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Perspective

Future Directions in Dopaminergic Nervous System and Dopaminergic Agonists

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Introduction

Physiology. Although a biochemical role for dopamine was suspected as early as 1911,[1] it was not until 1957 that Blaschko[2] proposed that, apart from its being a biosynthetic precursor to norepinephrine, dopamine might have a separate, independent peripheral physiological role. Carlsson et al.[3] suggested central actions for dopamine and presented biochemical–pharmacological evidence to confirm that, indeed, dopamine per se is involved in brain biochemistry. In 1959, Bertler and Rosengreen[4] found that the regional distribution of dopamine does not parallel that of norepinephrine, which further suggests a separate physiological role for dopamine. Hornykiewicz and coworkers[5] presented two significant observations in human neurochemistry: (1) dopamine levels are greatly decreased in the corpus striatum and substantia nigra of parkinsonian patients; and (2) L-Dopa (the immediate biochemical precursor to dopamine), injected intravenously, improves the symptomatology in parkinsonian patients. Biochemical studies on the regional distribution of dopamine supported the concept of its role as a transmitter in the central nervous system, and Falk's formaldehyde fluorescence technique[7] permitted identification of a specific dopamine neuron system in the brain, with ascending fiber projections from dopamine-containing areas in the midbrain to regions of the basal ganglia. It became possible to differentiate chemically between dopamine and norepinephrine at the cellular level.[8,9] Thus, biochemical data on the localization of brain dopamine can be interpreted in terms of well-defined topography of central dopamine neuron systems. The current literature now implicates central dopamine- or dopamine-related physiological mechanisms in schizophrenia,[10,11] Parkinson's disease,[12] neuroleptic-induced tardive dyskinesias,[13] Huntington's chorea,[14] and a variety of other neurological conditions.[12] It has been reported[15] that anorexigenic effects in rats of certain ergot alkaloid derivatives is due to stimulation of central dopamine receptors and does not involve α or β adrenoceptors. Dopamine inhibits the release of prolactin by the pituitary gland.[16,17] Peripherally administered dopamine has a vasodilator effect on the renal vascular system, due to interaction with specific receptors in the vascular tissue.[18] It seems likely that dopamine has a physiological role in the kidney, and Goldberg[18] has cited considerable evidence that implicates dopamine in the regulation of renal excretion of sodium.

Dopamine dilates the coronary, cerebral, and mesenteric arteries,[12] but it minimally dilates the skeletal muscular vasculature. Overall the hemodynamic responses to dopamine are dose dependent;[12] at doses less than 10 (μg/kg)/min, dopamine lowers systemic blood pressure via selective vasodilation. However, at higher infusion rates [>20 (μg/kg)/min], pressor responses predominate, and under these conditions, dopamine is useful in treatment of shock. While the depressor actions of dopamine are

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(2) Blaschko, H. *Experientia* **1957**, *13*, 9.
(3) Carlsson, A.; Lindquist, M.; Magnusson, T. *Nature (London)*, **1957**, *180*, 1200.
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dopaminergic (i.e., they involve interaction with dopamine-specific receptors, the pressor response has been attributed to excitation of α adrenoceptors.[12] Thus, in the cardiovascular system, dopamine is classified as both a dopaminergic and a sympathomimetic. Intravenous dopamine produces a dose-related increase in inotropy and chronotropy.[12] However, in contrast to epinephrine and isoproterenol, dopamine elicits only a small increase in heart rate for each incremental increase in contractile force.[12] These effects have been ascribed to direct interaction with β_1 adrenoceptors and to an indirect action of release of norepinephrine from adrenergic nerve terminals.[12]

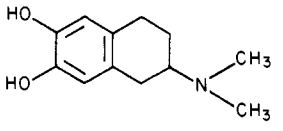
It would seem that dopamine would be a useful therapeutic agent. However, dopamine suffers some serious defects: (1) it is not dependably effective by the oral route and is best administered intravenously; (2) it is rapidly metabolically inactivated, and hence its systemic effects are transient; (3) it does not penetrate the blood–brain barrier; and (4) because of its broad variety of physiological actions (as described previously), administration of dopamine for correction of some specific defect can be expected to elicit a variety of additional responses, due to α and β adrenoceptor and dopaminergic receptor stimulation. Thus, side effects may be expected to be common and prominent in therapy with dopamine. Synthetic dopaminergic agonists now available or under study also suffer from some or most of these defects.

Dopamine Receptors

Classification. It is well established that there exist in animals (and, presumably, in humans) more than one type of dopamine receptor, differing physiologically and biochemically and also exhibiting qualitative and quantitative differences in response to different synthetic agonist molecules. Although the therapeutic significance of multiple dopamine receptors is not clear, it has been useful to subdivide them into D-1 and D-2 types: D-1 receptors are those which are linked to activation of adenylate cyclase (the stimulation of certain dopamine receptors results in the production of cyclic AMP); and D-2 receptors are not linked to this enzyme.[19] Despite the large numbers of synthetic dopamine analogues and congeners which have been studied, it has not yet been possible to design molecules which are consistently specific for D-1 or D-2 receptors, nor has it been possible to define a structure–activity relationship for D-1 or D-2 receptor agonists, which is generally applicable to the rather varied chemical structural types which show dopamine receptor-stimulant actions.

Langer and Dubocovich[20] have demonstrated the existence of presynaptic dopamine-specific receptors located on the axon terminals of postganglionic peripheral sympathetic neurons and have speculated as to the physiological significance of these presynaptic dopamine receptors. Long and co-workers[21] have established the presence of presynaptic dopamine receptors on an adrenergic nerve terminal (cardioaccelerator nerve) in the cat. Kohli et al.[22] have suggested that femoral vascular bed dilation in the dog produced by *N,N*-di-*n*-propyldopamine is due, at least in part, to effects of the drug on presynaptic dopamine receptors.

Presynaptic dopamine receptors ("autoreceptors") have been demonstrated in the central nervous system. Binding of agonists to pre- or postsynaptic dopamine receptors seems frequently to be a dose-dependent phenomenon. Thus, Seeman et al.[23] found that low concentrations of apomorphine bind primarily to presynaptic receptors in the striatum. It has been reported[24] that presynaptic binding of apomorphine is normal in schizophrenic brains, whereas postsynaptic binding of haloperidol (a dopamine blocker) is significantly elevated in the caudate and putamen of schizophrenic brains. Skirboll et al.[25] reported that the dopamine autoreceptor in the sustantia nigra is more sensitive to dopamine or to apomorphine (a classic exogenous dopaminergic agonist) than is the postsynaptic dopamine receptor in the striatum. Schizophrenia has been found to be dramatically improved by administration of low doses of apomorphine.[26] Since the underlying neurochemical defect in schizophrenia has been viewed as overactivity of dopamine neurons, apomorphine may exert its therapeutic effect through presynaptic inhibition of dopaminergic neurotransmission. Thus, physiologically, it may be inferred that the presynaptic dopamine receptors on a dopaminergic nerve terminal represent a negative feedback mechanism by which the neuron's own dopamine can interact with the presynaptic autoreceptors and shut down further nerve activity. Goodale et al.[27] have described central selective presynaptic dopaminergic agonist actions of TL-99 (1). Compounds of this pharmacologic



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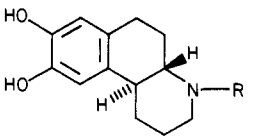

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type provide a unique alternative to classical neuroleptic therapy, not only of schizophrenia but also of other states, such as Huntington's chorea, hyperkinetic disorders, and tardive dyskinesias where dopaminergic neuronal hyperactivity is the pathophysiological alteration.

It is intriguing that dopaminergic agonists can, depending upon a predominant or exclusive pre- or postsynaptic locus of action, stimulate or inhibit the activity of a dopaminergic neuron.

Costall and Naylor[28] have noted that the literature describes numerous dopamine receptor subtypes based upon diverse techniques (behavioral, electrophysiological, biochemical, and others), using vertebrates and invertebrates. Evidence of classification is not always convincing, and correlation between the various subtypes is very difficult. Further, with terminologies ranging from DA-1, DA-2, D_1, D_2, DI, DE, DA_i, DA_e, DA_α, DA_β, D-1, D-2, and even D-3, the literature seems to be impossibly confusing. Costall and Naylor made a strong argument for indicating differences in dopamine receptors simply on the basis of their anatomic location (in which tissue; pre- or postsynaptic) and the spectrum of dopamine agonist–antagonist sensitivity.

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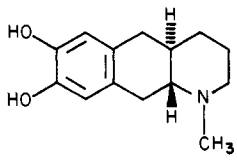
Design of Dopaminergic Drugs

General Comments. Cannon et al.[29] have reported synthetic dopamine agonists (e.g., 2) which exhibit some degree of selectivity and high potency at the presynaptic receptors on the cardioaccelerator nerve of the cat. The net effect is inhibition of cardioaccelerator nerve transmission and resultant slowing of heart rate. However, this presynaptic effect had not been predicted for these compounds, and it has not been possible to utilize these pharmacological and structural data to design additional compounds which are selective for pre- or postsynaptic sites. A number of chemical entities have been found (vide supra, vide infra) which exhibit mixed pre- and postsynaptic or predominant presynaptic effects, but attempts to prepare a "pure" postsynaptic dopaminergic agonist have not been successful.

Despite several attempts,[19,23,30,31] it has not been possible either to relate D-1 and/or D-2 receptors exclusively to pre- or postsynaptic loci or to identify and localize additional subtypes of multiple dopamine receptors.

Graphic Representation of Dopamine Receptors. An important aspect in the design of new dopaminergic agonists is to examine the possibility of finding agents which are relatively specific for a single subtype of dopamine receptor and to attempt to design dopaminergic agonists which lack adrenergic effects. A seeming prerequisite to these endeavors is the definition of the chemical details and the topography of dopamine receptors. Goldberg et al.[32] have presented a model for the renal vascular dopamine receptor, based upon studies of renal agonist activities of a considerable number of flexible, semirigid, and rigid dopamine congeners. This receptor model possesses defects, in that compound 3, which would



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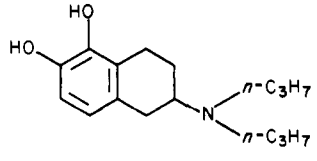

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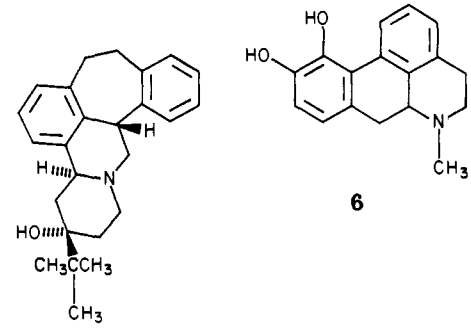
be predicted by the Goldberg model to be a potent renal vasodilator, is inert.[29] In addition, the aminotetralin 4, which would be predicted by the Goldberg model to exhibit at best a low activity, was reported by Goldberg[33] to be equipotent to dopamine in the renal vascular assay. The seeming anomalous renal vascular effects of 3 and 4 are not easily explained on the basis of a definition of some steric properties of the renal vascular receptor proposed by Grol and Rollema.[34] Structural–steric requirements for renal vascular dopaminergic agonist activity are as yet poorly understood, and it does not seem that any model of this receptor is adequate to explain observed agonist activity and inactivity of dopamine congeners, although Erhardt[35] has proposed a topographical model that permits rationalization of activities and inactivities of several different chemical structural types.

Humber et al.[36,37] have utilized an extensive structure–activity study of the dopamine antagonist butaclamol (5)



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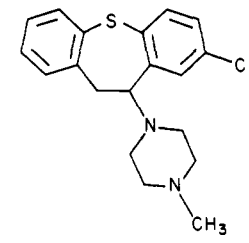

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to map the topography of "the" ("a"?) central dopamine receptor, using a cartesian coordinate model. This graphic model accomodates the dopaminergic agonist apomorphine (6), as well as the antagonists (+)-octoclothepin (7) and butaclamol (5). Moreover, this model reflects the observed inherent chirality of "the central dopamine receptor".[37] It may be erroneous (or, at least, premature) to define a dopamine receptor on the basis of subsite features that accomodate both agonist and antagonist molecules. There seem to be no conclusive data or evidence in the literature that confirm the hypothesis that both dopaminergic agonists and antagonists produce their in vivo effects by interaction at the same receptor site with the same set of subsites. Indeed, it seems equally possible, based upon the present state of knowledge, that dopamine antagonists may exert their blocking actions, including displacement of dopamine and of other agonists from their receptors, by alteration of the geometry of the agonist receptor site by allosteric attachment of the antagonist (i.e., at some site on the receptor protein molecule other than the agonist set of subsites). Seeman et al.[38] have cited biological data which are incompatible with the hypothesis that the "neuroleptic receptor" is the same as that which binds apomorphine, and Tedesco et al.[39] have concluded that "the identity of the [central] dopamine agonist receptor with the antagonist receptor, however, remains controversial". Until more is known about the biochemical nature of dopamine antagonism, it may be prudent to utilize only biological data on dopamine agonists in the definition and depiction of dopamine agonist receptors.

Prodrugs. The undependable, capricious, or poor absorption across the wall of the gut of dopamine, apomorphine, and catechol-derived congeners of these has been related to the undesirable partition properties con-

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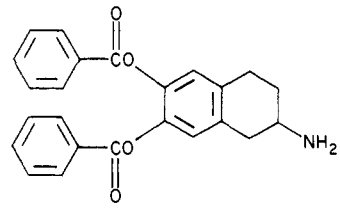
ferred upon the molecules by the highly hydrophilic, lipophobic catechol moiety. This moiety has also been implicated in the extremely short duration of action (rapid metabolic inactivation) and in the frequent inability of catechol-derived congeners (especially primary amines) to penetrate the blood–brain barrier. Borgman et al.[40] have described sterically hindered diester derivatives of apomorphine having properties of lipophilic prodrugs. These compounds provide decidedly prolonged activity as depot sources of apomorphine in the body. They are less potent than apomorphine and they exhibit a lag period before eliciting their CNS effects (sterotyped gnawing and unilateral rotation) similar to that produced by apomorphine. They owe their activity in vivo to ester cleavage to liberate apomorphine itself. Apomorphine and dopamine (but not their esters) stimulate adenylate cyclase activity in mouse striatal homogenates.[41] However, none of the esters demonstrated appreciable or consistent activities when given by gastric tube. Horn and co-workers[42] found that the dibenzoate ester of A-6,7-DTN (8), a potent dopami-



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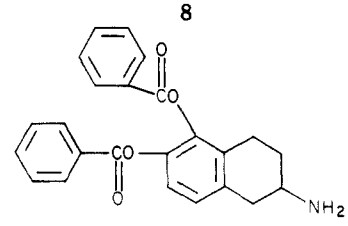

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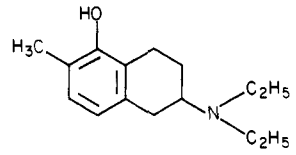
nergic agonist, provides for selective accumulation of free A-6,7-DTN in the corpus striatum (in contrast to the cerebellum) of rodents. Accumulation is slow but of long duration. Similar results have been reported[43] for the dibenzoate ester of A-5,6-DTN (9). It seems that catechol ester types of dopaminergic prodrugs suffer from inherent defects: erratic or poor absorption by the oral route and frequent poor water solubility, even of the salt form. In addition, apomorphine, most of the aminotetralins (typified by 8 and 9), and dopamine itself produce a broad spectrum of dopaminergic effects as well as some adrenergic actions. A greater degree of pharmacologic specificity would be highly desirable. This specificity seems best attainable with prodrugs which are new chemical entities, not merely latentiated forms of currently used dopaminergic drugs. A promising structural variant is the aminotetralin 10, which seems to be specific for peripheral (inhibition of cardioaccelerator nerve) and central (inhibition of CNS Dopa accumulation) presynaptic dopamine receptors but which has little effect on postsynaptic receptors, as manifested by its failure to induce stereotyped behavior in rodents and emesis in dogs.[44,45] Because 10



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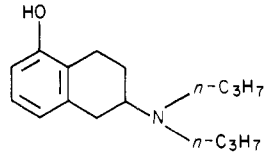
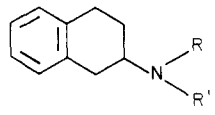
lacks a catechol moiety, it is chemically more stable and it shows a prolonged duration of action. It seems to be well absorbed across the wall of the ileum of the cat.[44] Binding studies[45] strongly suggest that 10 does not directly activate presynaptic dopamine receptors but that it is first metabolized in vivo to an active molecular species. Thus, it appears that it is possible to obtain novel dopaminergic prodrugs which deviate structurally from catechol systems and which may exhibit considerable specificity of action. Compounds like 10 further support findings that a catechol moiety is not essential for dopamine agonist effects. McDermed and co-workers[46] first reported potent dopamine receptor agonist activity for a 5-hydroxy-2-aminotetralin 11. This compound would be expected to display



11

chemical stability, improved resistance to metabolic inactivation ,and perhaps improved oral efficacy, although these properties have not been reported in the literature. However, 11 displays little specificity of effect, showing a variety of postsynaptic actions. It does not seem likely that 11 is a prodrug, being converted in vivo into a catechol system or other active metabolite. Rusterholz and coworkers[47] have found a variety of postsynaptic dopaminergic effects in a series of nonoxygenated 2-aminotetralins 12 and 2-aminoindans 13 and have presented the possi-



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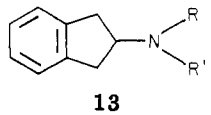

13

bility that these agents may be metabolically activated. Fuller, Baker, and Molloy[48] have previously suggested that systems like 12 and 13 may be metabolically ring hydroxylated. Wong and Bymaster[49] have found that a proposed metabolite of lergotrile (14), the 13-hydroxy derivative 15, is a more potent inhibitor of dopamine binding to calf caudate homogenates than is the parent compound 14, which leads to the speculation that a portion

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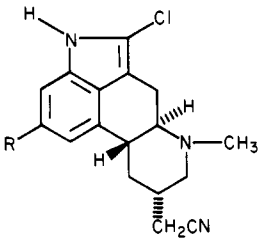
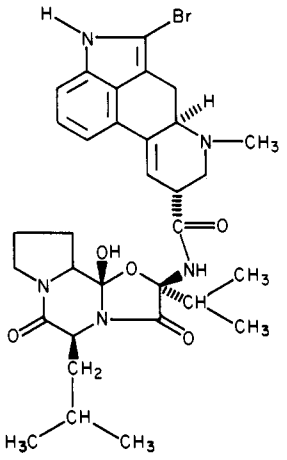


14, R = H
15, R = OH

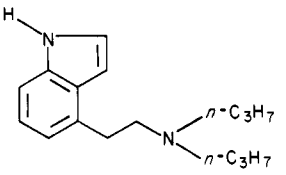
of the dopaminergic effect of lergotrile is produced by its metabolite and that lergotrile is, at least in part, a dopaminergic prodrug. Bromocriptine (16), a semisynthetic



16

ergot derivative bearing a complicated peptide moiety, has some clinically useful dopamine agonist properties.[50] Metabolic activation has been suggested for bromocriptine.[51] However, more recent studies cited by Thorner et al.[50] suggest that some dopaminomimetic effects of bromocriptine are due to the intact molecule and not to metabolites.

A fragment of the lergotrile molecule, 4-[2-(di-*n*-propylamino)ethyl]indole (17), exhibits some potent dop-

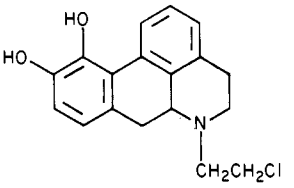


17

amine-like actions, including some at presynaptic receptor sites.[52] Like lergotrile, 17 required 30–40 min following intravenous administration to attain maximal pharmacologic effect. This may indicate metabolic activation, perhaps by hydroxylation of the benzene ring. Thus, this simple indole derivative may also represent a prodrug to a dopaminergic agonist.

It seems apparent that for drug design, a prodrug strategy, involving more than hydrolysis of ester-masked catechol systems, may be expected to provide orally effective, chemically stable, long-acting, pharmacologically specific dopaminergics which can display any of a wide variety of central or peripheral actions. It may be expected that even more novel dopaminergic prodrug structures will be found having even more interesting/useful therapeutic properties.

Irreversible Dopamine Receptor Blockade. A novel approach to dopamine antagonism is typified by Neumeyer's design of *N*-(chloroethyl)norapomorphine (18).[53]



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It is proposed[53] that this molecule alkylates the dopamine receptor(s) on dopamine-sensitive adenylate cyclase which normally interacts with dopamine itself. The compound is said to produce selective, potent, and long-lasting (up to 5 days) behavioral and biochemical effects in rodents, indicative of dopamine receptor blockade. More extensive studies[54] support the contention that 18 is a unique long-acting antagonist of dopamine in the brain. If selectivity for dopamine receptors can be further supported, 18 and similar agents should be useful tools in characterization and in isolation of dopamine receptors, both centrally and peripherally. Moreover, compounds typified by 18 may have clinical applications in a variety of psychotic, dyskinetic, and other neuropsychiatric disorders where blockade of dopamine receptors seems indicated. Usefulness of such dopamine receptor blockers will be enhanced by some degree of selectivity of action, which may be attainable by incorporation of the *N*-(chloroethyl) moiety into other dopaminergic ring systems. This seems a fertile field for chemical and biological research.

Future Directions for Therapeutic Exploitation of Dopaminergic Agents

The following represent some possibilities for therapeutic intervention with drugs affecting dopamine receptors.

Heart. Some dopamine receptor agonists decrease heart rate[55,56] and presumably they will decrease after-load and thus will decrease the oxygen consumption of cardiac muscle. It seems advantageous to develop dopaminergic drugs that lack a noradrenergic component of action and thus will produce a considerable decrease in heart rate without significantly decreasing cardiac output.

Blood Pressure. A number of dopamine receptor agonists (including some ergot alkaloid derivatives) have been demonstrated to lower arterial pressure by possible actions at many sites. Dopamine receptor stimulation in renal, mesenteric, and cerebral arterial vessels produces vasodilation. Many dopaminergic agonists have been found to interact with sympathetic nerve terminals to decrease norepinephrine release, and these agents are more effective at lower frequencies (2 Hz) of neuronal conduction than at higher frequencies (10 Hz). This frequency selectivity may be useful for developing agents with di-

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minished liability to produce postural hypotension. Also, dopamine receptor agonists have been shown to lower arterial pressure following injection of small doses into vertebral arteries.[57] The mechanism of site of action for decreasing the activity of the sympathetic nervous system by a central action is totally unknown, but it appears to involve dopamine receptors on neural elements within the brain.[58,59]

Kidney. A small number of dopamine analogues increase renal blood flow. Dopamine receptor activation in the kidney seems to increase excretion of sodium, but whether this response is related to increased renal blood flow or to some other physiological phenomenon remains to be established. It is possible that dopaminergic agonists may decrease plasma renin levels. In a clinical study involving only seven subjects, bromocriptine (16) reduced plasma renin activity by 20–40%.[60]

Central Nervous System. (a) Postsynaptic Sites. The relationship of degeneration of dopamine pathways in the substantia nigra to the etiology of Parkinson's disease is well established. Dopamine receptor agonists that act at postsynaptic sites in the caudate nucleus have shown efficacy in the therapy of Parkinson's disease. However, drugs do not exist which are selective for postsynaptic receptor sites, and such agents would be of great value.

(b) Presynaptic Sites. It seems possible to design agents which are selective for presynaptic sites of dopaminergic neurons within the central nervous system. Thus, it would be possible to design neuroleptic agents whose mechanism of action involves inhibition of transmission in dopaminergic pathways. Presumably, selectivity for the limbic system would be a desirable property, but whether such selectivity is possible has not yet been demonstrated.

Relationship of Dopamine to Other Neurotransmitters. Dopamine receptor agonists may modify the effect/function of other neurotransmitters (acetylcholine,[61,62] serotonin,[63,64] and γ-aminobutyric acid)[65] within the central nervous system. Whether equal or variable sensitivity to dopaminergic agonists will be exhibited by neurons whose effects are mediated by the various neurotransmitters will be an area for future investigation. Dopamine receptor agonists offer the possibility to modify various transmitter functions in a manner that has not been recognized for any other pharmacological class of drugs. The possibilities for modification of behavior seem almost limitless, and unique opportunities for advances in psychopharmacotherapy seem likely.

Endocrine System. The postsynaptic action of dopaminergic agonists in lowering prolactin levels has been cited above. Levels of other pituitary hormones (growth hormone, FSH) may also be altered.

Summary

The physiological and pharmacological roles of pre- and postsynaptic dopamine receptors in modification of neuronal transmission centrally and peripherally will be subjects for intense research during the next decade. As enumerated by Langer,[66] dopamine-sensitive receptors have been described that may inhibit or facilitate release of neurotransmitter substances. It is likely that dopaminergic agents that are highly selective for specific transmitters will be discovered. Likewise, dopaminergic agents that are nonselective (i.e., that modify the function of two or more neurotransmitters) may offer many opportunities for modification of behavior.

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