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THE ROLE OF STRIATAL AFFERENTS IN THE RESPONSE OF STRIATAL NEURONS TO DEXAMPHETAMINE IN FREELY MOVING ANIMALS

by

© MARCUS W. WARENYCIA

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DALHOUSIE UNIVERSITY JULY, 1984

Dedication

I would like to dedicate this thesis to two people. Firstly, my dear wife Lucille who has put up with me through all these years, and who became increasingly supportive during the last weeks of preparations of this thesis.

Secondly, to my supervisor, Dr. Gerald M. McKenzie, who contributed to the process of preparing this thesis immeasurably, and whose unwritten motto: "always try to prove your data wrong", I have consciously adopted.

TABLE OF CONTENTS

Table of Contents	i
List of Figures	iv
List of Tables	ix
Abstract	xi
Abbreviations and Symbols Used in This Thesis	xii
Acknowledgements	xiii
INTRODUCTION	1
THE BASAL GANGLIA	1
FUNCTION OF THE STRIATUM	3
Clinical Findings in Pathophysiological States	4
Behavioral Consequences of Intrastriatal Electrostimulation	8
The Relationship Between Unit Activity in the Basal Ganglia and Movement	9
STRIATAL AFFERENTS	10
Nigrostriatal Afferents	11
Anatomy	11
Electrophysiology of the Nigrostriatal DA System	13
The Effect of External Stimuli on DA Release in the Striatum	14
Is DA an Inhibitory or Excitatory Neurotransmitter in the Striatum?	15
Dopamine Receptors	18
Corticostriatal Afferents	21
Anatomy	21
Electrophysiology of the Cortico-Striatal System	23
Glutamate as the Neurotransmitter of Corticostriatal Afferents	23
Cortical Modulation of Striatal Neurotransmission	24
Striatal Afferents From The PF-CM Complex	26
Anatomy	26
Electrophysiology of the PF-CM Complex	26
The Transmitter for Fibers from the PF-CM Complex to the Striatum	27
DEXAMPHETAMINE AND THE STRIATUM	28
Release of DA by DEX	28
Stereotypy and the Striatum	28
Amphetamine and the DA Theory of Schizophrenia	29
Effects of DEX on Striatal Neuronal Activity	31
Single Unit Studies in Immobilized Animals	31
Effects of DEX on MUA of Striatal Neurons in Freely Moving Animals	33
Effects of DEX on SUA in Freely Moving Animals	33
OBJECTIVES OF THE PRESENT STUDY	35
MATERIALS AND METHODS	37

RESULTS 66
Striatal MUA in Freely Moving Animals 66
Changes in MUA Following DEX 66
Effects of Anaesthetics and Analgesics on MUA 75
Halothane 75
Pentobarbital 75
Urethane 79
Chloral Hydrate 79
Morphine 79
Ketamine 79
Nitrous Oxide 87
Effects of Morphine and Nitrous Oxide on the Striatal Neuronal Response to DEX 87
Morphine 87
Nitrous Oxide 90
Effects of Immobilization on the Response of Striatal Neurons To DEX 90
DEX Responses In Cortically Ablated Animals 99
Unilateral Ablation 99
Striatal Responses to DEX After Bilateral Cortical Ablation 107
Effects of Cortical Lesions on Drug-Induced Catalepsy 107
Responses of Striatal Neurons to DEX Following Lesions of the PF-CM Complex 115
DEX-Induced Activation of Neurons within the PF-CM Complex 115
Reversal of DEX-Induced Inhibition of Striatal Neurons in Lesioned Animals 122
Striatal Glutamate, GABA and Glutamine Levels Following Unilateral Cortical Ablation 122
Striatal Glutamate, GABA and Glutamine Levels Following Bilateral Cortical Ablation 129
Receptor Changes Following Bilateral Cortical Ablation 129
The Effects of 6-OHDA in the SNC on the Striatal DEX Response 129
The Effects of Intra-Striatal 6-OHDA on the Striatal DEX Response 135
The Effects of Specific Dopamine Agonists and Antagonists on Striatal MUA 141
Dopamine Agonists 141
Effects of Dopamine Receptor Antagonists on DEX-Induced Activation of Striatal Neurons 147
Single Unit Studies 147
Normal Animals 147
Lesioned Animals 157
Histology 157
Electrode Locations 157
Cortical Lesions 157
Fimbria-Fornix Lesions 165
PF-CM Lesions 165

DISCUSSION 170

SUMMARY OF THE PRESENT STUDY 189

iii

CONCLUSIONS 195

APPENDICES 196

BIBLIOGRAPHY 216

List of Figures

Figure		Page
Figure 1.	Anatomical and neurochemical relationships within the basal ganglia.	5
Figure 2.	Structure of specific D_1 and D_2 dopamine receptor agonists and antagonists.	38
Figure 3.	Schematic of signal processing and data collection.	47
Figure 4.	Chromatogram of amino acid separation.	56
Figure 5.	Standard curve for amino acid determinations.	57
Figure 6.	Standard curve for dopamine analysis.	60
Figure 7.	Oscilloscope traces of striatal multiple unit recordings in freely moving animals.	67
Figure 8.	Effect of lesioning current on striatal MUA.	70
Figure 9.	Striatal excitation in response to DEX in the freely moving animal.	71
Figure 10.	Activation of behavior and striatal MUA following DEX in the freely moving animal.	72
Figure 11.	Striatal neuronal response to DEX, 1 mg/kg in freely moving animals.	73
Figure 12.	Striatal neuronal responses to DEX in freely moving animals.	74
Figure 13.	Effects of halothane on striatal MUA.	78
Figure 14.	Effects of pentobarbital on striatal MUA.	80
Figure 15.	Effects of urethane on striatal MUA.	81
Figure 16.	Effects of chloral hydrate on striatal MUA.	82
Figure 17.	Dose-dependent effects of morphine on striatal MUA.	83
Figure 18.	Time course of morphine-induced depression of striatal MUA and catalepsy.	84
Figure 19.	Effect of naloxone on morphine and ketamine-induced changes in striatal MUA.	85

Figure		Page
Figure 20.	Efects of ketamine on striatal neurons.	86
Figure 21.	Comparison of the effects of nitrous oxide on spontaneous MUA in freely moving and immobilized animals.	88
Figure 22.	Effects of analgesic doses of morphine on striatal neuronal responses to DEX in freely moving animals.	89
Figure 23.	Striatal neuronal responses to DEX in freely moving animals in the presence of nitrous oxide.	91
Figure 24.	Effects of immobilization on striatal neuronal responses to DEX.	93
Figure 25.	A comparison of striatal responses to DEX in the same animal as either freely moving or immobilized.	94
Figure 26.	A comparison of striatal neuronal responses to DEX, in the same animal as either freely moving or immobilized.	95
Figure 27.	Comparison of striatal neuronal responses to DEX in the same animal as either freely moving or immobilized.	96
Figure 28.	Comparison of striatal neuronal responses to DEX in the same animal as either freely moving or immobilized.	97
Figure 29.	Comparison of no change responses to DEX in immobilized animals to immobilized control animals receiving saline only.	101
Figure 30.	Effects of ketamine on striatal MUA in an immobilized animal.	102
Figure 31.	Behavioral activation following DEX in a unilateral cortically ablated animal.	103
Figure 32.	Reduced excitations on the ablated side in unilateral cortically ablated animals.	106
Figure 33.	Behavioral activation following DEX in a bilateral cortically ablated animal.	109
Figure 34.	Ratemeter and behavioral record in a bilateral cortically ablated animals with a bilateral fimbria-fornix lesion.	112

Figure		Page
Figure 35.	Haloperidol and morphine catalepsy following bilateral cortical ablation.	113
Figure 36.	Ratemeter record of inhibition of striatal MUA in a PF-CM lesioned animal.	116
Figure 37.	Ratemeter record of the response of PF-CM neurons to DEX.	119
Figure 38.	Time course of striatal and PF-CM complex activation following DEX.	120
Figure 39.	Effects of DEX on neurons of the PF-CM complex.	121
Figure 40.	DEX-induced reversal of inhibition to DEX in unilateral cortically ablated animals.	123
Figure 41.	Lack of DEX-induced reversal of striatal inhibition to DEX in a bilateral cortically ablated animal.	125
Figure 42.	Lack of DEX-induced reversal of striatal inhibition to DEX in a unilateral PF-CM lesioned animal.	126
Figure 43.	Effects of unilateral cortical ablation of the striatal content of glutamate, GABA and glutamine.	128
Figure 44.	Effects of bilateral cortical ablation on striatal content of glutamate, GABA and glutamine.	130
Figure 45.	Effects of bilateral cortical ablation on the binding of [^{3}H]Met-enkephalin to striatal membranes.	131
Figure 46.	Effects of bilateral cortical ablation on dopamine D_1 receptor binding.	133
Figure 47.	Effects of bilateral cortical ablation on dopamine D_2 receptor binding.	134
Figure 48.	Response of striatal neurons to DEX in an animal with a unilateral 6-OHDA lesion of the SNC.	137
Figure 49.	Relationship between the excitatory striatal response to DEX and the dopamine content of the striatum.	138
Figure 50.	Relationship between striatal dopamine and the excitatory effects of DEX on MUA.	139

Figure		Page
Figure 51.	Behavioral and striatal MUA response to DEX following unilateral instriatal depletion of dopamine.	142
Figure 52.	Effects of intrastriatal depletion of DA on DEX-induced excitation of striatal neurons.	143
Figure 53.	Behavior and striatal MUA following DEX in an animal having received a unilateral control infusion into one striatum.	144
Figure 54.	Response to DEX in animals receiving intrastriatal control infusions.	145
Figure 55.	Dopamine content of several brain regions following unilateral intrastriatal depletion of DA.	146
Figure 56.	Behavioral activation following LY 171555.	148
Figure 57.	Effects of a specific D_1 antagonist, SCH 23390, on DEX-induced activation of MUA.	149
Figure 58.	Effects of haloperidol on DEX-induced activation of MUA and DEX-induced behavior.	150
Figure 59.	Effects of sulpiride on DEX-induced excitation of striatal neurons.	151
Figure 60.	Sulpiride antagonism of DEX-induced activation of striatal MUA.	152
Figure 61.	Effects of Ro 22-1319 on DEX-induced striatal excitation.	153
Figure 62.	Effect of Ro 22-1319 on DEX-induced activation of behavior and MUA.	154
Figure 63.	Oscilloscope trace of a single unit in a freely moving animal.	155
Figure 64.	Effects of DEX on SUA and behavior - freely moving.	158
Figure 65.	Striatal inhibition of SUA following DEX.	159
Figure 66.	Excitation of SUA following DEX.	160
Figure 67.	Inhibition of SUA following DEX in cortically ablated animals.	162

Figure		Page
Figure 68.	Location of striatal recording sites.	163
Figure 69.	Location of cortical lesions.	166
Figure 70.	Location of PF-CM lesions.	167
Figure 71.	Excitatory response to DEX in a unilateral cortically ablated animal.	192
Figure 72.	Striatal inhibition to DEX in a unilateral cortically ablated animal.	193
Figure 73.	No change in striatal MUA following DEX in a unilateral cortically ablated animal.	194
Figure 74.	Biphasic striatal response to DEX in a unilateral cortically ablated animal.	195
Figure 75.	Striatal excitation following DEX in a bilateral cortically ablated animal.	196
Figure 76.	Striatal inhibition to DEX in a bilateral cortically ablated animal.	197
Figure 77.	No change in striatal MUA following DEX in a bilateral cortically animal.	198
Figure 78.	Biphasic response to DEX in a bilateral cortically ablated animal.	199
Figure 79.	Excitatory response to DEX in an animal with a unilateral PF-CM lesion.	200
Figure 80.	Striatal inhibition in an animals with a unilateral PF-CM lesion.	201
Figure 81.	No change in striatal MUA following DEX in an animal with a unilateral PF-CM lesion.	202
Figure 82.	Biphasic response to DEX in an animal with a unilateral PF-CM lesion.	203

List of Tables

Table		Page
Table I.	Morphometric Characterization of Neuronal Sub-populations of the Striatum	2
Table II.	Effects of iontophoretically applied dopamine on caudate neurons (taken from Moore and Bloom, 1978)	17
Table III.	Classification and Properties of Striatal DA Receptors Based on Radioligand Studies	19
Table IV.	SUA of Striatal Neurons in Immobilized, Artifically-Respired Rats	32
Table V.	Electrode Manufacture	44
Table VI.	Criteria for Evaluating Striatal Neuronal Responses to Drug Treatments	50
Table VII.	Least squares analysis of standard curve calibrations for simultaneous amino acid analysis	58
Table VIII.	Protocol for Receptor-binding Assays	62
Table IX.	Comparison of the Spontaneous MUA and Peak Responses to DEX, 2.5 mg/kg, Between Left and Right Striata of Freely Moving Rats	76
Table X.	Summary to Striatal Neuronal Reponses to DEX in Freely Moving Animals	77
Table XI.	Paired Comparisons of Mean Spontaneous MUA under Different Experimental Treatments	92
Table XII.	Summary of Striatal Responses to DEX in Immobilized Animals.	98
Table XIII.	Comparison of Successive DEX Treatments in the Same Animal	100
Table XIV.	Comparison of Mean Spontaneous MUA of Striatal Neurons in Control and Unilateral Cortically Ablated Rats	104
Table XV.	Comparison of Striatal Neuronal Responses to DEX, 2.5 mg/kg, in Freely Moving Control and Unilateral Cortically Ablated Rats	105

Table		Page
Table XVI.	Analysis of Striatal Excitatory Responses to DEX, 2.5 mg/kg, in Unilateral Cortically Ablated Rats	108
Table XVII.	Comparison of Mean Spontaneous MUA of Striatal Neurons in Control and Bilateral Cortically Ablated Rats	110
Table XVIII.	Comparison of Striatal Neuronal Responses to DEX, 2.5 mg/kg, between Freely Moving Control and Bilateral Cortically Ablated Rats	111
Table XIX.	Comparison of Mean Spontaneous MUA of Striatal Neurons in Control and Unilateral PF-CM Lesioned Rats	117
Table XX.	Comparison of Striatal Neuronal Responses to DEX in Freely Moving Control and Unilateral PF-CM Lesioned Rats	118
Table XXI.	Summary of DEX-Induced Changes in Response to Second Administration of DEX in Unilateral Cortically Ablated Rats	124
Table XXII.	Comparison of Mean Spontaneous MUA in Lesioned Animals Between 1st and 2nd (48 hrs. later) Administration of DEX, 2.5 mg/kg	127
Table XXIII.	Receptor Binding Studies of Striata Following Bilateral Cortical Ablation	132
Table XXIV.	Comparison of Mean Spontaneous MUA in Control Rats and Rats with Unilateral 6-OHDA Lesions in the Substantia Nigra	136
Table XXV.	Reductions in Striatal Dopamine Levels Following 6-OHDA Lesions of the Substantia Nigra	140
Table XXVI.	Increased Incidence of DEX-Induced Innibition Recorded from Single Units in Lesioned Animals	161
Table XXVII.	Striatal Recording Sites	164
Table XXVIII.	Summary of the Present Study	191

ABSTRACT

The purpose of this study was to attempt to explain the difference in the response of striatal neurons to dexamphetamine in freely moving animals (excitation) versus immobilized animals (inhibition). This was accomplished by examining the role of striatal afferents in the response to dexamphetamine in freely moving animals using multiple unit recording techniques. Destruction of either cortical afferents by ablation, or thalamic afferents by radiofrequency lesioning, or nigral afferents with 6-hydroxydopamine markedly reduced the incidence of striatal neuronal excitation in response to dexamphetamine. However, none of the lesions affected dexamphetamine-induced activation of behavior, thus suggesting that in the normal animal, striatal afferents convey the sensory feedback arising from drug-induced behavior to the striatum, thus resulting in excitation of striatal neurons. In contrast, immobilized animals respond to dexamphetamine with striatal inhibition more frequently than excitation. Biochemical analysis following cortical ablation or 6-OHDA lesions demonstrated reductions in striatal glutamate and dopamine levels, respectively. Furthermore, the incidence of striatal excitation to dexamphetamine was found to be directly proportional to the dopamine content of the striatum. The excitatory effects of dopamine were found to be mediated by a D_2 receptor. Lastly, the inhibitory response to dexamphetamine in unilateral cortically ablated animals reversed to one of excitation following the second administration of dexamphetamine 48 hrs. later.

It is concluded that sensory feedback arising from drug-induced behavior is responsible for striatal activation in response to dexamphetamine. This feedback is conveyed to striatal neurons by striatal afferents originating in cortical, thalamic and nigral areas. Furthermore, these results support the concept that dopamine is an excitatory neurotransmitter in the striatum and are contrary to the widely-held view that dopamine is an inhibitory neurotransmitter.

List of Abbreviations used in This Thesis

Ach	Acetylcholine
ADTN	2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronapthalene
AP	Anterior posterior
AVT	Ventral tegmental area
CHaT	Choline acetyltransferase
CPM	Counts per minute
D_1	Adenylate cylcase-linked dopamine receptor
D_2	Dopamine receptor not linked to adenylate cyclase
DA	Dopamine
DA_e	Excitatory receptors for dopamine
DA_i	Inhibitory receptors for dopamine
DEX	Dexamphetamine
DOPAG	Dihydroxyphenylacetic acid
DPM	Disintegrations per mintue
DV	Dorsoventral
EDTA	Ethylene diamine tetra-acetate
EMG	Electromyograph
EPSP's	Excitatory postsynaptic potentials
FM	Freely moving
GABA	Y-aminobutyric acid
GAD	Glutamic acid decarboxylase
GDEE	Glutamic acid diethyl ester
5-HT	5-hydroxytryptamine
HPLC	High performance liquid chromatograph
HVA	Homovanillic acid
IMM	Immobilized
I.V.	Intravenously
K^+	Potassium
LY 141865	D_2 agonist, racemic mixture
LY 171555	D_2 agonist, active stereoisomer
ML	Mediolateral
MUA	Multiple unit activity
NEN	New England Nuclear
NMDA	N-methyl-d-aspartate
6-OHDA	6-Hydroxydopamine
P_2	Crude synaptosomal fraction
PCA	Perchloric acid
PF-CM	Parafascicular centromedian
Ro 22-1319	D_2 antagonist
SCH 23390	D_1 antagonist
SCR	Standard channels ratio
SKF 38393	D_1 agonist
SNC	Pars compacta of the substantia nigra
SNK	Student-Neuman-Keuls test
SUA	Single unit activity

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INTRODUCTION

THE BASAL GANGLIA

The caudate nucleus, the putamen and the pallidum are three large subcortical nuclear groups that are collectively called the basal ganglia. The basal ganglia and several associated subthalamic and mid-brain structures are known as the extrapyramidal system (Cote, 1981). The largest constituents of the basal ganglia, the caudate nucleus and putamen are anatomically indistinguishable in the rat; the resulting homogeneous structure is called the striatum. On the basis of light and electron microscopy (Kemp and Powell, 1971a,b,c,d,e; Mensah and Deadwyler, 1974) six neurons intrinsic to the striatum have been characterized on morphometric grounds (Table I). Of particular note is the finding that one type of neuron, classified as the medium spiny neuron, accounts for 96% of the total neuronal population. More recent studies have attempted to further differentiate the medium spiny neurons of the rat striatum into four subtypes (Dimova et al., 1980).

Consideration of axon lengths suggests that of the six cell types present only two, the medium long axon and the giant, accounting for less than 4% of the total population, appear to be suitable candidates for giving rise to efferent fibers from the nucleus. Furthermore, the medium long axon cell has also been shown to project to the contralateral striatum (Mensah and Deadwyler, 1974) via the ventral corpus callosum. The remaining four cell types may be properly designated as interneurons.

Table I - Morphometric Characterization of Neuronal Sub-populations of the Striatum

Cell Description	% of Total Population	Distinguishing Morphological Features
Medium spiny	96	Diameter of 12-18 μm 5-6 medium length dendrites Many spines Short axon; many collaterals
[illegible]ium long axon		Diameter of 16-18 μm 4-6 medium length dentrites Few spines Long axon; few collaterals
Medium smooth	3	Diameter of 16-18 μm 4-5 long dendrites Very few spines Short axon; many collaterals
Varicose dendrite		Diameter of 12-14 μm Many short dendrites Varicose; no spines Short axon; many collaterals
Giant	>1	Diameter of 22-30 μm Few long dendrites Few spines Long axon; few collaterals; choline-acetyltransferase positive (Kimura et al., 1980)
Small	<1	Diameter of 5-9 μm Many very short dendrites Few spines Axon?

Of interest also are the findings of several groups that striatal neurons are very often situated in groups or clusters; cells within these groups are in direct contact with each other (Adinolfi and Pappas, 1968; Kemp, 1968; Hassler et al., 1974). Furthermore, Dimova et al. (1980) have demonstrated that the large primary dendrites of the medium spiny cells are in direct contact with other neuronal cell bodies.

With the electron microscope, nine types of synapses have been observed (reviewed by Hassler, 1978). Eight of these synapses are associated with the medium spiny neuron; synapse types I, II, III, IV, and VII account for 75% of all observed synaptic contacts. The sources of the afferent projection to these synapses are respectively, the substantia nigra (Types I and II), the cortex (Types III and VII), and the parafascicular-centromedian complex (PF-CM) (Type IV). The afferent connections of the striatum will be described in more detail in subsequent sections.

FUNCTION OF THE STRIATUM

Determining the normal physiological role of the basal ganglia remains problematic (for a review see Marsden, 1982a) and the possible function of the striatum cannot be discussed in isolation with respect to the other components of the basal ganglia. The basal ganglia are characterized by many complex interconnections, both afferent and efferent, between different discrete nuclei. The core structure of the basal ganglia is the striopallidal complex, consisting of striatum and globus pallidus. In view of the considerable afferent connections onto striatal neurons, it is

evident that the striatum is a receiving area for convergent somatic, auditory, visual and olfactory polysensory inputs derived from wide bilateral receptive fields (Krauthamer, 1979). In contrast, efferent fibers from the striatum give rise to two pathways, one to the pars reticulata of the substantia nigra, and the second pathway to the pars externa and interna of the globus pallidus. In turn, the inner segment of the globus pallidus is known to project to three thalamic areas: 1) the nuclei ventralis lateralis and ventralis anterior, 2) the centromedian nucleus, and 3) the lateral habenular nucleus. The afore-mentioned relationships are schematically summarized in Figure 1.

The functions of the striatum have been investigated through a variety of approaches. In addition to the many pharmacological investigations in laboratory animals, three other lines of inquiry have been fruitful, viz.:

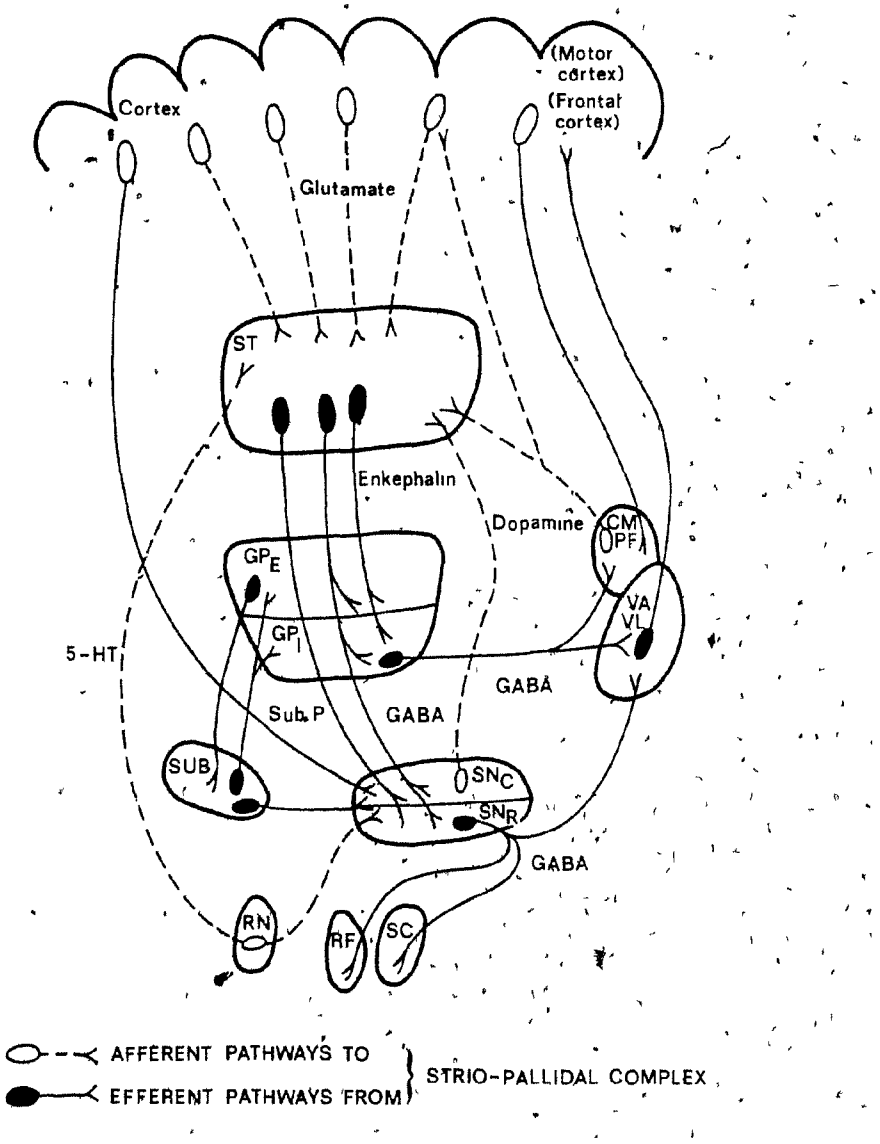
1) A survey of clinical findings in pathophysiological states with concomitant demonstrable neurochemical changes in the basal ganglia.
2) Analysis of behavioral effects of intrastriatal electrical stimulation.
3) Examination of unit recordings within the basal ganglia and their relationship to behavior.

Each of these approaches will be examined separately.

Clinical Findings in Pathophysiological States

Marsden (1982a) has concluded on the basis of data obtained from patients suffering from Parkinson's disease that the basal ganglia

FIGURE 1. Anatomical and neurochemical relationships of the basal ganglia adapted from Marsden (1982b). ST = striatum; GP_I = pars interna of the globus pallidus; GP_E = pars externa of the globus pallidus; SNC = pars compacta of the substantia nigra; PF-CM = parafascicular-centromedian complex; VA = nucleus ventralis anterior; VL = nucleus ventralis lateralis; RN = raphe nuclei; SUB = subthalamus; RF = reticular formation; SC = superior colliculus. $GABA_A$ = γ-aminobutyric acid; Sub. P = substance P; 5-HT = 5-hydroxytryptamine.


(Motor cortex)
(Frontal cortex)
Cortex
Glutamate
ST
Enkephalin
Dopamine
CM
PF
GPE
GPI
VA
VL
5-HT
GABA
Sub. P
GABA
SUB
SNC
SNR
GABA
RN
RF
SC
AFFERENT PATHWAYS TO
EFFERENT PATHWAYS FROM
STRIO-PALLIDAL COMPLEX

are responsible for the automatic execution of behavior. In Parkinson's disease the most observable symptoms include tremor, rigidity, and the inability to initiate movement (akinesia). It appears that the primary lesion in this disease involves degeneration of the dopaminergic cell bodies within the pars compacta of the substantia nigra (SNC) (Ehringer and Hornykiewicz, 1960). The biochemical features of this disease have been summarized by Marsden (1982b) and are as follows:

1) At least 80-85% of nigral neurons must be destroyed and the striatum 80% depleted of its dopamine (DA) content before overt symptoms appear.
2) The ratio of homovanillic acid to striatal DA content increases, indicating that the remaining nigral neurons increase their activity to compensate for the loss of dopaminergic tone.
3) Postsynaptic striatal DA receptors become supersensitive and as a consequence, the dopamine that is released exerts an enhanced postsynaptic action.

Although both presynaptic and postsynaptic compensation occurs, the severity of the disease is dependent upon the degree of striatal dopamine deficiency.

In contrast to Parkinson's disease, Huntington's chorea is characterized by neuronal cell death within the striatum and the substantia nigra, leading to considerable declines in striatal acetylcholine (ACh) and γ-aminobutyric acid (GABA) levels. These declines are matched by decreases in the activities of Glutamic Acid

Decarboxylase (GAD) and Choline Acetyltransferase (CHAT) the enzymes responsible for GABA and ACh synthesis respectively (Spokes, 1981). Clinically, patients suffering from Huntington's chorea present with choreiform (involuntary) movements.

It would appear then on the basis of clinical data that pathophysiological states involving the basal ganglia are characterized primarily by movement disorders.

Behavioral Consequences of Intrastriatal Electrostimulation

The relationship between behavior and caudate electrostimulation has shown that depending on the frequency of stimulation, various behavioral manifestations become apparent in the rat (Deadwyler et al., 1974). At low frequencies of stimulation (0.5 - 5.0 pulses/sec) ongoing behavior is inhibited; animal behavior slows and eventually ceases. This behavioral inhibition may be overcome by either changes in frequency of stimulation, novel environmental stimuli, or direct stimulation of primary sensory pathways. At frequencies of 10 to 30 pulses/sec all on going behavior is immediately halted ("arrest reaction"). Although this arrest state may be overcome by the animal, subsequent movements appear forced and unnatural and unilateral stimulation of the striatum at higher frequencies during the arrest reaction, results in contraversive circling. Lastly, at stimulus frequencies of 100 - 300 pulses/sec, sleeping or drowsy animals become alert; continued stimulation leads to circling movements or tremor. Based on similar considerations, Hassler (1978) has concluded that the function of the striatum is to focus attention onto a single event by simultaneously suppressing extraneous sensory

input. In contrast, the function of the pallidum is to co-ordinate locomotion by enhancing muscle tone and directing attention in anticipation of a given behavioral action.

The Relationship Between Unit Activity in the Basal Ganglia and Movement

Early single-unit studies in both conscious and chloralose-anaesthetized cats have demonstrated that caudate neurons are spontaneously active and display irregular rhythmic activity (Albe-Fessard et al., 1960; Sedgwick and Williams, 1967a,b). More sophisticated studies (Buser, 1974) of caudate single unit responses in awake monkeys (Macaca nemestrina), trained to perform a specific movement, have demonstrated the following:

1) Spontaneous firing rates of caudate neurons varied between 10-20 impulses/sec.
2) Cells activated only by the movement (ie, - silent in the absence of movement) could be detected.
3) Cells responding to the specific movement increased their discharge rates by 30-100%.
4) All cells were not activated at the same stage of the movement and could be activated either in the very early phases of movement (including prior to), during the movement itself, and after the movement.
5) Units could also be activated through presentation of novel visual or auditory stimuli in the absence of movement.

In another study, DeLong and Strick (1974) (confirmed by Liles, 1974) studied unit discharges in the monkey putamen as well as the globus

pallidus and were able to demonstrate that 45% of all the units studied in the putamen and 17% of all units in the globus pallidus discharged in relation to ramp (slow) movements. Less than 10% of all units in the putamen appeared to be related preferentially to ballistic (fast) movements. An analysis of EMG activity during ramp movements showed that the majority of neurons increased their discharge frequency before the actual onset of movement. These studies clearly indicate that caudate or putamen neurons have a high level of spontaneous activity and discharge in the course of motor behavior.

STRIATAL AFFERENTS

Striatal neurons receive afferent input from many areas of the brain. As mentioned earlier, 75% of the afferent input to the medium spiny neuron originates in three brain regions: the substantia nigra, the cortex, and the PF-CM. The remaining known afferents to the striatum arise from the raphé nuclei (Usunoff et al., 1974), the locus coeruleus (Kobayashi et al., 1975) and the amygdala (Kelley et al., 1982). Whereas the transmitter of afferent fibers from the amygdala is unknown, the projections from the raphé and locus coeruleus are thought to utilize 5-hydroxytryptamine and noradrenaline as transmitters, respectively (Steinbusch, 1981; Coyle and Henry, 1973).

Each of the three major striatal afferent systems will be considered separately.

Nigrostriatal Afferents

Anatomy

The dopaminergic innervation of the striatum was originally demonstrated by the formaldehyde-induced histofluoresence method of Falck and Hillarp (1962) and was shown to arise from mesencephalic nuclei (Andén et al., 1964, 1965). The cell bodies of the dopaminergic neurons projecting to the striatum are localized to the SNC and designated as the A9 cell group, as opposed to the A10 cell group within the ventral tegmental area (AVT) which was thought to project exclusively to limbic and cortical areas (Dahlstrom and Fuxe, 1964). However, with the advent of the more sensitive glyoxylic acid histofluoresence technique (Lindvall and Bjorklund, 1974a,b; Lindvall et al., 1974) as well as other tracer techniques, recent anatomical investigations have questioned the concept that SNC and AVT cells give rise to projections to anatomically separate areas of the telencephalon (Avendand et al., 1976; Domesick et al., 1976; Fallon and Moore, 1978; Fallon et al., 1978; Beckstead et al., 1979).

The projection from the SNC, consisting of a dense network of very fine nerve terminals (Hokfelt et al., 1969) is distributed throughout the striatum in an orderly medial-to-lateral arrangement, with the exception of the lateral quarter of the SNC which does not project to the extreme rostral pole of the striatum (Beckstead et al., 1979). In addition, the SNC does not project to the nucleus accumbens or olfactory tubercle. Both anatomical and functional studies have demonstrated that regardless of the anterior-posterior location of each SNC locus, that locus distributes fibers throughout

the striatum (Beckstead et al., 1979; Redgrave and Mitchell, 1982a).

The SNC projection to the striatum, however is inverted along the dorso-ventral axis such that cell bodies in the more ventrally placed pars compacta project to more dorsal striatal regions whereas the most ventral parts of the striatum receive fibers from more dorsal areas of the pars compacta (Beckstead et al., 1979). In animals pretreated with α-methyl-p-tyrosine, 250 mg/kg i.p., unilateral stimulation with medially-placed nigral electrodes resulted in maximal depletion of DA histofluoresence within anterior dorso-medial regions of the striatum, while laterally-placed electrodes produced maximum depletion of posterior, ventro-lateral areas (Redgrave and Mitchell, 1982b).

Studies on interhemispheric nigral projections in the rat have shown that approximately 5% of the nigrostriatal projection originates from the contralateral SNC (Pritzel et al., 1983a,b) and arises from bifurcating DA neurons. In addition to the well studied nigral DA system, other anatomical studies have shown that a non-dopaminergic nigrostriatal projection, comprising 5% or less of the total nigrostriatal projection, originates from the extreme medial edge of the SNC (Van Der Kooy et al., 1981; Pritzel et al., 1983a,b).

The DA neurons (A-10) in the AVT, distribute fibers to the entire ventromedial half of the striatum as well as the nucleus accumbens (Beckstead et al., 1979; Tassin et al., 1976).

Recent anatomical evidence based on multiple fluorescent tracers indicates that in contrast to AVT DA cells, cells of the SNC

collateralize extensively to both subcortical and cortical fields. It appears that cells in the SNC may be further categorized according to their cortical collateralization into three groups providing innervation to: 1) the cingulate cortex, 2) the prefrontal and suprarhinal cortices and 3) the entorhinal cortex (Loughlin and Fallon, 1984). Thus, DA neurons from the SNC appear to innervate not only the striatum but cortical areas as well.

Electrophysiology of the Nigrostriatal DA System

Grace and Bunney (1983a,b,c) have identified and studied nigral DA cells in the rat using both intracellular and extracellular recording and have shown that subsets of nigral DA neurons are electrotonically coupled. The presence of electrical synapses raises the possibility that the burst firing characteristic of these neurons may lead to the release of relatively large amounts of DA over a relatively long time (500 m.sec) at select projection areas. Bursting of nigral DA neurons increases following the administration of antagonists and decreases following agonists (Grace and Bunney, 1983c). Since nigral DA dendrites release DA (Leviel et al., 1979), the changes in nigral cell firing produced by agonists and antagonists could be due to stimulation of DA autoreceptors within the pars compacta.

If the DA neurons that comprise a single electrically coupled group project to the same postsynaptic site, a large facilitation of DA release may occur within a small region of the DA-innervated area. Alternatively, if the members of an electrically coupled group of DA neurons project to a variety of postsynaptic sites, it would be

conceivable that electrically coupled neurons could control neural subsets of a particular behavior through an action at different and discrete central nuclei.

Transitions from slow single spiking to rapid bursting have been observed for nigral DA neurons during the onset of orienting movement in the unanesthetized, freely moving rat (Meltzer and Bunney, unpublished observations; cited in Grace and Bunney, 1983c) suggesting that increased DA input necessary for the facilitation of movement may indeed arise as a result of synchronized burst firing of an electrically coupled network.

In contrast to the above findings, Steinfels et al. (1983) found that single unit activity (SUA) of DA neurons (3.68 ± 0.30 spikes/sec) in the cat SNC could not be correlated with phasic EMG changes, and that the most noticeable change in firing, a decrease in over 50% of all cells studied, occurred in association with orienting responses. After 2-4 trails, habituation was evident. Single unit activity was remarkably uniform and showed little relationship to overt behavior; neurons did respond however, to sensory stimuli such as an auditory or visual stimulus with excitation followed by inhibition. Habituation in response to sensory stimuli could not be demonstrated. The authors concluded that the stability of dopaminergic unit activity across a variety of behavioral states implies a tonic influence in contrast to direct mediation of a particular behavior.

The Effect of External Stimuli on DA Release in the Striatum

The release of dopamine from the striatum has been amply

demonstrated (McLennan, 1964; McKenzie and Szerb, 1968; Riddell and Szerb, 1971; Besson et al., 1971). More recently, it has been shown that dopaminergic neurons in the SNC, of both anaesthetized and freely moving rats, increase their rate of discharge in response to several sensory modalities (Harper et al., 1979; Hommer and Bunney, 1980; LeMoal and Olds, 1979); destruction of the nigrostriatal DA projection results in the appearance of a syndrome marked by neglect to sensory stimuli applied to the contralateral side of the body (Marshall et al., 1974). Similarly, specific depletion of DA using o-hydroxydopamine (6-OHDA) applied to the striatum also induces sensorimotor impairment (Marshall et al., 1980); recent evidence indicates that this sensorimotor impairment occurs irrespective of the location of the lesion within the anterior striatum (Dunnett and Iversen, 1982).

Using in vivo voltammetry to measure the release of DA, Keller et al. (1983) demonstrated in freely moving rats that intense environmental or exteroceptive stimuli will release striatal DA whereas homeostatic challenges do not.

Is DA an Inhibitory or Excitatory Neurotransmitter in the Striatum?

Electrical stimulation of the nigrostriatal pathway, either at the level of the substantia nigra or in the medial forebrain bundle, results in predominantly excitation of striatal neurons as seen with intracellular or extracellular recording (McLennan and York, 1967; Frigyesi and Purpura, 1967; Buchwald et al., 1973; Hull et al., 1974; Kitai et al., 1976, Norcross and Spehlmana, 1978a,b). In contrast,

in the majority of iontophoretic studies where DA was applied to striatal neurons, predominantly inhibitory responses have been observed (for a review see Moore and Bloom, 1978); exceptions to these observations have been studies in which chloral hydrate or halothane anaesthesia had been used (Table II).

Johnson et al. (1983) using urethane-anaesthetized animals, found that striatal neurons could be subdivided into two groups on the basis of their response latencies to cortical stimulation. Neurons in the "long-latency group" responded to DA more frequently with excitation as compared to the "short latency group".

Similarly, DA applied iontophoretically to striatal neurons in halothane-anaesthetized rats produced inhibition in 97% of spontaneously firing cells, 91% of glutamate-driven cells, but only in 57% of cells stimulated by cortical stimulation (Brown and Arbuthnott, 1983). Furthermore, sulpiride did not affect spontaneous activity or the inhibition produced by DA but did increase the response to cortical stimulation, suggesting that corticostriatal terminals contain DA receptors that are inhibitory on glutamate release.

Some reports in the literature suggest that the results of iontophoretic application of dopamine on striatal neurons may be explained on the basis of excitatory as well as inhibitory dopamine receptors (Norcross and Spehlmann, 1978). From behavioral studies, Cools and Van Rossum (1980) postulate the concept of excitatory (DA_e) and inhibitory (DA_i) receptors within the striatum. DA_e receptors are thought to be associated with nigrostriatal afferents originating

Table II - Effects of iontophoretically applied dopamine on caudate neurons (taken from Moore and Bloom, 1978)

Percentage of responding cells depressed	Number of cells tested	Animal	Preparation	Reference
96	50	Cat	Several anaesthetics	Bloom et al, 1965
78	55	Cat	Decerebrate	Bloom et al, 1965
87	130	Cat	Decerebrate	McLennan & York, 1967
84	81	Cat	Decerebrate	Connor, 1970
70	37	Rabbit	Gallamine paralyzed	Herz & Zieglgansberger 1968
100	(243)	Cat	Dial+urethane 6-OHDA	Feltz & De Champlain, 1972a
43*	136	Cat	Dial+urethane	Feltz & De Champlain, 1972a
86	(89)	Rat	Urethane	Gonzalez-Vegas, 1974
94	(91)	Rat	Halothane	Siggins et al, 1974
52	64	Cat	Cerveau isole	Spehlmann, 1975
28*	40	Rat	Chloral hydrate	Yarbrough, 1975
38*	51	Rat	Chloral hydrate, haloperidol	Yarbrough, 1975
92	103	Rat	Urethane	Stone, 1976, Stone & Bailey, 1975
90	40	Rat	Dial	Spencer & Havlicek, 1974
42	64	Rat	Penthrane	Spencer & Havlicek, 1974
34*	62	Rat	Halothane	Bevan et al, 1975
0*	26	Cat	Pentobarbitone	Kitai, et al, 1976

*Indicates studies where excitation was observed more frequently than inhibition following DA.

in the SNC whereas DA_1 receptors are associated with AVT neurons. In terms of fluoresence histochemistry, DA_e receptors are located within striatal areas marked by "diffuse" histofluoresence whereas DA_1 receptors, are thought to be located within striatal areas characterized by "dotted" histofluoresence (Cools, 1980). These patterns of histofluoresence, i.e. "diffuse" and "dotted", have been previously demonstrated suggesting heterogeneity of striatal dopaminergic innervation (Olson et al., 1972).

Dopamine Receptors

Multiple classes of striatal DA receptors are thought to exist on the basis of several different lines of experimental evidence. Ligand-binding studies (for a review see Seeman, 1980) have indicated the existence of three categories of dopamine receptor sites with distinct properties. These properties are summarized in Table III.

Similarly, behavioral studies with intrastriatal injection of dopamine agonists and antagonists have also indicated the existence of dopamine receptor subclasses (for a review see Costall and Naylor, 1981). In the rat, both classical neuroleptics e.g. haloperidol, and "atypical" neuroleptics e.g. thioridazine, clozapine and sulpiride, antagonize apomorphine-induced gnawing and locomotor activity (Ljunberg and Ungerstedt, 1977, 1978). In contrast, in the rat circling model, circling behavior induced by di-isobutylapomorphine was antagonized by haloperidol but not by clozapine; the circling response to lergotrile was inhibited by clozapine but not haloperidol (Tye et al., 1977). Although these findings suggest that DA receptor subtypes are present, any conclusions must be viewed

Table III - Classification and Properties of Striatal DA Receptors Based on Radioligand Studies

Receptor Designation and Biochemical Properties		Collateral Observations
D_1	Linked to adenylate cyclase. Stimulated by micromolar concentrations of dopamine and antagonized by micromolar concentrations of most neuroleptics.	All D_1 sites in the striatum are located on cell bodies within the striatum (Minneman et al., 1978)
D_2	Not linked to adenylate cyclase sensitive to micromolar concentrations of dopamine and nanomolar concentrations of neuroleptics	50-60% of D_2 sites located on striatal cell bodies (Minneman et al., 1978 and Schwarcz et al., 1980), 30-40% of D_2 sites are located on corticostriatal nerve terminals (Schwarcz et al., 1978; Garau et al., 1978).
D_3	Sensitive to nanomolar concentrations of dopamine but micromolar concentrations of neuroleptics.	Perhaps presynaptic on nigrostriatal nerve terminals. Decreases following nigrostriatal lesion (Nagy et al., 1978)

cautiously in light of the fact that although all stereotypic agents induce circling, drugs such as SKF 38393, bromocryptine and ergometrine all induce intense circling but not stereotypy (Costall and Naylor, 1981). It would appear then that DA receptors mediating stereotypy and circling behavior are not identical.

Biochemical and pharmacological criteria were used by Kebabian and Calne (1979) to differentiate DA receptors into two subclasses, D_1 and D_2. The D_1 receptor was defined as the receptor linked to adenylate cyclase and stimulated by micromolar concentrations of DA, whereas the D_2 receptor is not linked to adenylate cyclase.

The original concept of D_1 and D_2 receptors has been considerably augmented in recent years with the development of specific agonists and antagonists. SKF 38393, a specific D_1 agonist, stimulates adenylate cyclase as a partial agonist (ED_{50} = 0.075 μM versus an EC_{50} for DA of 3.5 μM), causes contralateral rotation in rats with unilateral nigral 6-OHDA lesions but does not cause stereotypy, emesis, or inhibition of prolactin release, and does not affect DA turnover (Setler et al., 1978). The specific D_1-antagonist, SCH 23390 blocks DA-stimulated adenylate cyclase (IC_{50} = 0.01 μM), antagonizes apomorphine-induced stereotypy, and conditioned avoidance but has no or little effect on emesis, prolactin release or DA synthesis.

LY 141865 does not stimulate adenylate cyclase, but does stimulate the D_2-receptor as judged by its ability to decrease either basal or isoprenaline-induced release of α-melanocyte-stimulating hormone from melanotrophs of the intermediary lobe of rat pituitary

(Tsuruta et al., 1981) and also its ability to lower serum prolactin in reserpine-treated male rats (Bach et al., 1980). In addition, this drug causes rotation in the rat turning model (Bach et al., 1980).

Specific antagonists for the D_2 receptor include (-) sulpiride and Ro 22-1319, both of which block apomorphine-induced stereotypy and are cataleptogenic at doses considerably higher than haloperidol (Worms, 1982; Elliot et al., 1977; Davidson et al., 1983).

The relationship between D_1 and D_2 receptors in the striatum is not clear. Stoof and Kebabian (1981) have suggested that stimulation of the D_2 receptor inhibits the formation of cyclic AMP resulting from stimulation of the D_1 receptor; their experimental evidence however, does not conclusively demonstrate that such a reciprical relationship exists within a given cell type within the striatum.

Lastly, recent behavioral evidence suggests that D_2 receptors alone, or in combination with D_1 receptors, but not D_1 receptors alone, are involved in goal-directed movements (Schmidt, 1983).

Corticostriatal Afferents

Anatomy

The anatomical studies of Webster (1961) demonstrated that the cortical projection to the striatum is topographically organized in both anteroposterior and mediolateral planes. Although this is true, considerable overlap of projection areas occurs, particularly in intermediate striatal regions. Studies on the cells of origin and the terminal distribution of corticostriatal fibers have shown that the medium size pyramidal cells of Layer V project to the striatum

predominantly in an ipsilateral manner (Wise and Jones, 1977). Furthermore, in the case of frontal cortex containing overlapping somatosensory and motor representations, which project to the anterior pole of the striatum, both ipsilateral and contralateral projections have been seen (Wise and Jones, 1977). Projections from more caudal cortical areas terminate in the dorsolateral striatum; projections from even more caudal cortical areas descend to the ventrolateral striatum but do not reach the posterior pole.

Patterns of terminal labelling indicate that corticostriatal fibers end in a very restricted manner and that the terminations are in the form of interrupted clusters and patches. Similar results are seen for the crossed corticostriatal projection; in morphological studies in animals with frontal cortex ablated, degenerating boutons, organized in patches, and exhibiting the features of Type III (axospinous) synapses, are seen in the striatum contralateral to the ablation (Hassler et al., 1982).

In addition to the projection from sensori-motor cortical areas, which is principally distributed to the dorsolateral quadrant of the anterior striatum (Webster, 1965; Carman et al., 1965; Wise and Jones, 1977; Kelley et al., 1982), the rostral striatum receives projections from the anteromedial or frontocingulate cortical area. This cortical region receives projections from the mediodorsal nucleus of the thalamus, and is a homologue of the prefrontal cortex of primates (Leonard, 1969). These cortical areas project to the entire ventromedial half of the anterior striatum as well as to a large portion of the dorsomedial striatum (Beckstead, 1979; Kelley et

al., 1982).

Electrophysiology of the Cortico-Striatal System

Blake, Zarzecki and Somjen (1976) studied evoked potentials within the caudate nucleus of cats after cortical stimulation and found by antidromic conduction that the cortico-striatal pathway was monosynaptic. Furthermore, the cortical projection appeared to be well organized topographically along the anterior-posterior axis and characterized by extensive overlapping. Summation of potentials at one point in the caudate nucleus could be evoked by stimulation of two widely separated cortical loci. Furthermore, evoked responses were also seen upon stimulation of the contralateral cortex.

Bishop et al. (1982) studied striatal neurons with a combination of intracellular recording and intracellular labelling with horseradish peroxidase. Two types of medium spiny cells and one medium aspiny cell all responded to either cortical or nigral stimulation with excitation; the giant aspiny neuron also responded to stimulation of the SNC with depolarization; the effects of cortical stimulation on this neuron were not determined.

Glutamate as the Neurotransmitter of Corticostriatal Afferents

Glutamate, an excitatory neurotransmitter (Curtis and Johnston, 1974; Krnjevic, 1974), was first implicated as the neurotransmitter of cortical afferents to the striatum by Spencer (1976) who showed that the excitation of striatal neurons obtained by cortical stimulation could be blocked by L-glutamic acid diethylester (GDEE). Biochemical studies of high-affinity glutamate uptake in anterior striatum following frontal cortical ablation showed that a reduction

in uptake accompanied the cortical lesion (Divac et al., 1977; McGeer et al., 1977). Similarly, it was also shown that frontal cortical ablation resulted in reduction of striatal glutamate levels (Kim et al., 1977).

Release of labelled L-glutamic acid from rat striatum following electrical stimulation of the frontal cortex has been demonstrated with push-pull cannula perfusion (Godukhin et al., 1980). Concurrent stimulation of the SNC did not enhance the release of labelled glutamate. Chronic dexamphetamine (DEX) treatment (5 mg/kg for 12 days) increased striatal glutamate levels, leading the authors to suggest that chronic DEX results in reduced glutamate release in the striatum, which is reflected in the observed increases in glutamate levels (Kim et al., 1981).

The literature regarding receptors for excitatory amino acids has been extensively reviewed (McLennan, 1981, 1982; Fagg and Foster, 1983) and electrophysiological experiments with agonists and antagonists have indicated the existence of three receptors. Both the N-methyl-D-aspartate (NMDA)-preferring and the glutamate/quisqualate-preferring receptors are present on striatal neurons (Lehmann and Scatton, 1982; Spencer, 1976).

Cortical Modulation of Striatal Neurotransmission

The role of the cortex on striatal cholinergic activity appears to be modulatory. Following unilateral cortical ablation the high affinity uptake of choline into striatal synaptosomes is decreased (Simon, 1982). However, neither Ach levels (Hassler et al., 1982) or CHAT activity (Scatton et al., 1982) appear to change. Furthermore,

the apomorphine-induced increase in striatal Ach levels, or the inhibition of K^+-evoked release of [H^3]-Ach from striatal slices preloaded with [H^3]-choline, as well as the apomorphine-induced decrease of striatal DOPAC (dihydroxyphenylacetic acid) were unaffected by bilateral cortical ablation. Unilateral or bilateral cortical ablation also failed to affect either DA levels (Hassler et al., 1982; Scatton et al., 1982) or the increase in DA turnover in response to haloperidol (Globus et al., 1983), suggesting that in cortically ablated animals, the dopamine-acetylcholine axis is not affected.

On the other hand, striatal glutamate binding has been found to increase approximately 30% following decortication but decreases 40% after nigral 6-OHDA lesions, suggesting the presence of glutamate receptors on DA nerve terminals (Roberts et al., 1982). In SNC lesioned animals 100 μM DA reduced the K^+-evoked release of endogenous glutamate to a greater extent in slices representing the lesioned striatum than in those from the intact side, suggesting supersensitivity of DA receptors on corticostriatal afferents. Others have demonstrated the reverse relationship, that is the ability of glutamate to enhance DA release (Giorgulieff et al., 1977; Marien et al., 1983). Thus it would seem that a reciprocal relationship between DA and glutamate release exists within the striatum. Not only can DA modulate the release of glutamate from corticostriatal afferents, but glutamate can also increase the amount of DA released from nigrostriatal nerve terminals.

Striatal Afferents From The PF-CM Complex

Anatomy

Striatal neurons receive a major afferent projection from the intralaminar complex of the thalamus, in particular, the PF-CM complex (Nauta and Whitlock, 1954; Jones and Leavitt, 1974). Like the cortical afferent projection, thalamostriatal fibers also exhibit patch-like terminal fields (Kalil, 1978). After thalamic (centromedian) lesions, degeneration of synapses at the level of the medium spiny neuron have been observed (Chung et al., 1977). As well as projecting to the striatum, the intralaminar nuclei also project to the cortex through branching axon collaterals (Jinnai and Matsuda, 1981); and Herkenham (1980) has shown that the entire neocortex of the rat receives projections from these nuclei.

Electrophysiology of the PF-CM Complex

Although Morrison and Dempsey (1942) first showed that stimulation of the intralaminar nuclei resulted in widespread recruitment (excitation) of cortical neurons, it was not until the pioneering work of Purpura and Malliani (1967) that it was demonstrated that there is an excitatory thalamostriatal projection. Buchwald et al. (1973) in the cat demonstrated with intracellular recording that caudate neurons respond to thalamic stimulation with excitation. Similarly, Kitai and associates (Kitai et al., 1976; Kocsis et al., 1976) stimulated the PF-CM complex and recorded monosynaptic EPSPs in caudate neurons of the cat. The striatal neurons being recorded were labelled with horseradish peroxidase and identified as medium spiny neurons. More recently, similar results

were also found in the rat (Van der Maelen and Kitai, 1981).

Most PF-CM neurons receive extensive bilateral inputs and have been characterized as polysensory, multimodal or sensory convergence neurons. Studies in chloralose-anaesthetized animals have demonstrated that 90% of these neurons are not spontaneously active but do respond to a wide range of sensory stimuli (somatic, auditory, visual) with a single spike or short burst discharge (Kruger, L. and Albe-Fessard, 1960).

The centromedian and parafascicular nuclei receive projections from the cortex; these projections arise from pyramidal cells in Layer V and are distributed over wide areas of cortex (Royce, 1983). The pattern by which cortical neurons impinge upon these nuclei bears a striking resemblance to that of the cortico-striatal projection (Royce, 1982).

The Transmitter for Fibers from the PF-CM Complex to the Striatum

On the basis of marked reductions in choline acetyltransferase activity in the head of the striatum 2-4 weeks after electrolytic lesions of the parafascicular nucleus, Simke and Saelens (1977) concluded that the fiber tract between the parafascicular nucleus and the striatum was cholinergic. Using a similar approach, Hassler (1975) had reached a similar conclusion. However, in a recent study (Barrington-Ward et al., 1984) no reductions in Choline Acetyltransferase (Chat) activity in the striatum could be demonstrated following lesions of the PF-CM complex. Furthermore, interruption of all afferent connections to the striatum does not

significantly alter striatal Ach levels (Kataoka et al., 1974), thereby supporting the concept that Ach functions only as the transmitter of interneurons of the striatum (Butcher, 1977; Misgeld and Bak, 1979).

DEXAMPHETAMINE AND THE STRIATUM

Release of DA by DEX

Since the original demonstration of the release of striatal dopamine by DEX using push-pull perfusion (McKenzie and Szerb, 1968), several groups have confirmed that DEX releases dopamine (Bartholini, 1980; Glowinski et al., 1979; Phillips et al., 1982). More recently, Zetterstrom et al. (1983), using the intracerebral dialysis technique have shown that in freely moving rats DEX produces a 14-fold increase in the release of endogenous striatal DA. Similarly, Forni and Nieoullon (1984), using *in vivo* voltammetry have shown that in the freely moving hamster, DEX enhances the release of DA. It is thus clear that DEX releases striatal DA both in freely moving and immobilized animals.

Stereotypy and the Striatum

Some authors argue that the striatum is the primary site of drug action for the induction of stereotyped behavior (Ernst and Smelik, 1966; Fog et al., 1970; Asher and Aghajanian, 1974; Creese and Iversen, 1974) while others maintain that mesolimbic nuclei are primarily responsible. McKenzie (1972) showed that bilateral destruction of the striatum did not affect stereotypy whereas lesions of the olfactory tubercle either eliminated or greatly reduced stereotypy. Direct injection of dopamine agonists into the nucleus

accumbens results in stereotypy and hyperactivity (Costall and Naylor, 1974). Lastly, enhancing GABA-ergic transmission in the striatum by pretreatment with aminooxyacetic acid or muscimol enhances DEX-induced stereotypy but inhibits striatal neuronal discharges (McKenzie and Hansen, 1980). Such evidence, taken collectively, argues against a primary role for the striatum in the induction of drug-induced stereotypies.

Amphetamine and the DA Theory of Schizophrenia

Repeated administration of amphetamines in humans may elicit a psychotic state akin to paranoid schizophrenia (Connell, 1958), leading many to hypothesize that DA holds a central position in the etiology of schizophrenia and possibly other affective disorders. In addition, in Parkinson's disease and Huntington's chorea where dysfunction of brain DA systems has been documented, affective disturbances and cognitive abnormalities have also been described (Marsden, 1982b).

The DA theory of schizophrenia is based on the following observations:

1) Schizophrenic symptomatology is greatly reduced by neuroleptic drugs such as the phenothiazines and butyrophenones, which are known to block DA receptors.
2) The relative potencies of neuroleptics in blocking D_2 receptors correlate very closely with their relative clinical potencies (Seeman et al., 1976).
3) Neuroleptic drugs enhance DA turnover in proportion to their clinical potencies (Carlsson and Lindqvist, 1963).

4) Agents that decrease functional levels of DA, such as reserpine (depletes dopamine) or α-methyl-p-tyrosine (inhibits catecholamine biosynthesis), lower the therapeutic dose of neuroleptics (Walinder et al., 1976). Similarly, low doses of apomorphine, which inhibit DA release, alleviates schizophrenic symptoms (Taminga et al., 1978).

5) Whereas neuroleptics diminish schizophrenic symptoms, amphetamines exacerbate them (Angrist et al., 1980); in fact chronic use of amphetamines leads to psychosis (Connell, 1958). Since DEX can release noradrenaline as well as DA (Carr and Moore, 1969) it may be argued that it is insufficient to assume that DA is responsible. However, that DA is more likely to be involved is supported by observations that l-dopa, which elevates DA levels in the brain aggravates schizophrenic symptoms (Angrist et al., 1973).

Although some authors (Snyder, 1982) contend that no unequivocal abnormalities in brain DA systems in schizophrenic patients have been demonstrated, others have demonstrated that striatal D_2 receptors are selectively increased in schizophrenic brains (Owen et al., 1978; Cross et al., 1981). More recent studies (Owen et al., 1984) have shown that nigral D_2 receptors also increase in schizophrenia; this increase is seen in brains of both neuroleptic-treated and untreated schizophrenics. Thus, the evidence implicating abnormalities of brain DA systems in schizophrenia suggests that D_2 receptor function has been altered.

Effects of DEX on Striatal Neuronal Activity

Single Unit Studies in Immobilized Animals

Throughout the last decade, Rebec, Groves, and co-workers have studied the responses of single neurons in the striatum to DEX (for reviews see Groves, 1983, and Groves and Tepper, 1983). These studies have all been carried out on immobilized, paralyzed, artificially respired rats. In the absence of behavior striatal neurons display little variation in spontaneous firing rates, the aggregate mean from 11 published reports (Table IV) being 2.05 ± 0.33 spikes/sec (range = 0.34-4.23 spikes/sec).

It was initially reported (Rebec and Segal, 1974) that striatal neurons respond to DEX only with inhibition preceded by a brief period (5-10 min) of increased firing; the duration of the inhibition appeared to be dose-dependent (0.5-4.0 mg/kg). Rebec and Segal (1978) reported that at a dose of 2.5 mg/kg of DEX, 83% of all neurons tested responded with inhibition, but at 5 mg/kg inhibition was seen in only 38% of all neurons. Moreover, at a dose of 7.5 mg/kg, inhibition could not be seen at all, having been replaced completely by excitation. In another report (Bashore et al., 1978) only 64% of striatal neurons responded with inhibition to DEX, 2.5 mg/kg. In contrast, Alloway and Rebec (1983) reported that only 36% of striatal neurons showed inhibition at a dose of 1 mg/kg but at the higher dose of 5.0 mg/kg, 64% of all neurons responded with inhibition. Thus it would seem that the estimates of striatal neurons responding to DEX with excitation or inhibition vary considerably from study to study and that more striatal neurons

Table IV - SUA of Striatal Neurons in Immobilized, Artificially-Respired Rats

Spontaneous Neuronal Activity (Range, mean or mean ± SEM in spikes/sec	Reference
3.0 ± 0.44	Groves, Rebec and Segal, 1974
3.12 ± 0.65	Rebec and Groves, 1975
2.27 ± 0.72	Rebec and Groves, 1975
1.10 - 1.95	Groves, Rebec and Harvey, 1975
1.63 - 6.83	Groves, Wilson, Young and Rebec, 1975
1.06 - 2.37	Rebec and Groves, 1976
0.08 - 13.9; 2.43	Wilson, Juraska and Groves, 1977
0.80	Rebec and Segal, 1978
1.52 ± 0.5	Bashore, Rebec and Groves, 1978
0.34 ± 0.16 - 0.61 ± 0.15	Rebec, Bashore, Zimmerman and Alloway, 1979
1.60 ± 0.28	Alloway and Rebec, 1983

respond with excitation as the dose of DEX is increased.

The role of dopamine in striatal neuronal responses to DEX in immobilized animals has not been adequately examined. In a study by Groves et al. (1975a), electrolytic lesions placed in the nigrostriatal DA bundle, (1) attenuated but did not abolish the inhibitory response, (2) did not affect spontaneous discharge rates of striatal neurons, (3) did not affect the transient excitatory response following DEX, and, (4) resulted in a decrease in telencephalic DA content of approximately 55%.

Effects of DEX on MUA of Striatal Neurons in Freely Moving Animals

Hansen and McKenzie (1979) found that in freely moving rats DEX produced excitation of striatal neurons as measured by multiple unit recording. The excitation of striatal neurons was dose-dependent and paralleled DEX-induced locomotor activity and stereotypy, leading the authors to point out that stereotypy is accompanied by striatal activation. However, in a further study, McKenzie and Hansen (1980) were able to abolish DEX-induced excitation of striatal neurons by enhancing striatal GABA-ergic transmission while at the same time observing an increase in stereotypy. Therefore, it appears that striatal activation can be dissociated from behavioral activation.

Effects of DEX on SUA in Freely Moving Animals

Hansen (personal communication) found that 90% of striatal neurons of freely moving rats increased their discharge rates in response to DEX. Similarly, Trulson and Jacobs (1979), found that in freely moving cats, 70% of all striatal neurons recorded, respond to

DEX with excitation in a dose-dependent manner. Furthermore, compared to spontaneous discharge rates in immobilized animals, striatal neurons in freely moving animals exhibit higher spontaneous discharge rates (4.4 - 18.4 spikes/sec; median = 7.6), suggesting that behavior played an important influence on spontaneous striatal neuronal activity. These observations are in accord with the concept that the striatum subserves sensory as well as motor functions (Krauthamer, 1979).

OBJECTIVES OF THE PRESENT STUDY.

The effects of DEX on striatal neuronal activity appear to be fundamentally different, depending on whether experiments are carried out in immobilized or freely moving animals. Whereas excitation is the prevalent neuronal response to DEX in freely moving animals, inhibition has been reported to be the more predominant neuronal response in immobilized animals. The most likely explanation for this marked difference may lie in the fact that the immobilized animal is incapable of expressing either normal or drug-induced behavior. In order to postulate a role for behavior, or for that matter sensory feedback arising from drug-induced behavior it is necessary to identify the possible neural substrate(s) capable of conveying feedback to the neurons of the striatum. Since striatal neurons receive considerable afferent projections from other brain regions the objectives of this study were defined as follows:

1) To delineate more precisely the effects of DEX on striatal neurons in freely moving versus immobilized animals using the multiple unit recording technique.
2) To assess the roles of the three major afferent projections to striatal neurons, ie. those originating in the cortex, the PF-CM complex of the thalamus, and the pars compacta of the substantia nigra, by examining the effects of lesions within these structures on the striatal neuronal response to DEX in freely moving animals.
3) To extend further the analysis of the role of striatal

afferent systems by attempting to understand the behavioral and neurochemical consequences of disruption of the three major afferent projections of the striatum.

4) To attempt to define pharmacologically the role of the nigrostriatal system in the DEX-induced activation of striatal neurons as it is well established that DEX releases striatal DA in freely moving animals.

MATERIALS AND METHODS

ANIMALS

Adult male Long-Evans hooded rats, weighing 240-400 g, were used. Animals were kept on a 12 hr day-night cycle and were given access to food and water ad libitum.

DRUGS, REAGENTS AND MATERIALS

Drugs, and reagents and materials used in this study are listed in Appendices II and III, respectively. The names and structures of DA agonists and antagonists are given in Figure 2.

STEREOTACTIC APPARATUS

A rat stereotactic apparatus (David Kopf Instruments) was used in this study. The incisor bar was set 5.0 mm above the interaural line when rats weighing 280 g or more were used. For animals weighing less than 290 g the height of the incisor bar was determined by the formula of Whishaw et al. (1977):

$$H_i = Dx$$

where H_i = height of incisor bar

D = distance from the back of the incisors to the interaural line with the incisor bar set at 0

x = sine of the mean angle between the horizontal plane of the interaural line and the incisor bar set at 5.0 mm ($x = 8°29'$; $\sin x = 0.147$)

The bregmoidal intersection was used as the anterior-posterior zero

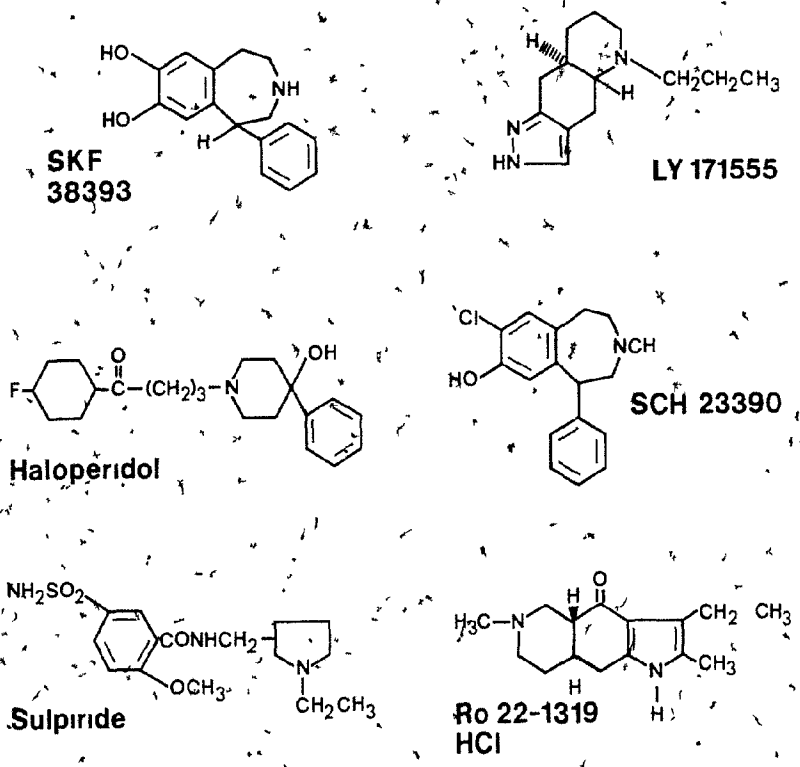


FIGURE 2. Structures of D_1 and D_2 DA receptor agonists and antagonists used in this study. D1 agonist = SKF 38393; D_2 agonist = LY 171555. D1 antagonist = SCH 23390. D1 and D_2 antagonist = haloperidol. D_2 antagonists = sulpiride and Ro 22-1319.

reference as well as the medio-lateral zero, and the surface of the dura taken as the dorso-ventral zero reference. All co-ordinates were taken from the atlas of Pellegrino and Cushman (1967).

LESIONING TECHNIQUES

Dopamine-Depleting Lesions

6-Hydroxydopamine (6-OHDA) solutions were infused into the brain through a 30-gauge cannula connected with polyethylene tubing (PE 10) to a 10 µl Hamilton syringe capable of accurately delivering 0.5-10 µl. Using this apparatus small volumes (2.0 or 4.0 µl) were infused slowly thus minimizing tissue damage at the infusion site.

Nigral Lesions

All animals used in this part of the study weighed 280-310 g to minimize stereotactic error. Unilateral 6-OHDA lesions (Setler et al., 1978) were placed in the SNC at two points, one rostral and one caudal to the midpoint of the nucleus (-3.0 AP, ± 2.4 ML, -8.0 DV and -3.8 AP, ± 2.2 ML, -8.5 DV). Each locus received 8 µg 6-OHDA (HBr salt) in 4.0 µl of 0.9% saline containing 1 mg/ml ascorbic acid. This volume of 4.0 µl was infused over 10 min. and the cannula left in place for an additional 10 min. to allow for adequate diffusion. Animals were treated with 30,000 I.U. penicillin G i.m. and given 15-21 days to recover before electrode implantation.

Control animals consisted of normal animals (N=2), normal animals bilaterally implanted with electrodes in the striatum (N=2), and animals in which unilateral sham cannulation of the substantia nigra was carried out (N=4).

Intrastriatal Lesions

Fifty µg of 6-OHDA (HBr salt) in 2.0 µl of 0.9% saline containing 0.00001 N HCl and 0.1 mg/ml sodium meta-bisulfite (final pH 6.6) was infused unilaterally into the anterior striatum (AP + 2.4, ML ± 2.5, DV - 4.5) over 20 min., and the cannula left in place for 5 min. to allow for diffusion. Ascorbate as an anti-oxidant was avoided because of the report of Waddington and Crow (1979) that ascorbate alone may be neurotoxic. The volume and dose of 6-OHDA chosen was selected on the basis of the work of Dunnett and Iversen (1982) where a volume of 2.0 µl containing 4.0 µg 6-OHDA was shown to deplete an area approximately 1/7 of the area of the entire striatum within a given coronal section. Animals then received a prophylactic i.m. injection of 30,000 I.U. Penicillin-G. Following recovery from anaesthesia (4-24 hrs.) animals were examined for turning preference. Control animals (N=4) received a unilateral intrastriatal infusion of 2 µl of 0.9% saline containing 0.1 mg/ml sodium meta-bisulfite, adjusted to pH 6.6 with 0.00001 N HCl.

In contrast to nigrally-lesioned animals, striatally-lesioned animals were given only 7 days to recover before electrode implantation. The allotted recovery time was shortened for two reasons:

1. The possibility of regeneration within the depleted striatum (Marshall et al., 1983).
2. The possibility of increased activity of nigro-striatal fibers originating from the contralateral substantia nigra (Agid et al., 1973).

Cortical Lesions

In all cases cortex was removed by aspiration through a curved blunt 18-gauge needle. Unilateral lesions were restricted to the left side as previous work indicated that suction lesions of the cortex on the right side or infarction of the right middle cerebral artery resulted in a behavioral syndrome of hyperactivity as well as decreases in subcortical catecholamine levels (Pearlson and Robinson, 1981; Robinson and Coyle, 1980). Topographically, lesions were restricted to the dorsal surface of the brain because it had been shown that focal ventrolateral lesions decreased monoamine levels in the striatum ipsilateral to the lesion (Finkelstein et al., 1983).

Unilateral Cortical Ablations

The calvarium overlying the area of cortex to be ablated was removed by means of a dental drill used in the manner of a router. The dura was cut and reflected, and cortex then removed by aspiration. The resulting cavity was packed with a piece of Gelfoam cut approximately 20% larger than the area of removed cortex. Skin was then approximated and sutured. Animals received 30,000 I.U. Penicillin G intramuscularly and were given 15-21 days to recover prior to electrode implantation.

Bilateral Cortical Ablations

Only one type of bilateral lesion was used throughout these studies. Bregma was marked with a fine dental drill before skull bone was removed. A midline strip of bone, approximately 2.0 mm wide was left in place for two reasons: 1) the marked bregma point was needed for future stereotactic procedures, and 2) the midline bone

strip served for anchoring of the electrode assembly with dental acrylic during subsequent electrode implantation 15-21 days post-ablation.

The dorsoventral extent of all cortical lesions was restricted at the level of the corpus callosum at the time of ablation.

Fimbria-Fornix Lesions

Before the calvarium was removed, a stereotactic measurement was carried out to locate a point 1.0 mm posterior to Bregma. This anterior-posterior point was then marked with a scalpel on the central suture of the midline. Once the skull had been removed (except the midline bone strip) a fine pair of iris scissors (Irex) was aligned with the bone marking on the central bone strip and lowered until the tip of the scissors was level with the fornix which was then severed. The co-ordinates for this lesion were taken from Waalas (1981).

Once the fimbria-fornix had been severed bilateral cortical ablation was carried out.

Parafascicular-Centromedian Complex Lesions

Electrolytic lesions using a radio-frequency generator (Radionics, Burlington, Mass) were placed at the following thalamic co-ordinates: AP - 2.5, LM ± 0.9 and DV - 6.0, which represented the approximate midpoint of the parafascicular-centromedian (PF-CM) complex. Lesioning parameters employed were as follows: 75-100 sec. at a probe tip temperature of 65°C. Animals were treated with a prophylactic injection of Penicillin G (30,000 I.U. given intramuscularly) and allowed to recover 15-21 days prior to electrode implantation.

ELECTRICAL RECORDING

Electrode Assembly

Electrodes were manufactured from the components listed in Appendix III and constructed according to the scheme of Table V.

Ground screws to be used during implantation (4/animal) were prepared by soldering treated (flamed to remove lacquer insulation) ground wires, approximately 4-5 cm in length, to pointed-end jeweller's screws (Lomat Watch Material Co., Montreal, Que.). Phosphoric acid was used to treat all surfaces being soldered to assure proper fluxing.

Electrode Implantation

Animals were anaesthetized with halothane and positioned in the stereotactic apparatus. A midline incision was made on the skull from the bone overlaping the olfactory bulbs to the posterior-most aspect of the central suture. All skin and connective tissue were reflected to the sides of the skull, and all wound edges treated with Styptic to prevent oozing into the operational field. The top of the skull was then swabbed with 70% ethanol to dry the surface and the bregmoidal intersection located. The electrode assembly was aligned with bregma and the corresponding zero references established. The electrode assembly was then moved to the desired anterior-posterior and medio-lateral co-ordinates overlying the striatum, and the points on the skull marked with a fine tip indelible marker. Using a dental drill, burr holes were made at the corresponding marked points, taking care not to pierce the dura. The dorso-ventral zero point on the surface of the dura was then determined, and the electrode

Table V. Electrode Manufacture

1. Twist teflon coated wire to make bipolar configuration.
2. Remove teflon coating at the end of electrode wire (1.0 - 1.5 mm).
3. Solder wire into amphenol tale pins.
4. Remove laquer insulation by flaming from ground wire.
5. Solder ground wire into amphenol tale pin.
6. Push ground wire and electrode pin assemblies into threaded male connectors.
7. Measure distance between the two electrode wires and set to 5.0 mm.
8. Apply orthodontic resin (mixture of powder and liquid) for cementing in place.
9. Cut electrode wires to desired length (7.0 - 9.0 mm).

assembly removed from the field.

Four holes were then made in the skull, two ahead and two behind the electrode assembly holes using a small hand drill. The ground screws, with attached ground wires, were then screwed into the holes. All four ground emplacements were covered with dental acrylic, care being taken not to occlude the burr holes designated for the electrode wires.

The dura was then pierced and the electrode wires lowered to the desired depth within the underlying striatum. Dental acrylic was then used to encapsulate the electrode assembly extending from the bottom of the connection to the skull surface. At the same time dental acrylic was also used to build a 'bridge' between the ground emplacements and the electrode assembly. Approximately 20 minutes were given for the entire shaped mass of dental acrylic to set properly. The ground wires were then bent along the contours of the electrode assembly-dental acrylic fixture and twisted together behind the fixture. This coil of wires was then cut with wire cutters and the common ends of the stump soldered. The ground was then bent into the downward contour of the fixture. Furacin powder (approximately 100 mg) was sprinkled along the wound edges and the skin re-opposed with simple discontinuous sutures both ahead and behind the fixture. Reinforcing sutures were placed immediately proximal and distal to the electrode fixture. Animals were then given 30,000 I.U. Penicillin G intramuscularly and allowed 5-7 days to recover prior to the acute recording experiment.

Identical implantation protocols were followed throughout these

experiments with two exceptions. First, in bilateral cortically ablated animals the absence of considerable bone surface area necessitated the use of larger amounts of dental acrylic on the ground emplacements and the bridge structure between them in order to anchor adequately the electrode assembly. Secondly, in experiments with intrastriatal 6-OHDA lesions, the burr hole for the infusion cannula was also used for the electrode. Dorso-ventral zero was obtained for the electrode wire on the contralateral dura.

Signal Processing

Neuronal action potentials were first amplified by a preamplifier (WPI Instruments Inc., New Haven, Conn) and then differentially amplified by a Tektronix oscilliscope (Tektronix Inc., Beaverton, Ore) before being passed to a band pass filter (0.3 - 10 kHz) (AP Circuit Corporation, New York, N.Y.). The filtered signal was then fed to a window discriminator (Mentor Corp., Minneapolis, Minn) and the multiplexed output displayed on an oscilliscope. Signal-to-noise ratios of less than 2.5:1 (peak to peak) were deemed unacceptable. Each standard pulse generated by the window discriminator, representing an action potential was recorded by an Ortec counter (Ortec Inc., Oakridge, Tenn.) and accumulated four-minute bin totals printed out on electrosensitive paper. A schematic summary of the recording and signal processing procedure is given in Figure 3.

In most experiments, an analog output was sent to a polygraph (Grass Instruments, Quincy, Mass.) to obtain a ratemeter record. Ratemeter calibrations were obtained from the test function of the

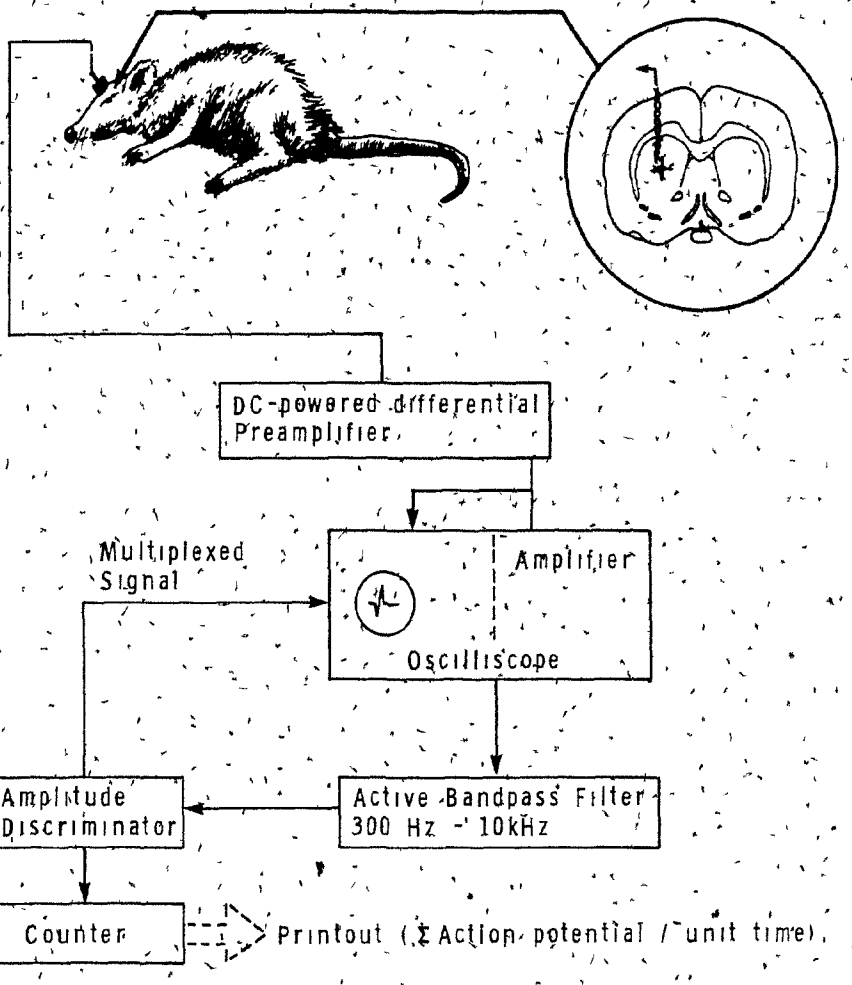


FIGURE 3. Schematic representation of signal processing and data collection used in this study.

window discriminator, which delivered a test signal at frequencies corresponding to 1800, and/or 3600 spikes/min.

Behavioral Recording

Behavioral activity was monitored in most experiments using a Grass Polygraph connected to the analog output of a Stoelting activity monitor (Stoelting Inc., Chicago, Ill.), placed under the recording chamber and set to detect movements larger than respiration.

Experimental Paradigm and Data Analysis

Once discrimination criteria were established recording of neuronal activity commenced. Freely moving animals were allowed to move freely in the test enclosure (cardboard cylinder - 25 cm Dx 30 cmH) for at least 32 min while recording SUA or MUA to establish a baseline. The bin totals from the 8 consecutive 4-min intervals immediately preceding any drug treatment were averaged to obtain spontaneous multiple-unit activity (MUA) and the mean value set as 100% (control). Throughout this thesis this value is referred to as spontaneous MUA. Spontaneous MUA of several animals were averaged to obtain mean spontaneous MUA. All data points were then expressed in terms of % of control.

For group comparisons % of control values were averaged to obtain a mean ± SEM. In evaluating drug treatments, post-drug values were compared to the value immediately preceding drug with an analysis of variance and the Student-Neuman-Keul test for multiple comparisons. A P value of 0.05 was considered significant. Statistical analysis showed that all the values obtained during the

control period, including the last interval, were equivalent.

In situations where data was evaluated qualitatively, such as in consideration of neuronal response patterns, the quantitative criteria of Table VI were used.

Statistical comparisons involving response pattern sub-types were carried out using 4 x 2 contingency tables and the χ^2-test for independence; a P value of 0.05 was considered significant. Throughout this thesis N = number of animals and n = number of recording sites.

Drug Administration

Unless otherwise stated, animals received DEX only once. With exception of the halothane and nitrous oxide-oxygen mixtures (70% N_2O-30% O_2) all drugs were given i.p. A mixture of 3% halothane in air was obtained using a Fluotec Mark-2 (Fraser Sweatman Inc., Buffalo, New York). The test cage was sealed within a plastic garbage bag (approximate volume 6-7 litres) and the halothane mixture delivered through one tube and evacuated through another tube at the bottom of the cage such that the rates of inflow and outflow were matched.

Nitrous oxide and oxygen mixtures were obtained with a Kinet-o-meter manifold (Ohio Chemical and Surgical Equipment Co., Madison, Wisconsin) to achieve a 70% N_2O-30% O_2 mixture. The mixture was delivered by a side-port to freely moving animals in the test cage sealed with a plexi-glass cover at a rate of 1500 ml/min. Ten minutes was considered sufficient time to fill the 6L volume of the test cage. In immobilized animals, the N_2O-O_2 mixture was delivered

Table VI. Criteria for Evaluating Striatal Neuronal Responses to Drug Treatments

Type of Response	Evaluation Parameters
Excitation	Sustained[+] increased in firing rate greater than 120% of control
Inhibition	Sustained decrease in firing rate less than 80% of control
No change	A maintained firing rate between 80 and 120% of control
Biphasic	Combinations of the above three

[+]The quantitative assignment of "sustained" was dependent on the dose of a given drug.

through a tracheal cannula using a small animal respirator (Harvard Apparatus, Dover, Massachusetts).

Immobilization Procedures

In animals anaesthetized with 3% halothane applied through a nose cone, the trachea was isolated, and a glass tracheal cannula inserted. Animals were then given a sub-cutaneous injection of 0.5 ml succinylcholine (100 mg/ml in 0.9% saline) and ventilated with 70% N_2O–30% O_2 delivered by a small animal respirator. Xylocaine ointment was applied to all wound surfaces and warm physiological saline applied periodically to the eyes to prevent corneal discomfort. Animals were blanketed with Kleenex and a circulating hot-water pad (Hamilton Industries, Cinncinatti, Ohio) controlled by a rectal thermistor (YSI telethermometer, Gorman Rupp Industries, Belleville, Ohio) used to maintain body temperature at 37 ± 0.5°C.

Behavioral Testing-Catalepsy

Catalepsy produced by haloperidol or morphine was measured by determining the amount of time animals remained motionless when their forepaws were placed on a box 4.5 cm high. Readings were taken every 30 min. and the upper limit cut-off was defined as 300 secs of catalepsy. Between observation periods animals were returned to their home cages. The behavioral observations on lesioned animals were conducted prior to electrode implantation, ie., 5-7 days prior to the acute electrophysiological experiment. Age-matched control animals were tested with the lesioned group. Catalepsy data were evaluated using the Mann-Whitney U test.

HISTOLOGY

Electrode Placements

At the completion of each experiment, lesioning current was passed through the electrode and animals anaesthetized with halothane. The rib cage was cut and the sides reflected to expose the pericardium. An incision was made in the right atrium and 50 ml of 0.9% saline infused through the apex of the left ventricle. This was followed with 50 ml of 10% formalin. Brains were stored in 10% formalin until verification of lesions and/or electrode sites could be made.

Brains were removed from the skulls and frozen and then sectioned on a cryostat (Reichert Instruments, Austria) to obtain consecutive 100 µm sections. Sections were then examined on a projector microscope and the electrode lesion located. Locations were determined by comparison to serial section photographs in the atlas of Pellegrino and Cushman (1967).

Cortical Lesions

Each lesion was examined morphometrically and the placement of the lesion determined to within 0.5 mm by measurements based on the following anatomical landmarks:

1. Distance from the anterior-most margin of the lesion to the frontal pole
2. Distance from the posterior-most margin of the lesion to the cerebellum
3. [illegible]tance from the medial margin of lesion to the midline
4. Width of the lesion from the medial margin to the lateral

margin

5. Depth of the lesion in relation to the corpus callosum.

Fimbria-Fornix Lesions

Lesion placement and depth were determined morphometrically using the guidelines established for cortical lesions and 100 µm sections examined for severing of the fimbria-fornix.

Parafascicular-Centromedian Complex Lesions

Lesions were verified histologically by examining serial 100 µm sections and determining the lesion size morphometrically using the following criteria:

1. Distance from the midline to the medial margin of the lesion
2. Distance from the overlying hippocampus to the dorsal-most margin of the lesion
3. Maximal medio-lateral width of the lesion
4. Maximal dorso-ventral extent of the lesion
5. Maximal anterior-posterior extent of the lesion

BIOCHEMICAL VERIFICATIONS OF LESIONS

Dissecting Technique

Striatal tissue samples after cortical ablation or nigral 6-OHDA lesions

After decapitation, brains were removed, put on ice, and separated into right and left halves. For striatal dissections, the genu of the corpus callosum was first located and a coronal cut made posterior to this point. A second cut, approximately 1.0 mm posterior to the first one, resulted in a slice containing anterior striatum (corresponding to approximately 2.0 - 3.2 mm anterior to

Bregma). First, the ventral quarter of the slice was removed, thus eliminating the nucleus accumbens. Then the tissue lateral and medial to the striatum was removed. Finally, overlying cortex with the underlying corpus callosum was removed, leaving a roughly square block of striatal tissue ranging in wet weight from 10 - 50 mg. The order of dissection (ie, right vs left) was varied uniformly within a given experiment so as to avoid lateral bias.

Tissue samples of striatum and other brain regions after intrastriatal 6-OHDA lesions

First, olfactory tubercles were dissected according to the guidelines of McKenzie (1972) and tubercles from 2 animals corresponding to the lesioned and intact sides were pooled respectively. Brains were then halved down the midline and individual striatal samples dissected out as described in the previous section. Samples of piriform and cingulate cortices corresponding to lesioned and intact sides were dissected according to the guidelines of Bannon et al. (1983) and were again pooled such that the material from 2 animals was represented in each sample.

Amino Acid Analyses

After obtaining wet weight, the tissue representing an individual striatal sample was placed in 2.0 ml of cold 80% ethanol (v/v) and homogenized in the cold with a Brinkmann Polytron (Brinkmann Instruments, Lucerne, Switzerland). One ml of this homogenate was then transferred to a 1.5 ml Eppendorf centrifuge tube (Brinkmann Instruments) and centrifuged at 4°C at 12,000 x g for 10 min in a Brinkmann microfuge. 100 µl of the resulting supernatants

were taken for subsequent analysis.

For amino acid analysis, the method of Turnell and Cooper (1982) was followed. 100 µl samples of striatal supernatants at an appropriate dilution were reacted with Reagent A (500 g o-pthalaldehyde in 10.0 ml methanol + 90.0 mls. 0.4 M Borate buffer to which was added 40.0 µl 2-mercaptoethanol) and applied 1.0 min after mixing to an OD-5A reverse phase C-18 column (spheri - 5 µm) (Brownlee Labs, Mississauga, Ont.) guarded by a pre-column (Brownlee Labs.) and in series with an HPLC pump (Waters Associates, Inc., Milford, Mass.) and an Aminco filter fluorimeter analyzer (Aminco, Silver Springs, Maryland). The mobile phase consisted of buffer of the following composition: 0.05 M Na_2HPO_4, 0.05 M Na acetate, 120 ml of methanol, 70.0 mls of acetonitrile and 20 mls of tetrahydrofuran, all adjusted to pH 7.5 with acetic acid. The temperature of the run was maintained at 35°C with an LC-22 temperature controller (Bioanalytical Systems Inc.). Flow rate was maintained at 1.5 ml/min and the detector set at 1000, which was equivalent to the analog output of a 10 mV baseline. Runs were carried out at an operating pressure of 2.5 - 3 thousand p.s.i. Quantification was obtained from a spectraphysics integrator-recorder (Spectraphysics, Piscataway, N.J.). A typical chromatogram is shown in Figure 4. A representative standard curve is shown in Figure 5; Table VII gives an index of the goodness of fit as determined by correlation analysis.

Dopamine Analysis

Individual striata were weighed, and homogenized with a Polytron in 2.0 ml of cold 0.1 N perchloric acid (PCA). Pooled olfactory

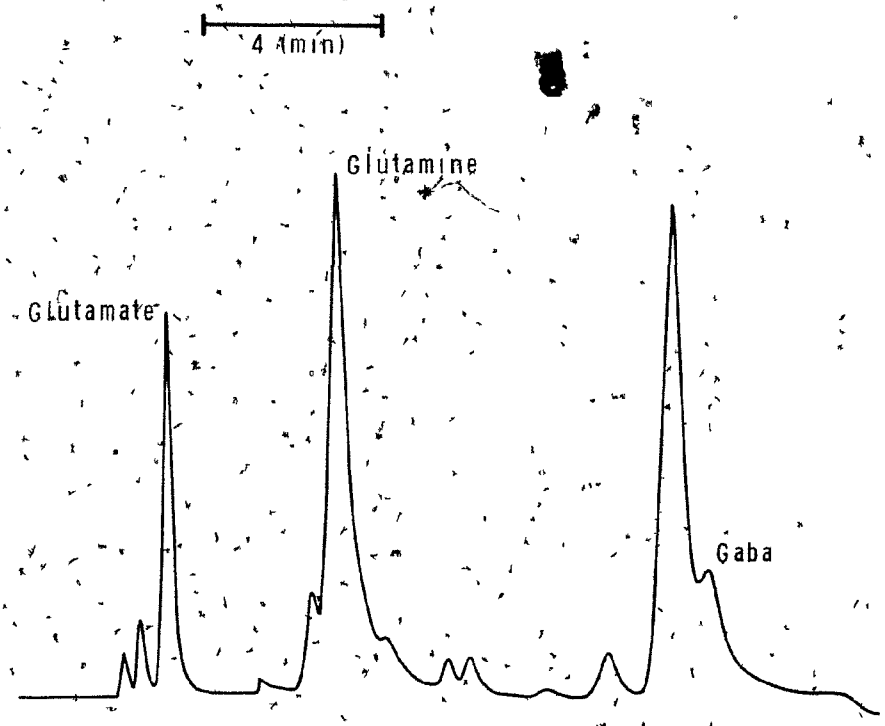


FIGURE 4. Representative chromatogram of amino acid separation using HPLC and fluorescent detection of the derivatized amino acid.

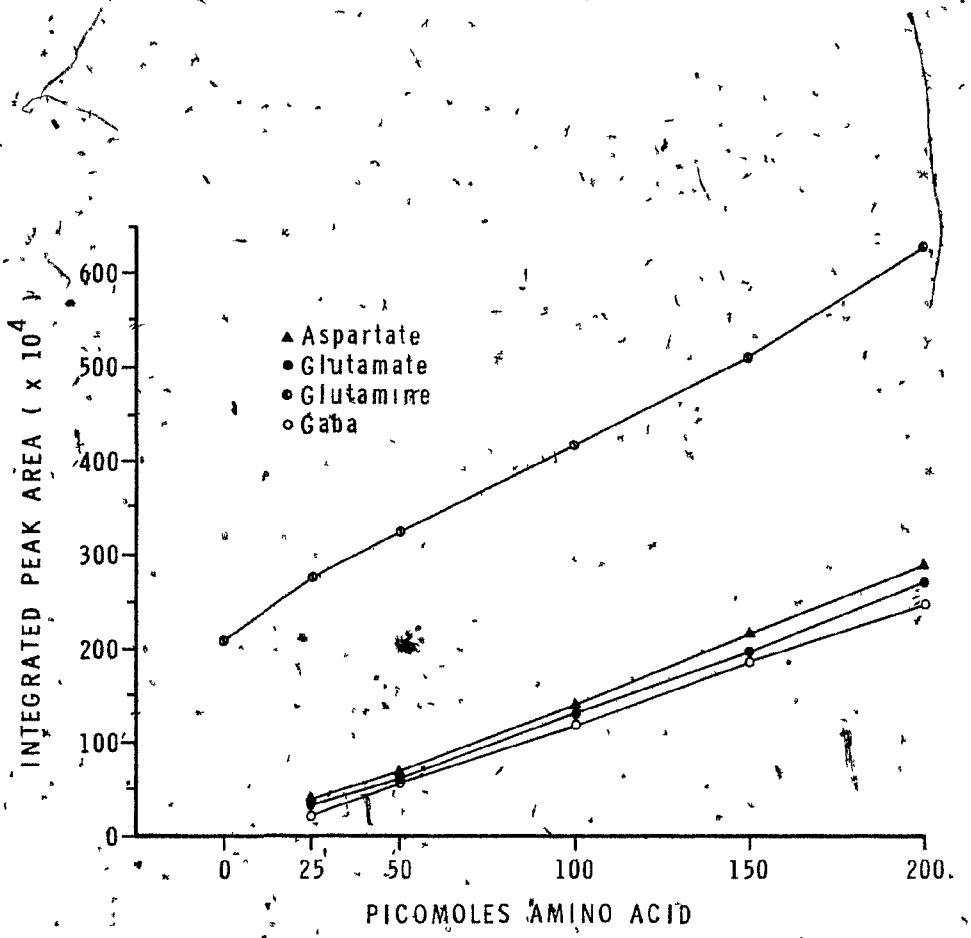


FIGURE 5. Standard curve for the simultaneous analysis of amino acids by HPLC.

Table VII. Least squares analysis of standard curve calibrations for simultaneous amino acid analysis.

Aspartate (4.4)[1]	Glutamate (5.4)	Glutamine (13)	GABA (20)
[2]r = 0.9998	r = 0.9995	r = 0.999	r = 0.999
[3]y = 1.4382x + 268.8	y = 1,351.3x + (-4,195)	y = 2.023x + 217,039.7	y = 1,255.6x + (-3,393)

[1]number in parenthesis under each amino acid is the retention time

[2]r = correlation coefficient

[3]y = equation of line (slope x + y-intercept)

tubercles, piriform or cingulate cortices were sonicated in 250 µl of 0.1N (Sonifer Cell Disrupter, Model W185; Heat Systems and Ultrasonics Inc., Plainview, N.Y.).

All samples were then centrifuged at 4°C at 12,000 x g for 10 min. 750 µl-aliquots of the supernatants from striatal and tubercular samples and 150 µl-aliquots of the cortical samples were frozen at -70°C until HPLC analysis.

Dopamine was quantified using HPLC with amperometric detection. 20 µl aliquots of PCA supernatants representing the various tissue samples or authentic standards were applied to a Lichrosorb RP-18 (5 µm) column hooked in series to a HPLC pump (Waters Associates Inc., Milford, Mass.) and an amperometric detector (Bioanalytical Systems Inc., West Lafayette, Indiana). The mobile phase consisted of buffer of the following composition: 0.1 M Na_2HPO_4, 0.1 M citrate, 0.1 mM EDTA and sodium octyl sulfate, 100 mg/l. pH was adjusted to 4.0 with NaOH.

Flow rate was set at 1.5 ml/min at an operating pressure of 2-3 thousand p.s.i. The detector potential was set at +0.70 mv with an offset of 0.004-0.006 and the sensitivity at 2-5 na/v. The analog output of the detector was recorded by a Kipp and Zonen BD-40 recorder (Amsterdam, Netherlands). A representative standard curve is shown in Figure 6.

Statistical Analysis

Right-left differences were evaluated using the paired t-test. Comparisons between groups were examined using the unpaired t-test.

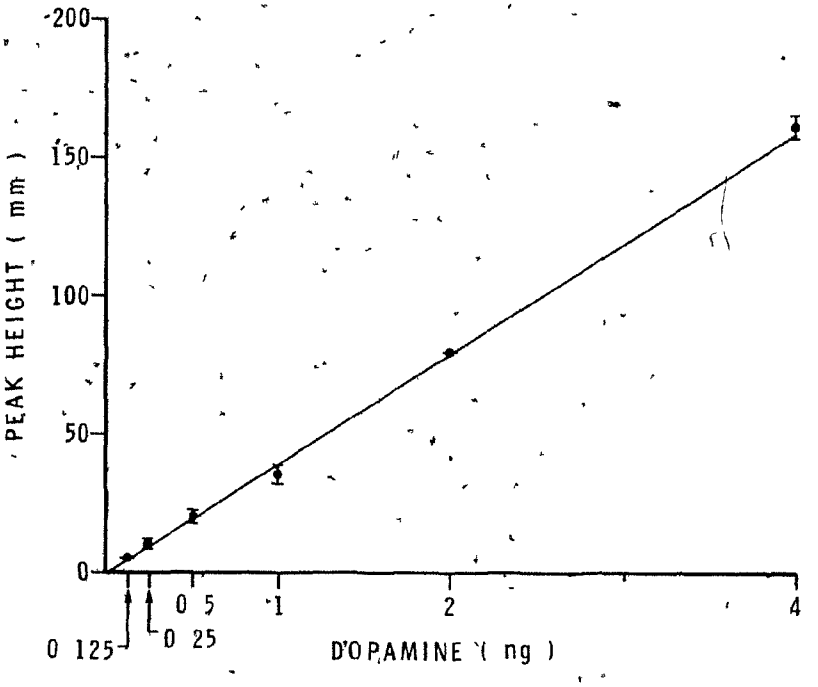


FIGURE 6. A representative standard curve showing the relationship of peak height to dopamine concentration as measured by HPLC with electrochemical detection. Each point represents the mean ± SEM of three replicate determinations at each concentration of dopamine. r (correlation coefficient) = 0.98.

Receptor-Binding Studies

Preparation of Striatal P_2 Fraction

Striata from sham-operated and bilaterally cortically ablated animals were dissected out as described previously. Striatal samples, representing each group were pooled, weighed and homogenized in 10 volumes (w/v) of cold 0.32 M sucrose with 10 strokes of a Teflon pestle homogenizer. The resulting homogenates were then centrifuged at 1000 x g for 10 min at 4°C. The supernatants were decanted and then centrifuged at 15,000 x g for 20 min at 4°C. The pellet, representing a crude synaptosomal fraction (P_2) was then resuspended in 0.32 M sucrose to give a solution containing 200-300 µg protein per 100 µl.

Binding Assays

The general protocol followed in the binding assays is given in Table VIII. Each binding assay is described separately below in terms of: type of radioligand, displacing agent, assay buffer, and conditions of assay.

Opiate Receptor Binding Assay

Radioligand: [^{3}H]met-enkephalin [Tyrosyl-3,5-^{3}H(N)]-enkephalin (5-L-methionine). Supplied by New England Nuclear (NEN), Boston, Mass. Specific activity = 30.5 Ci/mmol. Radioligand concentration was varied over the concentration range 1.6 - 55.5 nM.

Displacing agent: Methionine-enkephalin, 10^{-5} nM.

Assay buffer: Sodium-free buffer containing 5 mM HEPES (pH 7.6), 0.32 M sucrose, 0.5 mM $MgCl_2$, 0.5 mM $CaCl_2$ and 10^{-5} M puromycin. Puromycin, an aminopeptidase inhibitor, was included to

Table VIII. Protocol for Receptor-binding Assays

Tubes	
1 2 3	4 5 6
- displacing agent (Total binding)[a]	+ displacing agent (Non-specific binding)[b]
Each tube contained:	Each tube contained:
700 µl buffer	700 µl buffer
100 µl of appropriate solvent used to dissolve displacing agent	100 µl of solvent containing a known concentration of displacing agent[2]
100 µl of radioligand at the appropriate concentration	100 µl of radioligand at the appropriate concentration
100 µl of corresponding striatal P_2 fraction	100 µl of corresponding striatal P_2 fraction

[a], [b] Specific Binding = Total Binding − Non-specific Binding

prevent degradation of Met-enkephalin. Buffer was kept sodium-free because it has been shown that the presence of sodium significantly decreased specific binding of Met-enkephalin (Law et al., 1974).

Conditions of assay: The incubation mixtures (1000 µl total volume) in silanized tubes were incubated at 30°C for 20 min in a shaking water bath (Gallenkamp, England). The bound radioligand was separated from the free by rapid filtration under vacuum through GF/B (Whatman, England) glass fiber filters. Both tubes and filters were rinsed with 2 five ml aliquots of ice-cold 50 mM Tris-HCl buffer (pH 7.4), and when dry placed in mini-scintillation vials (Beckman Inc., Fullerton, CA.) to which was added 7.0 mls of Ready-solv fluor.

Dopamine D_1 Receptor Binding

Radioligand: [^{3}H]ADTN (2-[5,8-^{3}H]-amino-6,7-dihydroxy-1,2,3,4-tetrahydronapthalene. Supplied by NEN. Specific activity = 26.1 Ci/mmol. Radioligand was diluted to a specific activity of approximately 300 dpm pmol^{-1} with non-radioactive ADTN. Final radioligand concentrations lay in the range of 0.4 - 10 µM.

Displacing agent: dopamine, 10^{-3} M.

Assay buffer: Puck's D_1 saline solution containing 5 mM HEPES (pH 7.6), 137 mM NaCl, 5 mM KCl, 0.17 mM Na_2HPO_4, 0.22 mM KH_2PO_4, 6 mM glucose and 59 mM sucrose.

Conditions of assay: Incubation mixtures (1000 µl total volume) in 1.5 ml Eppendorf microfuge tubes were incubated at 30°C for 30 min in a shaking water bath. Bound radioligand was separated from the free by a 5 min centrifugation at 10,000 x g. Pellets were washed with ice-cold Tris-buffer, resuspended in 1% Triton x-100,

transferred to mini scintillation vials, and 7.0 ml of Ready-Solv added.

Dopamine D_2 Receptor Binding

Radioligand: [^{3}H]spiperone (benzene ring-^{3}H). Supplied by NEN. Specific activity 31.7 Ci/mmol. Radioligand concentration was varied over the range 0.2 - 12.0 nM.

Displacing agent: domperidone, 10^{-5} M dissolved in 1.5% tartaric acid solution in a volume equivalent to 10% of the final incubation mixture.

Assay buffer: Puck's D_1 saline solution.

Conditions of assay: Incubation mixtures (final volume 1000 µl in disposable glass tubes were incubated in a shaking water bath for 30 min at 30°C. Bound and free radioligand were separated by vacuum filtration through Whatman GF/B filters and tubes and filters rinsed twice with 5.0 ml aliquots of ice-cold 50 mM Tris buffer. Filters were placed in mini-scintillation vials and 7.0 ml of Ready-Solv added.

Counting of Samples and Analysis

Radioligand concentrations were determined by counting triplicate aliquots of radioligand at each of the concentrations used to establish binding isotherms. All samples were counted in a Mark III liquid scintillation spectrometer (Searle Analytic Inc., Des Plaines, Ill.). Efficiency of counting was 30-35%. Counts/min (CPM) were converted to disintegrations/min (DPM) using the standard channels ratio (SCR). Data were analyzed by the method of Scatchard (1949), plotting Bound versus Bound/Free. Protein content was

determined by the method of Lowry et al. (1951).

RESULTS

Striatal MUA in Freely Moving Animals

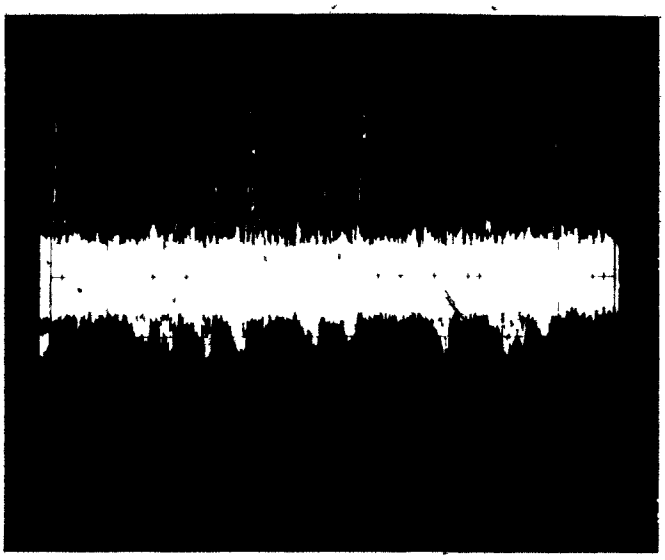
Examples of action potentials in a multiple unit recording from striatal neurons in freely moving animals are shown in Figure 7. Inspection of these records shows that these are typical extracellular action potentials - biphasic and assymetric about the zero potential line and having waveforms less than 0.5 msec duration. Passing a lesioning current through the electrode resulted in immediate disappearance of neuronal action potentials (Fig. 8), thus establishing that the waveforms observed were not artefactual, e.g. arising from recording-lead or muscle potentials.

Changes in MUA Following DEX

A representative experiment showing the response of striatal neurons as well as behavioral changes to DEX, 2.5 mg/kg, are displayed in Figures 9 and 10. Pooled data (N=5) showing the variability in the responses to DEX, 1 mg/kg, are shown in Figure 11. At a dose of 1 mg/kg, peak response, representing 130.2 ± 10.7% of control (mean ± SEM), was reached between 19 and 32 min. after injection. Discharge rates were no longer significantly different from pre-drug control values by 88 min. after drug.

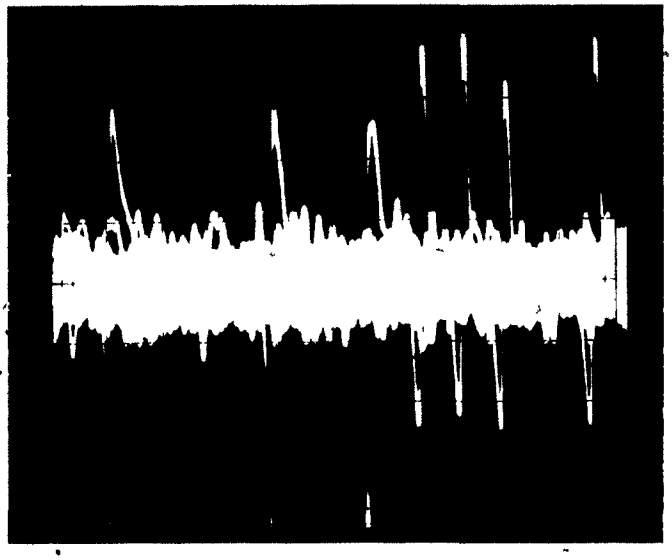
At the higher dose of 2.5 mg/kg a peak response of 171.8 ± 19.7% of control (N=5) was reached between 34 and 64 min. after DEX. As the drug-induced neuronal activation declined, discharge rates became progressively more variable (Fig. 12). However discharge rates were statistically indistinguishable from pre-drug control values by 164

FIGURE 7. Oscilloscope traces of striatal MUA recorded from a freely moving animal. The last panel depicts an example of the criteria used for discrimination.



50 μV

2 msec



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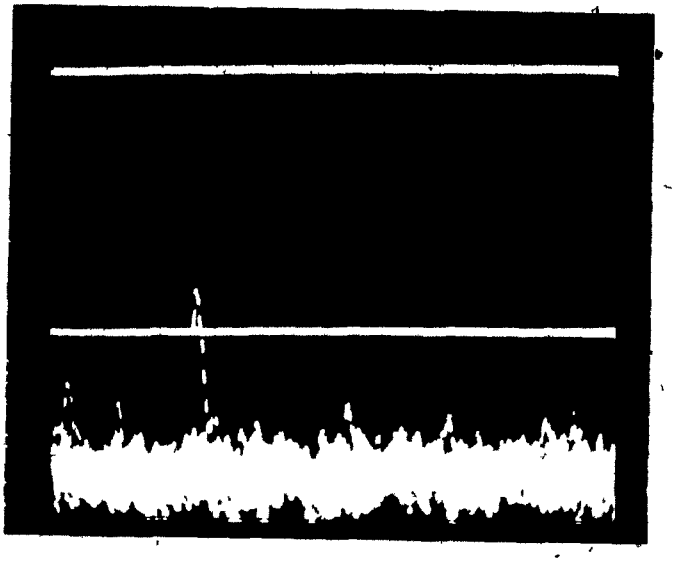
0·5 msec


50 μV
0.5 msec

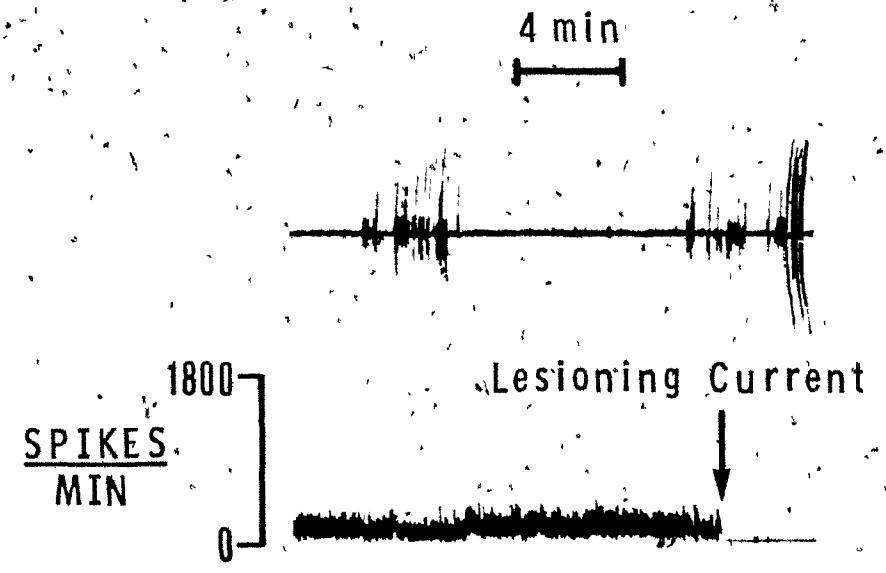


FIGURE 8. Effects of lesioning currents on potentials recorded from the striatum of a freely moving rat. Upper and lower traces are, respectively, the analog output of the activity monitor and the polygraph record of the discriminator output pulses expressed as spikes/min.

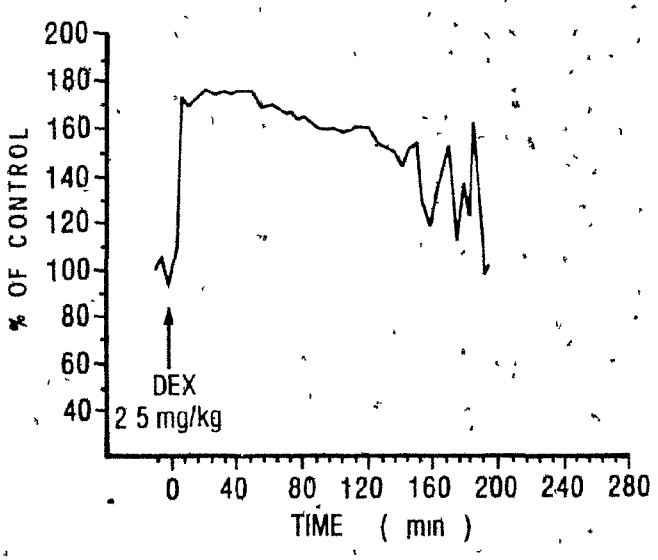


FIGURE 9. A representative experiment showing the characteristic excitatory response of striatal neurons to DEX. Peak response was 175% of control. Spontaneous MUA = 8367 ± 750 spikes/4-min.

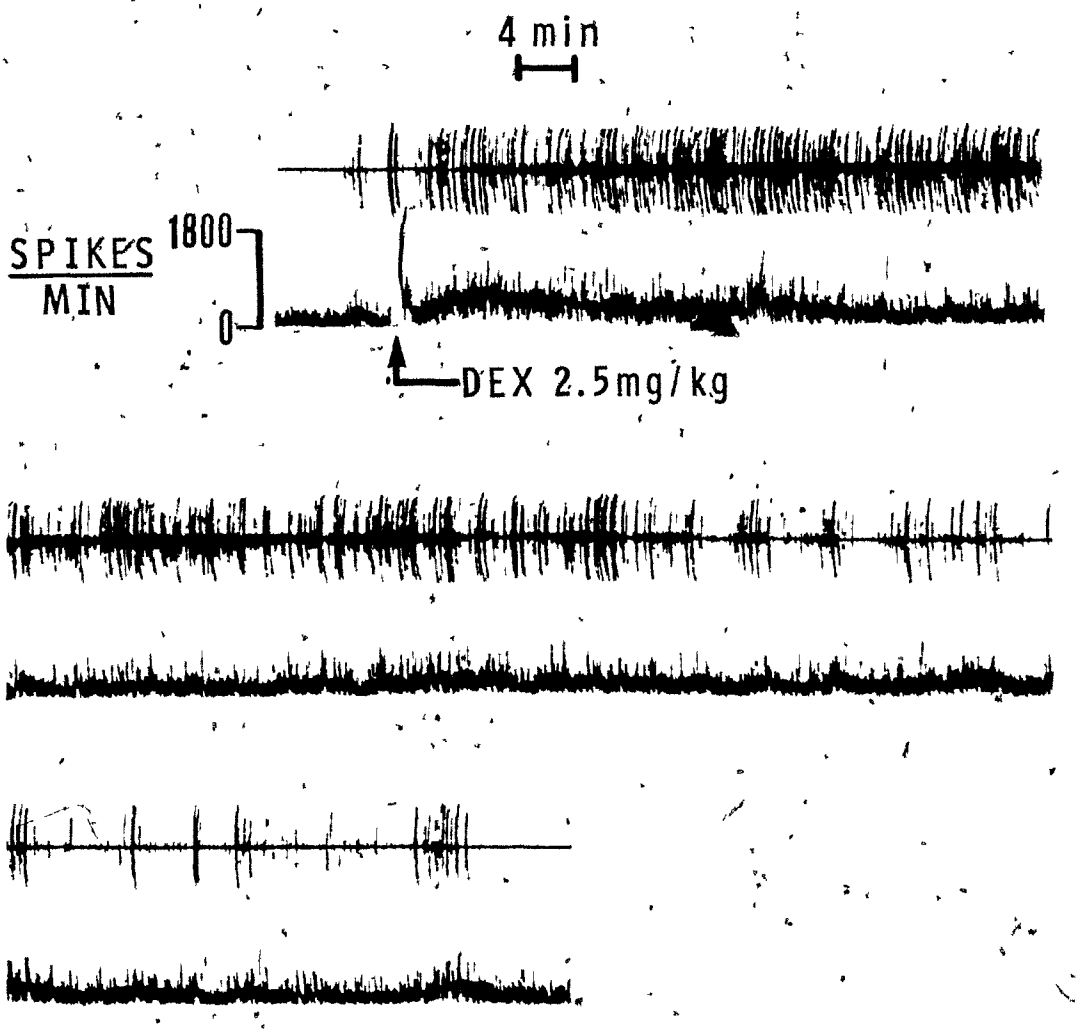


FIGURE 10. A representative experiment showing the effects of DEX on behavior (upper trace) and striatal multiple unit activity (lower trace). Both behavioural activation and striatal neuronal excitation were maintained for approximately 200 minutes.

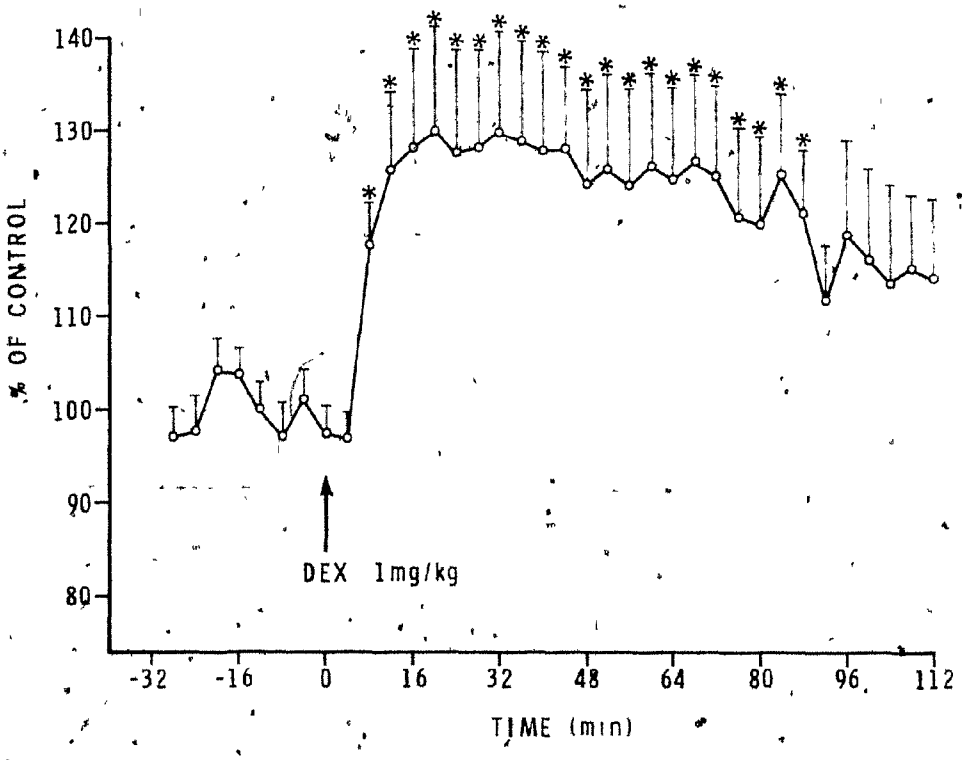


FIGURE 11. Striatal neuronal responses to DEX, 1 mg/kg in freely moving animals (N=5). Mean spontaneous MUA was 9538 ± 2127 spikes/4-min. *p = < 0.05, SNK test.

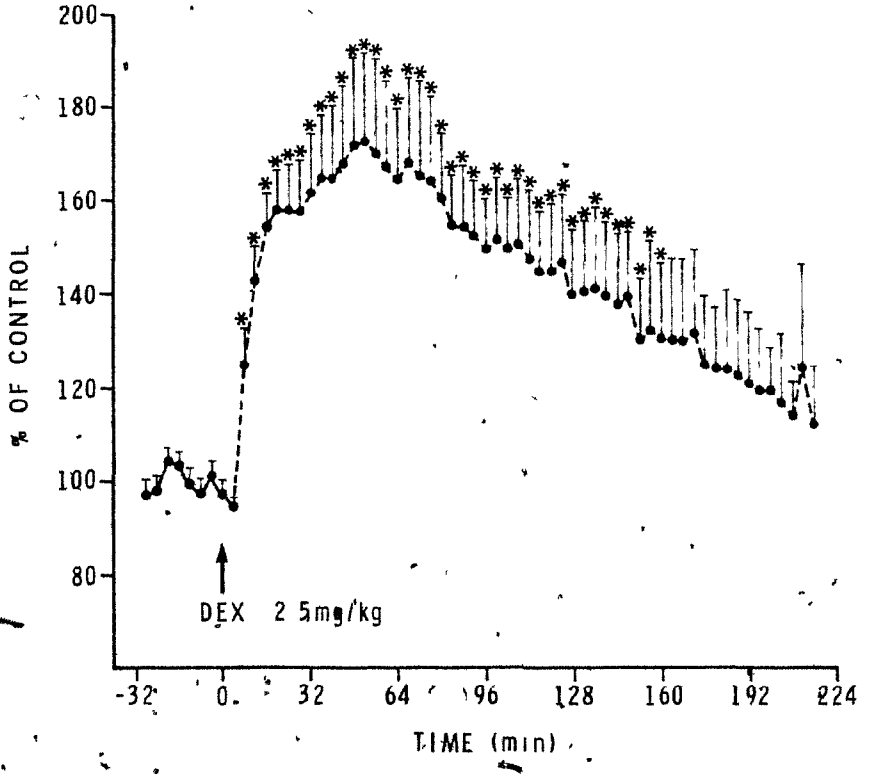


FIGURE 12. The excitatory response to DEX, 2.5 mg/kg, in freely moving animals (N=5). Mean spontaneous MUA was 5537 ± 970 spikes/4-min. * = $p < 0.05$, SNK test.

min. after DEX. Throughout this study, no differences in mean spontaneous MUA or peak response between left and right sides could be demonstrated (Table IX).

In 10% of all animals, the striatal response to DEX was not excitation. Table X summarizes the incidence of various response patterns in freely moving animals.

Effects of Anaesthetics and Analgesics on MUA

Before attempting immobilization studies, a suitable analgesic or anesthetic had to be identified which would, on the one hand, reduce the pain and stress accompanying immobilization procedures, but on the other, have no effect on spontaneous or DEX-induced MUA. To this end, several analgesics and anaesthetics, commonly used in electrophysiological studies, were screened for their effects on striatal MUA.

Halothane

Pooled MUA data showing the effects of 3% halothane are depicted in Figure 13. In the first 3 min. following introduction of halothane, animals underwent locomotor hyperactivity, with no change in striatal neuronal firing rates. As animals lost the righting reflex, striatal firing rates declined, reaching a maximum depression of 90 ± 4.5% (mean ± SEM) of control. Thirty four min. after discontinuation of halothane, discharge rates were no longer significantly different from pre-anaesthetic control values and all animals regained their righting reflex.

Pentobarbital

Pentobarbital's (35 mg/kg) effects on MUA were similar to

Table IX. Comparison of the Spontaneous MUA and Peak Responses to DEX, 2.5 mg/kg, Between Left and Right Striata of Freely Moving Rats

	Left (n=19)	Right (n=10)	Pooled
Spontaneous MUA[1]	5554 ± 667[a]	5594 ± 1660	5574 ± 702
Peak response[2]	183 ± 8.7[b]	188 ± 25.7	185.5 ± 10.3

[1]Spontaneous discharge rates of striatal neurons were determined by obtaining the mean ± SEM of the eight consecutive 4-min counts immediately preceding administration of dexamphetamine within each experiment. Mean values obtained in this way were then pooled and the resulting mean ± SEM expressed in this table. This convention is followed throughout this thesis.

[2]Peak response was determined as the maximum increase in discharge rates following drug and expressed as % of control based on the mean obtained from averaging the eight consecutive 4-min counts immediately preceding drug. Values obtained were then pooled and the resulting mean ± SEM expressed in this table. This convention is followed throughout this thesis.

[a],[b]Not signficantly different from the right side (unpaired t-test).

Table X. Summary of Striatal Neuronal Responses to DEX in Freely Moving Animals.

	Dose of DEX (mg/kg)	
	1.0 (n=5)	2.5 (n=33)
Excitation	5	29
Inhibition	0	1
No change	0	2
Biphasic	0	1

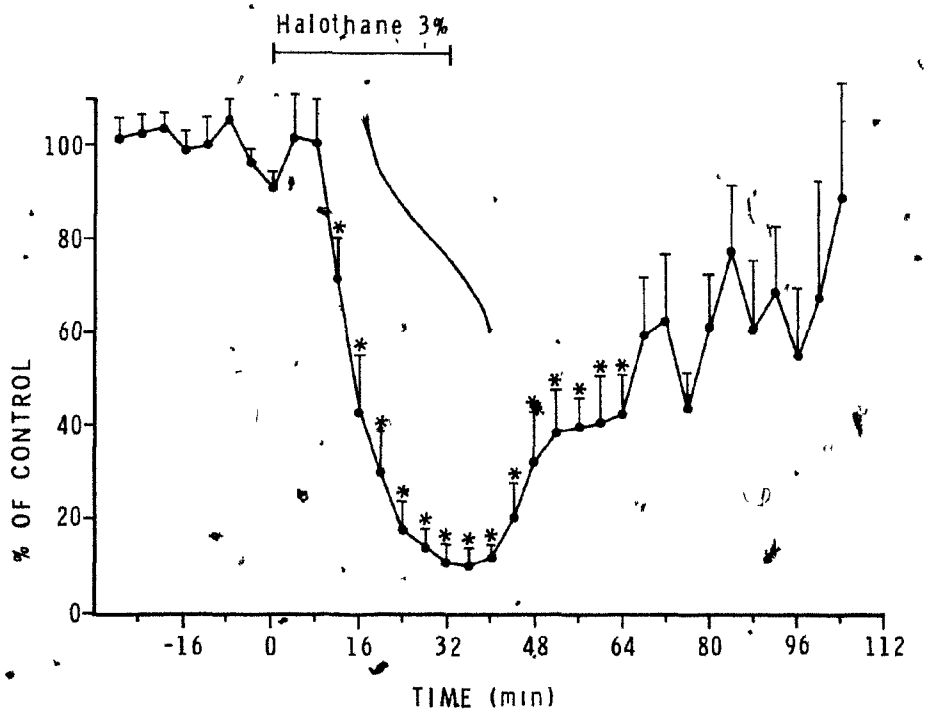


FIGURE 13. Effects of halothane on striatal MUA. Results shown here are based on 6 recordings (4 animals). Mean spontaneous MUA was 4267 ± 1342 spikes/4-min interval. * = $p < 0.05$, SNK test.

halothane, with discharge rates reduced to 5.7 ± 2.1% of control (N=4), by 20 min. after drug (Fig. 14). However, pentobarbital-induced depression of neuronal firing was more protracted than halothane, lasting 140 min.

Urethane

Urethane, 1.5 g/kg, depressed MUA to 9.3 ± 3.6% of control and remained depressed, i.e. below 25% of control, for 3.0 hrs (Fig. 15). Animals did not recover the righting reflex during this time.

Chloral Hydrate

Chloral hydrate, 400 mg/kg, depressed MUA to 5.2 ± 2.7% of control (Fig. 16). Peak depression occurred 8 min. after injection and essentially no recovery was evident by 3 hrs. Animals did not recover their righting reflex.

Morphine

The dose relationship between morphine and MUA is described in Figure 17. Whereas 15 mg/kg produced a peak depression of striatal neuronal firing of 44.3 ± 6.2% of control, 5 mg/kg did not significantly affect discharge rates. Depression of firing rate following 10 and 15 mg/kg morphine was accompanied by catalepsy. In a separate group of animals, morphine, 15 mg/kg, induced a cataleptic response, the time course of which paralled the depression of MUA (Fig. 18). The depression of MUA produced by 15 mg/kg of morphine were immediately reversed by 10 mg/kg of naloxone (Fig. 19). The catalepsy was also reversed.

Ketamine

Ketamine, 50 mg/kg, activated striatal neurons resulting in a

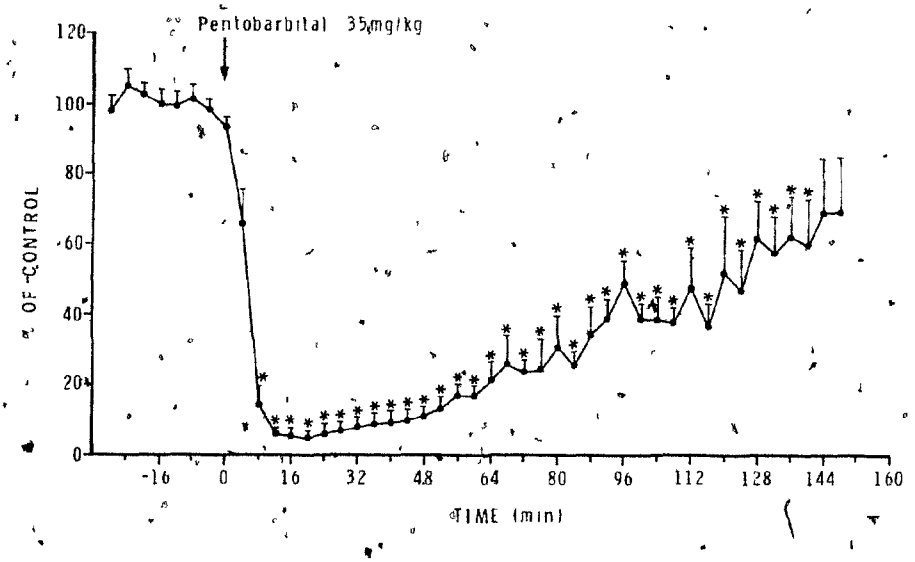


FIGURE 14. Effects of pentobarbital on striatal MUA (4 animals, 5 recording sites). Mean spontaneous MUA was 5910 ± 1054 spikes/4-min. * = $p < 0.05$, SNK test.

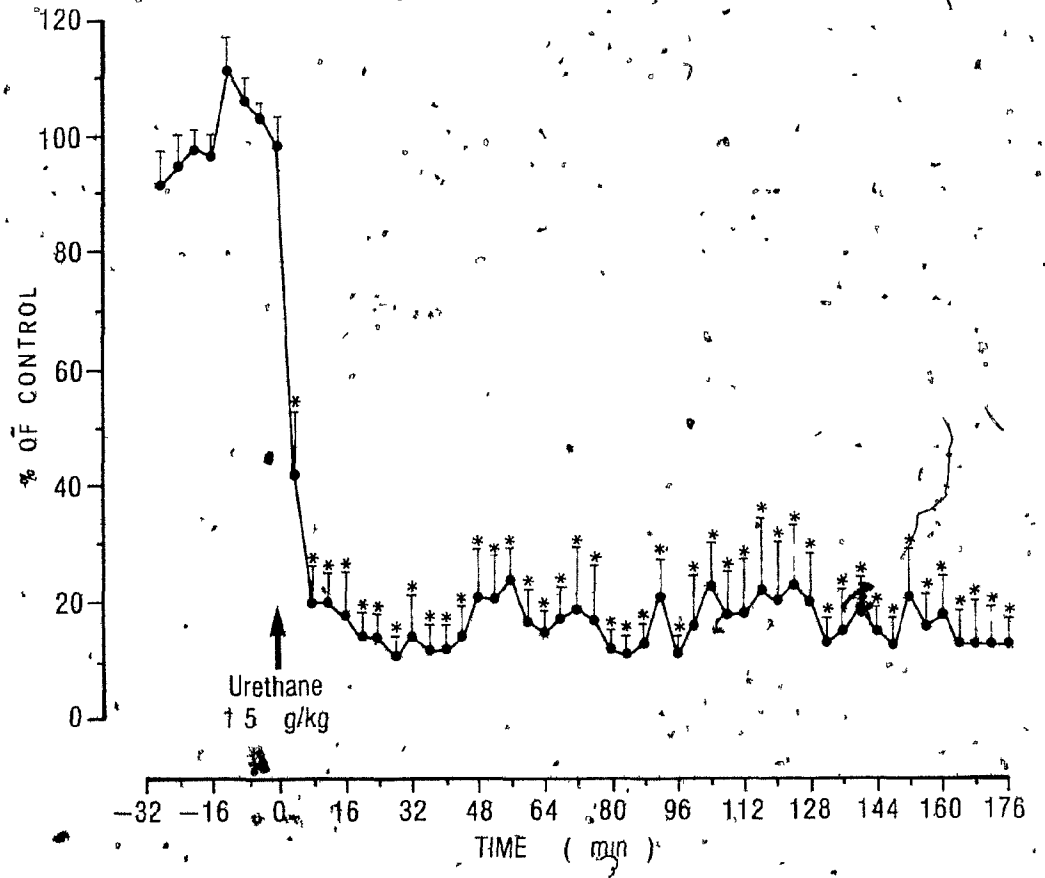


FIGURE 15. Effects of urethane on striatal MUA. Results from 3 animals (5 recording sites). Mean spontaneous MUA was 2108 ± 550 spikes/4-min interval. * = $p \leq 0.05$, SNK test.

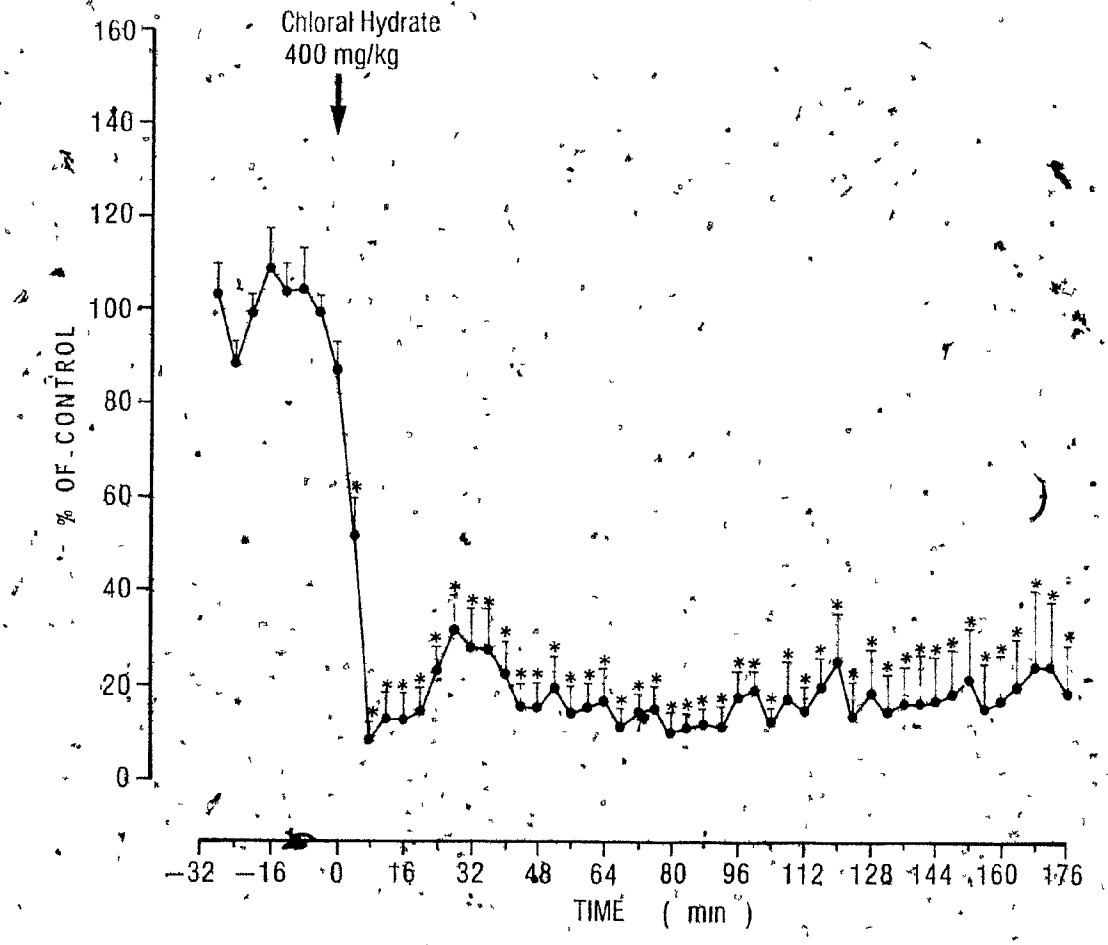


FIGURE 16. Effects of chloral hydrate on striatal MUA. Results from 3 animals (5 recording sites). Mean spontaneous MUA was 2217 ± 516 spikes/4-min. * = $p < 0.05$, SNK test.

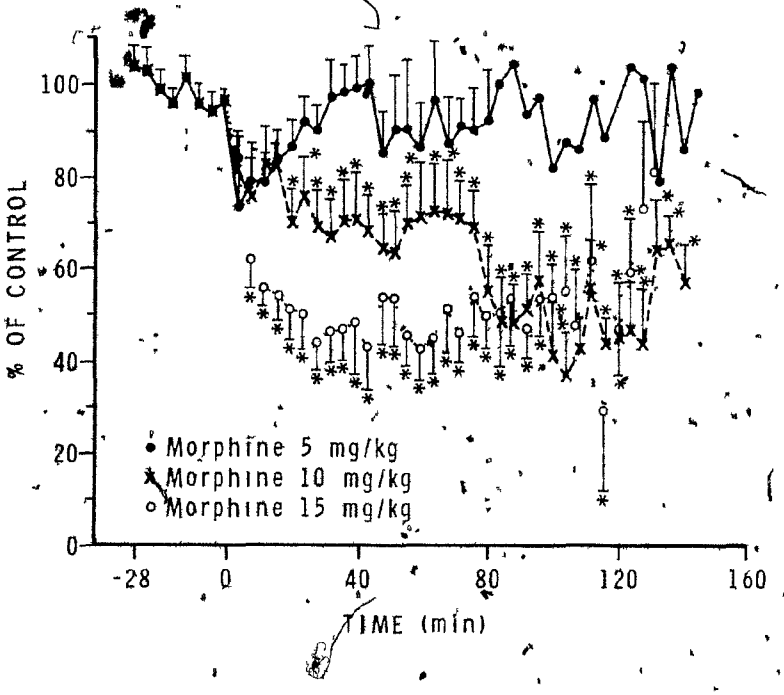
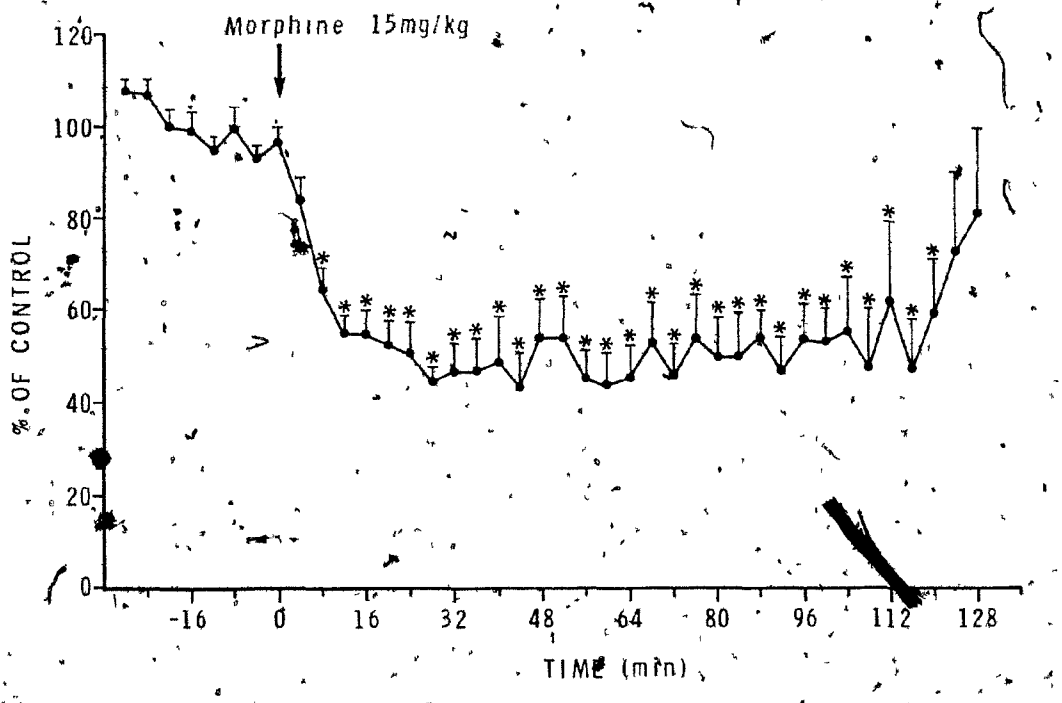


FIGURE 17. Dose-dependent reductions in striatal MUA following morphine; 5 mg/kg N=6; 10 mg/kg N=7; 15 mg/kg N=5. Control interval data for the three groups was pooled. Mean spontaneous MUA (5 mg/kg) was 3222 ± 703 spikes/4-min; mean spontaneous MUA (10 mg/kg) was 3438 ± 938 spikes/4-min, and mean spontaneous MUA (15 mg/kg) was 4252 ± 779 spikes/4-min. * = $p < 0.05$, SNK test.



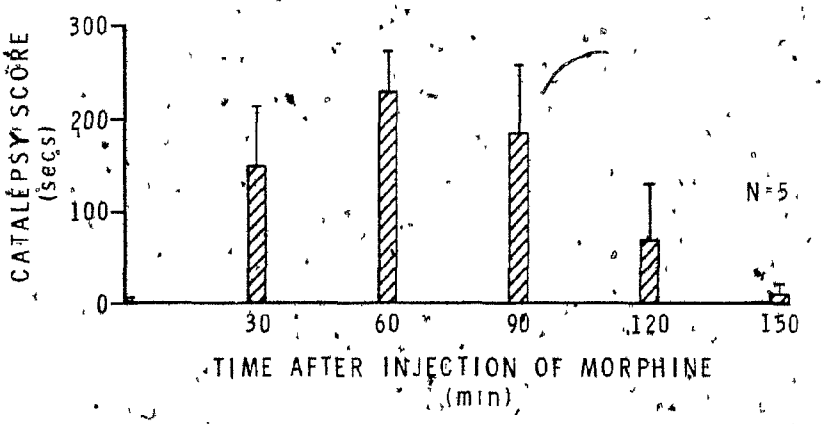


FIGURE 18. Comparison of the time course of the depression of striatal MUA and the catalepsy resulting from morphine, 15 mg/kg. Mean spontaneous MUA was 4252 ± 779 spikes/min (5 animals; 6 recording sites). * = $p < 0.05$, SNK test.

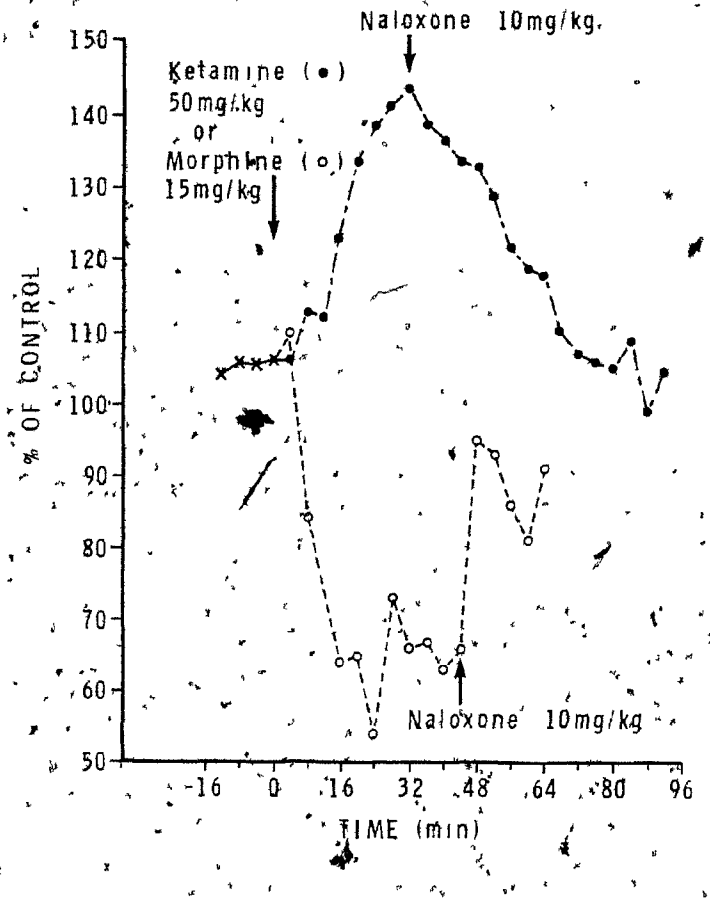


FIGURE 19. Representative experiments showing the effects of naloxone on morphine or ketamine-induced changes in striatal MUA. Pre-drug values from the two animals were pooled; spontaneous MUA (morphine) = 2746 ± 97 spikes/4-min; (ketamine) = 8429 ± 422 spikes/4-min.

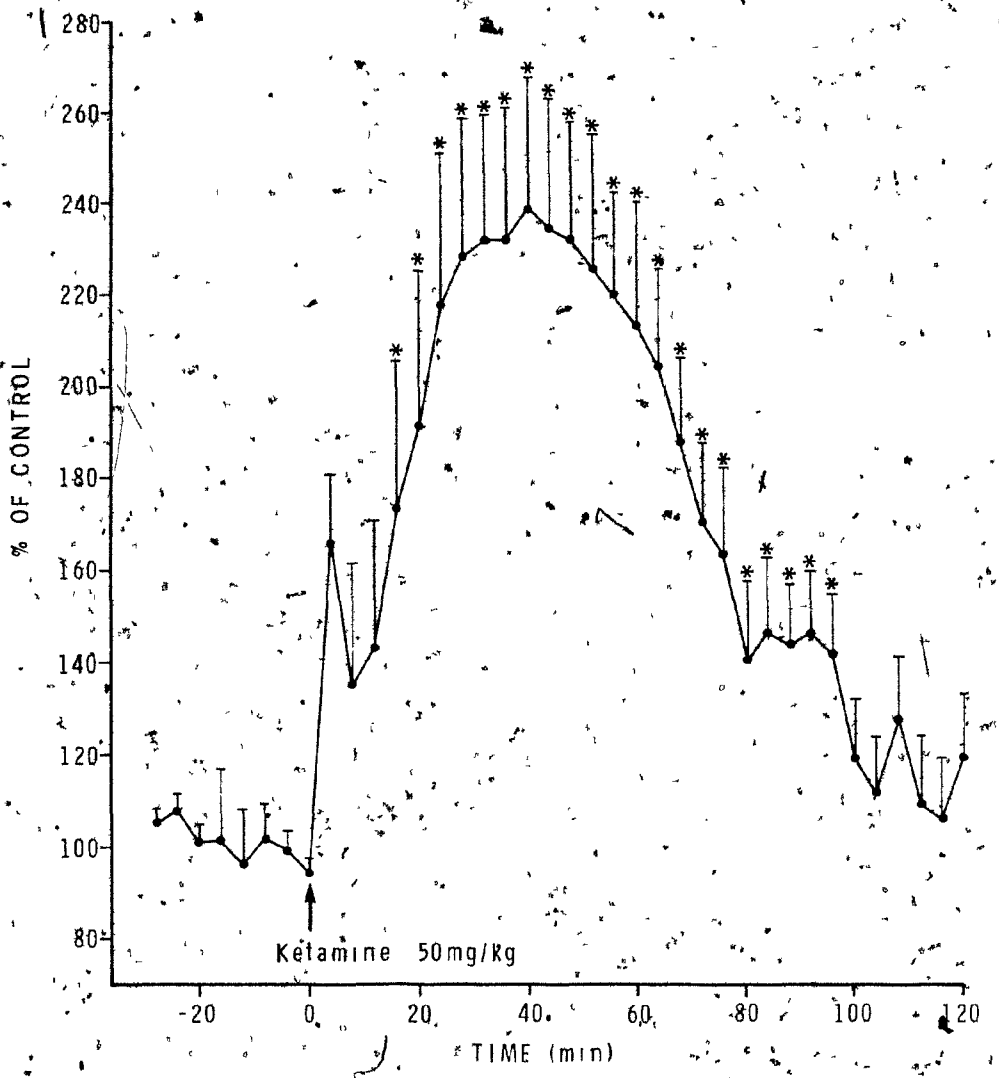


FIGURE 20. Response of striatal neurons to ketamine (5 animals, 6 recording sites). Mean [illegible] was 3003 ± 1018 spikes/4-min. [illegible] NK test.

peak increase in MUA of 236.4 ± 27.3% of control (mean ± SEM) (Fig. 20). With the onset of ketamine action, animals underwent a period of intense locomotor activity which appeared to subside as peak neuronal response was approached. As MUA returned to control values, a second episode of marked locomotor activity was observed. Neither ketamine-induced excitation of striatal neurons nor the locomotor response to ketamine were reversed by 10 mg/kg naloxone (Fig. 19).

Nitrous oxide

Administration of nitrous oxide-oxygen mixture (70% N_2O-30% O_2) to freely moving animals did not significantly alter spontaneous discharge rates of striatal neurons (Fig. 21). However, the variability of baseline firing did appear to be increased as compared to control animals.

During the administation of this gas mixture, animals appeared behaviorally normal.

Effects of Morphine and Nitrous Oxide on the Striatal Neuronal Response to DEX

Since halothane, pentobarbital, ketamine, chloral hydrate and urethane all produced marked alterations in MUA and behavior, only morphine and nitrous oxide were studied further for effects on DEX responses.

Morphine

Morphine pretreatment, 5 mg/kg (N=9) or 10 mg/kg (N=2), interrupted the normal striatal response to DEX (Fig. 22). In neither instance did DEX produce a sustained increase in MUA. On the contrary, MUA after DEX never exceeded pre-morphine control values.

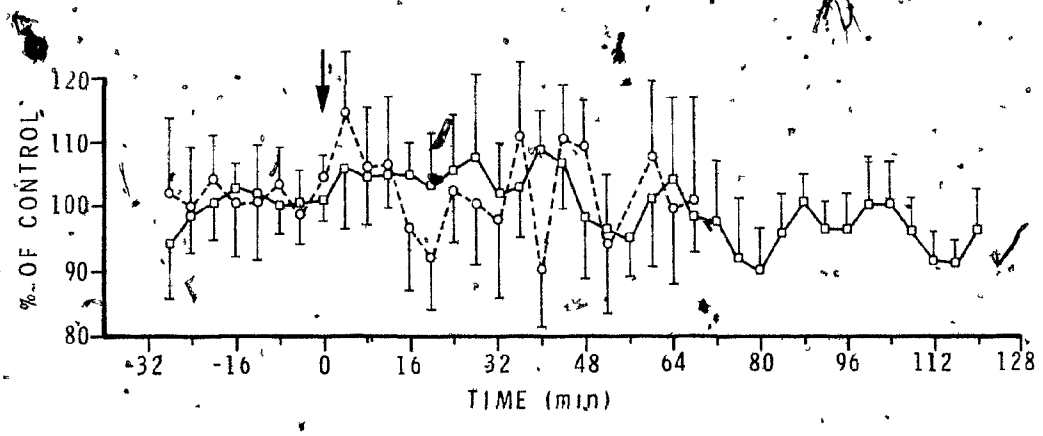


FIGURE 21. A comparison of the effects of nitrous oxide (70% N_2O/30% O_2) on spontaneous MUA in freely moving (o--o; N=5) and immobilized animals (□—□; N=5). At the arrow saline was given. Mean spontaneous MUA was 6722 ± 1511 spikes/4-min; mean spontaneous MUA (IMM) was 6462 ± 1337 spikes/4-min.

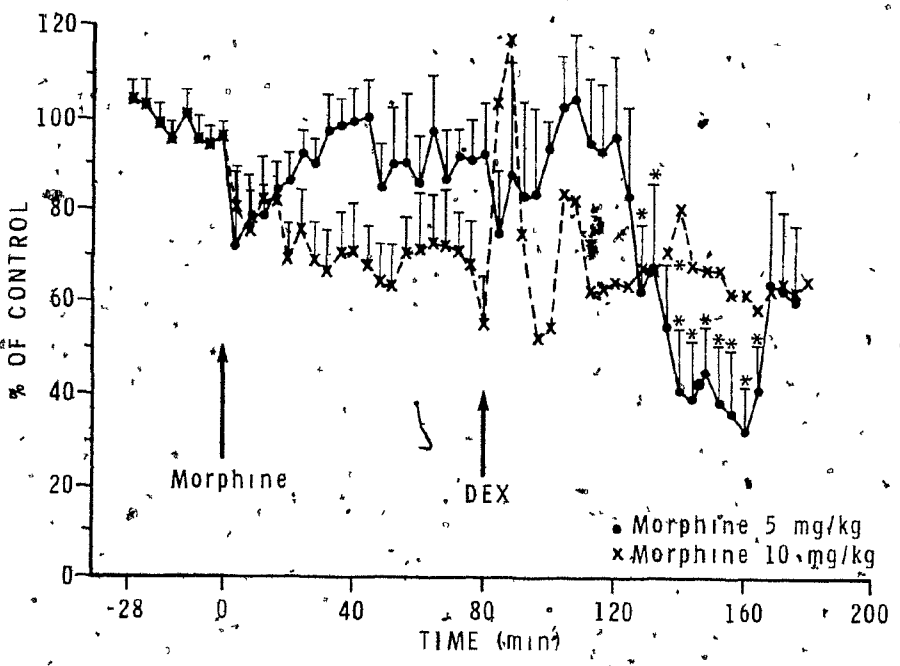


FIGURE 22. Alterations in the striatal response to DEX, 1 mg/kg, in freely moving animals that had been pretreated with 5 (●——●) or 10 (x--x) mg/kg morphine. Mean spontaneous MUA (5 mg/kg; N=5) was 3361 ± 893 spikes/4-min; mean spontaneous MUA (10 mg/kg; N=2) was 5394 spikes/4-min. Control interval data for the two groups was pooled. * = $p < 0.05$, SNK test.

Following either dose of morphine, animals became quiet but not cataleptic at the time of administation of DEX. Nevertheless, all animals responded to DEX with behavioral activation.

Nitrous oxide

DEX, [redacted] mg/kg, in freely moving animals and in the presence of 70% N_2O/30% O_2, produced a normal excitatory response, reaching 129.8 ± 10.9% of control (N=5; Fig. 23). For comparison, untreated animals gave a mean increase of 130.2 ± 10.7%. Striatal discharge rates returned to pre-drug values by 88 min. Again, the behavioral response to this dose of DEX was not different from untreated animals.

Effects of Immobilization on the Response of Striatal Neurons to DEX

Mean spontaneous MUA in immobilized animals was not different compared to MUA in the same animals while freely moving or while freely moving with nitrous oxide (Table XI). However, DEX 1 mg/kg, did not induce an excitatory response in the striatum when readministered to immobilized animals 48 hrs. after an initial trial with DEX while freely moving (Fig. 24).

To test the higher dose, 2.5 mg/kg, additional animals were again tested as freely moving and retested as immobilized 48 hrs. later. There was no change in spontaneous MUA between experiments, i.e. 5838 ± 1030 spikes/4 min. vs. 6602 ± 1110 spikes/4 min. However, at this dose of DEX, striatal neurons showed a multiplicity of responses, ranging from excitation (N=4) to inhibition (N=3) and including no change (N=5) as well as biphasic responses (N=6) (Figs. 25, 26, 27, and 28). No differences were found between animals which were immobilized without a previous DEX challenge (drug-naive animals) and those animals receiving two DEX treatments (Table XII).

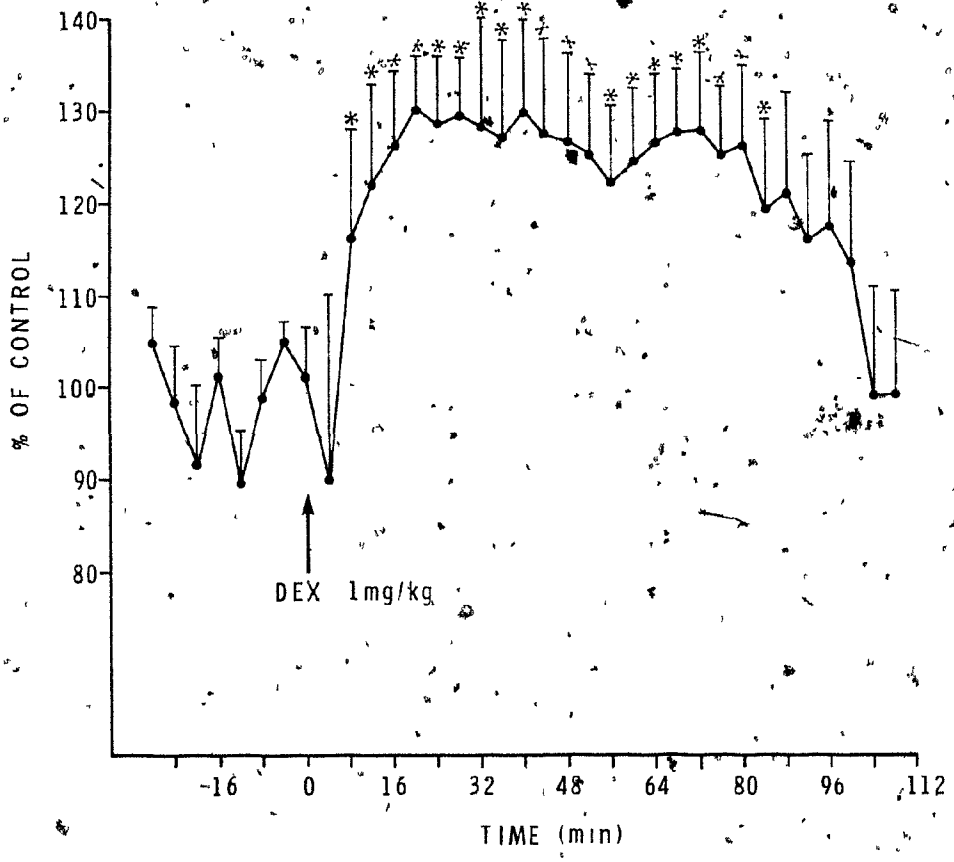


FIGURE 23. Striatal neuronal response to DEX, 1 mg/kg in the presence of nitrous oxide (70% N_2O/30% O_2) in freely moving animals (N=5). Mean spontaneous MUA was 7502 ± 1543 spikes/4-min. *=$p<0.05$, SNK test

Table XI. Paired Comparisons of Mean Spontaneous MUA under Different Experimental Treatments

Treatments being Compared	Mean spikes/4-min interval+	n	S.E.D.*	Significance**
1) Freely Moving	6941 ± 965	7(6)	184	N.S.
vs				
Freely moving in 70%N_2O/30%O_2	6787 ± 951			
2) Freely moving in 70%N_2O/30%O_2	9829 ± 1795	8(8)	243	N.S.
vs				
Immobilized and respired with 70% N_2O/30% O_2	9070 ± 1576			
3) Freely moving	6205 ± 696			
vs.				
Immobilized and respired with 70% N_2O/30% O_2	6966 ± 1021	8(8)	400	N.S.

+Neuronal activity is expressed as the mean spontaneous MUA.

n = number of recordings used for comparison; number of animals is indicated in parentheses.

*Standard error of the difference.

**Statistical difference was not observed between any of the conditions ($p>0.05$); calculated according to the 2-tailed Student's t-test for paired observations.

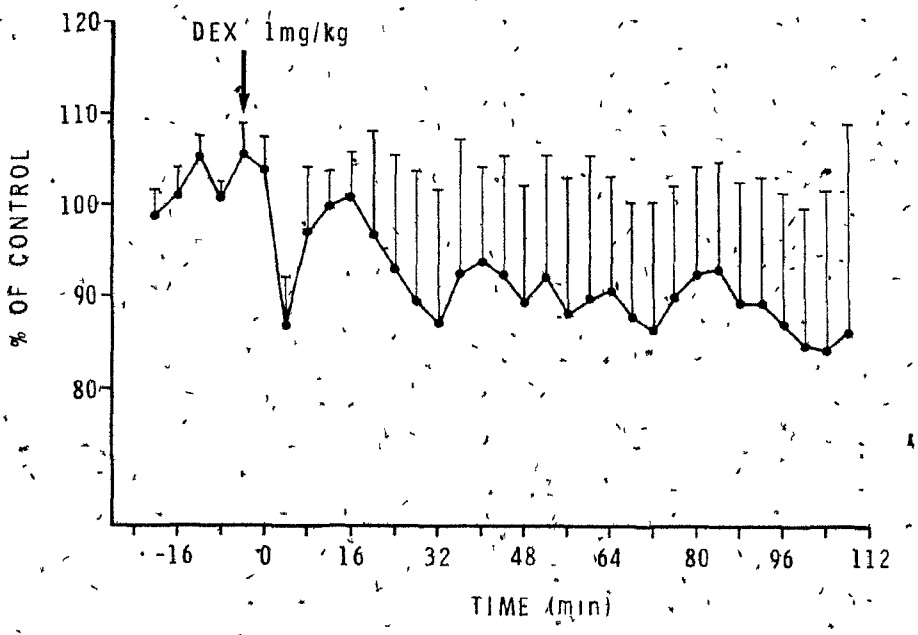


FIGURE 24. Effects of immobilization on striatal neuronal responses to DEX, 1 mg/kg in animals (N=5) that had previously (48 hrs.) responded to the same dose of DEX with excitation (peak response = 135 ± 8.6; mean ± SEM, expressed as % of control). Mean spontaneous MUA was 10628 ± 2076 spikes/4-min.

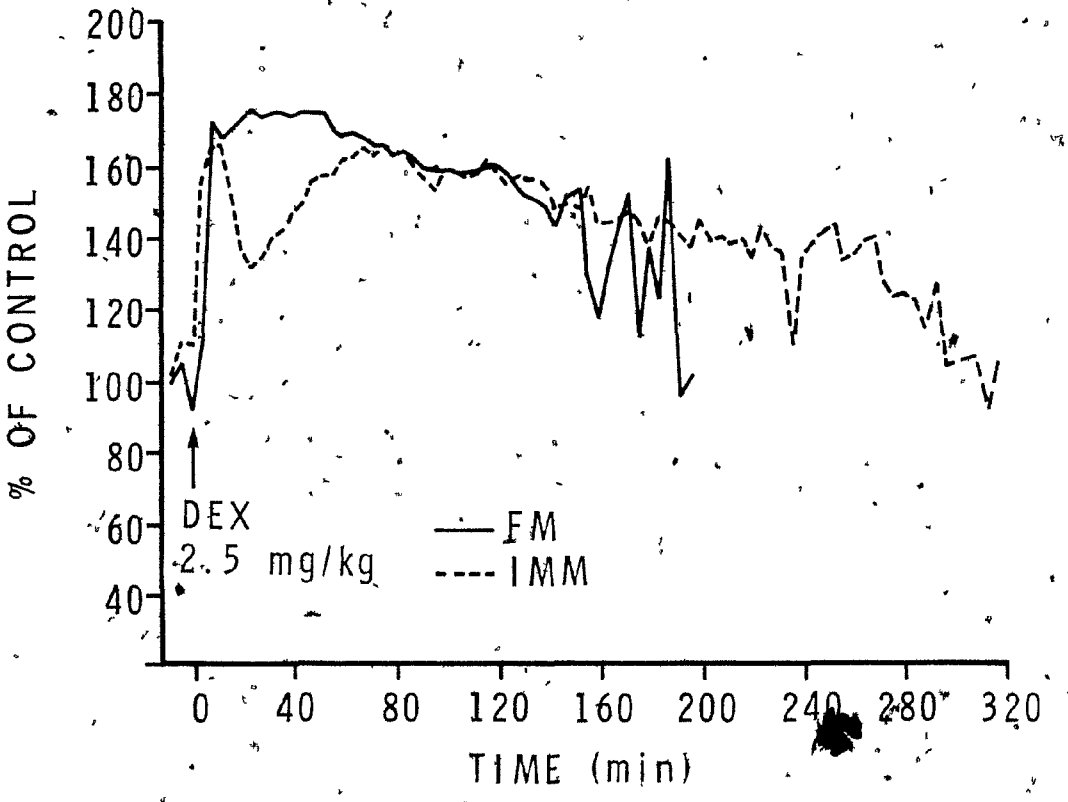


FIGURE 25. A comparison of striatal neuronal responses to DEX in the same animal during freely moving (FM) and immobilized (IMM) 48 hrs. later. In this instance the response in the immobilized animal consisted of excitation. Spontaneous MUA (FM) was 8367 ± 750 spikes/4-min; spontaneous MUA (IMM) was 5416 ± 429 spikes/4-min.

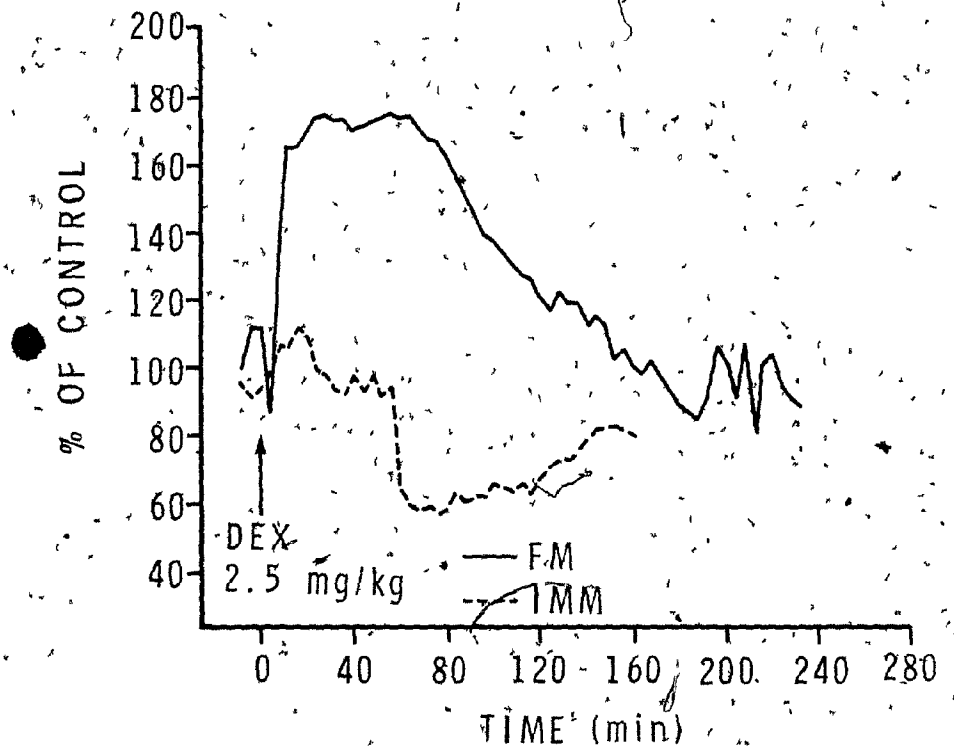


FIGURE 26. A comparison of striatal neuronal responses to DEX in the same animal during freely moving (FM) and immobilized (IMM) 48 hrs. later. In this instance the response to DEX in the immobilized animals was inhibition. Spontaneous MUA (FM) was 4891 ± 134 and spontaneous MUA (IMM) was 4272 ± 168 spikes/4-min.

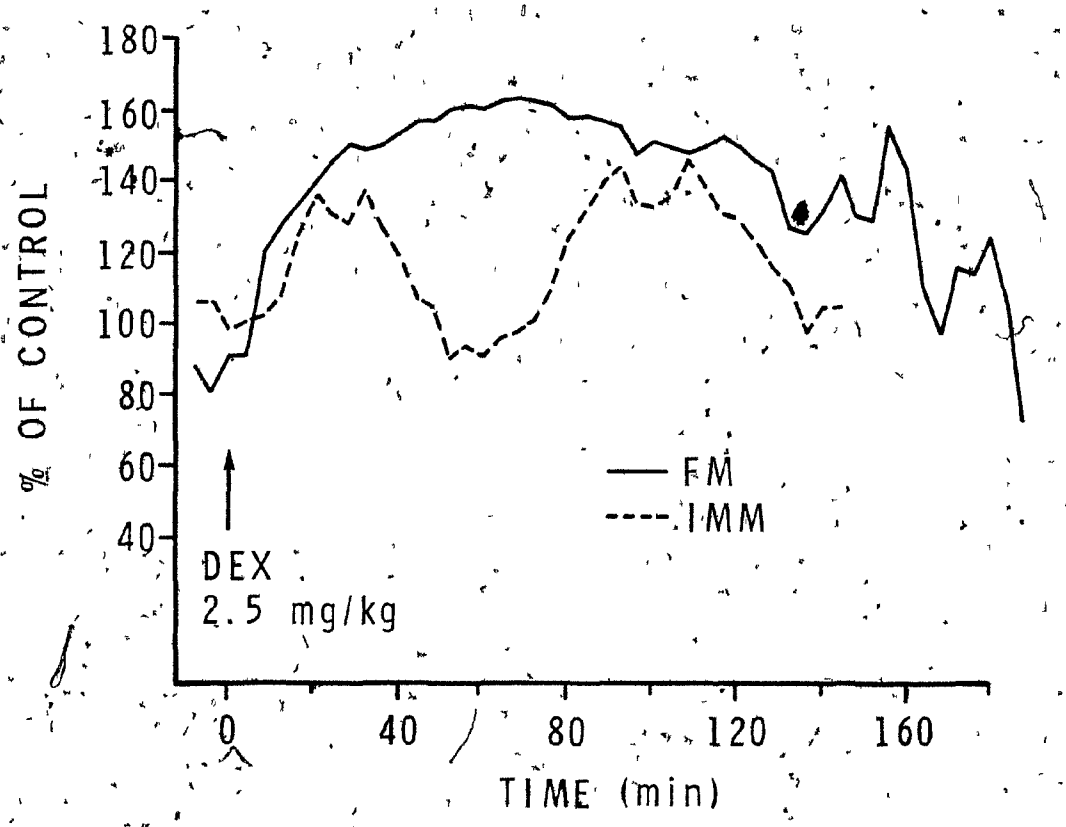


FIGURE 27. A comparison of striatal neuronal responses to DEX in the same animal during freely moving (FM) or immobilized (IMM). In this instance the response of the immobilized animal represents an example to one type of biphasic response. Spontaneous MUA (FM) was 6994 ± 485 spikes/4-min; spontaneous MUA (IMM) was 3598 ± 239 spikes/4-min.

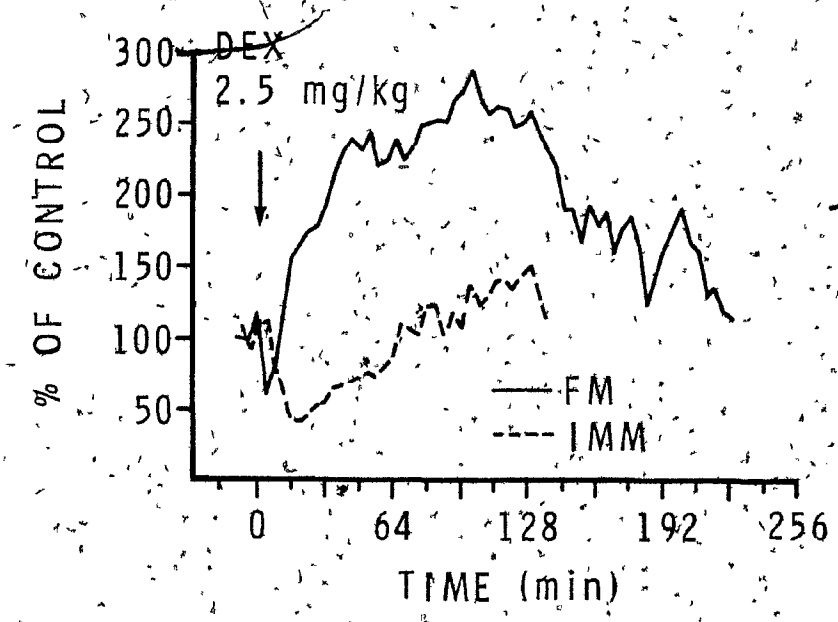


FIGURE 28. A comparison of striatal responses to DEX in the same animal as either freely moving (FM) or immobilized (IMM) 48 hrs. later. In this instance, the response in the immobilized animal represents a second type of a biphasic response. Spontaneous MUA (FM) 2119 ± 64 spikes/4-min; spontaneous MUA (IMM) 4828 ± 43 spikes/4-min.

Table XII. Summary of Striatal Responses to DEX in Immobilized Animals

Dose of DEX	Excitation	Inhibition	No Change	Biphasic	Total Recording Sites (n)
1 mg/kg (N=4)					
Drug-Naive (N=6)	2	1	–	1	4
Drug-Experienced[a]	–	2	4	–	6
2.5 mg/kg					
Drug-Naive* (N=13)	3	7	6	4	20
Drug-Experienced* (N=11)	4	3	5	6	18

[a]Animals first tested with DEX (2.5 mg/kg i.p.) in the freely moving state, immobilized 48 hr later, and tested a second time with the same dose of DEX.

N = number of animals.

*χ^2-square analysis showed no significant differences between the two groups ($p > 0.05$) of animals.

Table XIII demonstrates that the response of striatal neurons to DEX, either freely moving or immobilized animals, was not modified by the previous administration of DEX. Lastly, in immobilized animals receiving DEX, 2.5 mg/kg, and where no change in striatal neuronal discharge rates could be detected, this lack of change was indistinguishable from immobilized animals that had received saline only (Fig. 29).

However, neurons in these immobilized, saline-treated control animals still responded to ketamine, 50 mg/kg, with excitation (Fig. 30).

DEX Responses in Cortically Ablated Animals

Unilateral Ablation

The behavioral response to DEX, 2.5 mg/kg, was unchanged 21 days following unilateral cortical ablation (Fig. 31). Spontaneous MUA of lesioned animals was significantly decreased on the lesioned as compared to the intact side in animals with frontal but not parietal lesions (Table XIV). Striatal neuronal responses on both lesioned and intact sides no longer consisted predominantly of excitation. The various response patterns of striatal neurons were not unlike those seen in immobilized animals and are depicted in Appendix I, Figures 71, 72, 73 and 74. On the lesioned side the incidence of excitation was reduced to 35% of all observations (11/31) whereas the incidence of inhibition increased to 48% (15/31) (Table XV).

Of the 11 out of 31 ablated animals in which activation was seen on the lesioned side, 5 of the eleven showed peak DEX responses which were significantly less than normal animals (Fig. 32). Spontaneous

Table XIII. Comparison of Successive DEX Treatments in the Same Animal

Paradigm	Peak Response (% of Control)[a] 1st trial	2nd trial	N	S.E.D.+
DEX, 1.0 mg/kg i.p., 24 hr apart; freely moving under 70% N_2O/30% O_2 in each trial.	135.2 ± 5.3*	139 ± 4.4**	5(6)	2.7
DEX, 2.5 mg/kg i.p. 48 hr apart, animals freely moving in 1st trial and immobilized in 2nd trial	158.5 ± 6.7**	160.3 ± 12.9**	4(4)	8.8

[a]Peak response is defined as the maximal increase in striatal MUA activity following DEX.

N refers to number of animals; number of electrode sites in parentheses.

+Standard error of the difference.

**Peak responses were not statistically different as evaluated by the 2-tailed Student's t-test for paired observations ($p > 0.05$).

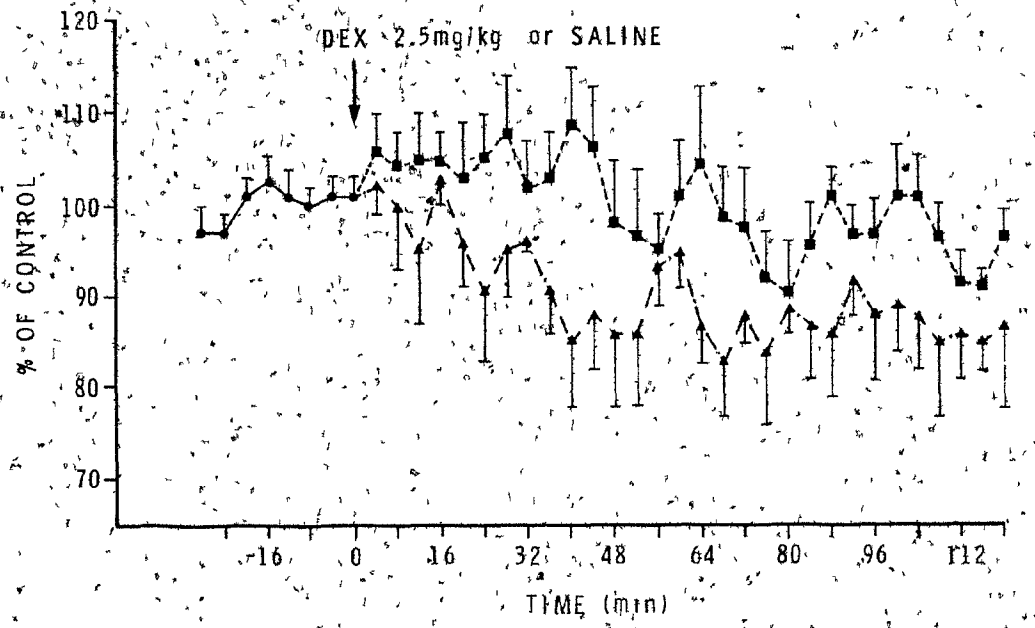


FIGURE 29. No change responses to DEX in immobilized animals (▲--▲; N=5) as compared to immobilized animals receiving saline only (■-■; N=5). Mean spontaneous MUA (no change group) 6300 ± 657 spikes/4-min; mean spontaneous MUA (saline group) 7667 ± 1800 spikes/4-min. Control interval data for the two groups was pooled.

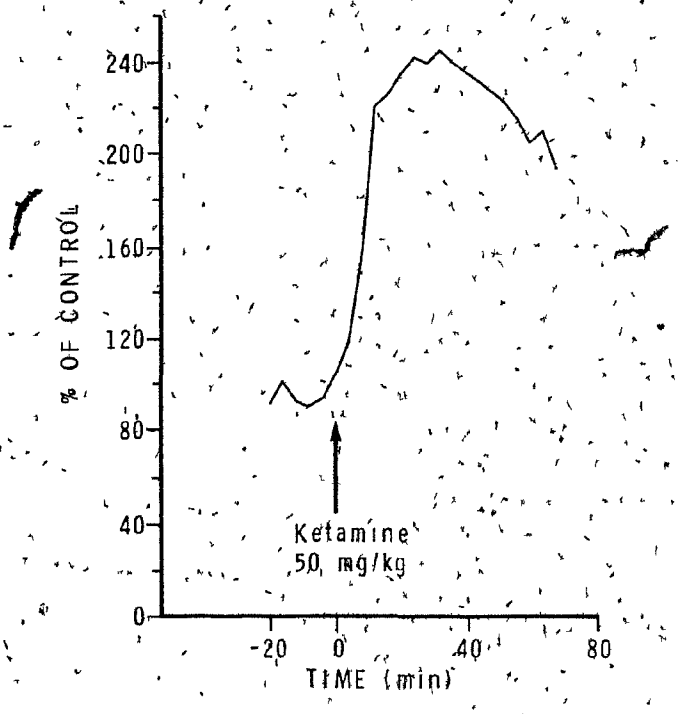


FIGURE 30. Representative experiment showing the response of striatal neurons in an immobilized animal following ketamine. Spontaneous MUA = 5231 ± 168 spike /4-min.

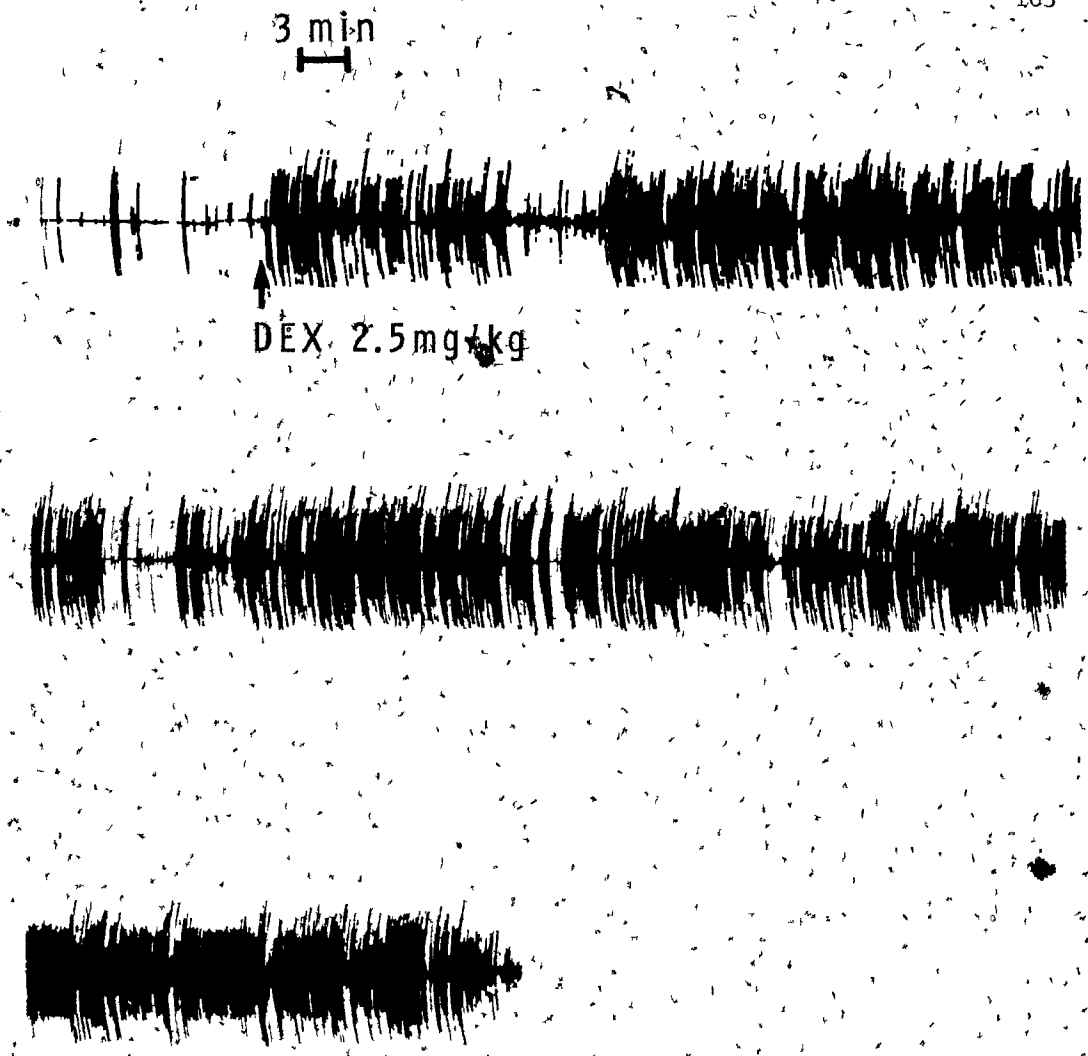


FIGURE 31. A representative trace of the behavioral response to DEX in a unilateral cortically ablated animal.

Table XIV. Comparison of Mean Spontaneous MUA of Striatal Neurons in Control and Unilateral Cortically Ablated Rats

Controls (n=29)	Frontal Cortical Lesion (n=17)	
	Ipsilateral (Lesion)	Contralateral (Intact)
5574 ± 702	3791 ± 659*	7645 ± 1477
	Parietal Cortical Lesion (n=13)	
	Ipsilateral (Lesion)	Contralateral (Intact)
	4455 ± 956	5616 ± 981

[1]Spontaneous discharge rates given as mean ± SEM of each group.

*Significantly different ($p<0.05$) from contralateral (paired t-test).

Table XV. Comparison of Striatal Neuronal Responses to DEX, 2.5 mg/kg, in Freely Moving Control and Unilateral Cortically Ablated Rats

	Controls (n=33)	Unilateral Cortically Ablated (n=31)+	
		Ipsilateral (Lesion)*	Contralateral (Intact)*,**
Excitation	29	11	8
Inhibition	1	15	9
No change	2	2	9
Biphasic	1	3	5

+Includes both frontal and parietal lesions.

**Not significantly different from ipsilateral ($p > 0.05$ χ^2-test).

*Significantly different from controls ($p < 0.05$ χ^2-test).

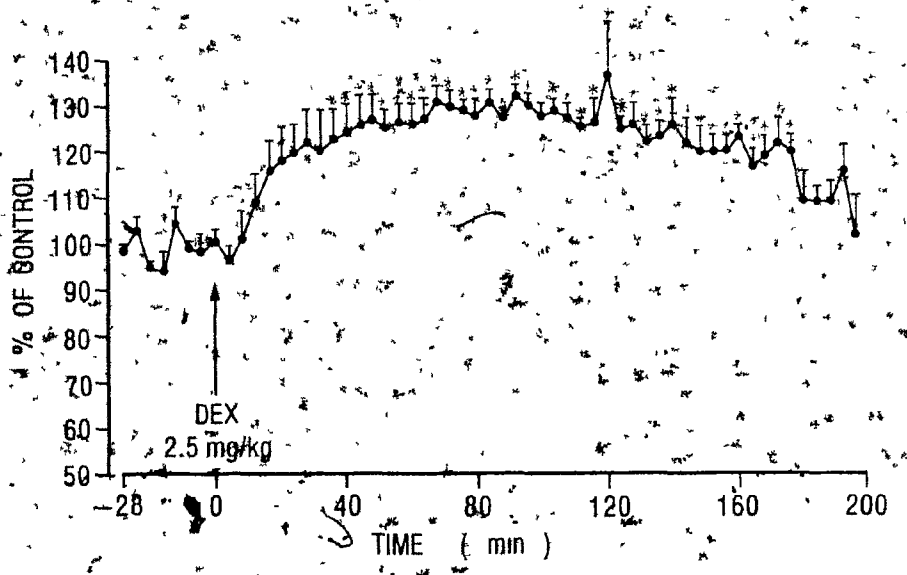


FIGURE 32: Reduced excitatory response to DEX in unilateral cortically ablated animals. Results show the response on the lesioned side in 5 animals. Mean spontaneous MUA 5544 ± 1104 spikes/4 min. * = $p < 0.05$, SNK test.

MUA of this group was unchanged compared to normal animals (Table XVI). In the remaining six animals, peak activation following DEX was significantly greater compared to non-ablated animals (Table XVI).

The spontaneous MUA activity on the lesioned side in those animals showing an increased response to DEX, was significantly reduced from 5554 ± 667 in normal animals to 2540 ± 1010 in ablated animals (Table XVI).

Striatal Responses to DEX After Bilateral Cortical Ablation

Bilateral cortical lesions did not alter DEX-induced behavioral activation (Fig. 33). However, mean spontaneous MUA in bilaterally cortically ablated animals was significantly decreased compared to normal control animals (Table XVII). Striatal neuronal responses to DEX were similar to those seen in animals with unilateral cortical lesions and could again be subdivided into four response patterns (Appendix I, Figures 75, 76, 77 and 78). The incidence of excitation was reduced to 21% in these animals such that in 15 out of 19 recording sites, responses other than excitation were seen (Table XVIII). Bilateral lesioning of the fimbria-fornix in addition to bilateral cortical ablation, did not further change either the DEX-induced behavior (Fig. 34), spontaneous MUA (Table XVII) or the responses to DEX as compared to those seen in bilateral cortical ablations only (Table XVIII).

Effects of Cortical Lesions on Drug-Induced Catalepsy

Haloperidol-induced catalepsy was significantly reduced in bilateral cortically ablated animals whereas the catalepsy produced by morphine was unchanged (Fig. 35).

Table XVI. Analysis of Striatal Excitatory Responses to DEX, 2.5 mg/kg, in Unilateral Cortically Ablated Rats

	Mean Spontaneous MUA	Peak Response
Controls (n=19)	5554 ± 667	183 ± 8.7
Unilateral Cortically Ablated[1]		
"Reduced Excitations" (n=5)	5544 ± 1104^{+}	137 ± 2.7**,$^{+}$
"Enhanced Excitations" (n=6)	2540 ± 1010*	264 ± 53*

[1]Units on ablated side only.

Data expressed as mean ± SEM.

*$p < 0.05$ compared to controls (two-tailed unpaired t-test).

**$p < 0.02$ compared to controls (two-tailed unpaired t-test).

$^{+}p < 0.05$ compared to "enhanced excitations" (one-tailed unpaired t-test).

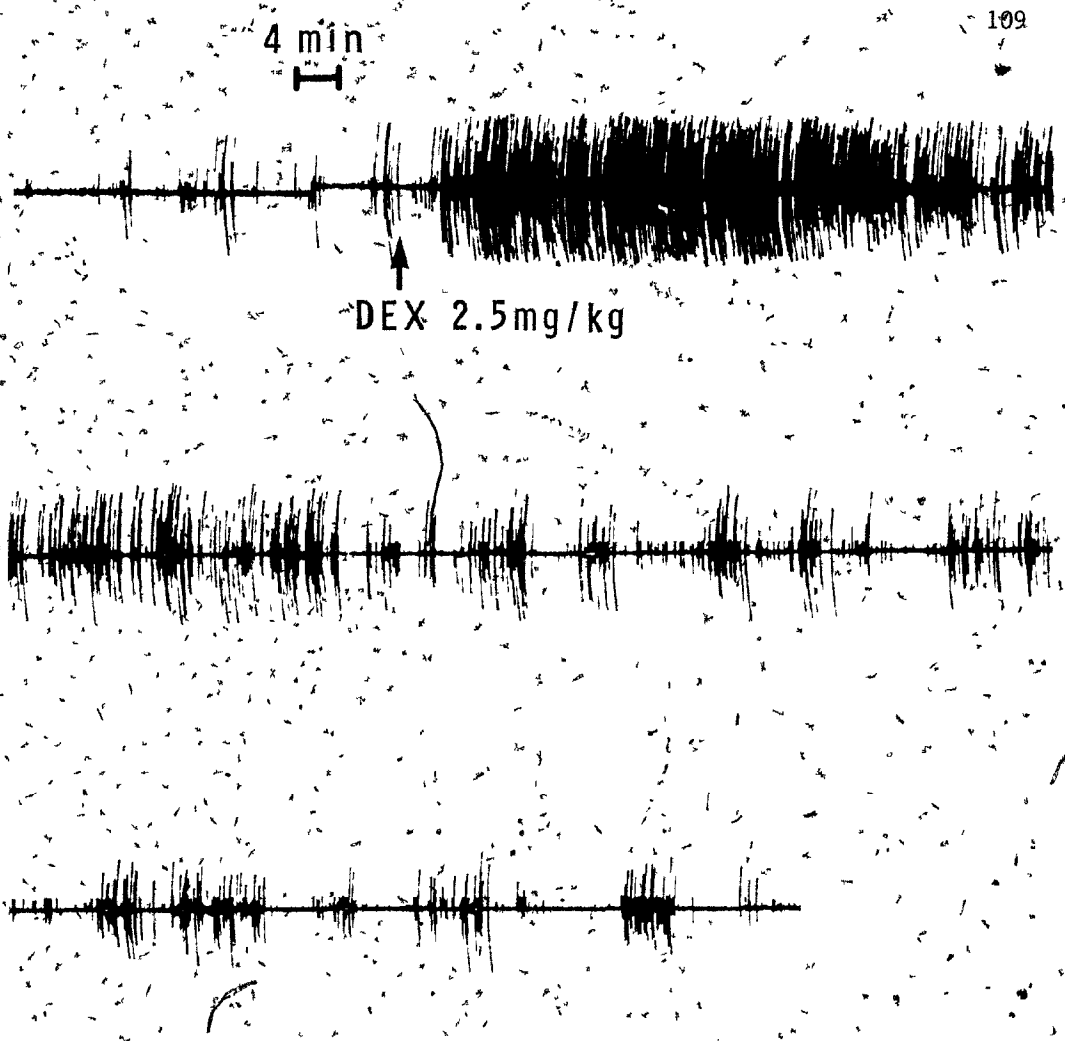


FIGURE 33. A representative trace of behavioral activation in response to DEX in a bilateral cortically ablated animal.

Table XVII. Comparison of Mean Spontaneous MUA of Striatal Neurons in Control and Bilateral Cortically Ablated Rats.

Controls (n=29)	Bilateral Ablation (n=19)	Bilateral Ablation + Fimbria-Fornix Transection (n=22)
5574 ± 702	2363 ± 692*,+	2371 ± 529*

[1]Data expressed as mean ± SEM.

+Not signficantly different from Bilateral Ablation + Fimbria-Fornix Transection (paired t-test).

*Significantly different ($p < 0.01$) from controls (unpaired t-test).

Table XVIII. Comparison of Striatal Neuronal Responses to DEX, 2.5 mg/kg, between Freely Moving Control and Bilateral Cortically Ablated Rats

	Controls (n=33)	Bilateral Cortically Ablated* (n=19)	Bilateral Cortically Ablated + Fimbria-Fornix Transection*,** (n=22)
Excitation	29	4	5
Inhibition	1	10	9
No change	2	2	2
Biphasic	1	3	6

**Not significantly different from bilateral cortically ablated ($p > 0.05$ χ^2-test).

*Significantly different from controls ($p < 0.05$ χ^2-test).

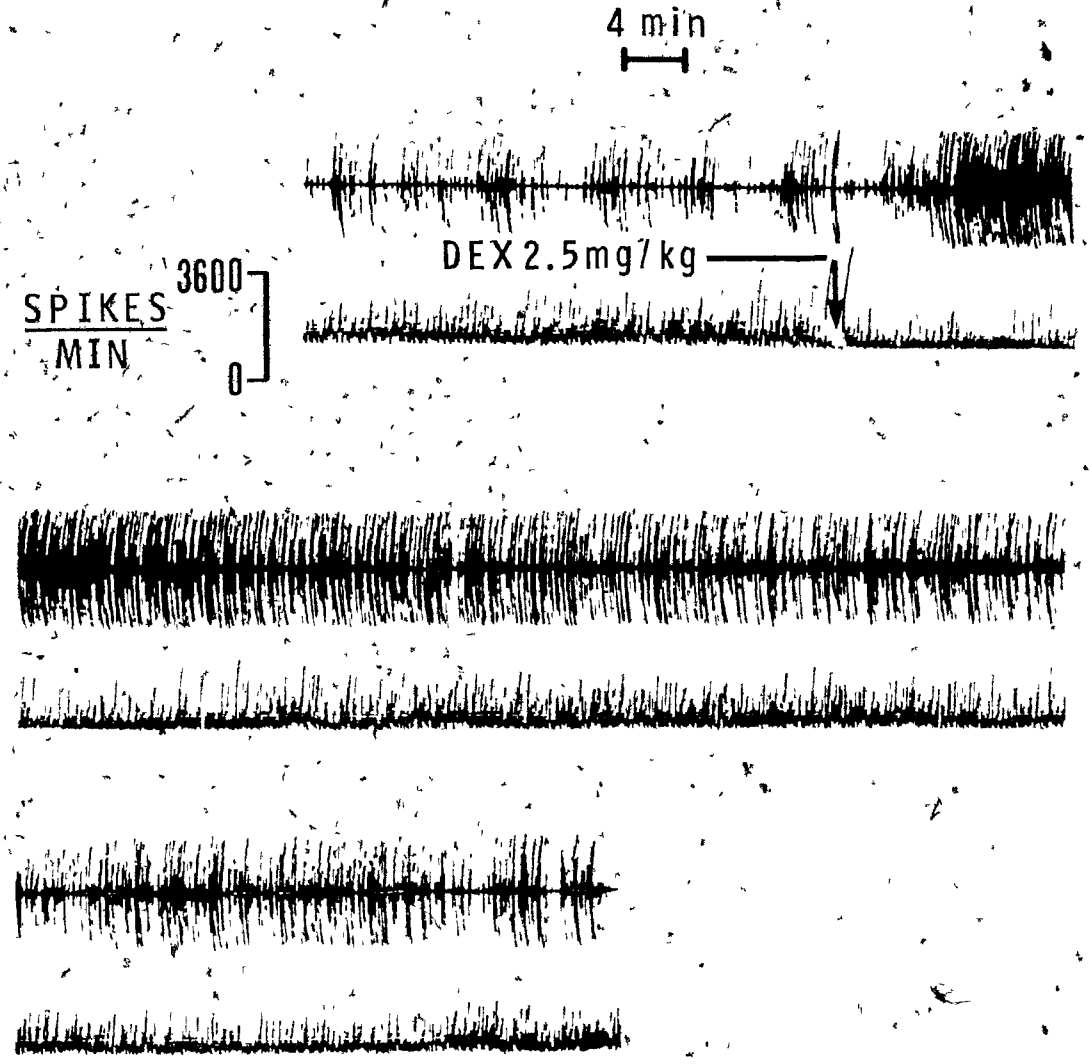
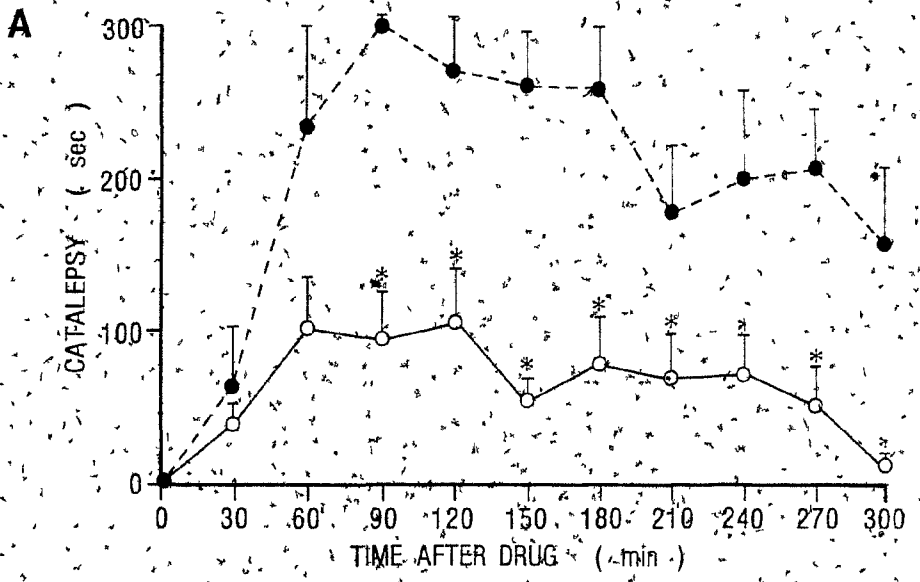
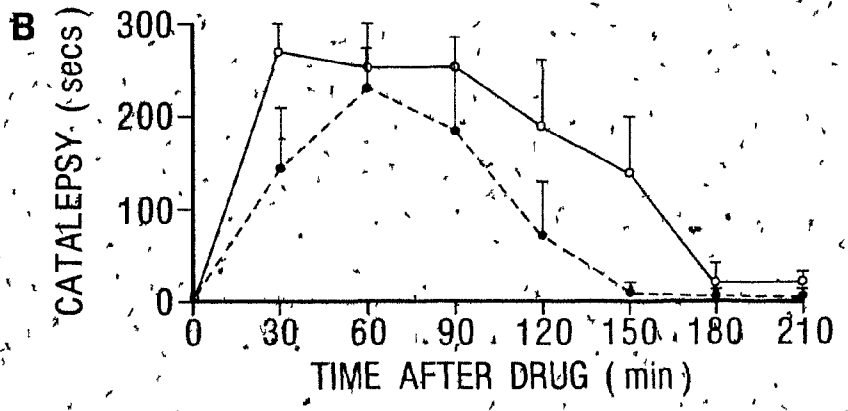


FIGURE 34. A representative trace of behavioral activation but no change in striatal MUA following DEX in a bilateral cortically ablated animal with bilaterally lesioned fimbria-fornix.

FIGURE 35. Catalepsy in animal with bilateral cortical ablation. A. Haloperidol, 2 mg/kg, controls = ●—●, N=4, lesioned = o——o; N=9. * = $p < 0.05$ compared to controls (Mann-Whitney U-test); B. Morphine, 15 mg/kg; controls = ●—●, N=5; lesioned = o——o, N=4.


A
CATALEPSY (sec)
300
200
100
0
0 30 60 90 120 150 180 210 240 270 300
TIME AFTER DRUG (min)


B
CATALEPSY (secs)
300
200
100
0
0 30 60 90 120 150 180 210
TIME AFTER DRUG (min)

Responses of Striatal Neurons to DEX Following Lesions of the PF-CM Complex

Lesions of the PF-CM complex produced contraversive body bias 4-24 hrs. after recovery from anaesthesia. By seven days this motor deficit was no longer apparent. Twenty-one to 28 days after lesioning, DEX induced the usual behavioral activation (Fig. 36).

A comparison of spontaneous striatal neuronal activity between the lesioned and intact sides, as well as comparison with normal control animals, showed that unilateral lesions decreased spontaneous MUA on both lesioned and intact sides (Table XIX). Striatal neurons on the lesioned side showed a variety of responses following DEX (Appendix I, Figures 79, 80, 81 and 82) with inhibition accounting for 11 out of 22 (50%) of all responses (Table XX). Furthermore, the striatal neuronal response to DEX, on the intact side (N=15), consisted mainly of excitation with inhibition accounting for only 20% of observed responses (Table XX).

DEX-Induced Activation of Neurons within the PF-CM Complex

Administration of DEX, 2.5 mg/kg, to animals where MUA was being recorded from neurons within the PF-CM complex, resulted in excitation of these neurons with a time-course somewhat shorter than that observed for striatal neurons (Figs. 37 and 38). Excitation reached a maximum of 187 ± 9% of control between 24 and 60 min. after drug and lasted approximately 1.5 hrs. compared to 2.5 hrs. in the striatum (Fig. 39).

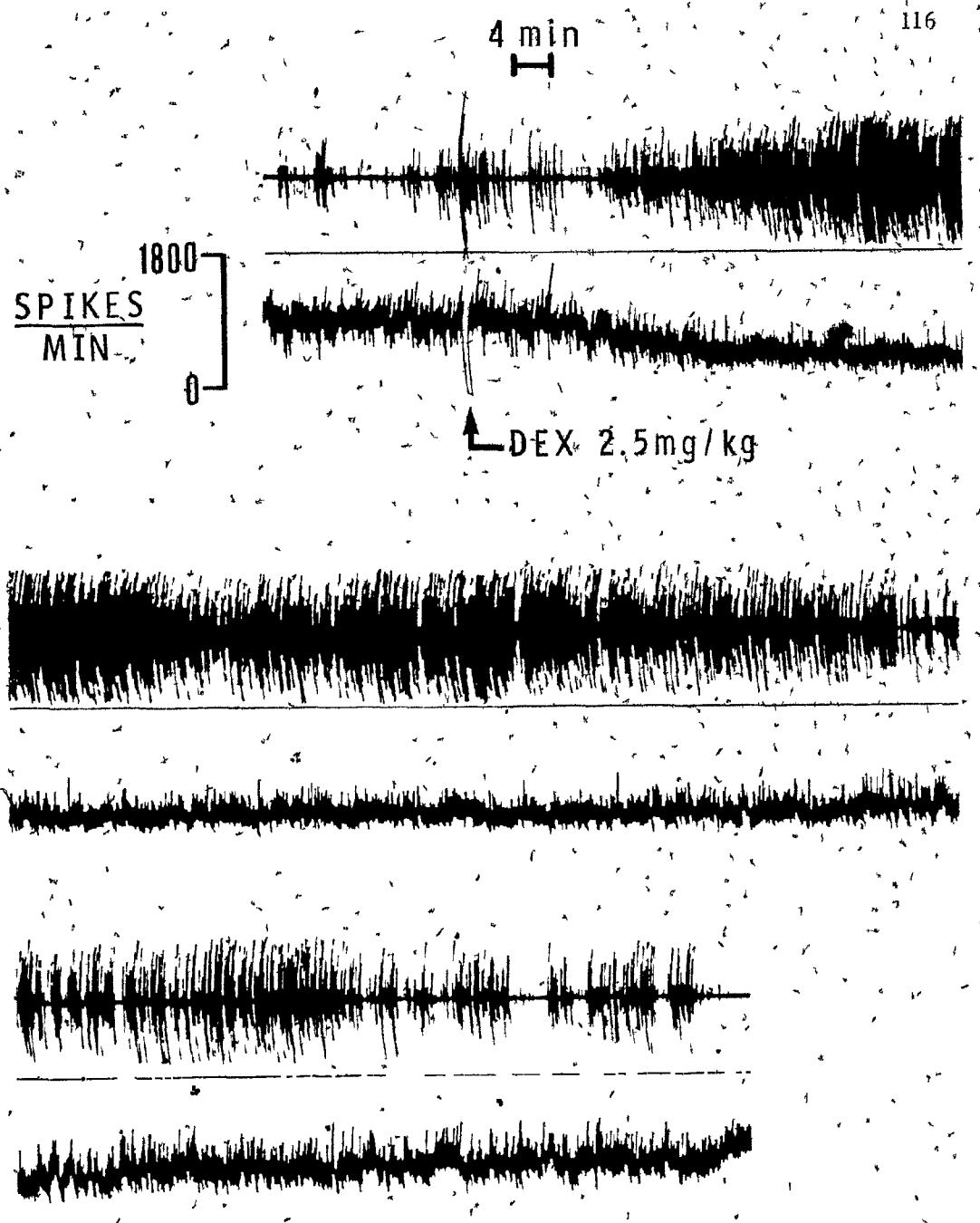


FIGURE 36. A representative record showing behavioral activation but inhibition of striatal MUA following DEX in an animal with a unilateral PF-CM lesion.

Table XIX. Comparison of Mean Spontaneous MUA of Striatal Neurons in Control and Unilateral PF-CM Lesioned Rats

	Unilateral PF-CM Lesions	
Controls (n=29)	Ipsilateral (Lesion) (n=22)	Contralateral (Intact) (n=15)
5574 ± 702	2203 ± 429*	2222 ± 543**

Data expressed as mean ± SEM.

*,**Significantly different ($p<0.01$) from controls (unpaired t-test).

Table XX. Comparison of Striatal Neuronal Responses to DEX in Freely Moving Control and Unilateral PF-CM Lesioned Rats

	Controls (n=33)	PF-CM Lesioned	
		Ipsilateral (Lesion) (n=22)*	Contralateral (Intact) (n=15)
Excitation	29	3	9
Inhibition	1	11	3
No change	2	4	-
Biphasic	1	4	3

*Significantly different from either controls or intact side ($p<0.05$; χ^2-test).

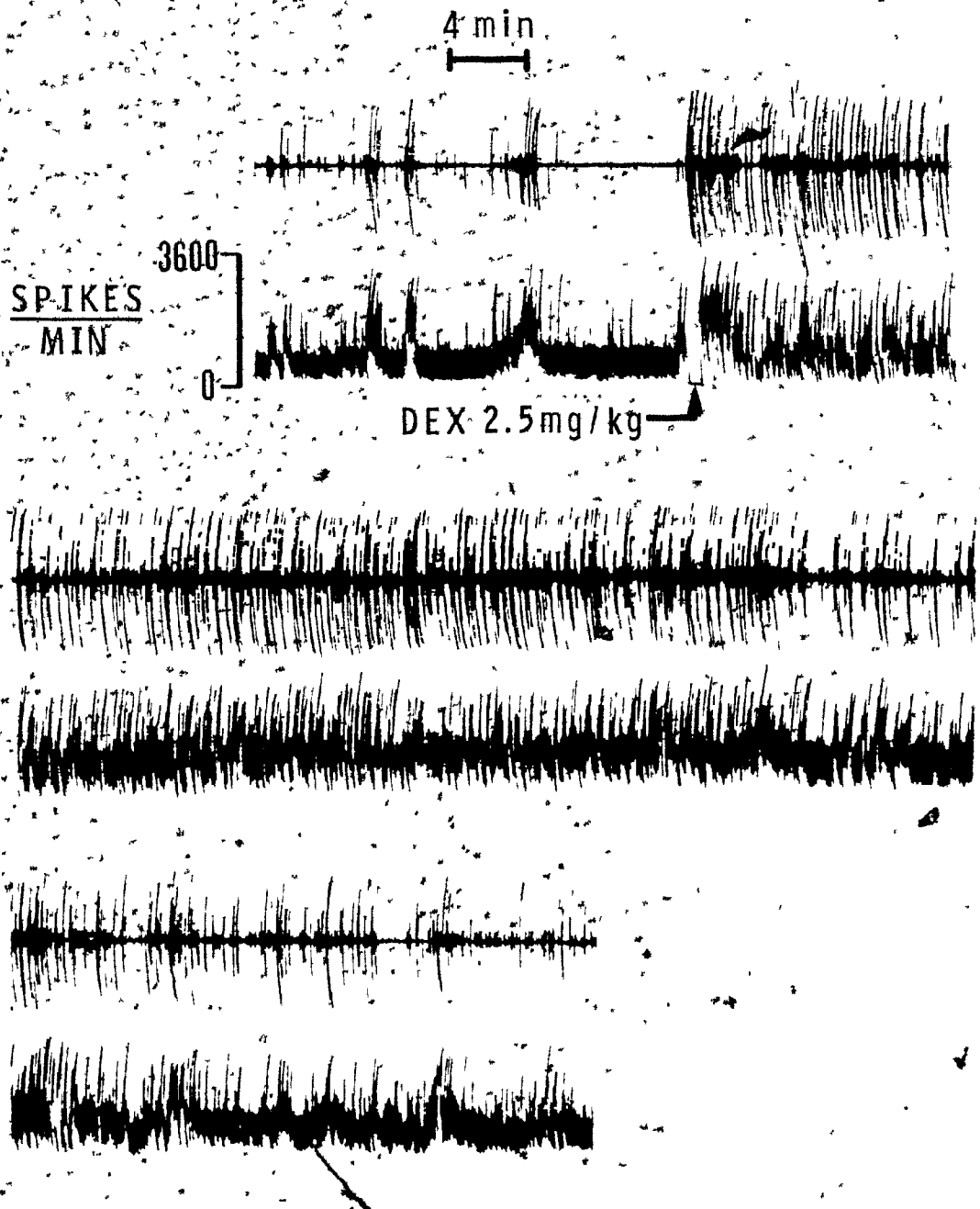


FIGURE 37. A representative record of an experiment in which the electrode was located in the PF-CM complex. Note that the transition to bursting of PF-CM neurons matches the onset of DEX-induced behavioral activation and shows the same time course.

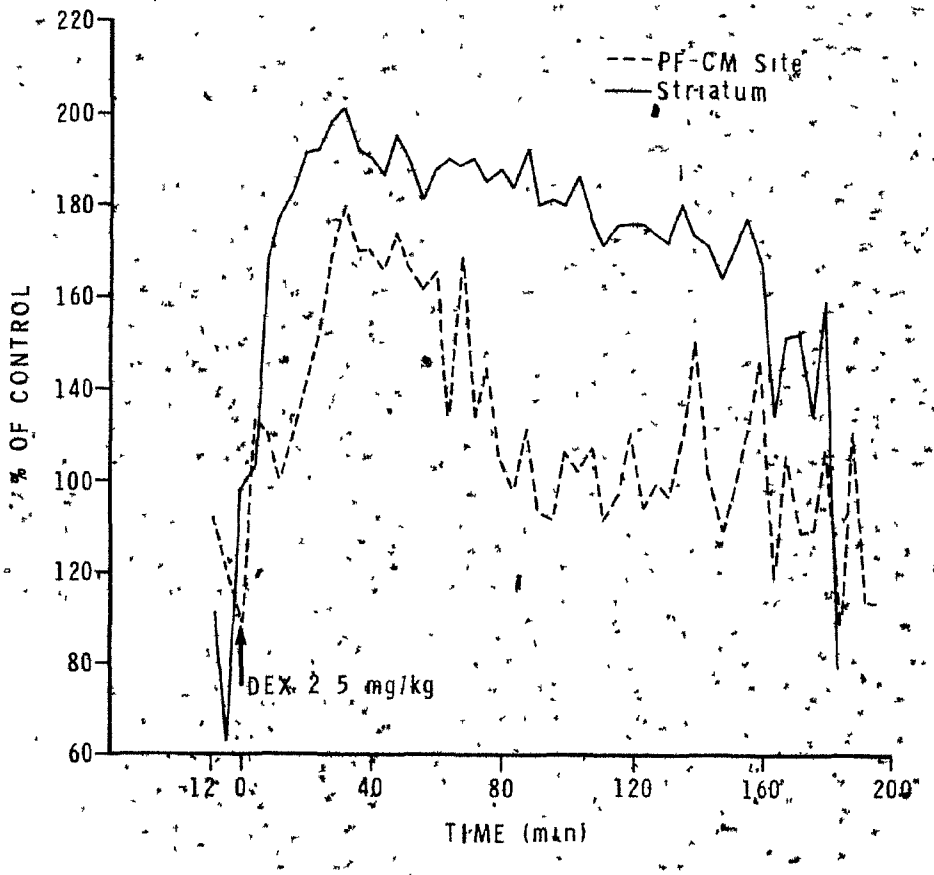


FIGURE 38. A representative experiment showing the similar time course between striatal activation of neurons in the PF-CM complex within the same animal. Spontaneous MUA in the striatum 4225 ± 287 spikes/4-min; PF-CM site 3259 ± 112 spikes/4-min.

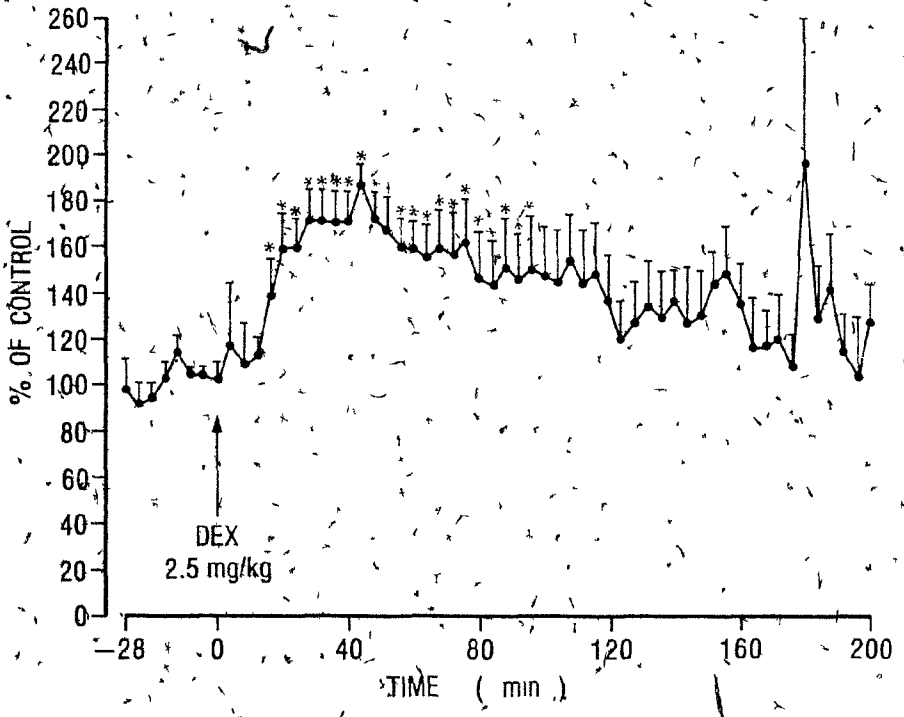


FIGURE 39. Activation of MUA in the PF-CM complex following DEX. Mean spontaneous MUA = 3246 ± 518 spikes/4-min (4 animals). * = $p < 0.05$, SNK test.

Reversal of DEX-Induced Inhibition of Striatal Neurons in Lesioned Animals

In six animals with unilateral cortical ablation, administration of DEX, 2.5 mg/kg, resulted in inhibition of striatal MUA on the ablated side (Fig. 40). This inhibition reached a maximum value of 58 ± 9% of control between 112 and 124 min. after drug, and gradually reversed over the next hour.

In contrast, re-administration of DEX, 2.5 mg/kg, forty-eight hrs. later to the same animals, resulted in activation of striatal neurons (Fig. 40). This activation of striatal neurons had a time course comparable to that seen in normal animals, with peak activity of 199 ± 53% of control (mean ± SEM) between 44 and 64 min. after injection. This reversal of the DEX response was seen in animals having either frontal or parietal lesions. Furthermore, this phenomenon was most prevalent in the ipsilateral striatum (Table XXI) and not seen in animals with either bilateral cortical or PF-CM lesions (Figs. 41 and 42). No difference in spontaneous firing rates for the various experimental settings could be detected (Table XXII).

Striatal Glutamate, GABA and Glutamine Levels Following Unilateral Cortical Ablation

Striatal glutamate, GABA and glutamine levels were measured in 19 animals age matched to animals in which electrical recording was carried out. Twenty one days after unilateral cortical ablation, striatal glutamate levels on the lesioned side (N=6) decreased significantly by 27% relative to the contralateral side, and by 44% compared to striata from sham-operated animals (N=8) (Fig. 43).

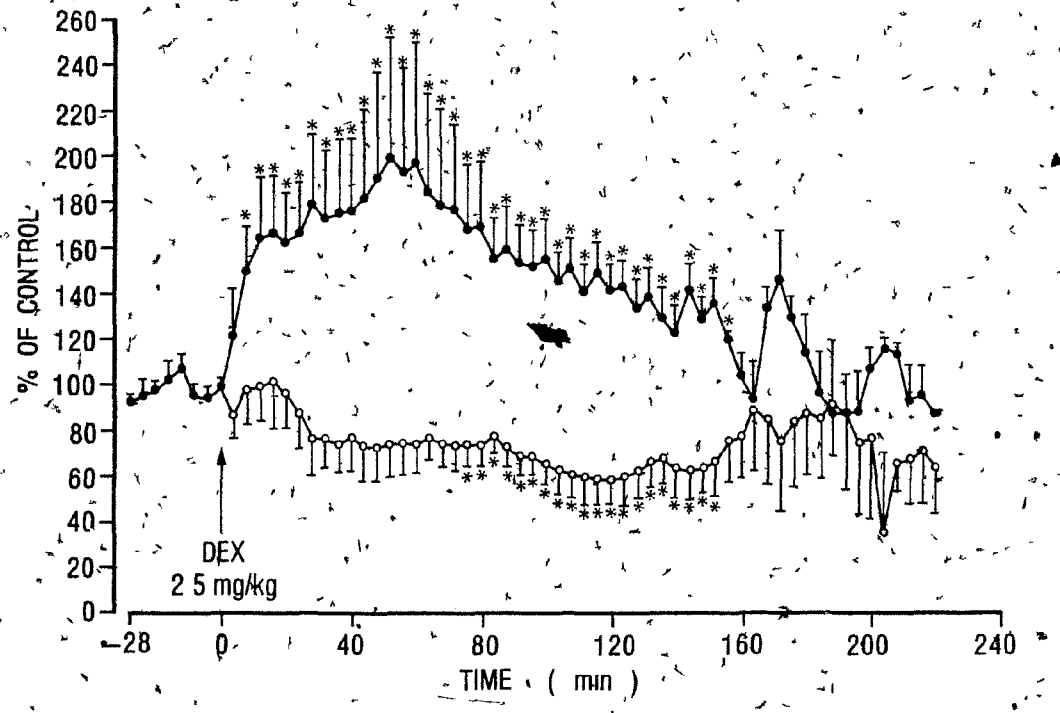


FIGURE 40. Reversal of DEX-induced inhibition of striatal neurons in unilateral cortically ablated animals. In the first experiment (o) DEX produced inhibition; 48 hrs. later (o) DEX re-administered to the same animals resulted in excitation. Results shown represent three frontal and three parietal ablations (6 animals). Mean spontaneous MUA in the first experiment was 5548 ± 1176 spikes/4-min; in the follow-up experiment mean spontaneous MUA was 6418 ± 1823 spikes/4-min. * = $p < 0.05$, SNK test.

Table XXI. Summary of DEX-Induced Changes in Response to Second Administration of DEX in Unilateral Cortically Ablated Rats

	Response Patterns of Units on Ablated Side			
	Excitation	Inhibition	No Change	Biphasic
Drug-naive	1	9	0	0
Drug 48 hrs. later	8*	0	1	1

	Response Patterns of Units on Intact Side			
	Excitation	Inhibition	No Change	Biphasic
Drug-naive	0	4	3	2
Drug 48 hrs. later	4	1	2	2

*$p < 0.05$ (χ^2-test with 4 x 2 contingency table).

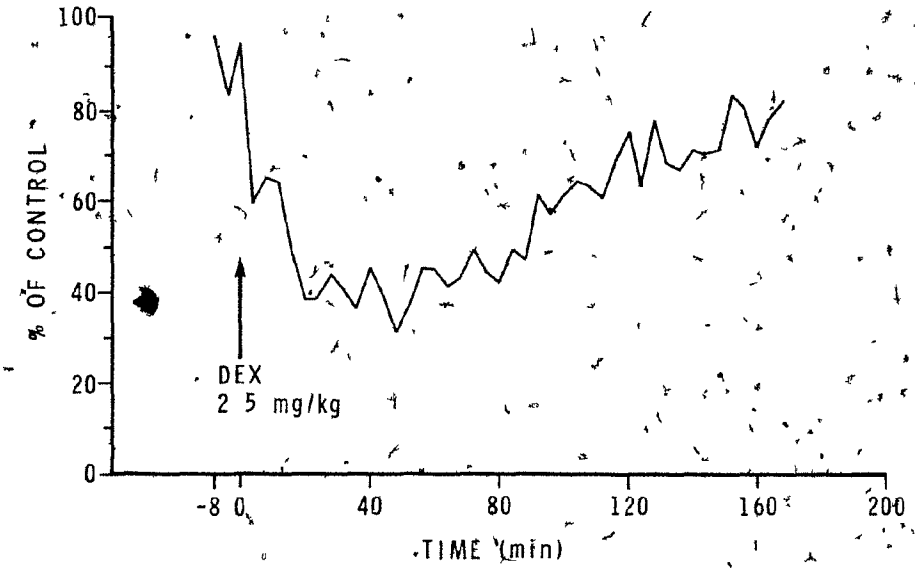


FIGURE 41. A representative experiment showing no DEX-reversal in a bilateral cortically ablated animal 48 hrs. after the first experiment, in which DEX produced inhibition of MUA. Spontaneous MUA in this experiment was 5392 ± 172 spikes/4-min.

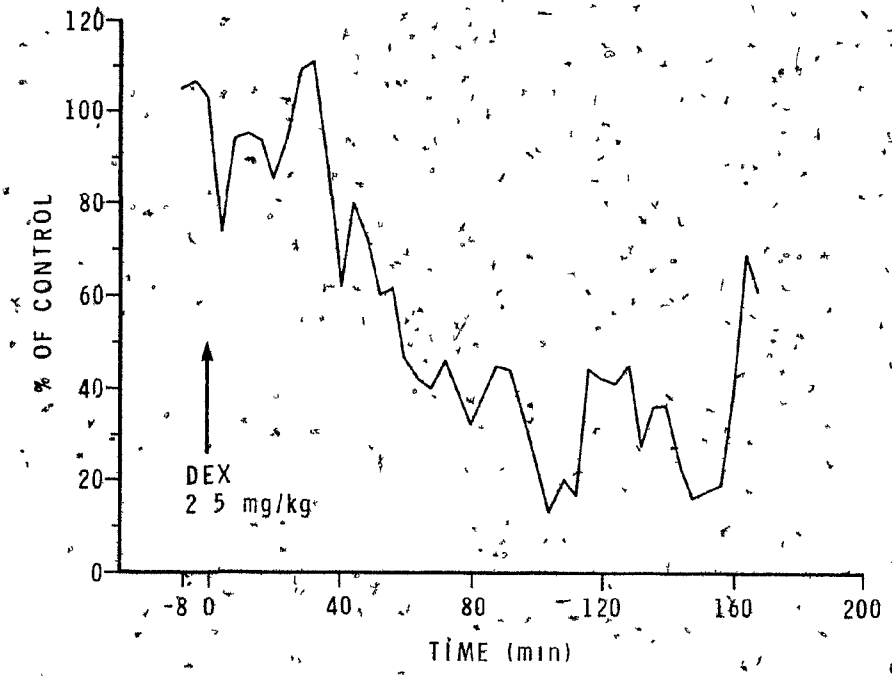


FIGURE 42. A representative experiment showing no DEX-reversal after 48 hrs. in an animal with a unilateral PF-CM lesion that had responded to DEX in the first experiment with inhibition. Spontaneous MUA in this experiment was 3344 ± 85 spikes/4-min.

Table XXII. Comparison of Mean Spontaneous MUA in Lesioned Animals Between 1st and 2nd (48 hrs. later) Administration of DEX, 2.5 mg/kg

	1st Experiment	2nd Experiment	n[1]	SED[2]	Significance*
Type of Lesion:					
Unilateral Cortical Ablation[3]	5937 ± 918	6377 ± 1397	8	906	N.S.
Bilateral Cortical Ablation[4]	2415 ± 662	2783 ± 755	11	406	N.S.
Unilateral PF-CM Lesion[5]	2337 ± 831	2305 ± 682	9	344	N.S.

[1]n = number of recording sites.

[2]SED = Standard Error of the Difference.

[3]Both frontal and parietal lesions; ablated side only.

[4]Includes Bilateral Cortically Ablated + Fimbria-Fornix Transection.

[5]Lesioned side only.

*No significant differences between 1st and 2nd treatments in any lesion group (paired t-test).

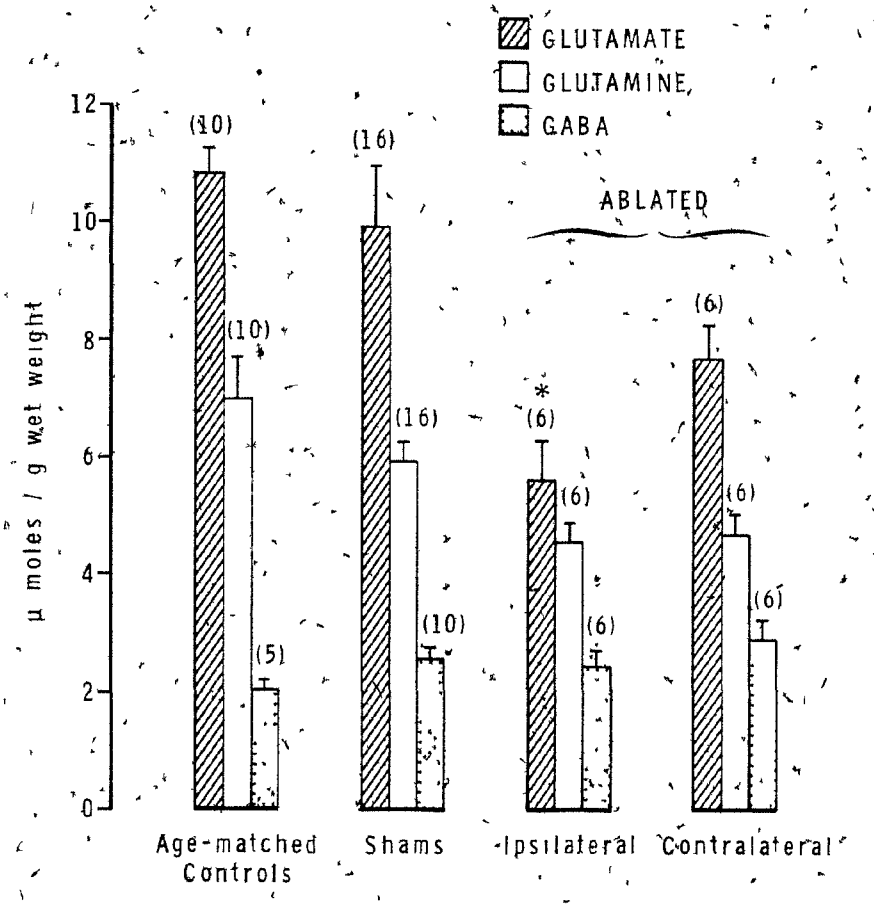


FIGURE 43. Reductions in striatal glutamate content following unilateral cortical ablation. Number of striata used in the analysis is indicated in parentheses. * = $p < 0.01$ ipsilateral compared to contralateral (paired-t-test).

Again, on the side contralateral to the lesion striatal glutamate levels also appeared to be somewhat lower than those of sham-operated animals (Fig. 43), but this decrease was not statistically significant ($0.2 \geq p \geq 0.1$). In contrast, striatal GABA and glutamine levels on either side were unchanged (Fig. 43).

Striatal Glutamate, GABA and Glutamine Levels Following Bilateral Cortical Ablation

Twenty-one days after bilateral cortical ablation in six animals, striatal glutamate was significantly decreased ($p < 0.05$) by 22% as compared to the appropriate sham-operated controls (Fig. 44). In contrast, striatal GABA and glutamine levels remained unchanged.

Receptor Changes Following Bilateral Cortical Ablation

Binding of [^{3}H]-Met-enkephalin to striatal opiate receptors did not change following bilateral cortical ablation. The results of a representative experiment are depicted in Figure 45. In three experiments, neither the density of binding sites (B_{max}) nor the affinity (Kd) were significantly different from those seen in sham-operated controls (Table XXIII).

Dopamine D_1-receptor binding was not systematically studied. However, in the single experiment in which [^{3}H]-ADTN binding was examined, there appeared to be an increase in B_{max} and a decrease in K_d as compared to shams (Fig. 46). In contrast, the B_{max} of dopamine D_2-receptor binding sites were found to decrease by 20-25% as compared to shams (Fig. 47 and Table XXIII).

The Effects of 6-OHDA Lesions in the SNC on the Striatal DEX Response

Immediately following the administration of 6-OHDA into the

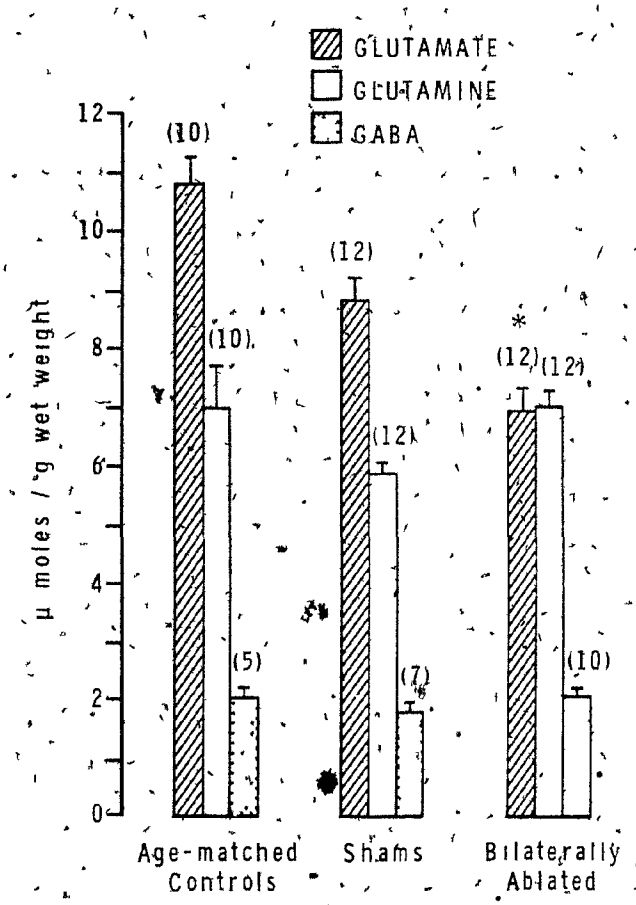


FIGURE 44. Reductions in striatal glutamate levels following bilateral cortical ablation. Number of striata used in the analysis is given in parentheses. * = $p < 0.05$ as compared to shams (unpaired-t-test).

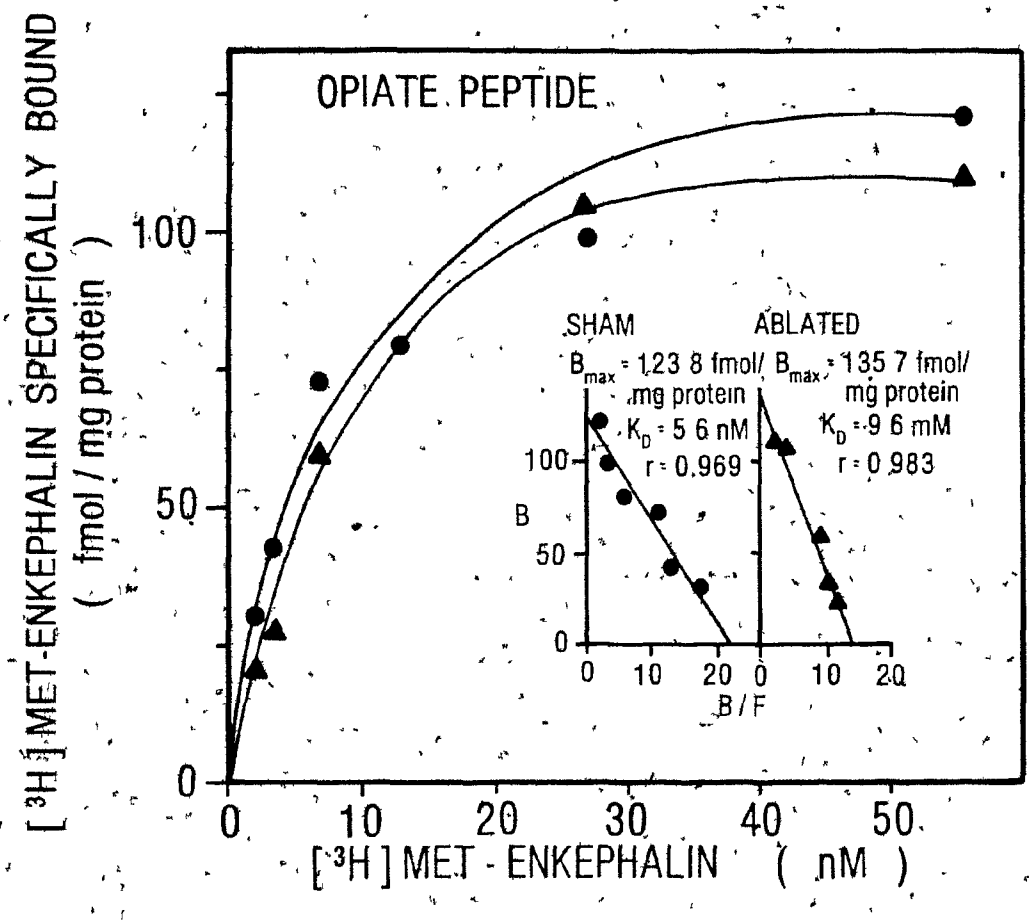


FIGURE 45. Binding isotherms and Eadie-Hofstee plots of a representative experiment showing the binding of (^{3}H)-Met-enkephalin to striatal P_2 fractions from sham-operated and bilateral cortically ablated animals.

Table XXIII. Receptor Binding Studies of Striata Following Bilateral Cortical Ablation

	SHAMS	BILATERALLY ABLATED
Striatal Opiate ([^{3}H]-Met-Enkephalin) Binding		
B_{max} (fmol/mg)	171.4 ± 23.9	175.1 ± 30.8
K_d (nM)	8.38 ± 2.1	12.14 ± 4.7
r^b	0.93 ± 0.05	0.96 ± 0.02
Striatal [^{3}H]-Spiperone Binding		
B_{max} (fmol/mg)	749.31 ±	604.3 ± *
K_d (nM)	2.48 ± 0.95	2.54 ± 0.96
r^b	0.81 ± 0.06	0.926 ± 0.01

Data expressed as mean ± SEM of three experiments.

[b]correlation coefficient

*$p < 0.05$ (one-tailed paired t-test).

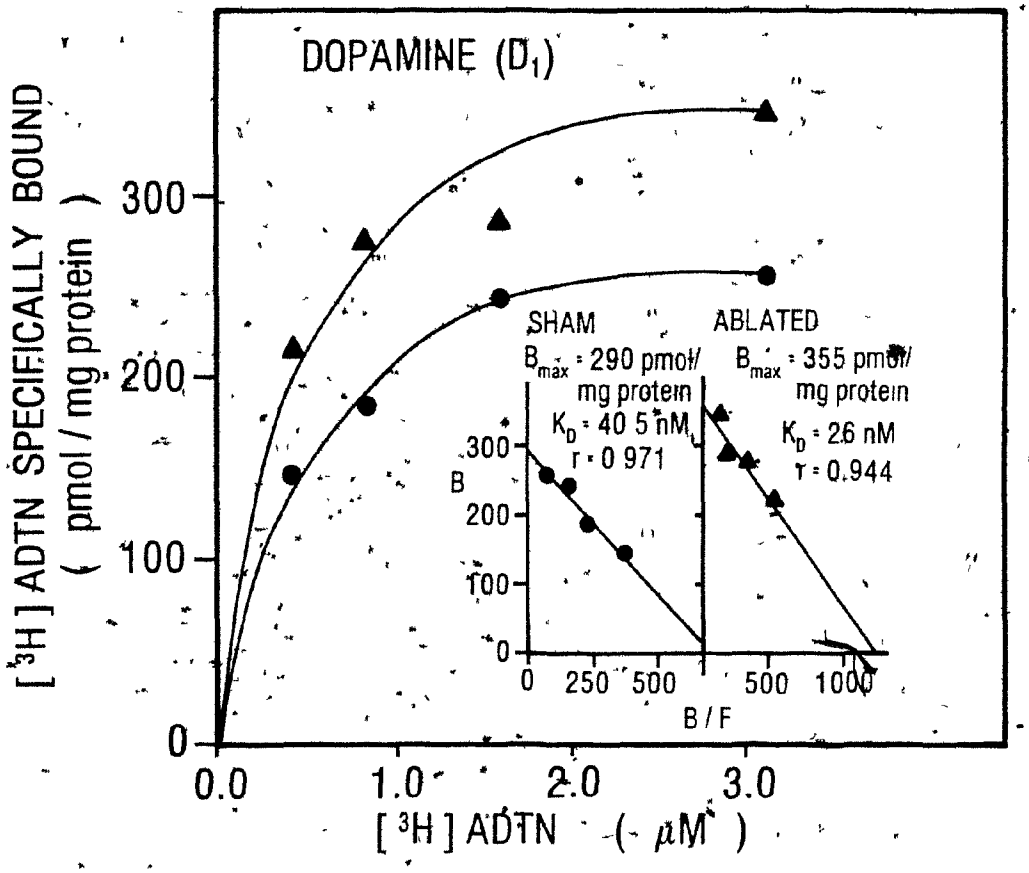


FIGURE 46. A single experiment showing binding isotherms and Eadie-Hofstee plots of (^{3}H)-ADTN, a dopamine D_1 receptor ligand in striatal P_2 fractions of sham-operated and bilateral cortically ablated animals.

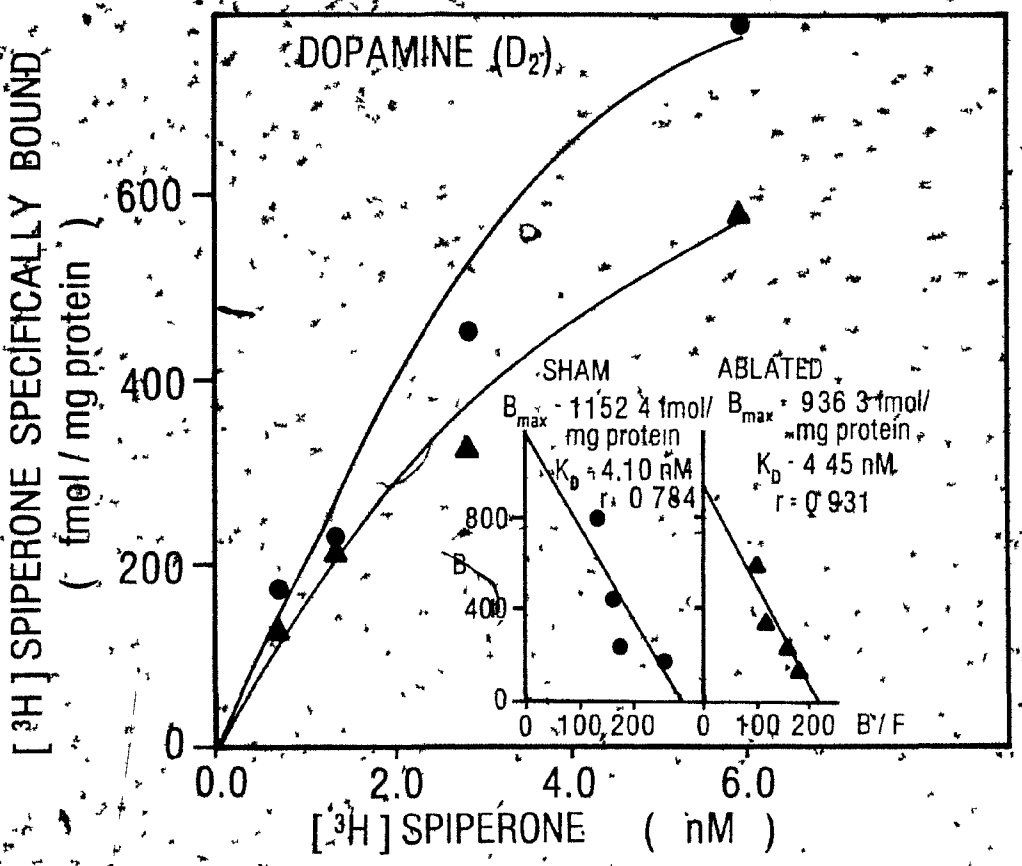


FIGURE 47. Binding isotherms and Eadie-Hofstee plots of a representative experiment showing binding of (^{3}H)-Spiroperidol, a dopamine-D_2 receptor ligand, to membranes of striatal P_2 fractions obtained from sham-operated and bilateral cortically ablated animals.

substantia nigra, and upon recovery from anaesthesia, most rats showed ipsiversive rotation, indicating successful lesioning. This spontaneous circling behavior had disappeared in all animals one week after lesion.

Spontaneous MUA was significantly reduced in lesioned animals in both the lesioned and intact striatum by approximately 50% (Table XXIV). Behavioral responses to DEX, 2.5 mg/kg, were qualitatively similar to those seen in normal animals in that increased locomotion and stereotypy of comparable duration were observed.

On the lesioned side, striatal neurons responded to DEX, 2.5 mg/kg, with response patterns predominantly other than excitation (Fig. 48), the direction of the response being dependent upon percent depletion of dopamine (Fig. 49). Whereas a 50-75% depletion of striatal dopamine reduced the incidence of excitation on the lesioned side from 88% to 50%, further depletion of striatal dopamine to 75-100% reduced the incidence of excitation to 22%. In contrast, striatal neurons on the contralateral side responded predominantly with excitation regardless of the percent depletion of DA on the other side (Fig. 50). Reductions in striatal DA levels reached a maximum of 85% (Table XXV) and in some animals striatal DA on the contralateral side was significantly elevated.

The Effects of Intra-Striatal 6-OHDA on the Striatal DEX Response

As in the case of nigral lesions, 6-OHDA applied directly to the striatum caused animals to circle to the side of the lesion (ipsilateral) upon recovery from surgery. Again, this behavior disappeared within one week. Administration of DEX, 2.5 mg/kg, 12-14

Table XXIV. Comparison of Mean Spontaneous MUA in Control Rats and Rats with Unilateral 6-OHDA Lesions in the Substantia Nigra

		6-OHDA Depleted	
	Controls (n=29)	Ipsilateral (Lesion) (n=15)	Contralateral (Intact) (n=9)
Spontaneous Discharge Rates	5574 ± 702	2820 ± 822**	2008 ± 337*,+

+Not significantly different from lesioned (paired t-test).

**Significantly different ($p < 0.02$) compared to controls (unpaired t-test).

*Significantly different ($p < 0.01$; unpaired t-test) from controls.

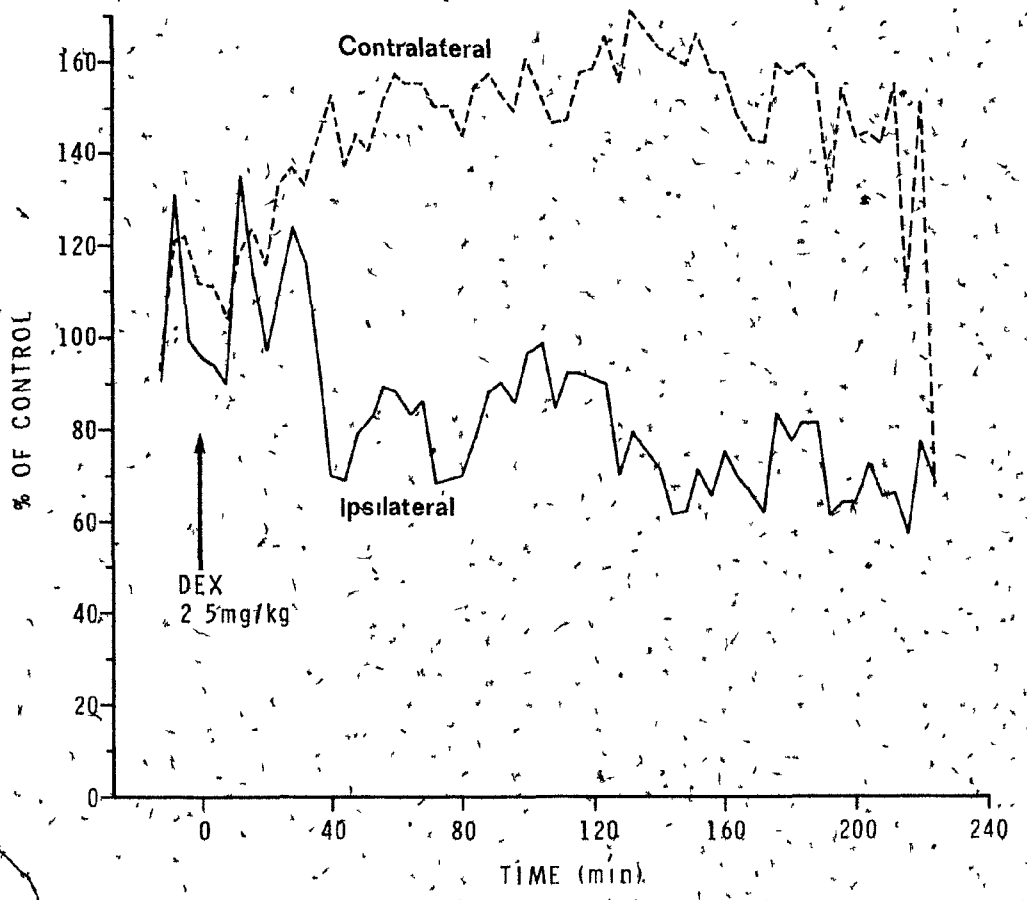


FIGURE 48. A representative experiment in an animal with a unilateral 6-OHDA lesion of the SNC showing the response of the control side (---) and the lesioned side (——). Dopamine depletion = 89%. Spontaneous MUA on the control side was 3304 ± 179 spikes/4-min, and on the lesioned side 2634 ± 126 spikes/4-min.

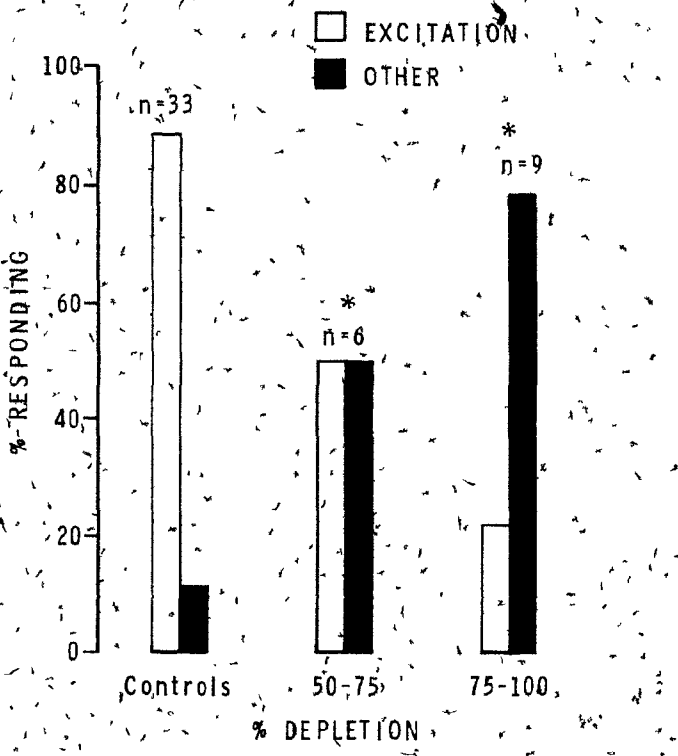


FIGURE 49. Relationship between the excitatory response to DEX and the DA content of the striatum. Results shown here depict this relationship in normal striata and those ipsilateral to a unilateral 6-OHDA lesion of the SNC. $p < 0.05$; χ^2-test.

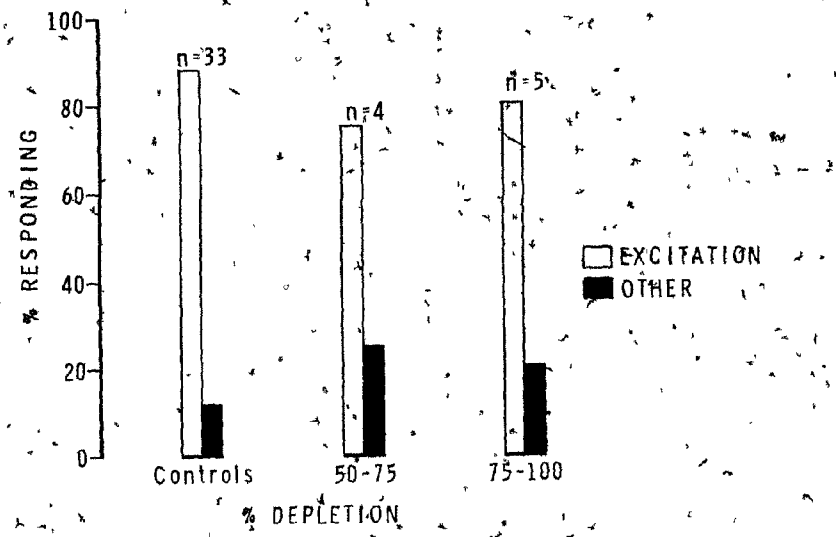


FIGURE 50. The relationship between the DA content of the striatum and the excitatory response to DEX in normal striata compared to striata contralateral to a unilateral 6-OHDA lesion of the SNC.

Table XXV. Reductions in Striatal Dopamine Levels Following 6-OHDA Lesions of the Substantia Nigra

	Controls	50-75% Depletion	75-100% Depletion
Ipsilateral (lesion)	6.74 ± 0.64 (N=16)	2.16 ± 0.45* (N=6)	1.36 ± 0.20** (N=9)
Contralateral (intact)		5.20 ± 0.86 (N=6)	9.23 ± 1.26 (N=9)
Mean depletion[2]		61.5%	85.3%

[1]Data expressed as the mean ± SEM.

N = number of striata assayed.

*Significantly different ($p < 0.01$) from controls (unpaired t-test) or contralateral side ($p < 0.005$; paired t-test).

**Significantly different ($p < 0.001$) from controls (unpaired t-test) or contralateral side ($p < 0.001$; paired t-test).

[2]% Depletion = $\frac{\text{Intact side} - \text{Lesioned side}}{\text{Intact}} \times 100\%$

days following lesions produced normal increases in behavior (Fig. 51). However, in the three animals so lesioned, DEX produced inhibition of striatal MUA on the lesioned side and activation of striatal neurons on the contralateral side (Fig. 52). In animals receiving only the control infusion (solvent less 6-OHDA into the striatum, N=4) striatal neurons still responded to DEX with excitation (Figs. 53 and 54). The duration of the excitatory response was similar to that seen in control animals receiving the same dose of DEX.

Examination of DA levels in striata, olfactory tubercles, and piriform and cingulate cortices of a parallel group of age matched animals shows that intra-striatal 6-OHDA specifically depleted striatal DA on the side of the infusion but did not alter the dopamine content in other regions innervated by nigral and/or AVT dopaminergic neurons (Fig. 55).

Spontaneous MUA on the lesioned side did not appear to be affected when compared to the intact side (intact = 4690 ± 1287 vs. 4057 ± 1117 lesion; N=3).

The Effects of Specific Dopamine Agonists and Antagonists on Striatal MUA

Since it appeared that striatal DA is essential for DEX-induced activation of striatal neurons, experiments were undertaken to determine which DA receptor, D_1 or D_2, is responsible to this effect.

Dopamine agonists

SKF 38393, a selective D_1 receptor agonist was unable to activate striatal neurons or elicit DEX-like behavior in 15 experiments at

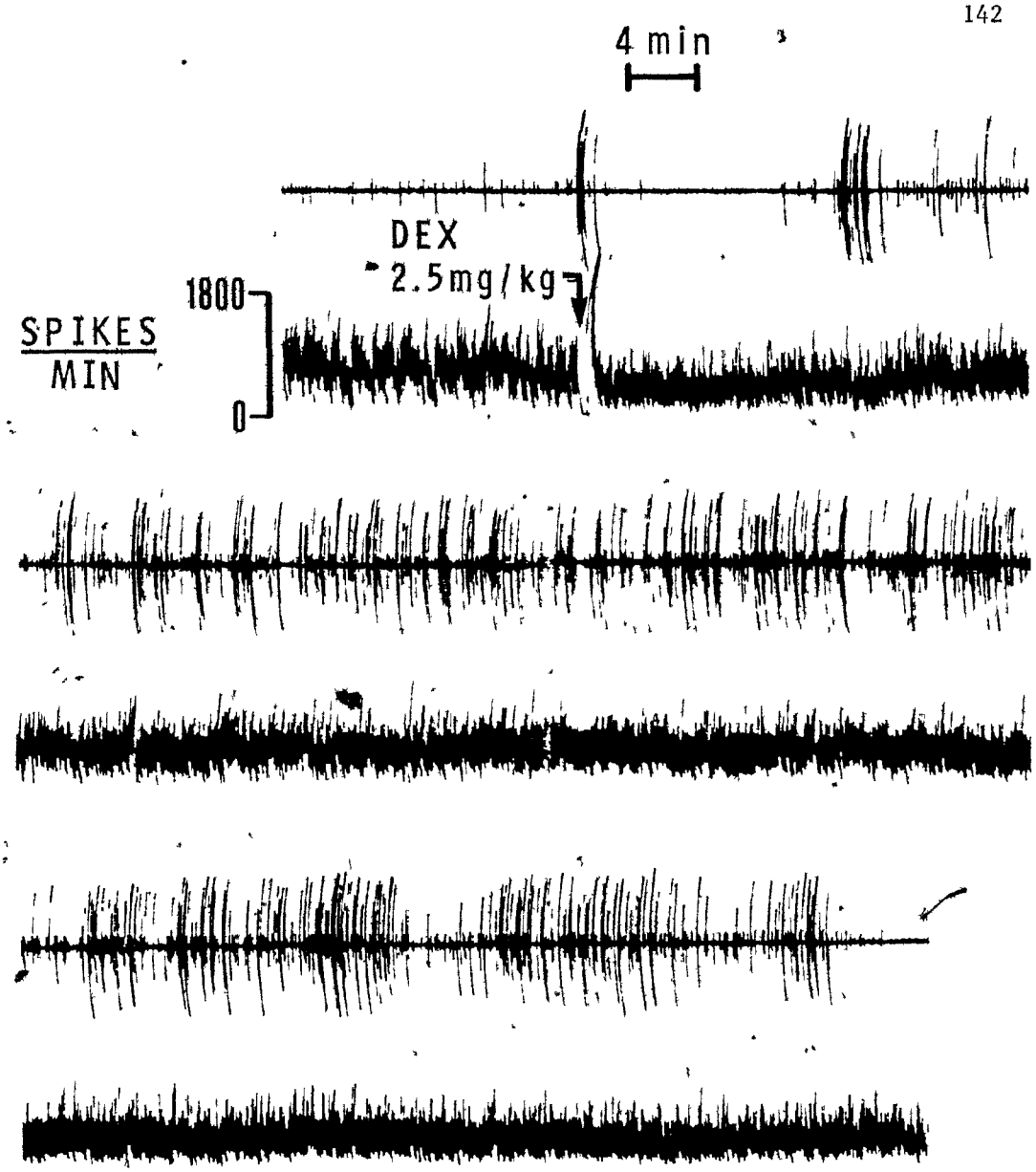


FIGURE 51. A representative record of inhibition of striatal MUA following DEX in an animal having received a unilateral infusion of 6-OHDA into the striatum. Note that DEX-induced activation of behavior was not abolished.

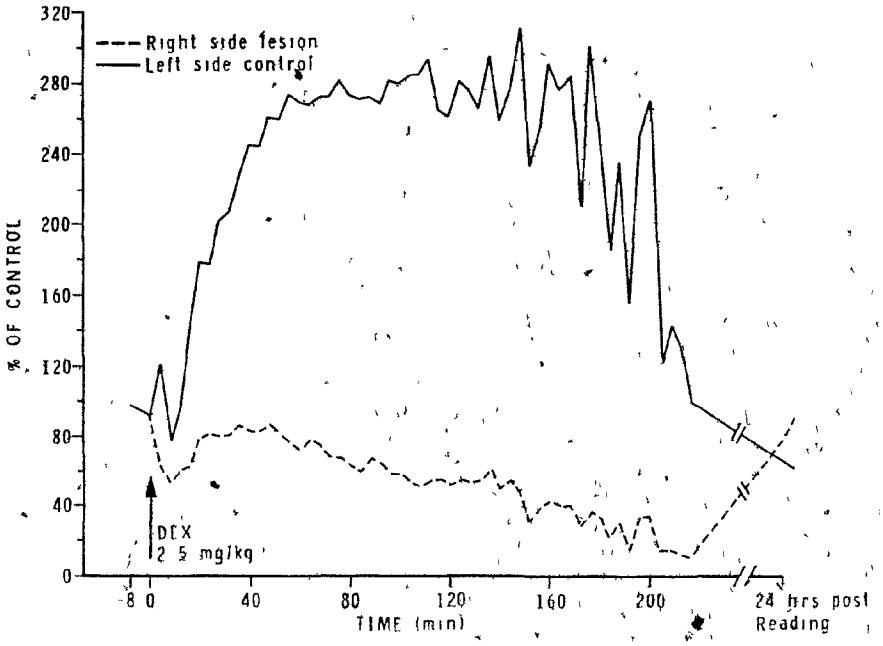


FIGURE 52. Representative experiment showing the effects of DEX on striatal MUA in an animal in which the right striatum was depleted of DA with previous 6-OHDA treatment. Spontaneous MUA on the lesioned side was 2783 ± 69 spikes/4-min; the control side spontaneous MUA was 4038 ± 197 spikes/4-min.

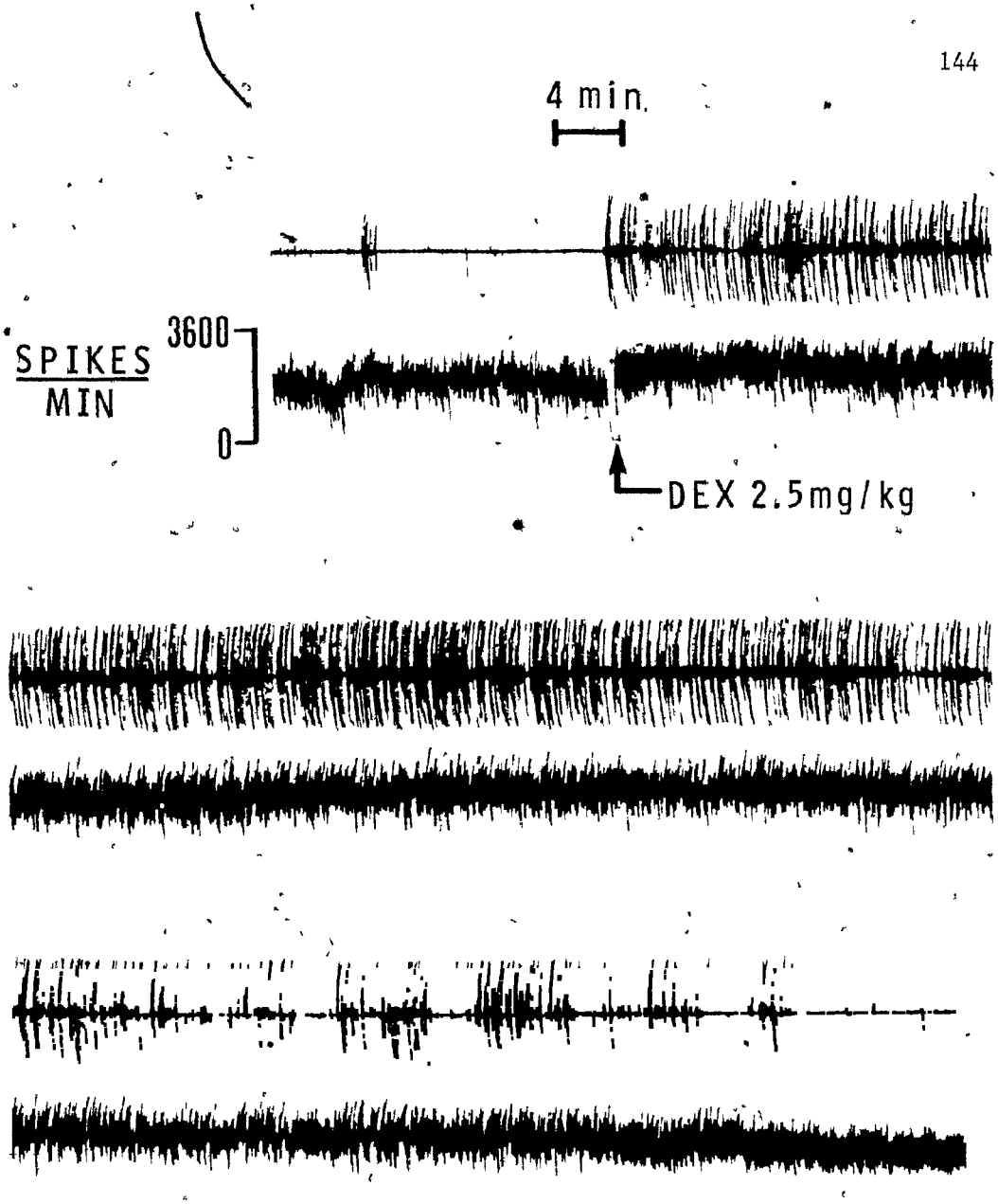


FIGURE 53. A representative record showing DEX-induced activation of behavior and striatal MUA in an animal that had received a unilateral control infusion into one striatum.

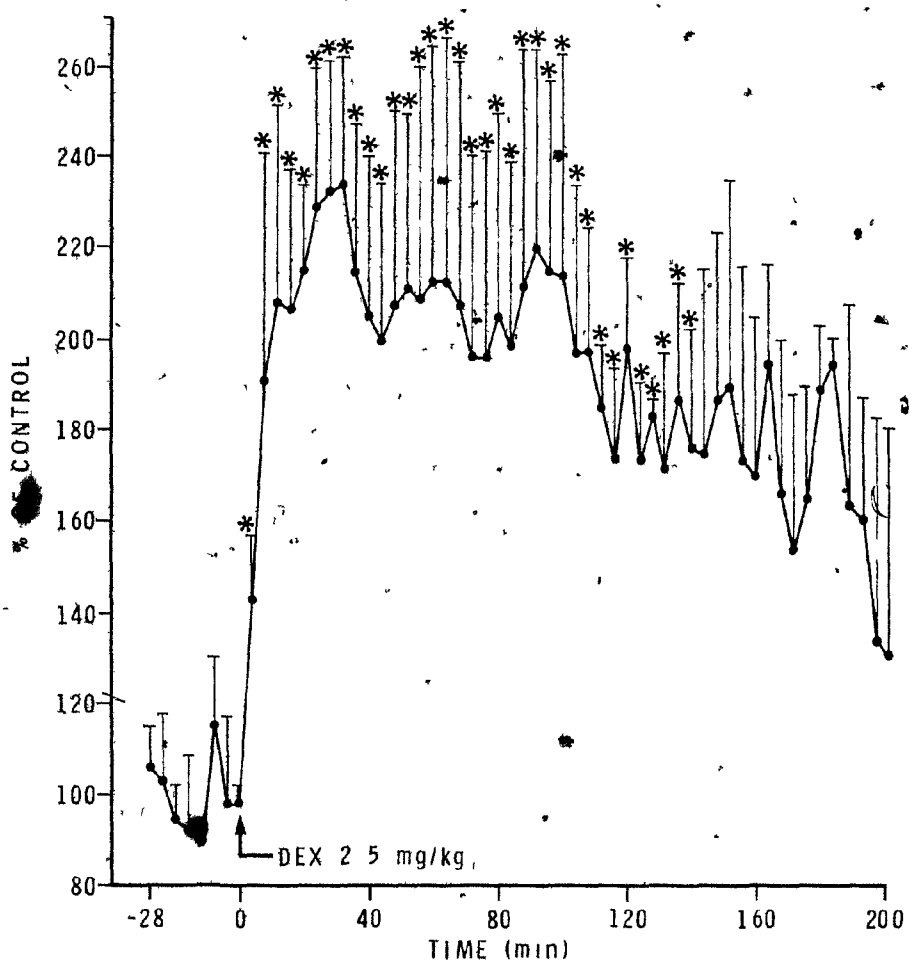


FIGURE 54. The response to DEX in 4 animals that had received an intrastriatal control infusion into one striatum. Mean spontaneous MUA was 1902 ± 681 spikes/4-min. (4 animals, n=4). * = $p < 0.05$; SNK test.

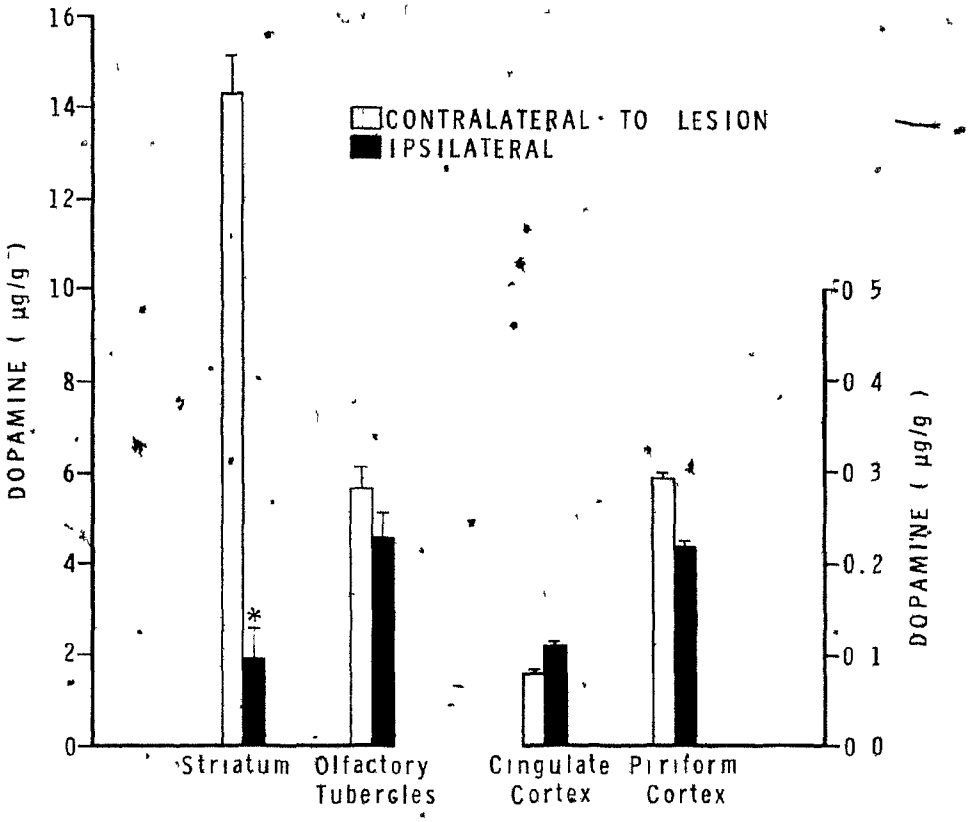


FIGURE 55. Effects of unilateral intrastriatal 6-OHDA on the DA content of the striatum, olfactory tubercles, and cingulate and piriform cortices (N=8). * = $p < 0.001$; paired t-test.

three doses (0.5, 1.0 and 2.0 mg/kg).

In contrast, the selective D_2 receptor agonist, LY-171555, although failing to increase striatal MUA did produce DEX-like behavioral activation (Fig. 56). This response was observed at all doses tested (0.25, 0.5, 1.0 and 2.5 mg/kg; N=12).

Effects of Dopamine Receptor Antagonists on DEX-Induced Activation of Striatal Neurons

In three experiments, the selective D_1 antagonist, SCH 23390, 4.0 mg/kg, produced a delayed antagonism of both DEX-induced behavior and activation of striatal neurons (Fig. 57). Again, haloperidol 2.5 mg/kg, presumed non-specific DA receptor blocker, antagonized the effects of DEX, 2.5 mg/kg (Fig. 58).

Pretreatment with the D_2 receptor antagonist, sulpiride, 100 mg/kg, prevented DEX-induced activation of striatal neurons (Fig. 59) but did not appear to block behavioral activation (Fig. 60). However a more selective D_2 receptor antagonist, RO 22-1319, 2 mg/kg, antagonized both DEX-induced activation of striatal neurons and behavioral activation (Figs. 61 and 62).

Single Unit Studies

Normal Animals

In the course of recording MUA, single units were encountered (Fig. 63) but the incidence in normal animals was low, accounting for less than 8% of all observations. Spontaneous SUA was 5.08 ± 1.05 spikes/sec (mean ± SEM).

In the 15 experiments in which DEX, 2.5 mg/kg, was given, inhibition of single unit activity (SUA) occurred 47% (7/15) of the

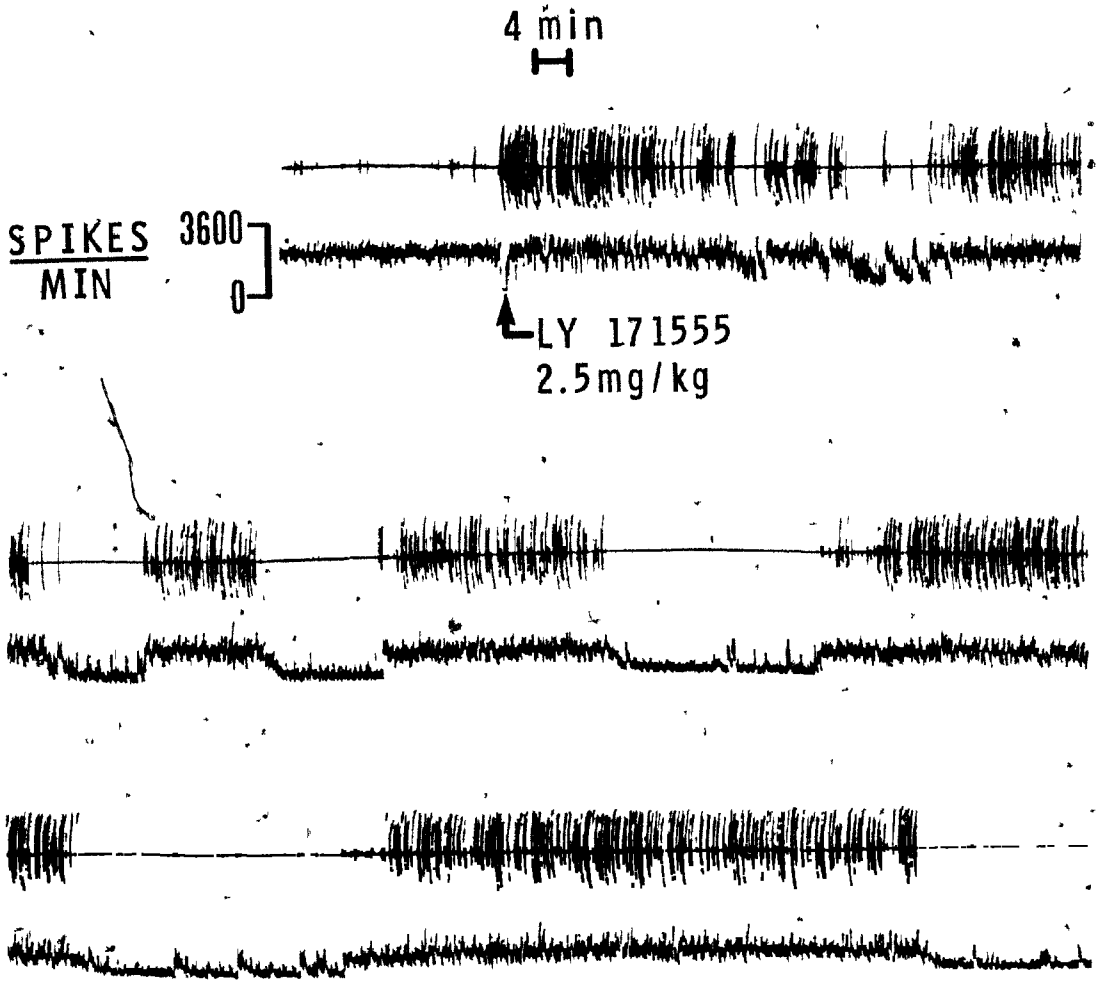


FIGURE 56. A representative record showing intermittent behavioral activation following the specific dopamine D_2 receptor agonist, LY 171555.

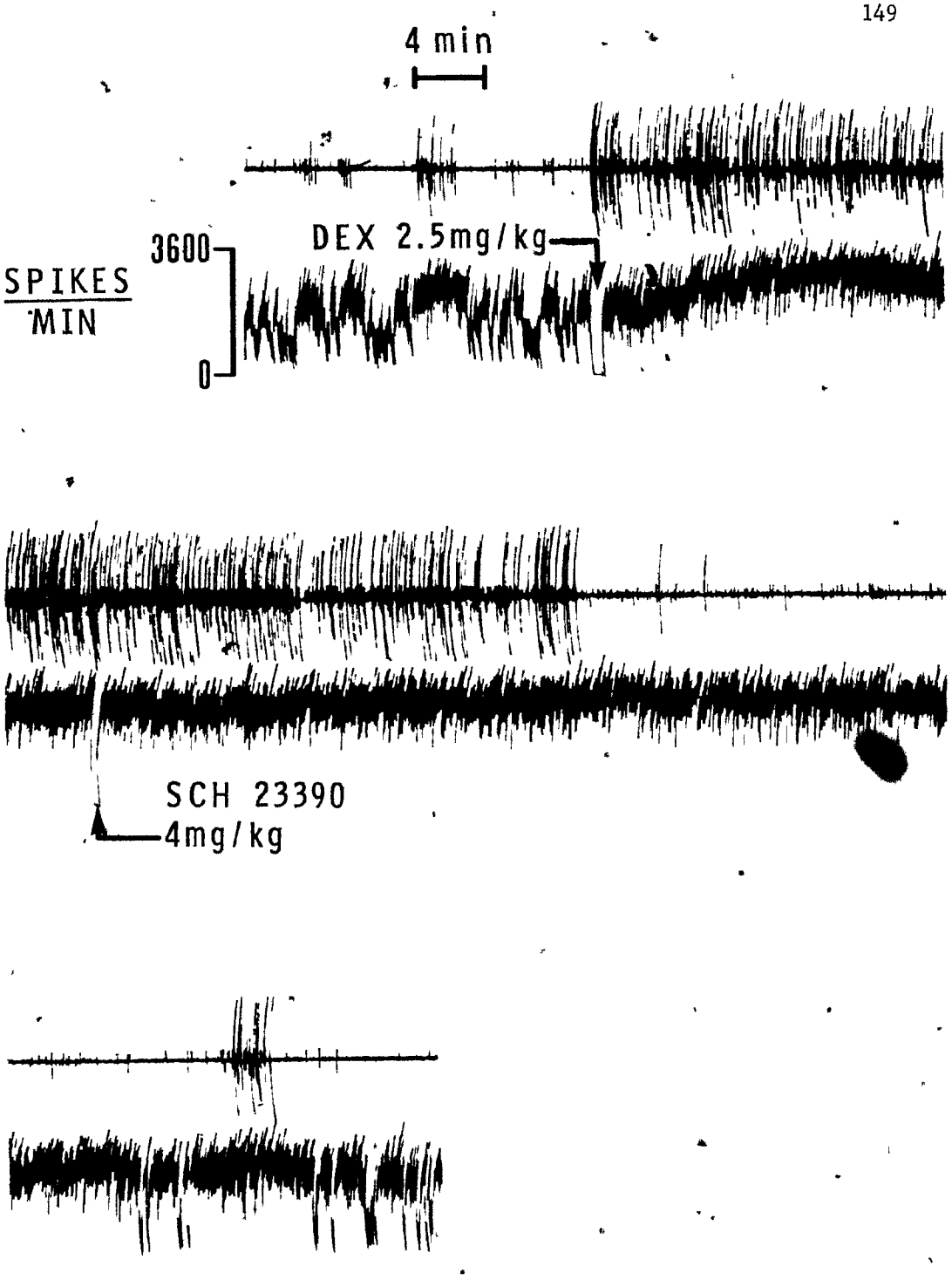


FIGURE 57. A representative record showing the delayed antagonism of DEX-induced behavior and the lack of antagonism of NMA by SCH 23390, the specific D_1 antagonist.

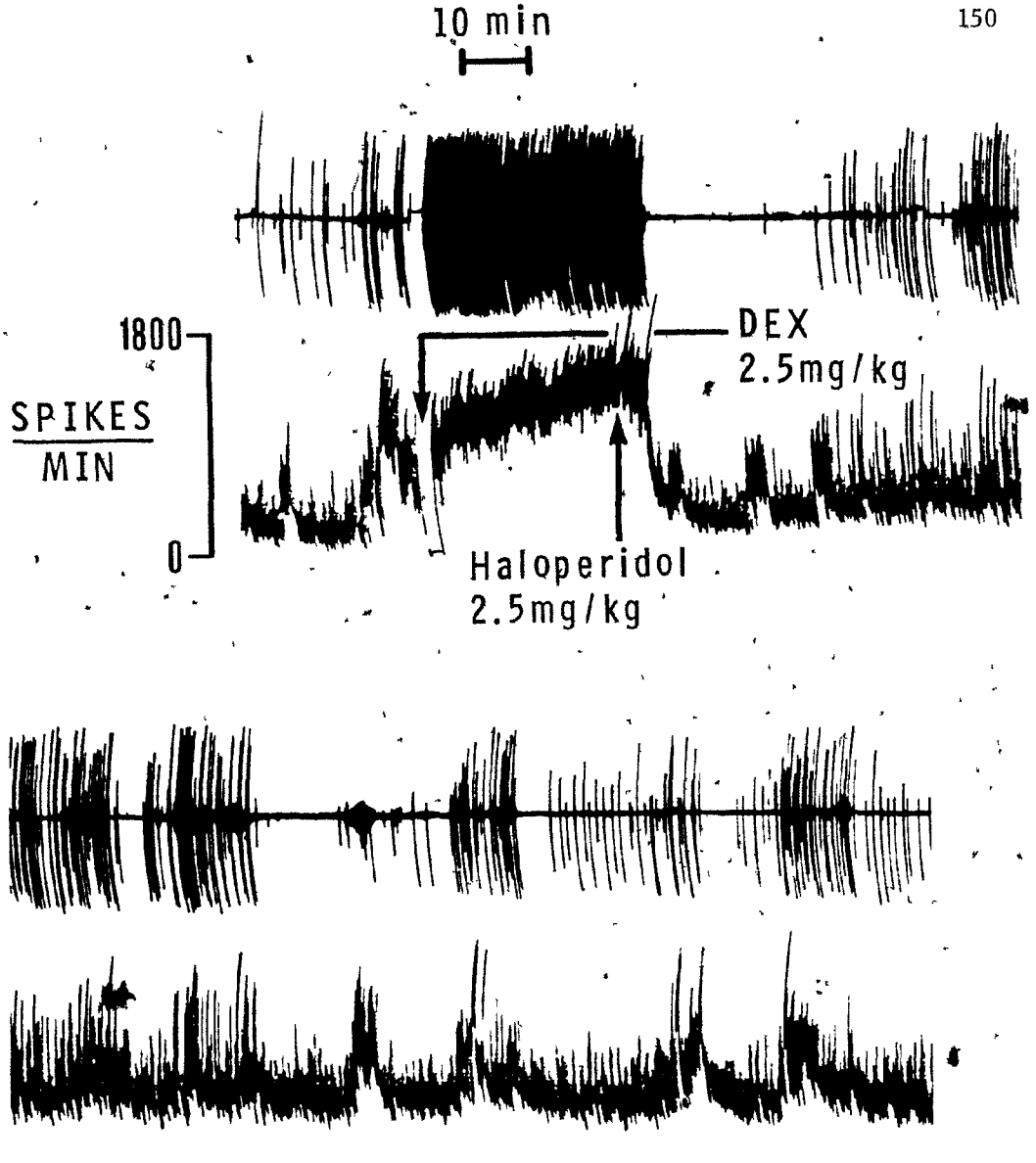


FIGURE 58. A representative experiment showing the blockade of both DEX-induced behavior and the activation of MUA following haloperidol.

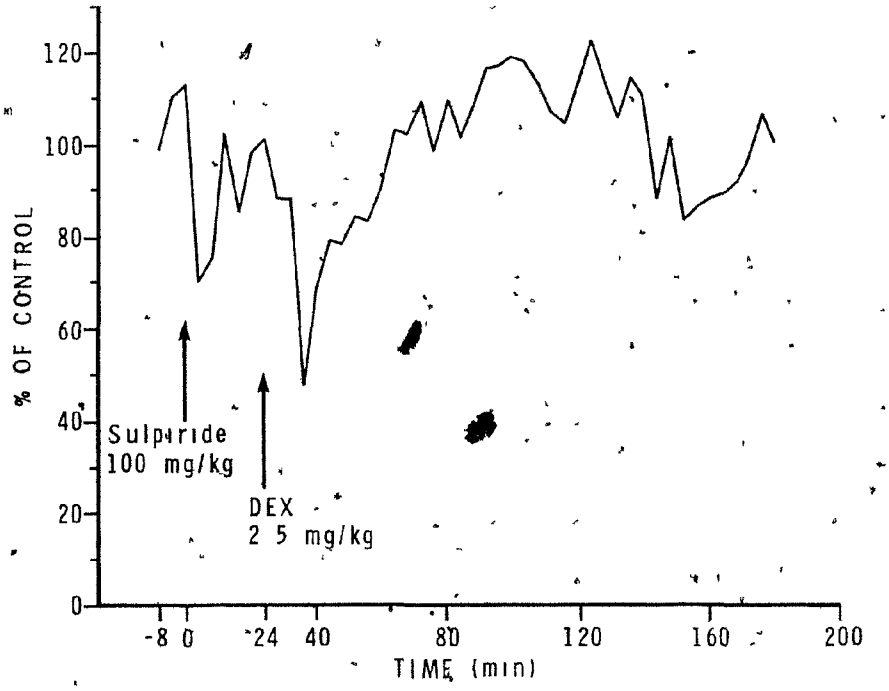


FIGURE 59. Representative experiment showing the effects of the specific D_2 receptor antagonist, sulpiride, 100 mg/kg, in preventing DEX-induced activation of striatal MUA. Spontaneous MUA was 3386 ± 151 spikes/4-min.

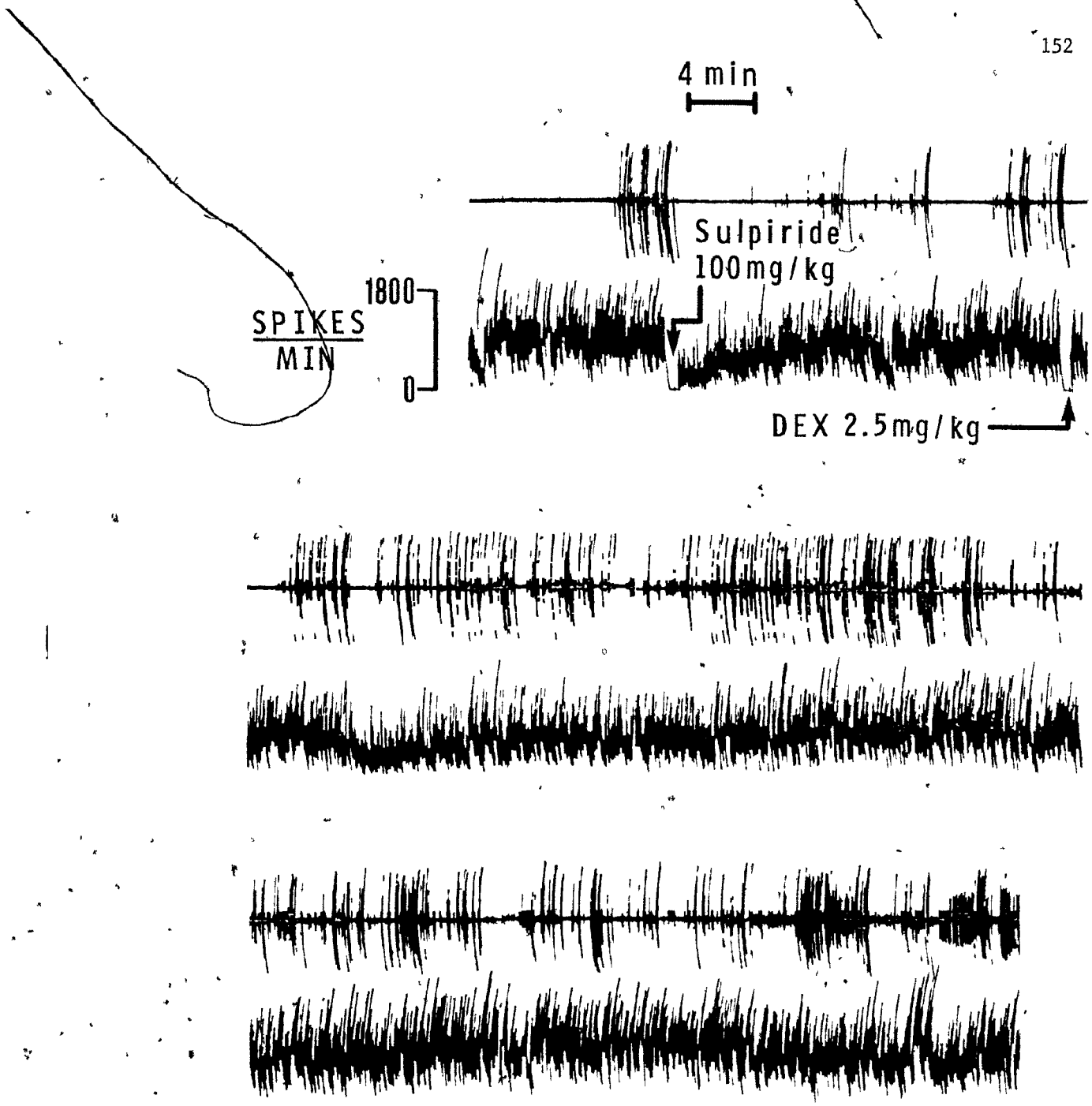


FIGURE 60. A representative experiment showing the lack of effect of pretreatment with sulpiride on DEX-induced behavior and the blockade of DEX-induced activation of MUA.

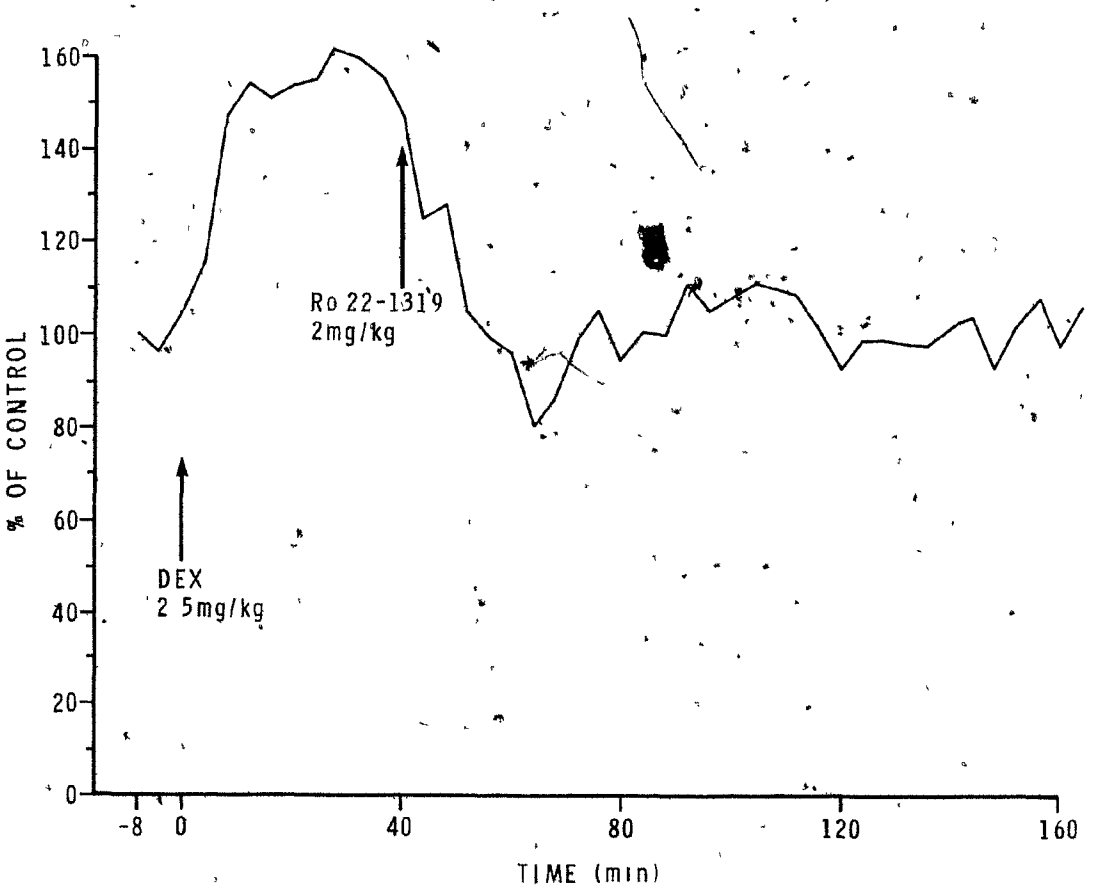


FIGURE 61. Representative experiment showing the antagonism of DEX-induced activation of MUA by the specific D_2 receptor antagonist, Ro 22-1319. Spontaneous MUA preceding DEX was 5292 ±°285 spikes/4-min.

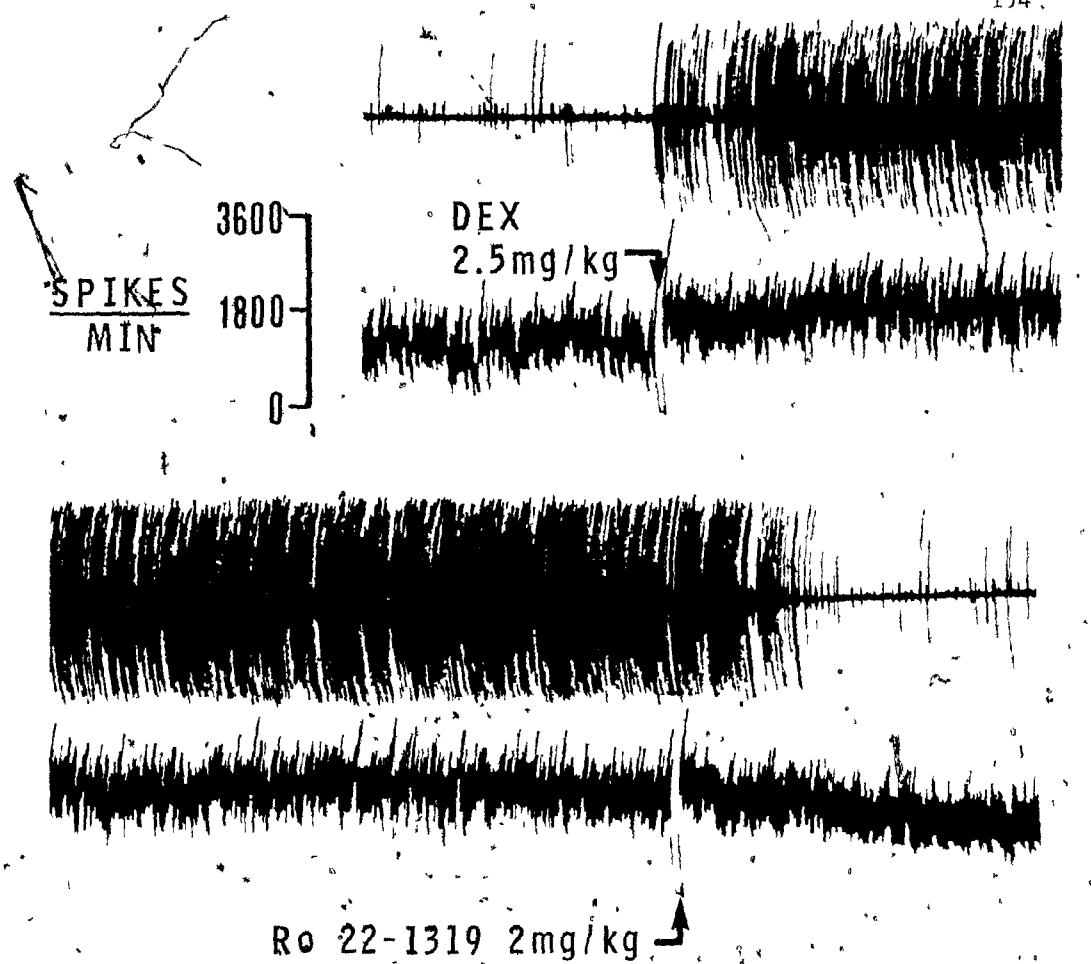
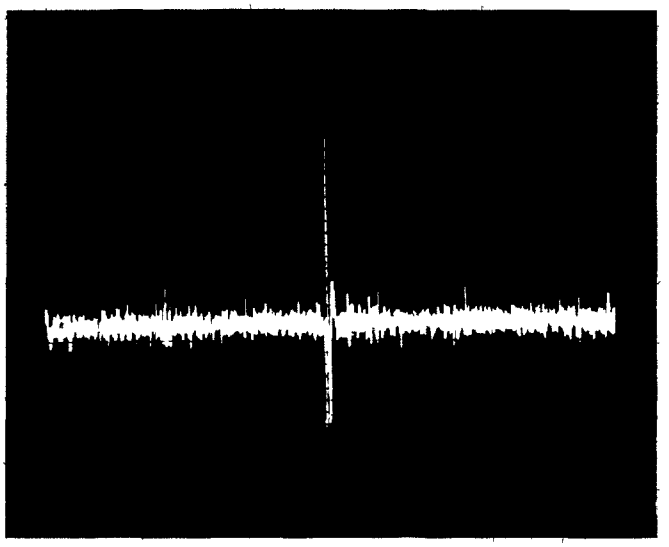


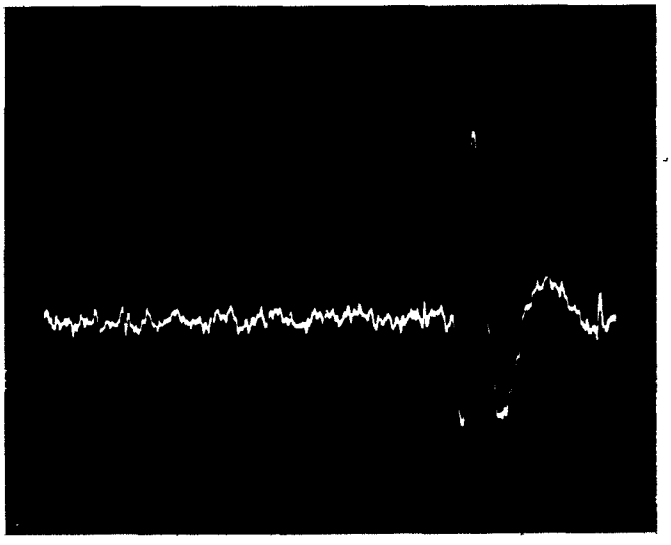
FIGURE 62. A representative experiment showing the effects of the specific D_2 receptor antagonist, Ro 22-1319 on DEX-induced activation of behavior and striatal MUA. Note the rapid antagonism of the effects of Ro 22-1319 on both behavior and MUA.

FIGURE 63. Oscilliscope traces of a representative single unit recorded in the striatum of a freely moving animal.



200 μV

20 msec



200 μV

2 msec

time and excitation 33% (5/15). Figures 64 and 65 give an example of DEX-induced inhibition of a single unit in a freely moving animal. In the instances where excitation was seen, striatal activation reached a maximum of 240 ± 58% of control between 40 and 80 min. after drug (Fig. 66). By 160 min. post-drug discharge rates were no longer significantly different from control values.

Lesioned Animals

Spontaneous SUA following lesions was not signficantly different from controls, i.e. lesioned 6.17 ± 0.98 vs. control 5.08 ± 1.05 spikes/sec (mean ± SEM). In contrast, the incidence of SU showing inhibition following DEX in lesioned animals (bilateral cortical ablation and PF-CM lesions), was significantly increased to 92% (12/13) (Table XXVI) whereas excitation was not seen at all.

Inhibition of SUA in response to DEX, 2.5 mg/kg, in animals with bilateral cortical lesions (N=7) reached a maximum of 47 ± 5% of control between 32 and 48 min. after DEX, and was maintained for approximately 200 minutes (Fig. 67).

Histology

Electrode Locations

Electrode locations in normal animals having either single or multiple unit responses to DEX are shown in Figure 68. The proven locations of all striatal recording sites are summarized in Table XXVII. In the case of PF-CM placements, all electrodes were located within the PF-CM complex.

Cortical Lesions

The full range of lesion sizes following unilateral and bilateral

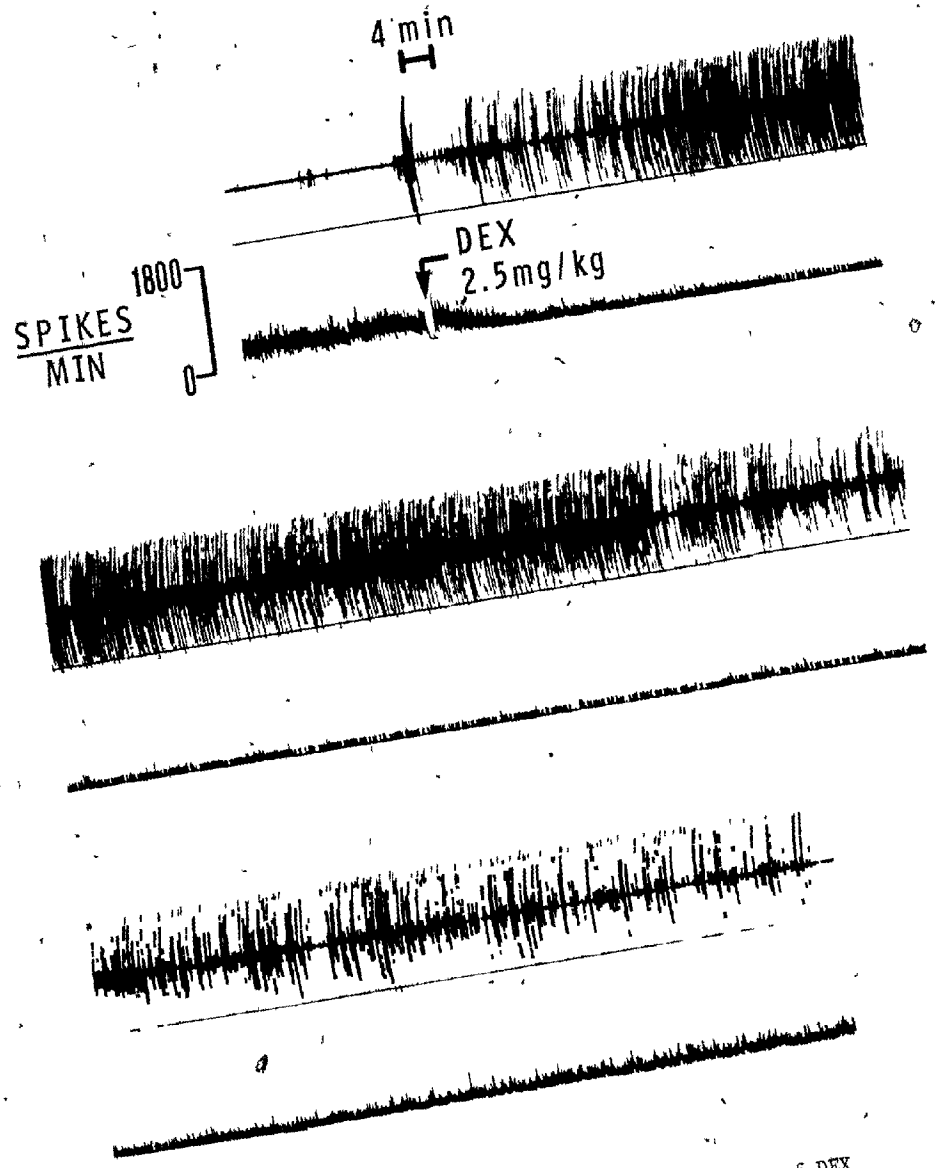


FIGURE 64. A representative record showing the effects of DEX on behavior and SUA. Note DEX produced inhibition in this unit, the time course of which parallels drug-induced behavior.

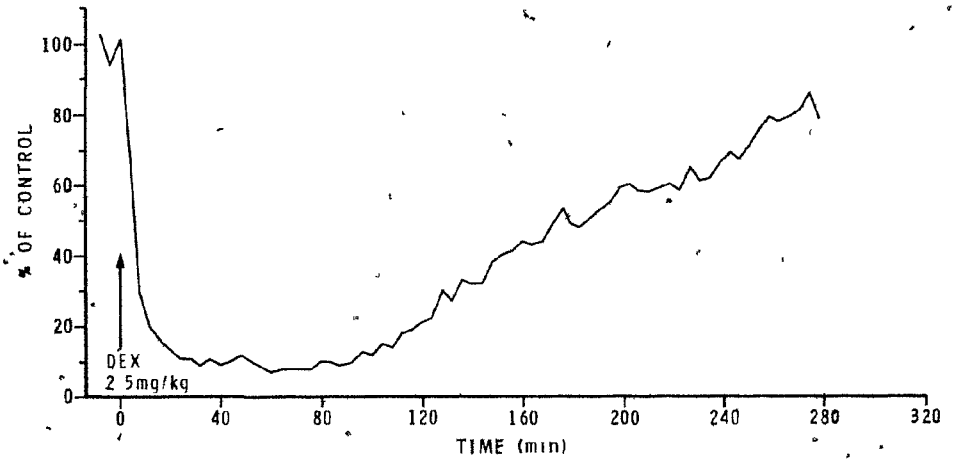


FIGURE 65. A representative experiment showing inhibition of SUA following DEX in a freely moving animal. Spontaneous MUA 5.42 ± 0,08 spikes/sec (= 1301 ± 19,2 spikes/4-min).

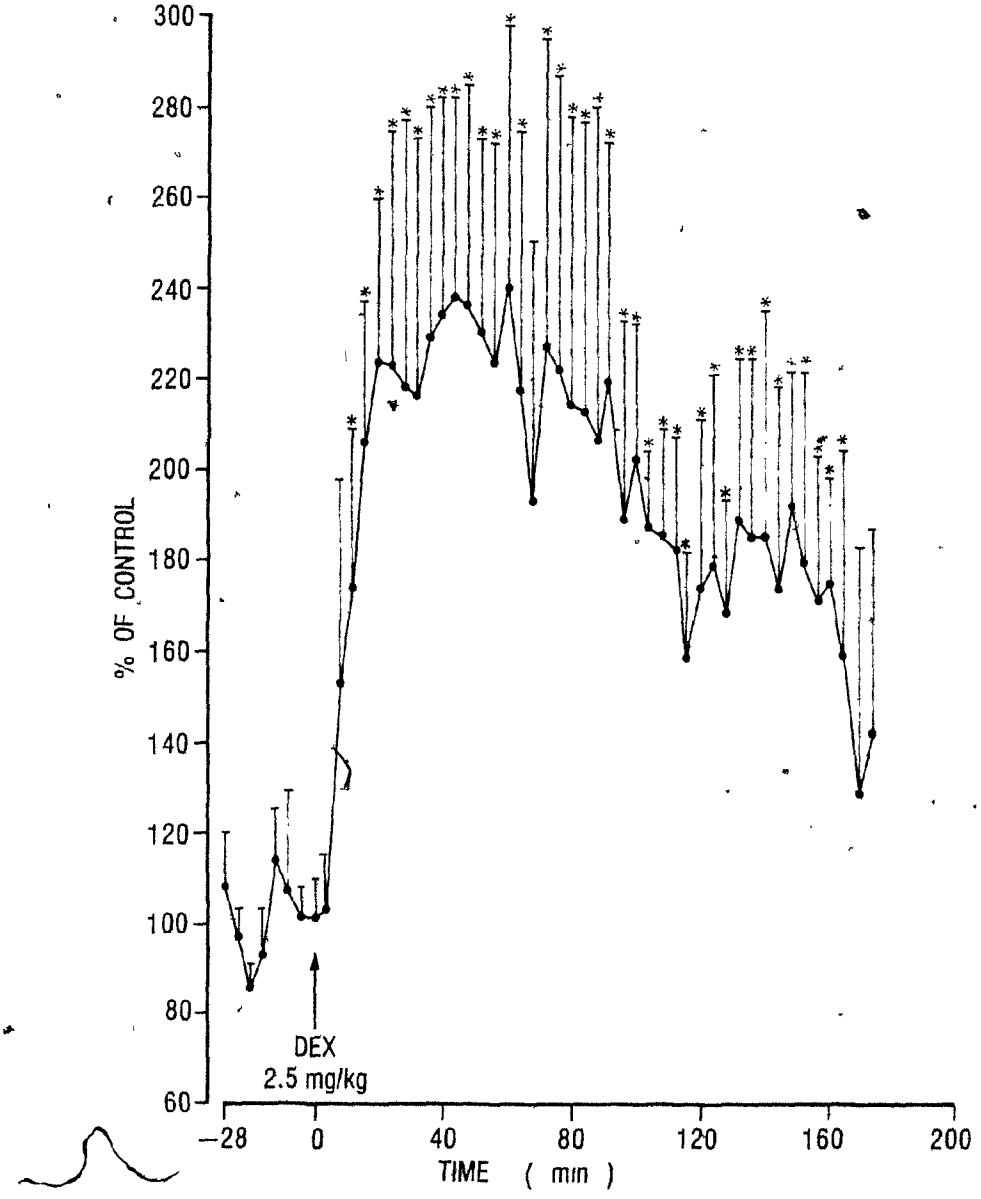


FIGURE 66. Excitation of striatal SUA in freely moving animals (N=5). Mean spontaneous MUA was 3.70 ± 0.99 spikes/sec (888 ± 238 spikes/4-min). * = $p < 0.05$, SNK test.

Table XXVI. Increased Incidence of DEX-Induced Inhibition Recorded from Single Units in Lesioned Animals

	Total Units	% Responding with Inhibition
Control	15	47%
Lesioned	13	92%*

*$p < 0.01$ compared to controls using χ^2-test.

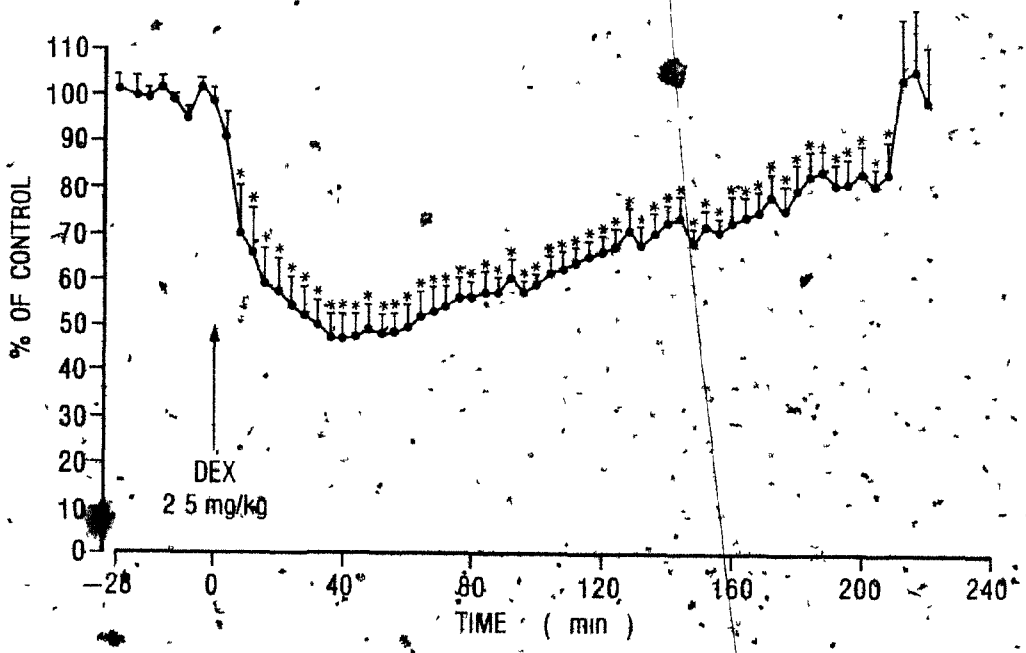


FIGURE 67. Inhibition of SUA in bilateral cortically ablated animals (N=7). Mean spontaneous SUA was 6.69 ± 1.14 spikes/sec. (1606 ± 274 spikes/4-min) * = $p < 0.05$, SNK test.

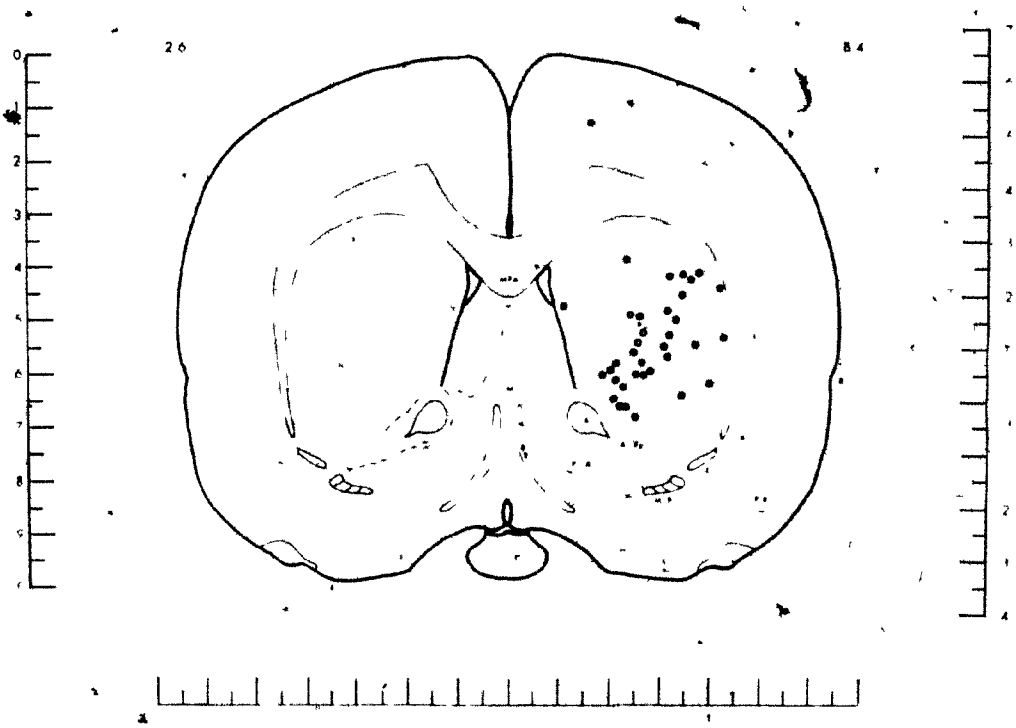


FIGURE 68. Recording sites in SUA (o) and MUA (●) experiments in which DEX, 2.5 mg/kg, excited striatal neurons (n=34). Recording sites from left striata have been transposed to the right for easy comparison. Similarly, recording sites lying anterior or posterior to the coronal section (+ 2.6 AP) have also been transposed for the sake of exposition.

Table XXVII. Striatal Recording Sites

Type of Experiment	AP[1] Extent	ML[2] Extent	DV[3] Extent
Controls	2.2 - 3.0	2.0 - 3.5	4.0 - 6.0
Unilateral Cortical Ablations	1.6 - 3.0	2.0 - 3.5	4.0 - 6.0
Bilateral Cortical Ablations	2.2 - 2.8	2.0 - 4.0	4.0 - 6.0
CM-PF Lesions	2.4 - 2.6	2.2 - 2.8	4.5 - 5.5
6-OHDA Lesions			
a) Intra Striatal	2.4 - 2.6	2.2 - 2.8	4.5 - 5.5

1 = Anterior-posterior; 2 = Mediolateral; 3 = Dorsoventral

cortical ablation is schematically summarized (Fig. 69).

In all cases, the dorso-ventral extent of the lesion could be traced to the level of the dorsal-most aspect of the corpus callosum. The lesions in which biochemical determinations parallel to the recording experiments were carried out are denoted by asterisks (Fig. 69).

Fimbria-Fornix Lesions

Histological analysis showed that the fimbria-fornix had been successfully severed bilaterally with little damage to adjacent (hippocampus) or underlying structures.

PF-CM Lesions

Serial reconstruction of lesions (Fig. 70) show that the lesion was confined primarily to the PF-CM complex with only minimal disruption of neighbouring thalamic nuclei.

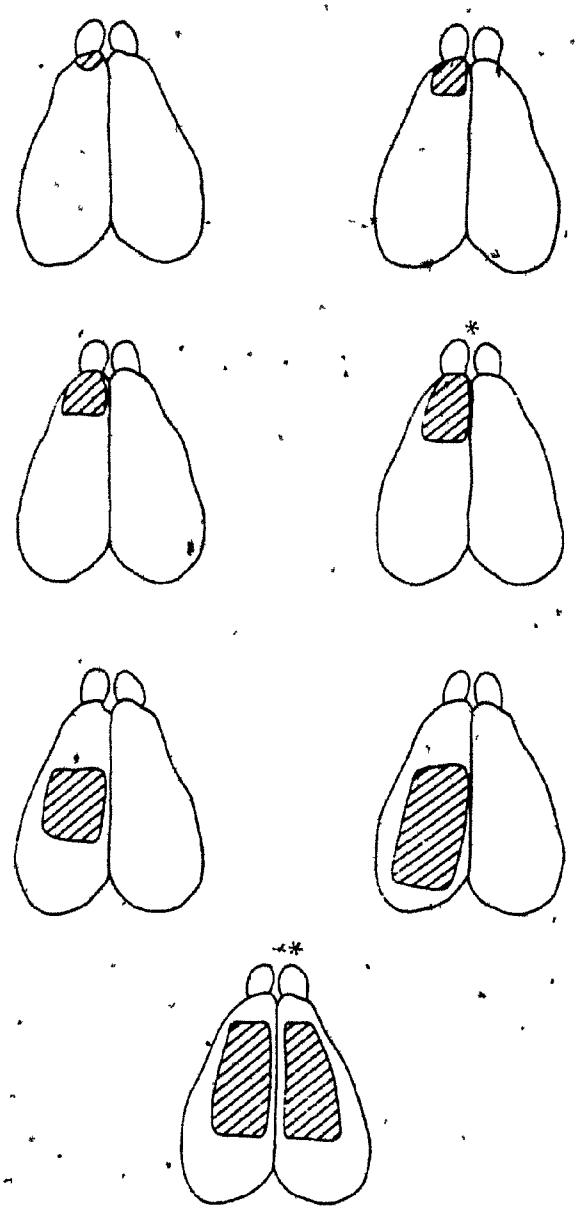
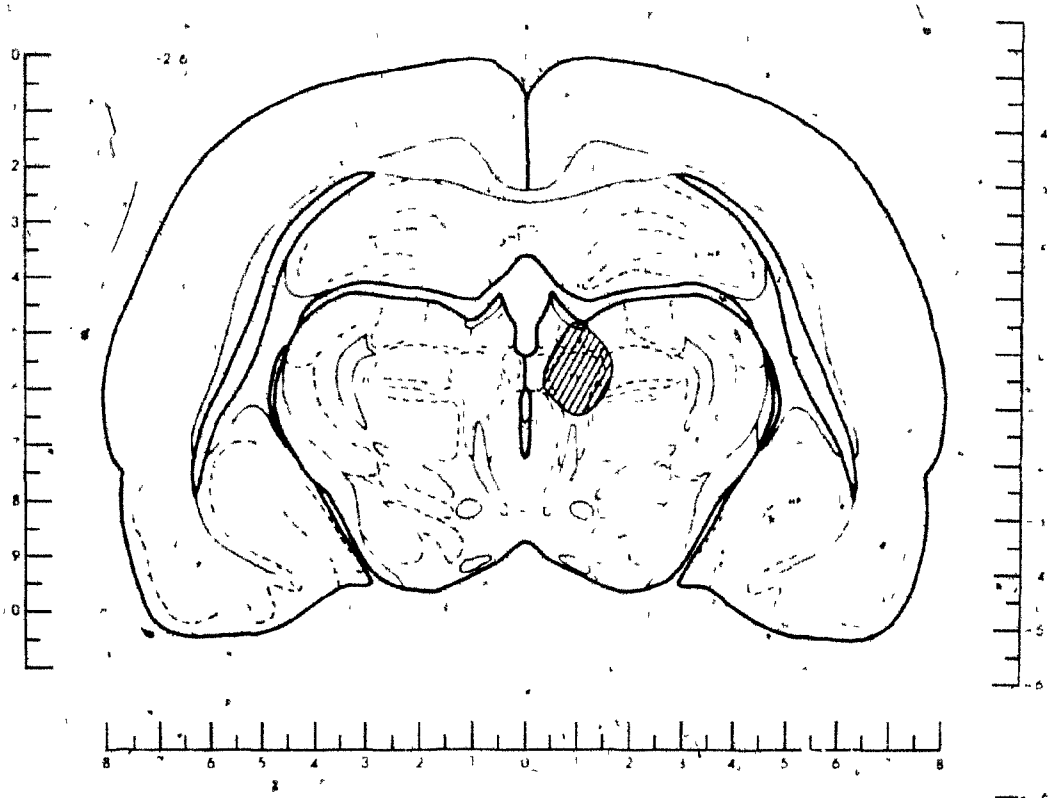
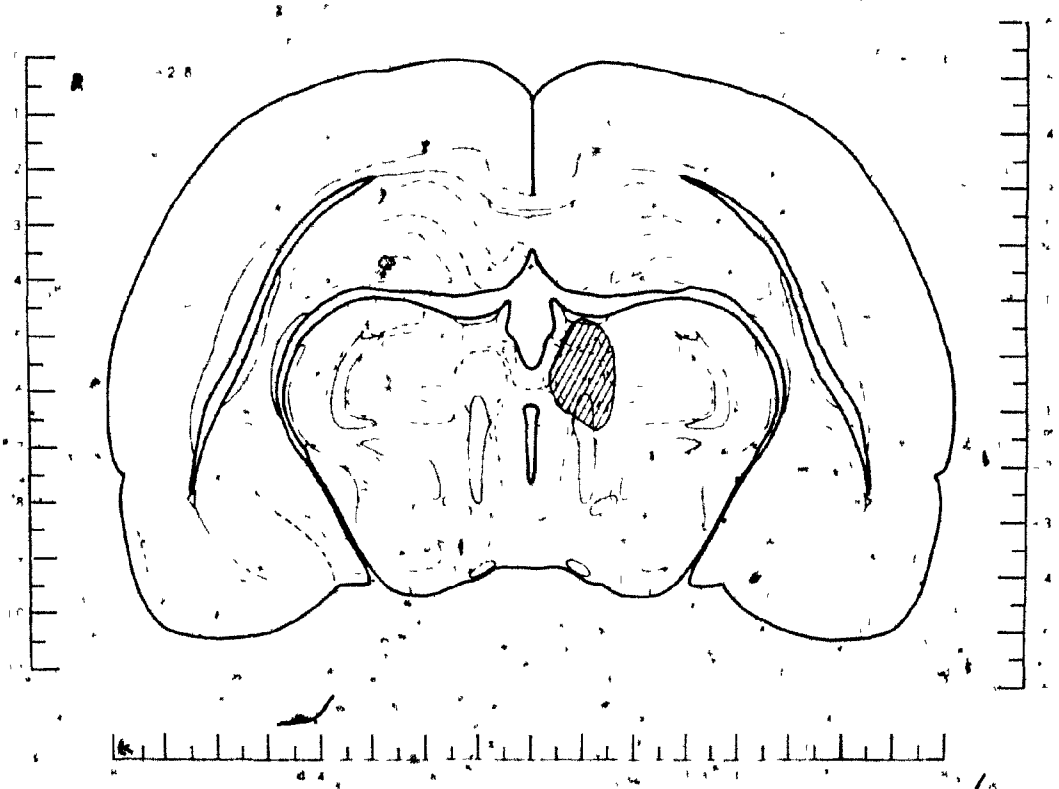
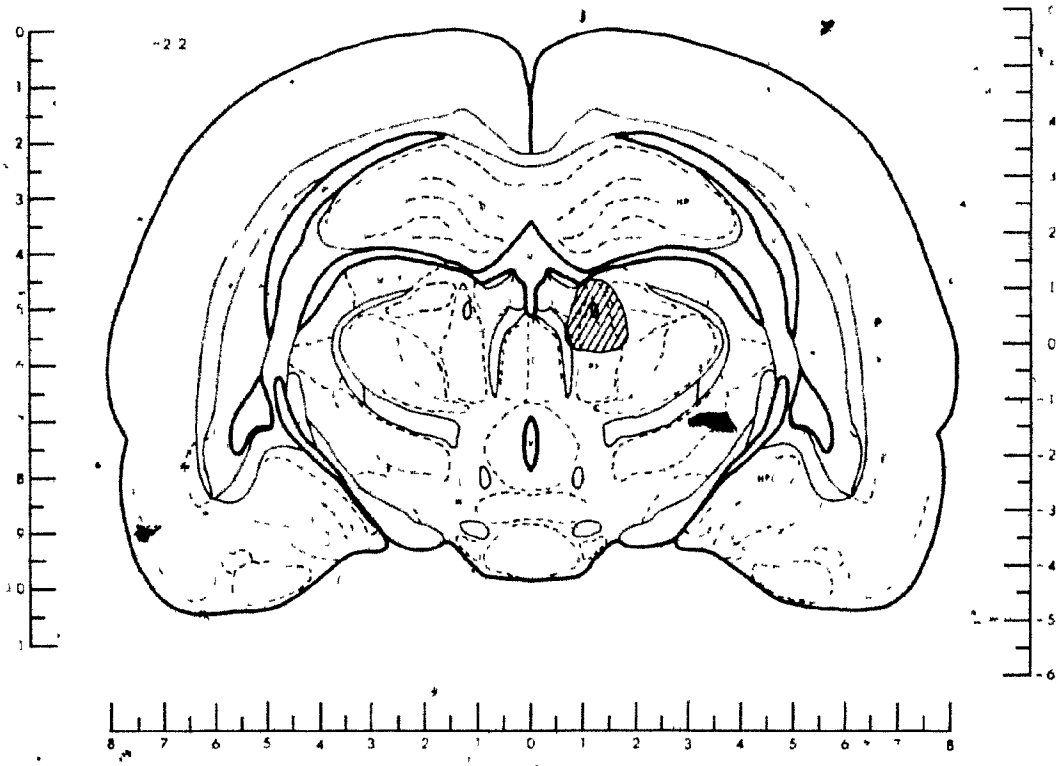


FIGURE 69. Location of unilateral and bilateral cortical lesions of this study drawn to scale. Asterisks indicate lesions in which biochemical as well as electrophysiological studies were carried out.

FIGURE 70. Serial reconstruction of unilateral PF-CM lesions. Extent of shaded areas represents the maximal observed lesion size at each coronal section.



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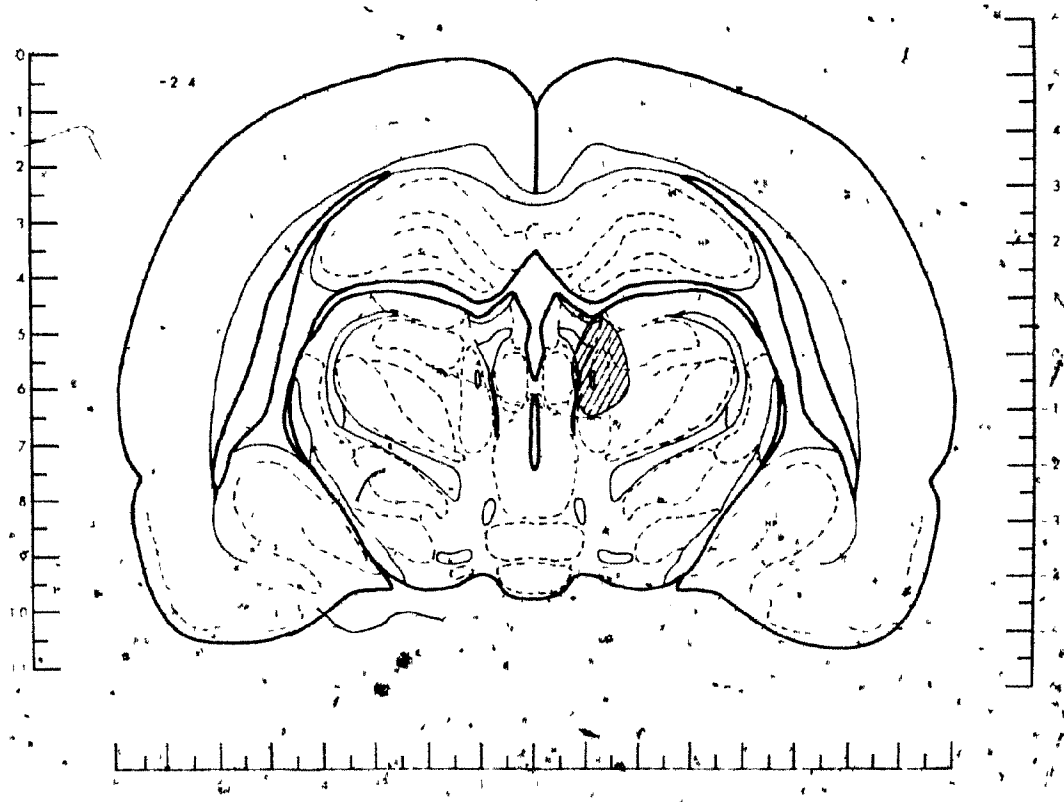
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DISCUSSION

The results of this study confirm and extend earlier work (Hansen and McKenzie, 1979; McKenzie and Hansen, 1980) demonstrating that in freely moving rats, most striatal neurons respond to DEX by increasing their rate of discharge. In addition, histological analyses of striatal recording sites confirm that DEX-induced activation of striatal neurons, whether recording SUA or MUA, are independent of electrode location in the striatum. This may seem somewhat surprising in view of the fact that most striatal afferent projections manifest a non-uniform distribution within the striatum (Groves, 1983). However, one notable exception to this non-uniformity is the nigrostriatal and AVT-striatal dopaminergic projections, which are known to produce a diffuse pattern of dopaminergic terminals in the striatum (Beckstedt, 1979; Fallon and Moore, 1978). Therefore, the consistency of the DEX response throughout the striatum in this study suggests that of the three major afferent projections to the striatum, the dopaminergic projection may be the most determinant with respect to the excitatory neuronal response following DEX.

The increase in striatal MUA in freely moving animals following DEX is in good agreement with the single unit data from freely moving animals (Trulson and Jacobs, 1979). These authors found that 70% of striatal neurons increase their rate of discharge after DEX. However, the results of both studies are in contrast with the results of most single unit studies by Rebec, Groves and co-workers, in which the predominant response to realistic doses of DEX, 0.5-5.0 mg/kg in

immobilized animals, was inhibition. This discrepancy cannot be explained by differences between studies, as regards recording technique, since the results of the present study clearly demonstrate that multiple unit recording in immobilized animals can in fact detect inhibition of striatal neurons following DEX. Indeed, inhibition was observed at 25% of the recording sites.

An important difference between the immobilization procedure used in this study and that used by other investigators is the presence of nitrous oxide, and, it is possible that nitrous oxide had some influence on the response to DEX. However, nitrous oxide, an anesthetic agent with strong analgesic effects in rats (Berkowitz et al., 1977) but with little effect on either cerebral metabolism (Carlsson et al., 1976) or cerebral blood flow (Dahlgren et al., 1981), did not significantly alter the spontaneous MUA of striatal neurons. Furthermore, spontaneous striatal MUA remained stable for over 2½ hr in immobilized animals receiving 70% nitrous oxide, which is in agreement with other reports that nitrous oxide has no consistent effect on the neuronal activity of the centromedian nucleus (Mori et al., 1972) or cortical neurons (Mandl et al., 1980). More importantly, nitrous oxide had no effect on the DEX response in freely moving animals. Therefore, it seems unlikely that nitrous oxide had any significant influence on striatal neurons or their responsiveness to DEX.

The two most obvious explanations for the preponderance of inhibition in immobilized animals, and the shift from excitation in freely moving animals to inhibition in immobilized animals in the

present study, are sampling bias and/or the absence of behavior in the immobilized state. It is conceivable that the neurons recorded in the freely moving state were not the same as those recorded in the immobilized state. In this study, spontaneous MUA did not change significantly as a result of immobilization whether the comparison was made between animal groups (freely-moving vs immobilized) or within the same animal. However, it is still possible that neurons which might have ceased to fire after immobilization could have also altered the discharge rates of the remaining neurons being recorded or causing a previously silent neuron to discharge. Though not possible to delineate from multiple unit data, it is possible that two neuronal populations exist, one active in the freely moving state and the other active in the immobilized state. The concept of two neurons in some kind of paired configuration has been raised by others (Moore and Bloom, 1978; Johnson et al., 1983) and is supported by anatomical evidence indicating that striatal neurons are often clustered together (Adinolfi and Pappas, 1968). Furthermore, iontophoretic evidence indicates that excitatory and inhibitory neuronal responses to DA may be dependent upon electrode positioning relative to the neuron recorded (Johnson et al., 1983). Therefore one might expect that, in addition to active neurons at the recording site in freely moving animals, there are also closely adjacent but unrecorded, "silent" neurons which may become active upon immobilization and it is these "silent" neurons which respond with inhibition following DEX.

Since all of the iontophoretic studies showing inhibitory responses to DA have been carried out on anaesthetized animals

(reviewed by Moore and Bloom, 1978), it is also possible that the spontaneously active neurons that are recorded in these anaesthetized animals are the neurons that are "silent" in the freely moving state. Indeed, the present study has demonstrated that striatal neurons displayed high levels of spontaneous activity which was profoundly depressed by all commonly used anaesthetics. This suggests that striatal sensory input, mediated presumably through afferents, may control the discharge rates of striatal neurons in freely moving animals. In the immobilized animals of this study spontaneous MUA did not change as compared to freely moving animals; however, the incidence of the characteristic excitatory response to DEX was grossly reduced from 90% in freely moving animals to 19% in immobilized animals (Table XII). Since immobilization precludes behavior, it is possible that behavior, or feedback from DEX-induced behavior, plays an important role in striatal neuronal responses to DEX in the freely moving animal.

That cortical afferents in the freely moving animal may influence the spontaneous discharge of striatal neurons is supported further by the present observation that unilateral destruction of cortical striatal fibers results in a 50% slowing of striatal MUA on the side ipsilateral to the lesion as compared to the contralateral side. A similar result using single unit recording in the cat has been reported (Garcia-Rill et al., 1979).

In contrast, striatal neurons contralateral to the lesion show increased MUA relative to normal control animals, possibly due to a compensatory increase in cortical striatal afferent activity following

ablation. This compensatory increase in activity would be initiated presumably through cortical afferents from the contralateral cortex (Wise and Jones, 1977). Thus, this compensatory increase is not seen in bilateral cortically ablated animals where there is a further decrease in striatal MUA, again presumably caused by the destruction of these contralateral cortical striatal afferents. Since this phenomenon was only observed in cortically ablated animals and not PF-CM or nigrally-lesioned animals, it can be argued that this compensatory effect may represent some type of physiological process brought into play by unilateral cortical damage and unrelated to destruction of striatal afferents. However, the PF-CM does not project contralaterally (Veening et al., 1980) and nigral afferents from the contralateral side represent only 5% of the total DA fibers (Pritzel et al., 1983b) favouring the initial idea that contralateral corticostriatal fibers are involved.

In contrast to control animals where only 10% of all recording sites responded to DEX with inhibition, 48% responded with inhibition in unilateral cortically ablated animals. In these animals spontaneous MUA was not different from the remainder of this unilateral cortically ablated group. This response is not unlike the inhibitory response observed in immobilized animals. However, there was no evidence of disruption of the behavioral response to DEX in the ablated animal. Therefore, it seems that, in some animals at least, removal of a major afferent system such as the corticostriatal system may be sufficient to convert an excitatory response to inhibition in the striatum. Alternatively, and as discussed earlier, different

striatal neurons may be producing the two responses.

However, in instances where excitation was observed, peak responses could be further subdivided into two groups based on peak response to DEX, as well as spontaneous MUA. In the first group, peak responses were less than those observed in control animals, but spontaneous MUA was not different from controls. This may indicate that the neurons being recorded have suffered only a partial loss of their cortical afferent supply, resulting in no changes in spontaneous MUA but a reduced excitatory response to DEX. Such an interpretation is consistent with the finding that a given striatal neuron may receive cortical afferents originating from widespread areas of the cortex (Webster, 1961). In the second group where peak DEX responses were considerably increased relative to control animals, spontaneous MUA was significantly reduced compared to controls. This finding may indicate that these neurons have lost all or the greater portion of their cortical supply resulting in decreased spontaneous MUA. The apparent enhancement seen in the DEX response may indicate that these neurons have become supersensitive to the normal transmitter of the corticostriatal pathway, presumably glutamate; and is in accord with the observation that striatal neurons in unilateral cortically ablated animals respond to lower amounts of iontophoretically applied glutamate (McLennan, 1980).

Interestingly, the response patterns on the contralateral side following DEX were actually very similar to those seen on the lesioned side, suggesting that the striatal projection from the contralateral cortex interdigitates with that from the ipsilateral cortex.

Anatomical studies have demonstrated this arrangement in rat striata (Hassler et al., 1982) although the present results suggest that the extent of this crossed, corticostriatal projection may have greater functional significance than previously demonstrated. Some investigators maintain that up to 1/3 of the corticostriatal afferent supply originates in the contralateral cortex (W.G.H. Nauta, personnal communication).

Following bilateral cortical ablation the incidence of excitation of striatal neurons in response to DEX was reduced (22%) whereas the incidence of inhibition increased (45%), results comparable to those observed with unilateral cortical ablation. However, spontaneous MUA in these animals was significantly lower compared to normal animals, thus providing further evidence that interruption of cortical afferents results in decreased spontaneous activity of striatal neurons. This is not to imply that striatal MUA is totally glutamate-dependent, since bilateral section of the fimbria-fornix, an area known to carry glutamatergic fibers from the hippocampus to the striatum (Waalas, 1981) did not produce a further decrease in spontaneous MUA beyond that produced by cortical ablation alone. Neither was the incidence of inhibition after DEX further increased.

The behavioral response to DEX was not affected by bilateral cortical ablation; in fact, others have reported that bilateral lesions enhance DEX-induced stereotypy and locomotion (Adler, 1961; Lynch et al., 1969; Glick, 1972). However, haloperidol-induced catalepsy was reduced in the present study, an observation previously made by others (Bartholini et al., 1981; Scatton et al., 1982) and

suggesting that glutamate-containing corticostriatal afferents mediate, at least in part, neuroleptic catalepsy. Neuroleptic-induced catalepsy is similar to the akinesia seen in Parkinsonism and one is tempted with the speculation that akinesia, whether haloperidol-induced or pathological, may result from overactivity of corticostriatal afferents. Alternately, the reduction in haloperidol-induced catalepsy may be due to changes in striatal DA receptors following cortical ablation. This is borne out by the observation that D_2 receptor binding sites decreased as a result of bilateral cortical ablation. This idea fits well with the currently held concept that Parkinson's disease involves degeneration of DA neurons which innervate D_2 receptors in the striatum (Lee et al., 1978).

Although decreases in D_2 receptor binding after unilateral cortical ablation have been reported (Garau et al., 1978; Schwarcz et al., 1978; Freedman et al., 1981) haloperidol-induced catalepsy is not reduced, and may in fact be potentiated (Sandberg, 1980). This is difficult to reconcile with the present observations. However, in the unilateral cortically ablated animal, the crossed corticostriatal projection may in itself be sufficient to prevent any noticeable change in catalepsy.

In contrast to a reduction in haloperidol-induced catalepsy in bilateral cortically ablated animals, morphine catalepsy was unchanged, thus implying that non specific changes in the striatum, or elsewhere in the brain, as a result of ablation, were not responsible for the reduction in haloperidol-catalepsy. Moreover, the lack of change in morphine-catalepsy is paralleled by the lack of change in

striatal [^{3}H]Met-enkephalin binding.

The 27% reduction in striatal glutamate levels after unilateral cortical ablation is in good agreement with that previously reported (Fonnum et al., 1981; Hassler et al., 1982) and is the expected result, given that glutamate-containing glia comprise a large portion of the cellular population of the striatum. The lack of change in GABA levels is also in agreement with the results of others (Hassler et al., 1982), and contributes to the idea that destruction of corticostriatal fibers, though obviously a non-specific and crude procedure, may indeed produce a somewhat selective neurochemical lesion in the striatum . However this lack of effect on GABA levels does not rule out the possibility that the increase in the incidence of inhibition following DEX does not involve changes in striatal GABAergic transmission, since unilateral cortical ablation alters striatal GABA turnover (Moroni et al., 1979).

In parallel to the reduction in dopamine D_2 receptor binding sites, and similar to that seen with unilateral cortical ablation, striatal glutamate levels decreased as a result of bilateral cortical ablation. Once again GABA content remained unchanged. Although striatal glutamate levels in bilaterally ablated animals were decreased relative to sham-operated animals, this decrease was not significantly different from the decreases observed in unilaterally ablated animals. It is possible that the extensive surgical procedure used to prepare shams did result in some cortical damage, thus making the decrease in striatal glutamate levels somewhat less apparent than in unilaterally cortically lesioned striata. Alternatively, the

placement of the lesion left some anterior cortex intact, and therefore, the lack of a greater decrease in glutamate levels following bilateral lesions might be accounted for by the remaining intact corticostriatal fibers.

The altered responsiveness of striatal neurons to DEX in cortically lesioned animals is best accounted for by assuming that the destruction of the monosynaptic corticostriatal tract was responsible for the observed responses. However, it is not possible to rule out that some of the observed responses could be due to disruption of cortical fibers projecting to other areas which in turn send afferents to the striatum. In particular, both the SNC and the PF-CM complex receive projections from the cortex (Carter, 1982; Royce, 1983).

Unilateral PF-CM lesions resulted in significant decreases in striatal spontaneous MUA on both the intact and lesioned sides. This finding is in contrast to other work in the cat where unilateral PF-CM lesioning had no effect on striatal spontaneous SUA on either the lesioned or the contralateral side (Levine et al., 1977). The reason for this disparity between studies is not readily apparent, however the cat data was recorded during immobilization, and may not be comparable to data derived in the freely moving state. As regards the decrease in spontaneous MUA on the contralateral side, it is possible that unilateral PF-CM lesion resulted in destruction of afferents known to project from the PF-CM complex to the cortex. Since the intralaminar nuclei have been shown to activate large areas of cortex (Morrison and Dempsey, 1942), and the cortex in turn projects to both ipsilateral and contralateral striatum, unilateral damage to the PF-CM

complex could conceivably alter spontaneous MUA in both striata. In addition to this possibility, it has also been found that unilateral PF-CM stimulation affects caudate [^{3}H]-DA release both ipsilateral and contralateral to the stimulation site (Cheramy et al., 1983), thus showing information transfer from one side of the thalamus to the other. This too could conceivably explain why unilateral PF-CM lesions affected spontaneous MUA of both striata.

DEX-induced behavior was not altered by lesions of the PF-CM complex, but again the striatal neuronal response was changed from one of excitation to predominantly inhibition on the lesioned side. This may indicate that a unilateral lesion at any site in the brain may be capable of altering DEX-induced behavior. However, these results demonstrate that during DEX-induced behavior, the PF-CM afferent pathway is involved in the activation of striatal neurons.

Unlike the neuronal responses in animals with thalamic or cortical lesions, where the incidence of excitation was reduced but not eliminated, unilateral 6-OHDA lesions resulted in a more dramatic reduction in the incidence of DEX-induced striatal activation. The incidence of striatal activation following DEX decreased proportionately as the degree of DA depletion increased. The direct relationship between excitation in response to DEX and DA content raises two possibilities, ie - that 1) DA is excitatory on most striatal neurons or, 2) the lack of DA results in disinhibition of neurons that now respond to DEX with responses other than excitation.

The decrease in spontaneous MUA in nigrally lesioned animals is compatible with an excitatory status for DA. This idea is supported

by the observation that stimulation of the substantia nigra invariably leads to EPSP's in caudate neurons of normal animals (Buchwald et al, 1973; Kitai et al., 1976).

The reduction in striatal DA levels following nigral 6-OHDA lesions is in good agreement with others (Hull et al., 1974; Marshall et al., 1983; Altar et al., 1983). In particular, the increase in contralateral DA in contrast to the marked reductions (75% or greater) in the ipsilateral striatum, appears to have been described but not commented on (Hefti et al., 1980; Marshall et al., 1983). Such an increase in contralateral content may reflect decreased release of DA on that side as a compensatory mechanism for the absence of DA on the lesioned side. In contrast, there are indications that, on the lesioned side, the surviving DA neurons become hyperactive, resulting in increased release as judged by the increase in the ratio of HVA to DA (Bernheimer and Hornykiewicz, 1965), as well as an increase in tyrosine hydroxylase activity (Agid et al., 1973). Upon first inspection, the contralateral striatal DA content in the 50-75% depletion group appears lower than the controls. However, Hefti et al. (1980), using 8 µg of 6-OHDA per nigra, observed that in rats with DA levels between 50 and 100% of control, DOPAC and HVA concentrations were reduced to a lesser extent than DA levels and tyrosine hydroxylase activities, thus suggesting an increase in DA release from surviving neurons. Therefore, the reduction in contralateral DA levels in the 50-75% depletion group in the present study may reflect on the mechanism by which the nigrostriatal DA system compensates for partial damage, that is, by an increase in DA release. This increase,

even if occurring in the presence of increased DA synthesis, would then result in lowered DA levels such as were seen in the present experiments.

From the experiments using intrastriatal 6-OHDA it is apparent that depletion of DA within the striatum itself is sufficient to abolish excitatory responses to DEX. Furthermore, this rules out the possibility that nigral lesions could have concommitantly disrupted the dopaminergic innervation of other brain regions (Bannon and Roth, 1983; Loughlin and Fallon, 1984) and indirectly alter striatal activity. This is an important observation in light of the findings that 6-OHDA lesions of the medial prefrontal cortex have been reported to enhance behavioral responses to DEX as well as increase striatal DA binding and DA turnover (Pycock et al., 1980). However, following unilateral intrastriatal depletion of DA in the present study, DA levels in the olfactory tubercles and piriform and cingulate cortices were unchanged, and control values were similar to other published work (Neve et al., 1982; Bannon et al., 1983).

Although not totally comparable as to time course, changes in MUA, similar to those seen in striata contralateral to SNC lesions, were also seen in striata contralateral to locally-depleted striata. Such observations may suggest that the surviving nigrostriatal DA neurons compensate for marked assymmetries between sides in striatal DA levels by reducing the amount of DA release in the contralateral striatum, a reduction which is reflected in increased content. A similar proposal regarding compensatory increase in contralateral DA levels following unilateral lesions has recently been raised

(Dickinson and Slater, 1982).

DEX-induced activation of striatal MUA was blocked, in the present study, by specific D_2 receptor antagonists, thus providing a clear delineation for the receptor mediating excitation. The selective dopamine D_2 receptor agonist, LY 171555, although unable to increase spontaneous striatal MUA, nonetheless did produce some behavioral activation. The lack of an excitatory effect on striatal MUA may be explained on the basis that LY 171555 stimulates DA autoreceptors which are pharmacologically indistinguishable from dopamine D_2 receptors (Stoof et al., 1982; Starke et al., 1983). Thus, LY 171555 may inhibit the release of DA by either a direct presynaptic effect on DA terminals, or by inhibition of nigral DA cell firing. However, at other brain sites, such as in the prefrontal cortex where terminal autoreceptors are absent (Bannon and Roth, 1983), LY 174555 may be able to initiate behavior normally resulting from DEX-induced release of DA. The pharmacological dissociation of the behavioral response from the striatal response induced by DEX was also observed in this study following sulpiride and has been produced by other investigators using GABA agonists (McKenzie and Hansen, 1980).

The role of behavioral sensory feedback in DEX-induced activation of striatal neurons is supported by examination of various dopaminergic mechanisms in freely moving versus either anaesthetized or immobilized animals. Both anaesthesia and immobilization greatly reduce the amount of DA released in response to DEX, relative to the amount released by DEX in freely moving animals, presumably by

interfering with the function of striatal afferent systems (Zetterstrom et al., 1983; Phillips et al., 1982; Clemens and Phebus, 1983; McCown et al., 1983; Mereu et al., 1983; Gauchy et al., 1974; Riddell and Szerb, 1971; Chiueh and Moore, 1973; Schwarcz et al., 1980; Robinson et al., 1982; Caviness and Wightman, 1982; Takano et al., 1983). It seems, therefore, quite likely that these reductions in DA release following DEX result from the elimination of the DEX-induced behavioral feedback, normally operative in the intact, freely moving animal. As regards the present study, degeneration of DA striatal terminals would be expected to interrupt the DEX-induced release of DA in the striatum as well as the release of DA produced by behavioral-sensory feedback to the striatum.

The single units recorded in this study were characterized by large amplitude, 300-500 μV, whereas most multiple units rarely exceeded 100 μV (Fig. 7). Again, mean spontaneous SUA in freely-moving animals in this study was three times higher than that reported for immobilized rats (Table IV), but consistent with that reported in freely moving cats (Trulson and Jacobs, 1979). Furthermore, these single units, though of small sample size relative to multiple units, showed an increased incidence of inhibition following DEX in lesioned animals compared to normal animals. This may be explained on the grounds that the medium spiny neurons of the striatum, which are the most likely candidates being recorded from in the freely moving state, normally inhibit the discharge of these larger neurons. Destruction of striatal afferent systems may result in disinhibition of this large cell type which responds to DEX only with inhibition. Such a

conclusion is consistent with the observations that spiny Type I neurons possess many collaterals thereby influencing substantial numbers of adjacent cells (Difiglia et al., 1976). Similarly, Richardson et al. (1977) have described inhibition of the activity of large amplitude neurons following stimulation of the substantia nigra, but excitation of small amplitude neurons thought to be inhibitory striatal interneurons. Thus, Richardson et al. (1977) were able to make a distinction between recording of unit activity and neuron size. In this regard the literature contains many suggestions that there is a sub-class of striatal neurons that receive an excitatory orthodromic input from the substantia nigra, and that these cells are smaller, and therefore more difficult to record from (Hull et al., 1970, 1974; Marco et al., 1973).

The DEX reversal of DEX-induced striatal inhibition in unilateral cortically ablated animals is an intriguing observation. Both electrophysiological studies (Alloway and Rebec, 1983) and behavioral studies (Conway and Uretsky, 1982) using chronic DEX pretreatment, have reported both reversal and facilitation, respectively, of DEX responses, and have concluded that these changes cannot be attributed to changes in nigrostriatal afferent activity, or changes in striatal DA receptors. These conclusions, however, are difficult to reconcile with the finding that repeated DEX administration results in destruction of nigrostriatal nerve terminals (Ricaurte et al., 1983; Nwanze and Jonsson, 1981; Ellison et al., 1978). The reversal observed in the present study was observed 48 hr after a single dose of DEX and not chronic treatment. Single injections of DEX can impart

long-lasting enhancement of rotational behavior in the rat, as well as in DEX-induced striatal DA release (Robinson et al., 1982; Robinson and Becker, 1982).

The phenomenon of DEX reversal is consistent with several literature reports, including clinical reports, on the use of DEX or L-Dopa in cerebral trauma cases. Furthermore, in rats previously trained to negotiate a narrow beam, unilateral ablation of the cortex resulted in considerable impairment in carrying out this motor task. However, a single injection of DEX, 2 mg/kg, given 24 hrs. following surgery remarkably improved motor performance (Feeney et al., 1982). Clinical reports also attest to catecholamine involvement in recovery from brain damage. A case of chronic post-traumatic organic brain syndrome, in which the cortex had been damaged, was successfully treated with DEX, 5 mg p.o., twice daily for 14 days (Lipper and Tuchman, 1976). Similarly, in two children with progressive neurological disorders, treatment with L-Dopa resulted in immediate recovery of normal motor functions (Bugiani and Gatti, 1980).

Plasticity in the central nervous system has been observed in response to lesions which destroy afferent projections to a brain region, i.e. area "deafferentation". Although plasticity has been noted in the adult rat, particularly in the hippocampus (Tsukahara, 1981), it does not seem to have been reported for the striatum. Previous studies on plasticity have shown that when cortical lesions are made in the neonate, development of corticofugal projections becomes aberrant (reviewed by Castro and Mihailoff, 1983). Furthermore, it has been demonstrated that following destruction of

cholinergic septal afferents, noradrenergic fibers of sympathetic origin will sprout (Peterson and Loy, 1983).

Nevertheless, in the striatum, 96% of all cells present are medium spiny neurons, and cortical ablation results in deafferentation of at least some of these neurons (Hassler et al., 1982). Since in the present study, where striatal deafferentation is confidently presumed, DEX reversal was most prevalent in the striatum ipsilateral to the lesion and, was not seen in bilaterally ablated animals or in animals with unilateral PF-CM lesions. It would not be unreasonable therefore, to suggest that plasticity involving fibers from the contralateral cortex has occurred; however, it is not clear whether such changes involve neuronal sprouting or re-innervation processes. Although corticostriatal afferents account for a larger share of the afferent input onto medium spiny neurons than either thalamic or nigral afferents (rank order: cortex, thalamus, substantia nigra) the size of terminal fields as well as their degree of collateralization is of the reverse order (nigra, thalamus, cortex) (Fisher et al., 1983). Since studies of sprouting have shown that this phenomenon appears more likely to involve neurons with large terminal fields, it is possible that DEX-reversal is not due to sprouting per se, but rather that the crossed corticostriatal projection, which may or may not be physiologically functional in the intact animal, has been activated as a result of the DEX treatment. Such an interpretation would avoid the difficulty of having to postulate sprouting within 48 hr. after DEX treatment. Alternatively, of course, sprouting of fibers from the contralateral cortex may have occurred following

cortical ablation, and DEX treatment has made these pathways physiologically functional.

However, several arguments mitigate against both these possibilities. The presence of so-called "silent" synapses, although demonstrated in the peripheral nervous system and spinal cord, has not been shown in the CNS. Secondly, and perhaps more important, is that sprouting of glutamate fibers has not been reported in the literature. Lastly, the possibility that sprouting of nigrostriatal DA neurons in areas vacated by corticostriatal fibers cannot be dismissed, although the literature contains little evidence on this point.

SUMMARY OF THE PRESENT STUDY

In concluding then, insofar as that the objectives of the present study may have been partially realized, the following summation highlights the findings:

1) Striatal neurons in freely moving animals respond to DEX in a manner qualitatively different from that seen in immobilized animals.
2) Destruction of corticostriatal and thalamostriatal afferents reduces the incidence of excitation in response to DEX in freely moving animals, the resulting neuronal responses being qualitatively similar to those seen in immobilized animals.
3) Destruction of nigrostriatal afferents abolishes the DEX-induced activation of striatal neurons; and, the percent depletion of striatal DA is inversely proportional to the incidence of excitation of striatal neurons following DEX. Furthermore, excitation appears to be mediated through a dopamine D_2 receptor.
4) Cortical lesions and unilateral lesions of either the PF-CM complex or SNC did not appreciably affect DEX-induced behavioral activation but consistently reduced or abolished the incidence of striatal activation on the lesioned side.
5) Immobilization of animals, thereby preventing behavior, reduces the incidence of DEX-induced striatal activation.
6) The effects of unilateral cortical ablation on DEX-induced changes in striatal MUA can be reversed by a second treatment with DEX.

The main findings of this study have been compiled and are summarized in Table XXVIII.

Table XXVIII - Summary of the Present Study

Experimental Protocol(s)	n	Spontaneous MUA	Drug and dose	Results[1]
Freely moving	6	4267 ± 1342	Halothane, 3% for 32 min.	90% inhibition of striatal MUA
Freely moving	5	5910 ± 1054	Pentobarbital, 35 mg/kg	95% inhibition of of MUA
Freely moving	5	2108 ± 550	Urethane, 1.5 g/kg	85% inhibition of striatal MUA
Freely moving	5	2217 ± 516	Chloral hydrate, 400 mg/kg	80% inhibition of striatal MUA
Freely moving	6	3222 ± 703	Morphine, 5 mg/kg	No effect
Freely moving	7	3438 ± 938	Morphine, 10 mg/kg	30% inhibition of striatal MUA
Freely moving	5	4252 ± 779	Morphine, 15 mg/kg	50% inhibition of striatal MUA
Freely moving	6	3003 ± 1018	Ketamine, 50 mg/kg	Excitation reaching 230% of control
Freely moving in the presence of 5 or 10 mg/kg morphine	5 (5 mg/kg)	3361 ± 893	DEX, 1 mg/kg	Excitation blocked
	2 (10 mg/kg)	5394	DEX, 1 mg/kg	inhibition
Freely moving in the presence of 70% N_2O/ 30% O_2	5	7502 ± 1543	DEX, 1 mg/kg	Excitation reaching 130% of control

Table XXVIII (con't)

Freely moving	5	9538 ± 2127	DEX, 1 mg/kg	Excitation reaching 129% of control
Immobilized in the presence of 70% N_2O/ 30% O_2	5	6722 ± 1511	Saline	No effect over 120 min.
Freely moving in the presence of 70% N_2O/ 30% O_2	5	6462 ± 1337	None	No effect over 68 min.
Immobilized	10	9602 1482	DEX, 1 mg/kg	20% excitation 30% inhibition 40% no change 10% biphasic
Freely moving	33	5574 ± 702	DEX, 2.5 mg/kg	88% excitation 3% inhibition 6% no change 3% biphasic
Immobilized	38	5162 ± 606	DEX, 2.5 mg/kg	18% excitation 27% inhibition 29% no change 26% biphasic

		Ipsi[2]	Contra[3]	DEX, 2.5 mg/kg	Ipsi	Contra
Freely moving unilateral cortical ablation						
a) Frontal ablation	17	3791 ± 659	7645 ± 1477		35% Excitation 48% Inhibition 7% No change 10% Biphasic	26% Excitation 29% Inhibition 29% No change 16% Biphasic
b) Parietal ablation	13	4455 ± 956	5616 ± 981			

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Table XXVIII (con't)

Freely moving bilateral cortical ablation			DEX, 2.5 mg/kg		
a) Ablation only	19	2363 ± 692		22% Excitation 46% Inhibition 10% No change 22% Biphasic	
b) +fimbria-fornix transection	22	2371 ± 529			
Freely moving unilateral PF-CM lesion	Ipsi=22 Contra=15	2203 ± 429 2222 ± 543	DEX, 2.5 mg/kg	Ipsi 14% Excitation 50% Inhibition 18% No change 18% Biphasic	Contra 60% Excitation 20% Inhibition 0% No change 20% Biphasic
Freely moving unilateral nigral lesion	Ipsi=15 Contra=9	2820 ± 322 2008 ± 337	DEX, 2.5 mg/kg	Ipsi Excitation reduced to 22% when dopamine depletion 75% Excitation reduced to 50% when dopamine depletion 50-75%	Contra 80% Excitation 75% Excitation
Freely moving unilateral intrastriatal lesion	Ipsi=3 Contra=3	4690 ± 1287 4057 ± 1117	DEX, 2.5 mg/kg	Ipsi Excitation abolished	Contra 33% Excitation 33% Inhibition 33% Biphasic

Table XXVIII (con't)

[1]Response pattern subtypes have been quantified by expressing the incidence of a particular response subtype as a percentage of the total number of observed responses.

[2]Ipsi = ipsilateral to the lesion.

[3]Contra = contralateral to the lesion.

CONCLUSIONS

1) Nigrostriatal DA is essential for DEX-induced activation of striatal neurons in freely moving animals.
2) Dopamine is an excitatory neurotransmitter in the striatum.
3) The excitatory effect of DA are mediated through D_2 receptors.
4) Corticostriatal and thalamostriatal afferents are involved in the DEX-induced activation of striatal neurons.
5) Sensory feedback, through cortico- and thalamostriatal afferents, and particularly nigrostriatal afferents, as a result of DEX-induced behavior, is required for the activation of striatal neurons.
6) Dopamine receptors may mediate plasticity in the central nervous system.

Appendix I. Representative experiments of striatal MUA responses following DEX, 2.5 mg/kg in lesioned animals.

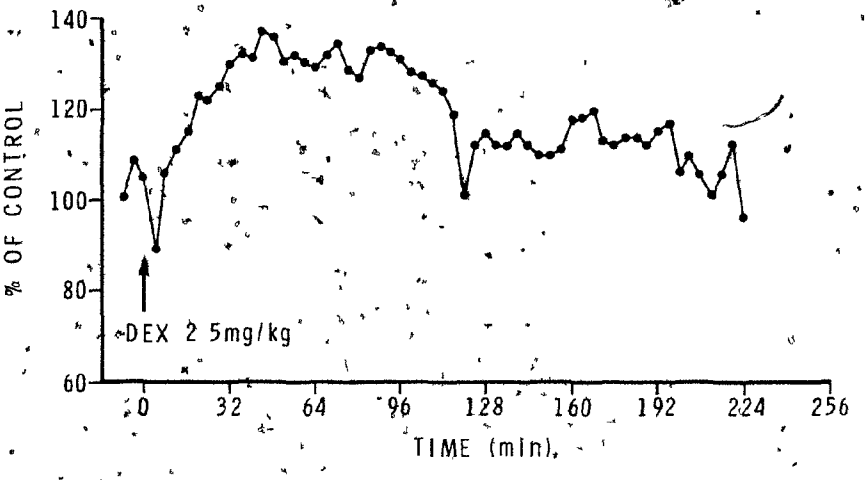

FIGURE 71. A representative experiment showing an excitatory striatal response to DEX on the lesioned side in a unilateral cortically ablated animal. Spontaneous MUA was 4988 ± 123 spikes/4-min. The response of the contralateral side was inhibition. The cortical lesion involved frontal cortical areas.

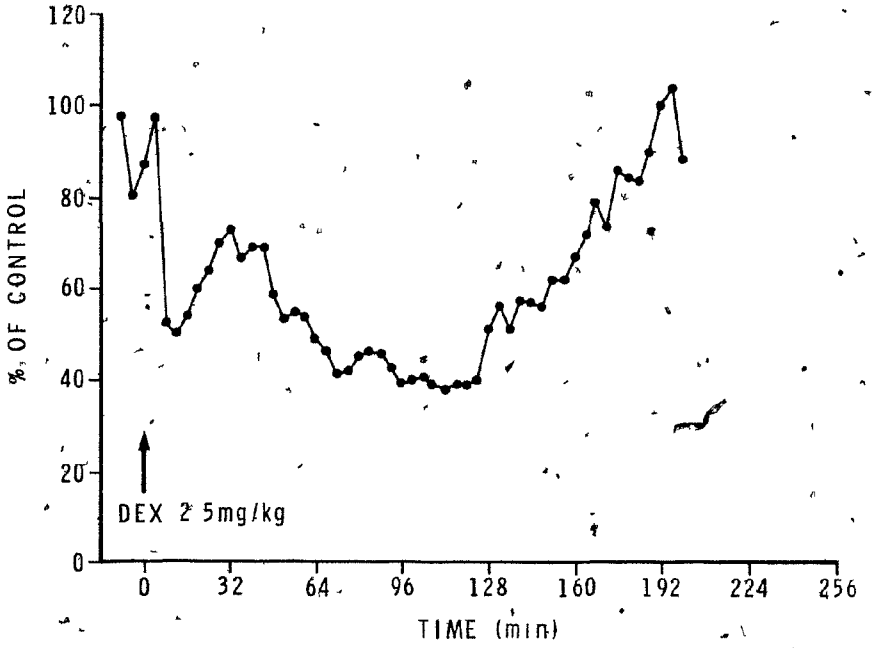

FIGURE 72. A representative experiment showing inhibition of striatal MUA following DEX on the ablated side in a unilateral cortically ablated animal. Spontaneous MUA was 4057 ± 196 spikes/4-min. The response of the contralateral side was biphasic. The cortical lesion involved frontal cortical areas.

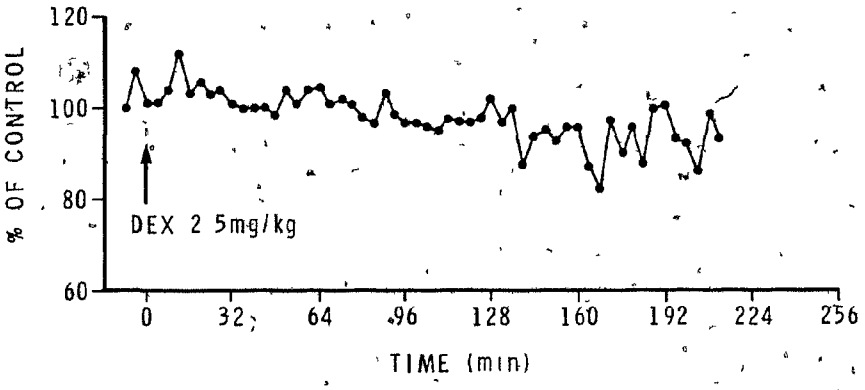

FIGURE 73. A representative experiment showing no change in striatal MUA on the ablated side following DEX in a unilateral cortically ablated animal. Spontaneous MUA was 6338 ± 190 spikes/4-min. The contralateral side also responded with no change. The cortical lesion involved frontal cortical areas.

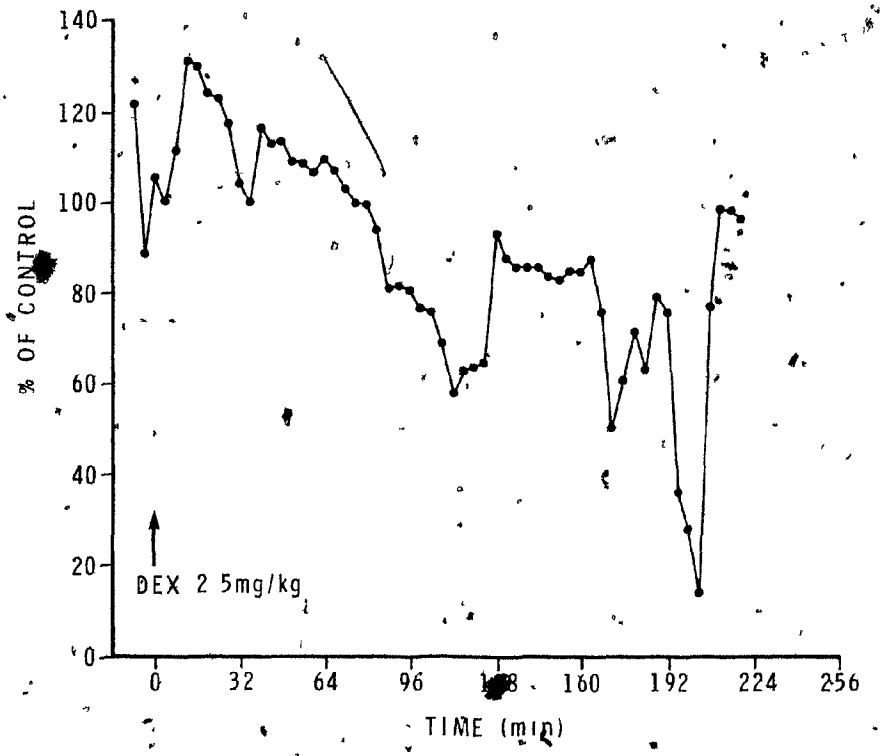

FIGURE 74. A representative experiment showing a biphasic striatal response to DEX on the ablated side in a unilateral cortically ablated animal. Spontaneous MUA was 8317 ± 487 spikes/4-min. The response of the contralateral side was excitation. The cortical lesion involved frontal cortical areas.

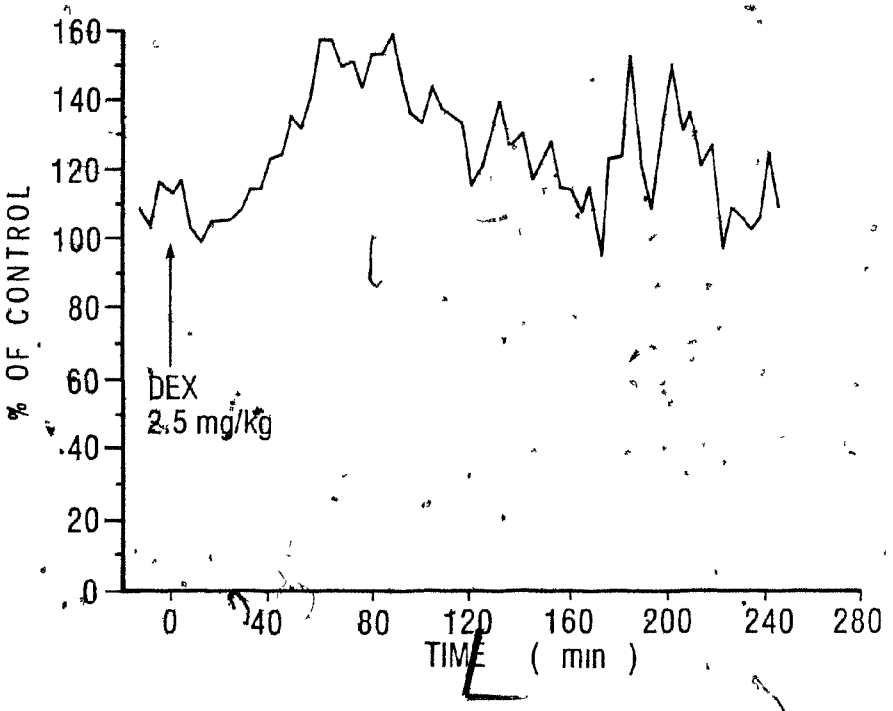

FIGURE 75. A representative experiment showing an excitatory striatal response to DEX in a bilateral cortically ablated animal. Spontaneous MUA was 703 ± 35 spikes/4-min.

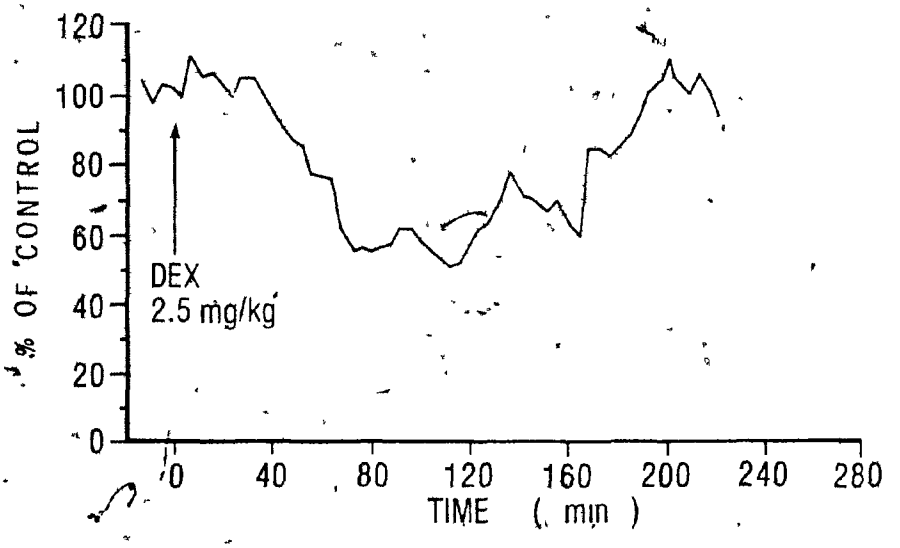

FIGURE 76. A representative experiment showing inhibition of striatal MUA following DEX in an animal with bilateral cortical ablation. Spontaneous MUA was 7701 ± 78 spikes/4-min.

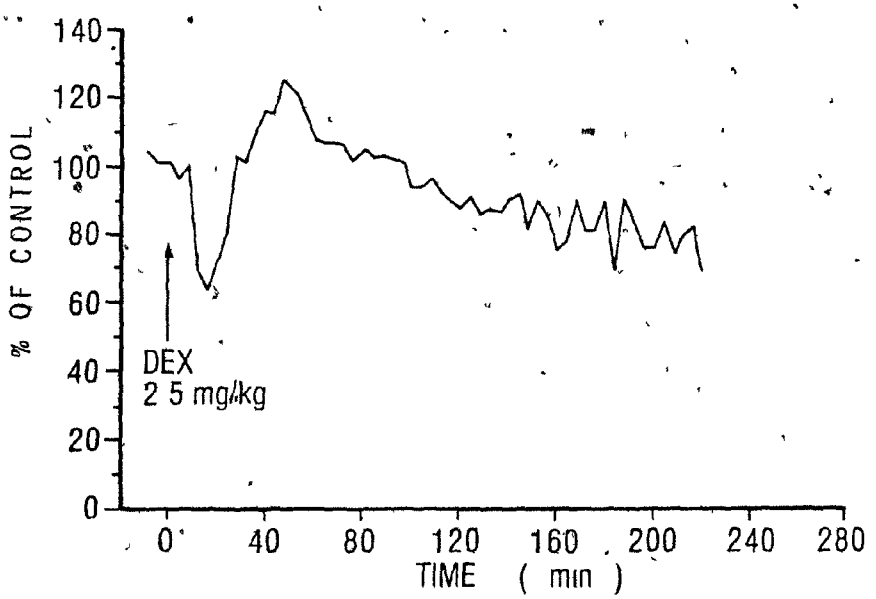

FIGURE 77. A representative experiment showing no change in striatal MUA following DEX in an animal with bilateral cortical ablation. Spontaneous MUA was 3990 ± 34 spikes/4-min.

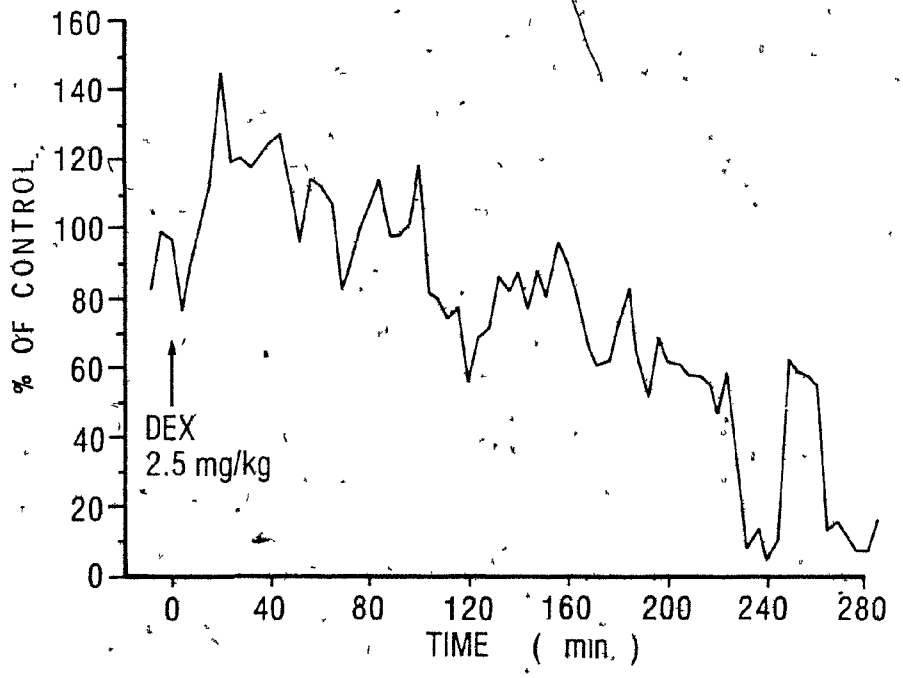

FIGURE 78. A representative experiment showing a biphasic response to DEX in a bilateral cortically ablated animal. Spontaneous MUA was 2178 ± 184 spikes/4-min.

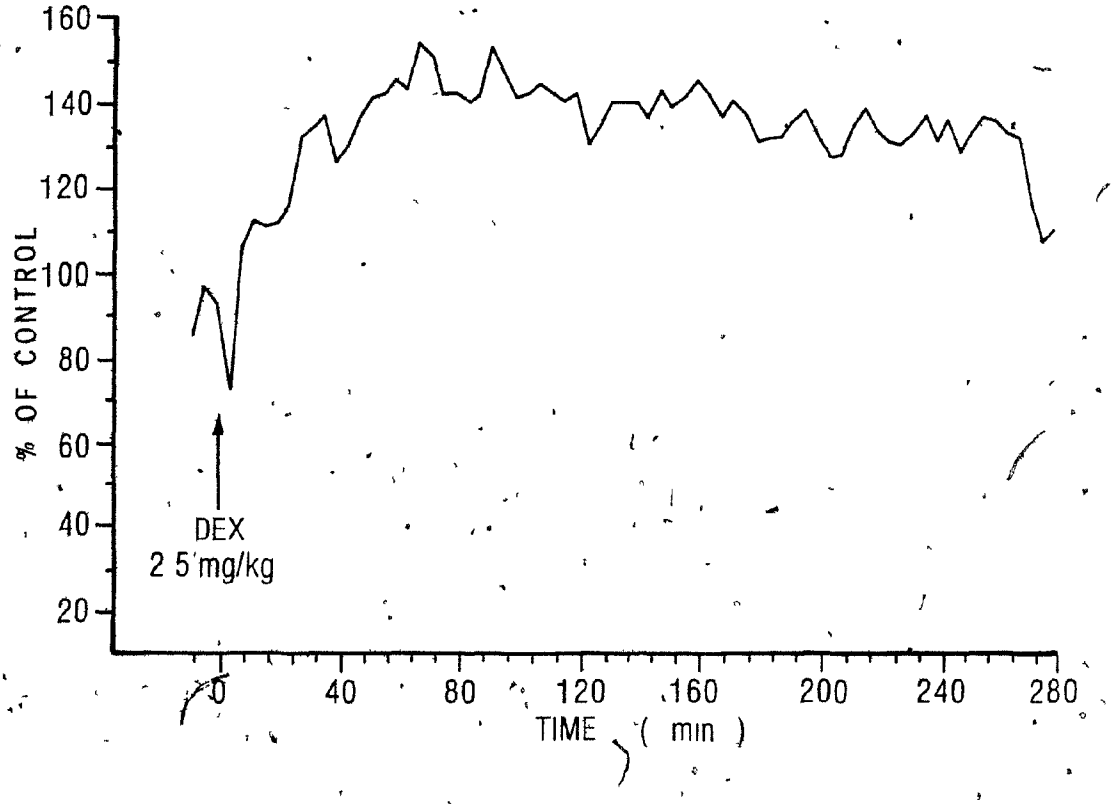

FIGURE 79. A representative experiment showing an excitatory response to DEX in an animal with a unilateral PF-CM lesion. Spontaneous MUA was 6297 ± 199 spikes/4-min.

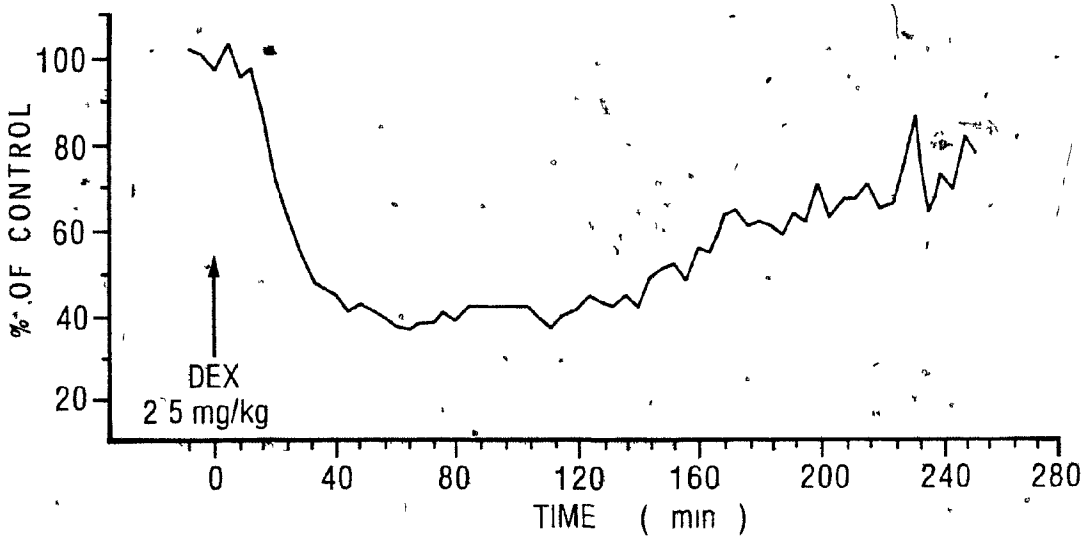

FIGURE 80. A representative experiment showing striatal inhibition following DEX in an animal with a unilateral PF-CM lesion. Spontaneous MUA was 2096 ± 21 spikes/4-min.

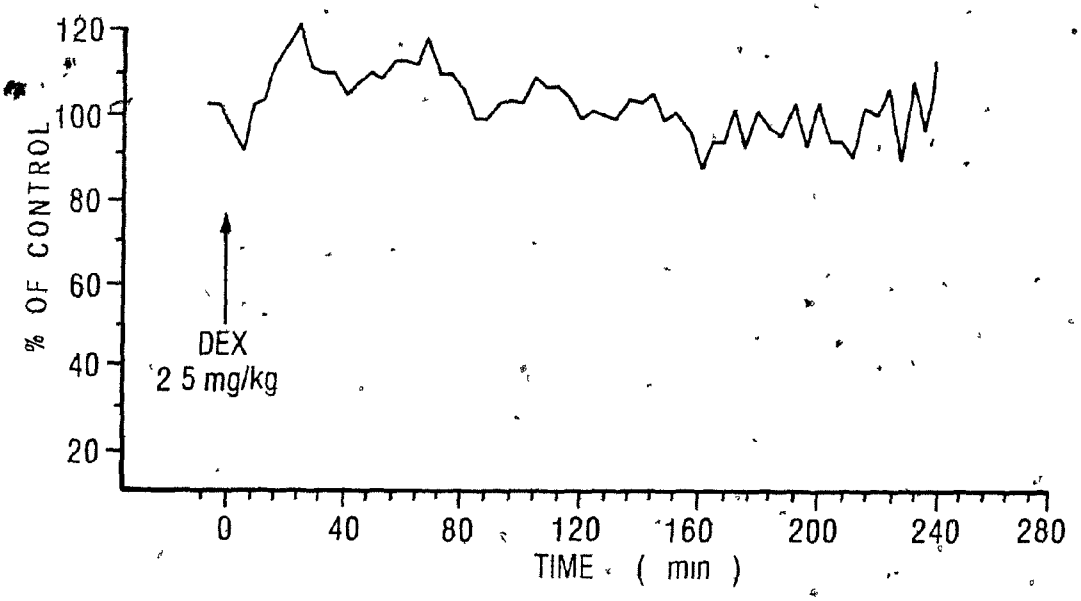

FIGURE 81. A representative experiment showing no change in striatal MUA in an animal with a unilateral PF-CM lesion. Spontaneous MUA was 2030 ± 29 spikes/4-min.

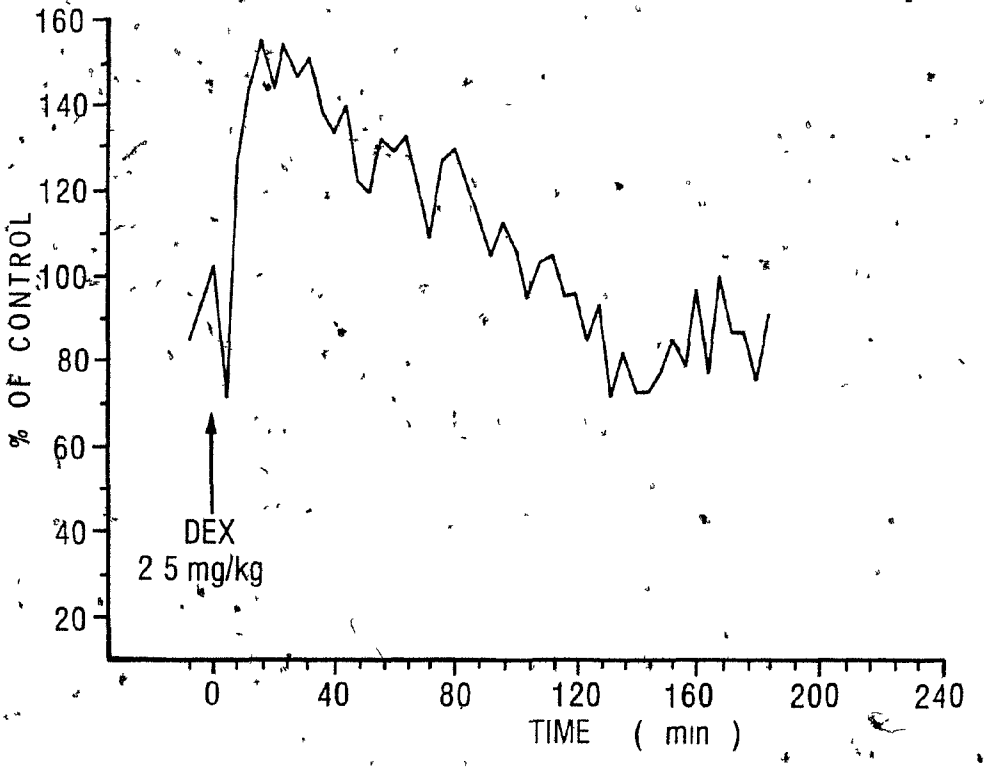

FIGURE 82. A representative experiment showing a biphasic response to DEX in an animal with a unilateral PF-CM lesion. Spontaneous MUA was 950 ± 28 spikes/4-min.

Appendix II. Drugs and Sources

Supplier	Drug	Solvent
May and Baker	D-Amphetamine Sulfate	0.9% saline
Merck	Chloral Hydrate	0.9% saline
Austin Laboratories	Furacin	N/A; powder
McNeil Laboratories	Haloperidol	1.5% tartaric acid
Ayerst Laboratories	Halothane	N/A
Sigma Chemical	6-Hydroxydopamine hydrogen bromide	a) 0.9% saline containing 1 mg/ml ascorbic acid b) 0.9% saline containing 0.1 mg/ml sodium meta bisulfite and 0.00001 N HCl, final pH 6.6
Parke-Davis	Ketamine	0.9% saline containing 0.01% Phemoral as preservative
Eli Lilly Company	LY-171555 (D_2-agonist)	0.9% saline
British Drug Houses	Morphine sulfate	0.9% saline

Appendix II (con't)

Rogar/STB	Pencillin G (Penlong-XL)	Suspension containing 300,000 international units of Penicillin G (Benzathine Penicillin G + Procaine Penicillin G)
MTC Pharmaceuticals	Pentobarbital	Sodium salt in aqueous propylene glycol base containing 2% benzyl alcohol as preservative
Hoffmann-LaRoche	RO 22-1319 (D_2-antagonist)	Distilled water
Schering Laboratories	SCH 23390 (D_1-antagonist)	0.4% aqueous methylcellulose
Smith, Kline and French	SKF-38393 (D_1-agonist)	0.9% saline
Sigma Chemical	Succinylcholine chloride	0.9% saline
Sesiif Laboratories	Sulpiride	1.5% tartaric acid
Sigma Chemical	Urethane	Distilled water
Astra Pharmaceuticals	Xylocaine	Sterile ointment - 2% lidocaine

Appendix III. Reagents, Materials and Their Application(s)

Reagent	Supplier	Use
Acetate (Na^+ salt)	British Drug Houses (BDH) Toronto, Ontario	in mobile phase for HPLC amino acid analysis
Acetic acid	BDH	for pH adjustment of mobile phase used in HPLC amino acid analysis
Acetonitrite (HPLC grade)	BDH	in mobile phase for HPLC amino acid analysis
L-Ascorbic acid	Fisher Scientific Ltd., Halifax, Nova Scotia	anti-oxidant
L-Aspartate (Na^+ salt)	Sigma Chemical Co., St. Louis, Missouri	amino acid standard for HPLC
Borate (Na^+ salt)	BDH	in mobile phase for HPLC amino acid analysis
Calcium chloride	Sigma Chemical Co.	in assay buffer for opiate receptor binding
Citric acid	BDH	in mobile phase for HPLC analysis of dopamine
Domperidone	Janssen Pharmaceuticals Inc.	displacing agent in D-2 receptor assay
Dopamine (3-Hydroxytyramine; HCl salt)	Sigma	standard for HPLC

Appendix III (con't)

Ethanol (HPLC grade)	Consolidated Alcohols Ltd., Toronto, Ontario	80% solution (v/v) used to homogenize tissues for subsequent amino acid analysis
Ethanol		70% solution (v/v) used to dry skull surfaces prior to electrode placement with dental acrylic
Ethylene diamine tetraacetic acid (EDTA) (Na^+ salt)	Sigma Chemical Co., St. Louis, Missouri	in mobile phase for HPLC analysis of catecholamines
Formaldehyde (37% v/v stock solution)	Fisher Scientific	for intracardiac perfusion of animals
GABA (Y-aminobutyric acid) (Na^+ salt)	Sigma	amino acid standard for HPLC
Glucose	J.T. Baker Chemical Co.	in assay buffer for D_1 and D_2 receptor binding
Glutamate (Na^+ salt)	Sigma	amino acid standard for HPLC
Glutamine	Calbiochem-Boering Inc. La Jolla, California	amino acid standard for HPLC
HEPES (N-2-Hydroxy-ethylpiperazine-N-2-ethanesulfonic acid)	Sigma	in assay buffers for receptor binding
Hydrochloric acid	Fisher	for acidifying 6-OHDA solutions used for intrastriatal lesioning.

Appendix III (con't)

Magnesium chloride	Anachem, Montreal, Quebec	in assay buffer for opiate receptor binding
Metabisulfite (Na^+ salt)	Sigma Chemical Company	to prevent degradation of 6-OHDA used for intrastriatal lesioning.
Methanol (HPLC grade)	BDH	a) in mobile phase for HPLC analysis of dopamine b) in mobile phase for HPLC analysis of amino acids
Methylcellulose (1500 centipoises)	Fisher	for making suspension of the D_1-antagonist SCH-23390
2-Mercaptoethanol	Sigma	part of reagent used for derivatizing amino acids prior to HPLC analysis
Octyl sodium sulfate	Eastman Rodak, Rochester, New York	in mobile phase for HPLC analysis of dopamine
Perchloric acid	Fisher	0.1 N solution used to homogenize tissues for subsequent dopamine analysis
Potassium chloride	J. T. Baker Chemical Co.	in assay buffer for D_1-D_2 receptor binding
Potassium phosphate	Sigma	in assay buffer for D_1 and D_2 receptor binding
o-Pthalaldehyde	Fisher	derivatizing reagent for HPLC analysis of amino acids

Appendix III (con't)

Puromycin	Sigma	in assay buffer for opiate binding
Ready-Solv	Beckman Incorporated Fullerton, California	fluor for scintillation counting
Sodium chloride	J. T. Baker Chemical Co., Phillipsburg, New Jersey	a) to make up physiological (0.9% saline b) in assay buffer for D_1 and D_2 receptor binding
Sodium phosphate (mono and di-basic Na^+ salts)	Fisher	in mobile phase for HPLC analysis of dopamine
Sucrose	Sigma	a) homogenization for preparing striatal P_2 fraction b) in assay buffer for receptor binding
Tartaric acid (Na^+ salt)	Matheson, Coleman and Bell Ohio, U.S.A.	as a solvent for haloperidol and sulpiride
Tetrohydrofuran (HPLC grade)	BDH	in mobile phase for HPLC analysis of amino acids
Triton X-100	Sigma	non-ionic detergent for resuspension of pellet in D_1-receptor binding assay
Trizma base (Tris Hydroxymethyl) aminomethane	Sigma	in rinse buffer for receptor-binding assays

Appendix III (con't)

Electrode Assembly

Component	Supplier
Magnetic Wire (Ground)	Electro Sonic Incorporated 1100 Gordon Baker Road Willowdale, Ontario
Male Electrode Pins (Amphenol)	Electro Sonic Incorporated 1100 Gordon Baker Road Willowdale, Ontario
Orthodontit Resin Powder & Liquid	Dental Depot 5443 Rainnie Drive Halifax, Nova Scotia
Teflon Coated Nicrome Wire (Electrode wire - 75 μ)	Medwire Corporation 121 So. Columbus Avenue Mount Vernon, New York
Threaded Male Connectors	Science Workshop Carleton University Ottawa, Ontario

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