Brain Neurotransmitters and Hormones

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Preface

Only in the past two decades have researchers from disparate clinical and experimental fields pooled their common interest in the brain and its role in neuroendocrine and behavioral physiology and pathology to create a new discipline called "psychoneuroendocrinology." Although the interrelationship between gonadal steroid hormones and brain functions was well established in the early 1960s, the recent demonstration that several neuropeptides and neurotransmitters produced by the brain may influence its function has opened an entire new field of clinical and experimental research.

In view of the breathtaking pace with which a vast number of new data are presently produced, it is of the utmost importance that the accumulating body of knowledge in psychoneuroendocrinology be examined periodically so that all new acquisitions as well as speculations be critically assessed. It is hoped that this book, based on the Proceedings of the XII Congress of the International Society of Psychoneuroendocrinology held in Montreal in May, 1981, will accomplish this goal.

Several topics are extensively covered in this volume; Non-striatal dopaminergic systems; GABA and benzodiazepines; Brain peptides; Clinical psychoneuroendocrinology; Chronobiology of affective disorders; Stress; and Ethanol. Foremost experts in the field discuss the pharmacological basis of present-day hypotheses on schizophrenia, tardive dyskinesia, and depression as well as on the mechanism of action of antianxiety drugs. Recent advances in the elucidation of the biosynthesis of endorphins and in the understanding of the physiological role of several brain peptides such as neurotensin, bombesin, and ACTH are reported. Careful analysis is also made of the clinical applications of newly acquired knowledge in psychopharmacology and neuroendocrinology. Finally, the importance of chronobiology in the study of affective disorders is stressed by some of the outstanding pioneers in the field, while the effects of stress and ethanol on the endocrine system are reviewed in detail.

The up-to-date content of this book makes it invaluable for clinicians and researchers who are actively engaged in psychiatry, psychopharmacology, endocrinology, and neuroscience.

R. Collu
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Foreword

The International Society of Psychoneuroendocrinology was founded to further the understanding of normal and abnormal brain function by bringing together laboratory and clinical investigations in neurobiology engaged in the study of brain–hormone and hormone–brain interaction. The annual meetings, although in the spirit of the Society, are marked by the "couleur locale" and, therefore, are subject to variation in topics and speakers. In this respect, the meeting held in Montreal has been no exception. The Society is grateful to Drs. R. Collu, J. C. Ducharme, G. Tolis, and A. Barbeau for the organization of an excellent meeting. They provided the setting that is characteristic of the Society meetings, relatively small in size, extremely pleasant and highly informal, thus facilitating maximal interaction among participants. I hope that the proceedings of the meeting reflect the good memories we all have of the meeting in Montreal.

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Non-Striatal Dopamine Receptors

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INTRODUCTION

Few would question that one of the most important developments in neurochemistry and neuroendocrinology has been the emergence of an established role for dopamine as a regulator of neuronal and endocrine function. Much of the interest in dopamine can be traced back to the early work of Fuxe, Hokfelt, Ungerstedt and others who developed neurochemical techniques which identified discrete dopaminergic pathways in the brain (3,32,37,61). These developments made it possible to study the dopamine receptor and its response in well-defined areas in the central nervous system (35,38,51,58,65,66).

Two biochemical markers have been used successfully in recent years to study the dopamine receptor. They are dopamine-sensitive adenylate cyclase activity and radioligand binding assays. These techniques provide a reliable and consistent approach to the study of the dopamine receptor. The results from these studies have contributed to a better understanding of the biochemical characteristics of the dopamine receptor in the brain.

Historically much of our knowledge about the biochemical action of dopamine receptors in the central nervous system has come from the study of its properties in the striatum. Foremost among these studies was the observation that dopamine activates the enzyme, adenylate cyclase (13-15,35,38). Initially, it was believed that the enzyme itself was the receptor or recognition site for dopamine but this idea was abandoned after it was determined that the receptor binding properties of dopamine could be separated from cyclase activity (13,14, 17). Another important discovery that occurred at about the same time as the report on dopamine activation of adenylate cyclase was the observation that certain ligands labeled specific dopamine receptors which had very little activity in the cyclase assay (7-10,22,47,48). This observation plus the discovery that some non-striatal areas responded physiologically to dopamine but did not contain, a dopamine-sensitive adenylate cyclase. This led a number of investigators to propose a subclassification for the dopamine receptor into two types (for review see 39;17,20,22,53-55,59,60): one type of dopamine receptor that is coupled to adenylate cyclase (D_1) and the other type (D_2) that is uncoupled to the enzyme. This proposal has been supported by kinetic studies which show a heterogeneous population of dopamine

receptors that are characterized by high and low affinity binding of specific dopamine agonists (17,41,46). Also, recent studies on the solubilization of the dopamine receptor show that multiple binding sites can be identified after gel filtration chromatography (19,43). Although these data support the suggestion that the dopamine receptor has multiple components, they do not rule out the possibility that the dopamine binding site is one molecular entity and that the heterogeneity that has been described for the receptor is a function of its interaction with other membrane components in the receptor complex.

The purpose of this commentary is to provide an overview of the biochemistry of dopamine receptors in the brain and to describe a number of chemical tools that may be useful for studying the coupling of the dopamine receptor to adenylate cyclase.

D_1:DOPAMINE RECEPTORS THAT ARE COUPLED TO ADENYLATE CYCLASE

Dopamine has been implicated as a neurotransmitter in several nonstriatal regions of the mammalian central nervous system. Recently, the amygdala, cerebral cortex, and median eminence have been identified as regions receiving dopaminergic innervation (32,37). Previous studies have supported the correlation between dopaminergic innervation of the limbic system and the extrapyramidal motor system and the occurrence of dopamine-sensitive adenylate cyclase in these non-striatal areas (13,38). Thus, it was of interest to verify the presence of a dopamine-sensitive adenylate cyclase in these dopaminergic areas (14). A study of the effects of various concentrations of dopamine, norepinephrine and l-isoproterenol on adenylate cyclase from the median eminence reveal that adenylate cyclase activity was stimulated by low concentrations of dopamine; a half maximal increase in enzyme activity was observed with 5 μM dopamine. In contrast, the β-adrenergic agonist l-isoproterenol had no significant effect on adenylate cyclase activity with concentrations as high as 1000 μM. l-Norepinephrine stimulated adenylate cyclase activity in the median eminence to the same maximal level as did dopamine. A greater concentration of l-norepinephrine than of dopamine was required to achieve a given increase in enzyme activity. Half maximal stimulation of the enzyme was obtained with 30 μM l-norepinephrine and maximal stimulation was obtained with 300 μM l-norepinephrine. Similar results were observed in the olfactory tubercle, nucleus accumbens and frontal cortex and retina (6,13,16,38). The increase in enzyme activity in the presence of a combination of dopamine and l-norepinephrine, each at a concentration causing maximal enzyme stimulation, was no greater than with either agent alone. This suggests that l-norepinephrine interacts with the same receptor as does dopamine in the median eminence.

The effect of dopamine on adenylate cyclase from selected dopaminergic areas is shown in Table 1. Low concentrations of dopamine were found to stimulate the adenylate cyclase from a number of nonstriatal dopaminergic areas in a comparable manner to that observed in the striatum. Fluphenazine, one of the most potent phenothiazine compounds, and clozapine, a potent antipsychotic with low extrapyramidal side effects, inhibited adenylate cyclase activity measured in the presence of dopamine. A summary table (Table 2) lists the nonstriatal areas in the central nervous system and pituitary that contain a dopamine-sensitive adenylate cyclase.

TABLE 1. Calculated inhibition constants (K_i) from several dopaminergic areas of the brain for representatives of the phenothiazine, butyrophenone, dibenzodiazepine and dibenzoxazepine classes

Source of enzyme	Enzyme activity (pmol/mg/min) Control	+Dopamine (40 μM)	K_i*(nM) Chlorpromazine	Fluphenazine	Clozapine
Caudate nucleus	105.1	280.0	90	8.0	60
Olfactory tubercle	50.9	109.8	60	7.0	60
Nucleus accumbens	80.0	120.2	75†	7.5†	59
Median eminence	83.2	125.6	70†	7.5	61†
Amygdala	103.8	180.6	80		
Retina (a)	39.1	73.5	50	5.5	

*The K_i value was calculated from the relationship K_m/K_m, where K_m and K_m are the concentrations of dopamine required to give half-maximal activation of the enzyme, in the presence and absence of test substance, respectively, and I is the concentration of the inhibitor except where indicated.

†Where daggers appear, the K_i value was calculated from the relationship $I_{50} = K_i\ (1+S/K_m)$, where I_{50} is the concentration of drug required to give 50 per cent inhibition of the enzyme activity, and S is the concentration (40 μM) of dopamine (13). (a) taken from reference (16).