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Advances in Dopamine Research

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ADVANCES IN DOPAMINE RESEARCH

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Volume 37

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Preface

This volume is based on the proceedings of a Symposium on Dopamine held in Okayama, Japan, in 1981.

The importance of dopamine in brain function is reflected in this book by chapters on the neurochemical, behavioural, neuroanatomical and electrophysiological aspects of dopamine in the central nervous system. Dopamine receptor agonists and antagonists enjoy widespread use in the treatment of various brain disorders. A comprehensive account of recent research on the actions and mechanisms of action of drugs which affect central dopaminergic pathways is included in this volume. Also included are accounts of the importance of dopamine and dopamine receptors in the periphery.

It is hoped that this volume will be of interest to neuroscientists and pharmacologists, and indeed to all who are interested in clinical and scientific aspects of dopamine and other neurotransmitters.

The Editors.

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Plenary Lecture on Dopamine Receptors

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ABSTRACT

An account is given of some early functional tests that were used in the evaluation of dopamine receptor agonists and antagonists. Using pharmacological, biochemical and electrophysiological studies, ADTN and certain ergot alkaloids have been shown to be potent dopamine receptor agonists. ADTN is considerably more active than iso-ADTN in all tests so far studied. This suggests that the receptor-preferring conformation of dopamine is the extended form, β rotamer. Ergot alkaloids differ from catechol type agonists in their effects on the dopamine sensitive adenylate cyclase in homogenates of rat striatum or nucleus accumbens. The benzamide derivative sulpiride which has neuroleptic properties in a number of tests, differs from classical neuroleptics in that it does not block effects of dopamine on the dopamine sensitive adenylate cyclase. This had led to the concept of D1 and D2 receptors. Our results, however, are not in accordance with the current concept of D1 and D2 receptors. Receptor binding studies have shown that sulpiride is a very useful ligand for dopamine receptor binding studies. It is more selective than spiroperidol but similar to the latter ligand in terms of regional distribution of binding and susceptibility to displacement by agonists and antagonists. It differs from conventional neuroleptics, however, in that there is a unique requirement for sodium ions in sulpiride binding. Our results using N-ethylmaleimide suggest that a sulphydryl group is associated with the sulpiride binding component of the dopamine receptor.

KEYWORDS

Dopamine receptors; ADTN; sulpiride; receptor binding; adenylate cyclase; conformation of dopamine.

INTRODUCTION

Dopamine was first synthesised by Barger and Ewins (1910) and by Mannich and Jacobsohn (1910). Some of its actions were described in the same year in a paper by Barger and Dale (1910) in which they described its weak peripheral sympathomimetic activity. In addition to its activity on α and β adrenoceptors, dopamine causes changes in the cardiovascular system that are quite distinct from those produced by adrenaline or noradrenaline. In 1942, Holtz and Credner showed that in the guinea-

pig and rabbit dopamine causes a fall in the arterial blood pressure, although the significance of this finding was not realised for many years to come. Indeed, it was not possible to further characterize the cardiovascular action of dopamine until the much later discovery of specific β blockers which could eliminate the possibility of dopamine mediating its effects via β receptors. Fifteen years later a proposal that 'dopamine has some regulating functions of its own which are not yet known' in a paper by Blaschko (1957) coincided with the beginnings of a vast amount of research on the physiological and pharmacological implications of dopamine, first in the CNS, and later in the periphery. The presence of dopamine in the brain was first demonstrated biochemically by Carlsson and others (1958), Montagu (1957) and Weil-Malherbe and Bone (1957). Using histochemical techniques, Carlsson, Falck and Hillarp (1962) showed that brain dopamine was localized intraneuronally. Since this time numerous histochemical studies have been carried out in combination with mechanical or chemical lesioning. These studies have revealed a detailed knowledge of the organization and projection of central dopaminergic neuronal systems (review by Lindvall and Bjorklund, 1978).

The finding by Ehringer and Hornykiewicz (1960) that the dopamine content of the corpus striatum is drastically depleted in patients with Parkinson's Disease led eventually to the successful use of Dopa in the treatment of this disorder (Cotzias, Van Woert and Schiffer, 1967). A considerable amount of research has subsequently been directed towards the discovery of potent and selective dopamine receptor agonists which can be used as anti-Parkinson drugs. The first dopamine receptor agonist, apart from dopamine itself, was apomorphine. Ernst, in 1965, proposed that the behavioural actions of apomorphine were due to the ability of the drug to stimulate central dopamine receptors. Although this proposal was based on the scantiest of evidence, apomorphine was soon firmly established as a potent and selective dopamine receptor agonist. Fortunately, subsequent work has confirmed the agonist activity of apomorphine at dopamine receptors. Neuroleptic drugs have been used in the treatment of schizophrenic states since the early 1950s. It is now generally accepted that these compounds act by blocking CNS dopamine receptors, although, again, the earlier suggestions for the mode of actions of these drugs were mainly hypothetical (Van Rossum, 1965; 1966).

METHODS OF INVESTIGATING DOPAMINE RECEPTORS

One of the difficulties encountered in dopamine receptor research has been the lack of convenient model test systems on which to evaluate the activities of dopamine receptor agonists and antagonists. The ultimate consequence of dopamine receptor activation should be the eliciting of a biological response. In the CNS, this would be expected to be either a change in neuronal firing or a change in transmitter release or perhaps some long-term metabolic change. Unfortunately, the tests available for measuring CNS dopamine receptor activity are often indirect and not based on a sound pharmacological characterization of the responses being measured. This is particularly important in attempts to classify or characterize multiple dopamine receptors.

Multiple receptors for neurotransmitters seems to be the rule rather than the exception. By analagy with the muscarinic and nicotinic acetylcholine receptors, the α_1 and α_2 and β_1 and β_2 adrenoceptors and the H_1 and H_2 histamine receptors, one would expect there to be multiple dopamine receptors, which we could call D_1 and D_2. These have been looked for and apparently found (Kebabian and Calne, 1979). Furthermore, D_3 and D_4 dopamine receptors have also been claimed (Sokoloff, Martres and Schwartz, 1980; Seeman, 1980). Dopamine receptor classification has however been carried out without a proper knowledge of selective agonists and antagonists. Let us take as an example of a successful area of receptor classification, the field of histamine H_1 and H_2 receptors. Histamine is known to have

a number of pharmacological actions in the periphery. The traditional anti-histamines, such as mepyramine and diphenhydramine, were shown to competitively inhibit the effects of histamine in causing contractions of smooth muscle. The inhibitory effect of histamine on the rat uterus and the stimulatory effect of histamine on gastric secretion were, however, unaffected by mepyramine or diphenhydramine. Ash and Schild (1966) defined the pharmacological receptors involved in the mepyramine-sensitive histamine responses as H_1 receptors. They also suggest a common receptor-mediating mepyramine-insensitive histamine responses in gastric secretion and rat uterus inhibition. However, they were unable to comment further on this presumed second type of histamine receptor because there were no available antagonists. In 1972 it was shown that burimimide competitively inhibits the stimulatory effects of histamine on gastric acid secretion whilst also blocking the inhibitory effect of histamine on the rat uterus (Black and others, 1972). This allowed the definition and characterization of this second receptor which became known as the H_2 receptor. Many important developments have since taken place in this field and there are now available a considerable number of selective agonists and antagonists for both H_1 and H_2 receptors. Using these selective compounds, and utilising receptor binding techniques and adenylate cyclase assays, the histamine receptors in the brain have been successfully characterized as H_1 and H_2 (Schwartz, Garbarg and Quach, 1981). Attempts to classify multiple dopamine receptors on the other hand, have been seriously hindered by the lack of specific agonists and antagonists, by the lack of knowledge on order of potencies of agonists and antagonists and, as previously mentioned, by the lack of suitable test systems. Some of the test systems which have been used are outlined below.

Invertebrate Neurones

Nearly fifteen years ago we investigated the possibility of using the isolated brain of the snail, Helix aspersa, as a model system on which to study dopamine receptor agonists and antagonists. Individual neurones can be recorded with intracellular microelectrodes and dopamine induced hyperpolarizations (or depolarizations) can be measured. This model has been largely superceded by more appropriate mammalian preparations. Its use did, however, lead to some important developments.

In 1968 we were able to show for the first time an interaction of ergot alkaloids with dopamine receptors. Ergometrine (ergonovine) was shown to be a potent antagonist of the inhibitory effect of dopamine on the Helix neurones. We later showed that lysergic acid diethylamide is similarly a potent and long-lasting dopamine antagonist in this system (Walker and others, 1968; Woodruff, Walker and Kerkut, 1971; Woodruff, 1971). More recently these and other more potent ergot alkaloids have been shown to have dopamine agonist-like properties in the mammalian CNS. We also used the isolated brain of Helix to characterise the dopamine receptor in terms of the structure activity requirements for dopamine agonist activity (Woodruff and Walker, 1969). The major findings have previously been discussed in review articles (Woodruff, 1971; 1978; 1980). Briefly, the most potent agonists were found to be dopamine epinine and later, ADTN. The dopamine receptor in this preparation was shown to be quite distinct from either the α or the β adrenoceptor and there was a high degree of structural specificity.

Dopamine Receptors in the Kidney

At the same time that we were working on Helix dopamine receptors, Goldberg and his colleagues were studying dopamine receptors mediating renal vasodilatation in the dog (Goldberg, Sonneville and McNay, 1968; Goldberg, 1979). The structural requirements for dopamine-like activity in this preparation were very close to

those reported in the Helix brain preparation. The only active compounds contained hydroxyl groups in the 3 and 4 positions of the benzene ring. Indeed, of the 44 amines tested in the original study, only epinine produced dopamine-like effects. The renal vasodilator action of dopamine could be antagonised by haloperidol, although specificity was demonstrated only in a narrow dose range (Yeh, McNay and Goldberg, 1969).

Dopamine-Sensitive Adenylate Cyclase

Kebabian, Petzold and Greengard (1972) showed that homogenates of rat striatum contain an adenylate cyclase that is stimulated by low concentrations of dopamine. A similar dopamine-sensitive adenylate cyclase has been shown to occur in other regions of the brain which receive a dopaminergic innervation, for example, the nucleus accumbens (Horn, Cuello and Miller, 1974; Watling, Woodruff and Poat, 1979). It was suggested that the actions of dopamine in the brain are mediated by an increased synthesis of cyclic AMP and that the dopamine receptor is closely linked to adenylate cyclase (Kebabian, Petzold and Greengard, 1972). Structure activity studies on the affects of dopamine receptor agonists on the dopamine sensitive adenylate cyclase were carried out in a number of laboratories. One of the most striking findings was that the structure activity requirements for the dopamine activity in this preparation were very similar to those previously reported by Goldberg in his dog kidney preparation and by our own group on invertebrate neurones (Woodruff, 1978). The view that dopamine receptors are linked to adenylate cyclase has not, however, been supported in a number of other experiments. For example, the role of cyclic AMP in mediating the physiological effects of dopamine has not been demonstrated and a number of problems have arisen in attempting to explain the central actions of a number of dopamine agonists and antagonists in terms of an effect on adenylate cyclase. This point will be discussed later.

Electrophysiological Studies in the Mammalian CNS

One of the major physiological roles of dopamine is undoubtedly to modify the firing rate of neurones in the brain. One of the most appropriate methods of classifying and characterizing dopamine receptors would therefore be based on the effects of a series of agonists and antagonists on the firing rate of neurones in the CNS. There are many technical difficulties associated with this type of approach which doubtless explains why this has not been satisfactorily carried out. However, with the development of tissue slice preparations of mammalian brain and with the development of methods for accurately measuring the release of amines from micropipettes, further advances can be anticipated. The electrophysiological approach can be used to study the properties of postsynaptic dopamine receptors and of so-called dopamine autoreceptors.

Postsynaptic dopamine receptors. Neurones in the caudate putamen and nucleus accumbens receive a dopaminergic projection from the substantia nigra (zona compacta) and the A10 cell group respectively. The postsynaptic receptors in the caudate putamen and the nucleus accumbens are difficult to study because of the smallness of the cells and because most of the neurones in these brain regions of anaesthetised animals are either silent or fire extremely slowly (Crossman, Walker and Woodruff, 1974). The size of the neurones also makes intracellular recording extremely difficult and so the majority of studies in these brain regions have been carried out using extracellular recording techniques. In our own studies of the effects of iontophoretically applied dopamine on neurones in the rat nucleus accumbens and caudate nucleus, the majority of cells studied were depressed by iontophoretically applied dopamine (Woodruff, McCarthy and Walker, 1976). These

results are similar to those reported by Gonzalez-Vegas (1974) and Siggins, Hoffer and Ungerstedt (1974). A systematic study of the structure activity requirements for dopamine-like activity in striatal and nucleus accumbens neurones has not yet been carried out. The responses to dopamine in the brain regions have however been shown to be blocked by neuroleptic drugs (Gonzalez-Vegas, 1970; McCarthy, Walker and Woodruff, 1977; Bunney, 1979).

Dopamine autoreceptors. The dopamine-containing neurones in the nigro-striatal pathway contain dopamine receptors on their cell bodies in the zona compacta of the substantia nigra. These soma-dendritic dopamine receptors are often referred to as autoreceptors (Bunney, 1979). In addition, it is likely that the same neurones have presynaptic dopamine receptors at their terminals in the striatum. These presynaptic dopamine receptors which modulate dopamine release are also referred to as autoreceptors (Carlsson, 1975; Bunney, 1979). It might be predicted that the soma-dendritic autoreceptors in the substantia nigra would be similar to the presynaptic receptors on the striatal nerve terminals, since both types of receptor would be present on the same cell. Electrophysiological studies on these neurones would therefore be expected to yield important information. The dopaminergic neurones in the zona compacta (and the A10 cell group) can be identified by their firing pattern, by their responsiveness to intravenous apomorphine and by antidromic stimulation (Bunney and others, 1973; Guyenet and Aghajanian, 1978; Bunney, 1979). These neurones will respond to intravenous applications of dopamine receptor agonists or antagonists (Bunney, 1979), providing, of course, that the drugs cross the blood brain barrier with ease. It is possible on these cells to distinguish between the direct and indirect actions of drugs such as apomorphine and amphetamine (Bunney, Aghajanian and Roth, 1973). In spite of all the advantages that these neurones offer, a detailed account of the structure activity requirements for dopamine-like activity has not yet been published.

Behavioural Studies

A number of important behavioural tests have been used in the evaluation of dopamine receptor agonists and antagonists (reviews by Costall and Naylor, 1980, 1981). The use of several of these tests has led to major advances in our knowledge of the physiology and pharmacology of central dopaminergic systems. Problems such as metabolism, distribution and non-specificity of action, however, require caution when interpreting the results of such tests in terms of dopamine receptor mechanisms (Woodruff, 1978; Woodruff and colleagues, 1979).

Drug-induced rotations. One of the most widely-used behavioural models for studying dopamine receptor agonists or antagonists is the 6-hydroxydopamine rotational model, developed by Ungerstedt (1971). In this test, unilateral lesions of the nigro-striatal tract are produced in rats by the local injection of 6-hydroxydopamine, unilaterally, into the substantia nigra. Several days later, if the animals are injected intraperitoneally with amphetamine, a drug that releases dopamine from nerve terminals and inhibits the uptake of dopamine, the rats rotate vigorously towards the lesioned side. If, on the other hand, the lesioned rats are injected with apomorphine, the rats rotate towards the innervated side. It is believed that this action of apomorphine is due to a compensatory increase in the sensitivity of the dopamine receptors on the denervated side, together with the loss of presynaptic apomorphine sensitive dopamine receptors (Ungerstedt, 1971).

Locomotor stimulation. It has long been known that the intraperitoneal injection of amphetamine in rats causes stimulation of locomotion. Although early studies suggested that the locomotor stimulant action of amphetamine is mediated by noradrenaline (Randrup and Scheel-Krüger, 1966; Pfeifer, Galambos and Gyorgy, 1966; Taylor and Snyder, 1971), later studies suggested that this effect involved an

action on central dopaminergic systems (Rolinski and Scheel-Kruger, 1973; Creese and Iversen, 1972; Van Rossum, 1970). The demonstration by Pijnenburg, Woodruff and Van Rossum (1973) that the bilateral injection of ergometrine into the nucleus accumbens of conscious rats causes a strong and long-lasting stimulation of motor activity provided the first clue to the site of action of locomotor stimulant drugs and provided evidence that brain dopamine receptors could be stimulated by certain ergot alkaloids. More recently, it has been shown that a number of other dopamine receptors agonists injected into the nucleus accumbens cause a potent and long-lasting stimulation of motor activity. ADTN is one of the most potent agonists in this respect (Elkhawad and Woodruff, 1975; Woodruff and Andrews, 1979). The ADTN hypermotility test represents a useful and selective method for evaluating neuroleptic activity (Woodruff and Andrews, 1979).

Receptor Binding Studies

One of the major growth areas in central dopamine receptor research has come with the advent of receptor binding techniques. A number of tritiated ligands have been used in attempts to localize and characterize CNS dopamine receptors. The ligands used have included the antagonist [^{3}H]-haloperidol (Seeman and others, 1975; Creese, Burt and Snyder, 1975), [^{3}H]-spiroperidol (Leysen, Gommeren and Laduron, 1978), [^{3}H]-cis(z)-flupenthixol (Hyttel, 1980), [^{3}H]-domperidone (Baudry, Martres and Schwartz, 1979) and [^{3}H]-sulpiride (Theodorou and others, 1979; Freedman and Woodruff, 1981a; Woodruff and Freedman, 1981). The agonists used have included dopamine (Creese, Burt and Snyder, 1975), [^{3}H]-apomorphine (Seeman and others, 1976) and [^{3}H]-ADTN (Roberts, Woodruff and Poat, 1977; Davis , Poat and Woodruff, 1979; Woodruff and others, 1979). Dopamine receptor labelling studies have been fully reviewed in the comprehensive article by Seeman (1980). Receptor binding studies are often regarded as the panacea for central dopamine receptor research and as the direct method of studying dopamine receptors. Results obtained in binding assays, however, can only be interpreted with confidence if detailed knowledge is already known of the pharmacological properties of the ligands used and of the structure activity profile of the receptor under study. Specific binding sites for tritiated ligands in the brain can be distinguished from non-specific binding by carrying out the incubations in presence and absence of a non-radioactive drug which has high affinity for the receptors. The use of (+) and (-) butaclamol has been important in this respect. Specific binding can, however, occur to enzyme binding sites, to uptake sites or to other membrane components (or even to glass filters) which are quite unrelated to the receptor. Binding can also occur to other types of receptor. For example, spiroperidol, used as a label for dopamine receptors, also labels serotonin receptors (Leysen and others, 1978). Of course, there is also the possibility that there might be types of dopamine receptor which are quite unaffected by spiroperidol or butaclamol. Bearing all of these points in mind, it is obvious that receptor binding techniques have made important contributions to the field and are likely to be of greater importance in the future.

DOPAMINE RECEPTOR AGONISTS

In recent years, there has been considerable interest in the development of potent and selective dopamine receptor agonists. As I have already mentioned, drugs which stimulate postsynaptic dopamine receptors in the striatum have potential use in the treatment of Parkinson's Disease. In addition to the postsynaptic dopamine receptors, there is also evidence for the presence in the CNS of dopamine autoreceptors, either located on dopamine-containing terminals, or located on the soma or dendrites of dopamine containing neurones. Drugs acting as selective agonists at dopamine autoreceptors would be expected to inhibit the release of dopamine.

Such drugs might be of potential value as anti-psychotic drugs (Langer and Dubocovich, 1979). In the pituitary, dopamine receptors seem to be involved in regulating the release of hormones such as prolactin. Dopamine receptor agonists reduce prolactin secretion and are of potential clinical usefulness in the treatment of certain endocrinological disorders such as hyperprolinactinaemia. Dopamine receptor agonists may also be of value for their peripheral, cardiovascular and renal actions. For example, in the treatment of congestive heart failure and shock (Goldberg, 1972). Presynaptic dopamine receptors also occur on sympathetic nerve terminals in the periphery. The activation of these receptors leads to inhibition of dopamine release and this has led to the realisation that peripherally-acting dopamine receptor agonists might be of value as anti-hypertensive drugs (Langer and Dubocovich, 1979). Apart from their clinical usefulness, dopamine receptor agonists can tell us much about the topography and organization of the dopamine receptor, and of the physiological role of dopamine in, for example, the CNS.

ADTN

ADTN is the abbreviated name for 2-amino-6,7,-dihydroxy-1,2,3,4,-tetrahydronaphthalene, a potent dopamine receptor agonist which was developed in our own laboratories (Woodruff, 1971, 1978; Woodruff and others, 1979). ADTN is one of the most potent dopamine receptor agonists known in a whole variety of test systems. Its use has given us important clues to the active conformation of dopamine when it is acting at its receptor (or receptors).

From the following account, unless designated, all compounds referred to are the racemates. Dopamine can exist in extended (anti) or folded (gauche) conformations (Woodruff, 1971; Bustard and Egan, 1971; Rekker, Engel and Nys, 1972). In the extended conformation, there is the possibility of rotation about the phenyl-carbon bond which leads to the existence of two rotameric extremes, α and β (Cannon, 1975). Several years ago we studied the active conformation of dopamine at its receptor site, using rigid analogues of dopamine which contain the dopamine side chain in a fixed conformation. Thus, norsalsolinol contains the dopamine skeleton in a folded conformation whereas the extended conformations of dopamine are contained in the molecules of ADTN (β-rotamer) and the 2-amino-5,6,-dihydroxy-1,2,3,4,-tetrahydronaphthalene (iso-ADTN) (α-rotamer).

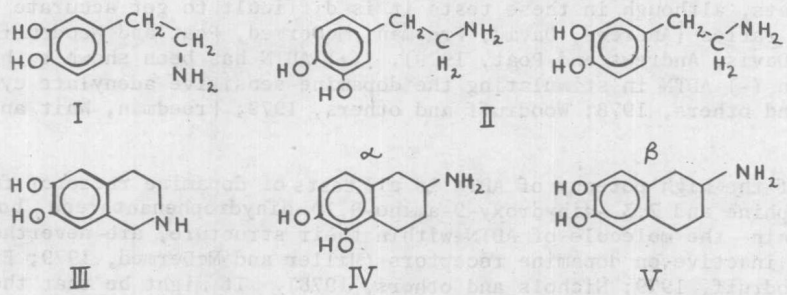

Fig. 1. Conformers of dopamine (I,II) and the structures of 3 rigid analogues. Norsalsolinol (III) corresponds to the folded conformer. ADTN (V) and iso-ADTN (IV) correspond respectively to the β and α rotamers of the extended form (II).