Ann. Rev. Pharmacol. Toxicol. 1978. 18:57–79

A COMPARISON OF THE VASCULAR DOPAMINE RECEPTOR WITH OTHER DOPAMINE RECEPTORS

❖6705

Leon I. Goldberg, Paul H. Volkman, and Jai D. Kohli
Committee on Clinical Pharmacology, Departments of Pharmacological and Physiological Sciences and Medicine, University of Chicago, Chicago, Illinois 60637

INTRODUCTION

The dopamine (DA) receptor has had an interesting history. Unusual actions were attributed to the catecholamine for many years, but these effects were generally considered to be manifestations of activation of α- and β-adrenergic receptors rather than results of action of DA on a specific receptor (1). The pendulum now has swung the other way. The literature is replete with papers reporting the existence of DA receptors subserving specialized functions in a wide variety of organs and species (2–4). A pertinent question which must be answered is whether the same DA receptor subserves all reported functions or whether there is a family of specific, but different, DA receptors (5). In this review we are concerned primarily with similarities and differences in the effects of agonists and antagonists acting on the DA receptor in the canine renal vascular bed and on selected DA receptors described in other organs and species. The actions of DA on a specific vascular receptor and on other receptors in the cardiovascular system have been the subject of previous reviews (1, 6, 7).

VASCULAR DA RECEPTOR

Methods

The experimental procedures for investigating putative DA agonists and antagonists in the canine renal vascular bed have been used with minor modifications for the past 15 years (8, 9). Specific details are presented because variations in technique have, on occasion, resulted in contrary data (1, 10, 11). Mongrel dogs are anesthetized with pentobarbital, 30 mg/kg intravenously, or a combination of pentobarbital, 15 mg/kg, and barbital, 20 mg/kg. Supplemental anesthetic is administered as

0362-1642/78/0415-0057$01.00

needed to maintain light anesthesia. The kidney is exposed by flank incision and retroperitoneal dissection and an electromagnetic flow probe is placed on the renal artery. A 23-gauge hypodermic needle, bent to an angle of approximately 80° and connected to a constant infusion system, is inserted into the artery, proximal to the flow probe. The system is arranged for injection of drugs through appropriate stopcocks. Arterial blood pressure is measured from a femoral or carotid artery, and blood flow and blood pressure are simultaneously recorded on an appropriate polygraph, the pens of which are carefully aligned to produce synchronized recordings. Simultaneous measurement of blood pressure and blood flow is essential to distinguish effects due to drugs on the renal vasculature from possible changes in flow resulting from alterations in arterial blood pressure. When DA is injected into the renal artery, a biphasic effect is usually observed. With smaller doses initial transient vasoconstriction is seen and then more prolonged vasodilation. With larger doses, vasoconstriction predominates. The vasoconstrictor effect can be eliminated by phenoxybenzamine (POB). Accordingly, in our studies of the vasodilating actions of DA and potential DA agonists, POB is administered intraarterially in a dose of 5 mg/kg over a 15–30 min period. If the vasoconstrictor effect of *l*-norepinephrine (1 μg) injected intraarterially is not reversed, an additional 5mg/kg of POB is administered. After POB, a complete dose-response curve of DA can be recorded without interference from opposing vasoconstriction.

Figure 1 illustrates tracings of renal blood flow recordings obtained from two experiments to demonstrate how a new chemical entity, X, is characterized as a DA vascular receptor agonist and how vasodilating actions by other mechanisms are ruled out. After administration of POB, DA, isoproterenol, bradykinin, compound X, and acetylcholine produced approximately equivalent increments in renal blood flow. After administration of propranolol, 2.5 mg/kg intraarterially, only the effects of isoproterenol are antagonized. After administration of atropine, only the effects of acetylcholine are blocked. Simultaneous administration of haloperidol, 1.4 X 10^{-7} M, selectively attenuates only DA and compound X. Effects of histamine can be ruled out in a similar manner by using antihistaminic agents. Serotonin does not produce DA-like renal vasodilation.

DA and other agonists active on the renal vascular receptor exhibit the same order of potency as vasodilators of the mesenteric bed, indicating that the same receptor is present in both vascular areas (9, 12). In contrast, DA is an extremely weak vasodilator when injected into the POB-treated femoral vascular bed, provided that care has been taken to eliminate effects of cutaneous shunts by occluding the paw circulation and to minimize neurogenic effects by cutting the femoral and sciatic nerves.

An estimate of relative vasoconstrictor activity can be obtained by administering the compounds into the femoral vascular bed without prior administration of POB. Relative β_2-adrenergic activity can be determined by injecting the compounds into the femoral vascular bed after administration of POB (8, 13). For estimation of relative β_1-adrenergic activity, the drugs are administered intravenously to an anesthetized dog prepared for measurement of right ventricular contractile force with a Walton-Brodie strain gauge arch (14).

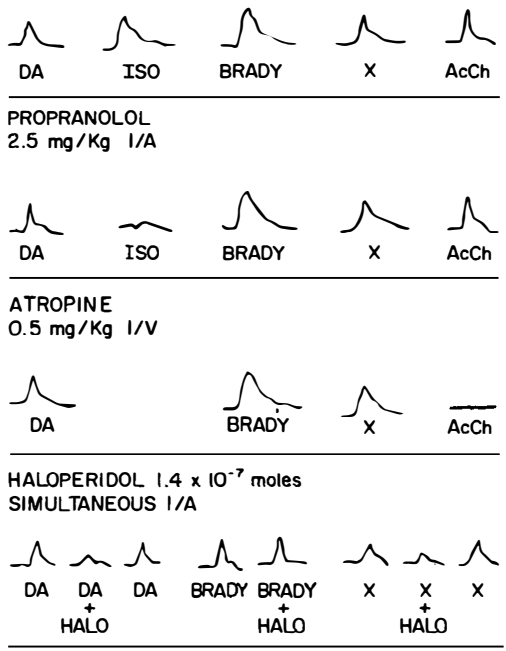

Figure 1 Effects of dopamine (DA), isoproterenol (ISO), bradykinin (BRADY), a dopamine-like drug (X), and acetylcholine (AcCh) on renal blood flow in phenoxybenzamine-treated dogs (5 mg/kg intraarterially). For details see text.

Agonists

The chemical requirements for agonists active on vascular DA receptors have been investigated by the procedures described above. Active compounds and their relative potencies are shown in Table 1. Selected inactive compounds are also shown in Table 1. A compound was considered as inactive if in at least two experiments it did not cause DA-like renal vasodilation in doses 1000 times the threshold dose of DA.

In the first structure-activity investigation, 44 phenylethylamines were studied (15). Only epinine (N-methyl dopamine) was active. Benzene ring substitutions, other than OH groups at the 3 and 4 positions, and substitutions at the α- or β-carbon resulted in inactive compounds. Mono substitution of the amino group with hydrocarbons larger than methyl (ethyl, *n*-propyl, isopropyl) yielded inactive compounds. N,N-dimethyl DA was inactive, as was N,N,N-trimethyl DA. We recently reported that N,N-di-*n*-propyl DA was an active agonist with an ED_{50} approximately 30-fold higher than that of DA (16). Interestingly, this analogue differs from DA and epinine in lacking β_1-adrenergic activity. Finally, analogues of DA with either 1, 3, or 4 carbon atoms on the side chain are inactive (J. D. Kohli, P. H. Volkman, L. I. Goldberg, and R. M. Pinder, unpublished data).

The results demonstrate that only a few substitutions on the phenylethylamine molecule result in active DA vascular receptor agonists. However, they provide little insight into the conformational requirements of the receptor, since the side chain of DA possesses unlimited flexibility and unrestricted rotation around the β-carbon-phenyl bond. Accurate estimation of the conformation at the vascular DA receptor could be obtained by investigating a series of analogues in which the side chain is fixed into a particular conformation.

The apomorphine molecule contains the structure of N-methyl DA with the side chain fully extended and the amino group *trans* to the catechol moiety, in an α-rotameric conformation (Figure 2). Apomorphine is active on vascular DA receptors, although it is much weaker than DA and appears to be a partial agonist (15, 17, 18). 6-N-*n*-propylnorapomorphine is more potent than apomorphine and appears to be a full agonist at vascular DA receptors with one thirtieth to one fiftieth the potency of DA (12). Isoapomorphine contains the structure of N-methyl DA in a β-rotameric conformation (Figure 2); this compound was inactive as a vascular DA agonist (18).

On the basis of the above results alone, it would appear that the preferred conformation for activation of the vascular DA receptor is the α-rotamer. However, a recent investigation (13) of a series of 2-aminotetralins demonstrated that the β-rotamer is the active conformation. 2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (A-6,7-DTN) (Figure 2) produces renal and mesenteric vasodilation with a potency equivalent to DA (12). This compound does not act on β_2-adrenergic receptors. The semi-rigid analogue of the α-rotamer, 2-amino-5,6-dihydroxy-1,2,3,4,-tetrahydronaphthalene (A-5,6 DTN) (Figure 2) is inactive on the DA vascular receptor, but is active as a β_2-adrenergic agonist. As demonstrated with the phenylethylamine molecule, N-methyl-A-6,7-DTN is also active at the vascular dopamine receptor while N,N-dimethyl-A-6,7-DTN is inactive. These data indicate that the preferred conformation for activation of the vascular DA receptor, at least with respect to the aminotetralin series, is the β-rotamer, while the preferred conformation for activation of β_2-adrenergic receptors is the α-rotamer.

Obviously, the above generalization does not apply to the apomorphines. As already mentioned, the β-rotamer, isoapomorphine, is inactive while the α-rotamer, apomorphine, is at least partially active. Other factors may be involved in the

Table 1 Agonists acting on the vascular dopamine receptor and their relative potency and selected inactive compounds[a]

Agonists	Potency		Inactive compounds			
Dopamine	1.0	(15)	Norepinephrine	(15)	Bromocryptine	(133)
Epinine (n-methyldopamine)	1.0	(15)	Epinephrine	(15)	Lergotrile	(133)
A-6,7-DTN	1.0	(12, 13)	α-Methyl dopamine	(15)	Piribedil	(133)
N-methyl-A-6,7-DTN	0.5–1	(13)	N,N-dimethyl dopamine	(15)	S-584	(133)
N,N-di-n-propyl dopamine	0.03	(16)	A-5,6-DTN	(13)		
6-N-n-propylnorapomorphine	0.02	(12)	N-methyl-A-5,6-DTN	(13)		
Apomorphine	0.01	(12, 18)	N,N-dimethyl-A-5,6-DTN	(13)		
	(partial agonist)		Amphetamine	(15)		

[a]Reference numbers are listed in parentheses.

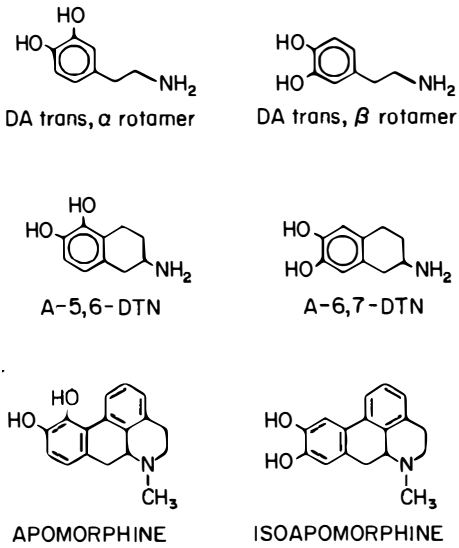

Figure 2 Conformations of dopamine and their structural relationships with 2-amino-dihydroxytetralins, apomorphine, and isoapomorphine.

inactivity of isoapomorphine, such as steric hindrance to interaction with the amino group, or inability of the unshared pair of electrons on the nitrogen moiety to rotate to the proper orientation for interaction with the receptor. Further studies with other rigid DA analogues will be required to elucidate this point.

Antagonists

Study of antagonists is more difficult than agonists because of the necessity of proving that attenuation of DA-induced renal vasodilation is due to antagonism of DA receptors and not to other actions of the drug. The first antagonist investigated, haloperidol, was found to be a specific antagonist, but its specificity was limited to a relatively narrow range (9). When a dose of haloperidol, 2×10^{-7} M, was injected immediately prior to the injection of the vasodilator, the renal vasodilation produced by DA was attenuated (not completely blocked) without affecting the vasodilation produced by isoproterenol or bradykinin. If a larger dose of haloperidol was used, a greater attenuation of the DA-induced renal vasodilation occurred, but the effect of the other vasodilators was also reduced. In these initial studies it was found that haloperidol produced a transient effect and, thus, subsequent experiments were carried out with simultaneous injections of haloperidol and the vasodilators. With this procedure, the maximum dose of haloperidol that could be used was 1.4×10^{-7} M because larger doses also attenuated the effects of bradykinin and isoproterenol. In the same study, haloperidol was found to attenuate selectively the effects of DA-induced superior mesenteric vasodilation and to attenuate selectively the vasodilation produced by epinine to the same extent as DA.

The above discussion should make it apparent that two parameters are important in the consideration of antagonists: potency and specificity. In an attempt to deal with this point, we have defined the range of specificity of an antagonist as the minimum dose needed to block isoproterenol or bradykinin divided by the minimum dose needed to block responses to DA. Table 2 lists antagonists studied, relative potency, and limits of specificity. It should be noted that haloperidol is approximately twice as potent as chlorpromazine (19). Both agents have a narrow range of specificity. Bulbocapnine is an active vascular DA antagonist (20, 21) with a range of specificity greater than haloperidol. Day & Blower (22) reported that intravenous administration of metoclopramide antagonized DA-induced renal vasodilation. We have confirmed the efficacy of metoclopramide with intraarterial administration and have shown that this antagonist and the structurally related sulpiride have a greater range of specificity than haloperidol (23). Bell et al (17) reported that ergometrine, administered into the aorta, produced a specific and long-lasting blockade of responses to intraaortic administration of DA. We have been unable to confirm these data utilizing our techniques with injections into the renal artery. Setler et al (21) and Imbs et al (24) reported that the butyrophenone, pimozide, was inactive as a vascular DA antagonist. Because pimozide is insoluble in aqueous solutions and solutions used to dissolve the drug affect renal blood flow, we could not perform adequate experiments with intrarenal injections of this agent.

DA RECEPTORS IN THE GASTROINTESTINAL TRACT, PANCREAS, AND SUBMANDIBULAR GLAND

The preceding section defines the responses of the renal vascular DA receptor which is clearly in a postsynaptic location (1). Several recent studies have suggested the presence of postsynaptic DA receptors in the gastrointestinal tract and exocrine glands. DeCarle & Christensen (25), in a study of isolated smooth muscle strips taken from the distal esophagus and the cardioesophageal junction of opossum, found that DA and epinine caused a dose-related inhibition of lower esophageal sphincter (LES) tone and dose-related inhibition of the esophageal body "off" response (the contraction occurring at the end of electrical field stimulation). The above effects of DA and epinine were inhibited by bulbocapnine and haloperidol, but not by propranolol or POB. In two in vivo studies of the esophageal body and LES of opossum (26, 27), DA, isoproterenol, and phenylephrine produced dose-related relaxations of the LES, but the responses to isoproterenol and phenylephrine were blocked by propranolol and phentolamine, respectively, while the responses to DA were unaffected by the α and β antagonists or by atropine or tetrodotoxin. The responses to DA were attenuated by haloperidol and bulbocapnine. Valenzuela (28), in an in vivo study of the effect of DA on canine intragastric pressure, found that both DA and norepinephrine produced dose-related decreases in intragastric pressure, but the effects of norepinephrine were blocked by propranolol plus POB, which did not affect responses to DA. Pimozide and metoclopramide completely antagonized the effects of DA (28). In two recent studies of the pharmacology of metoclopramide on isolated strips of guinea pig ileum (29) or stomach (30), the authors

Table 2 Antagonists of the dopamine vascular receptor with relative potency and ranges of specificity[a]

Antagonist	Relative potency[b] (mol)	Range of specificity[c]
Haloperidol	1.4×10^{-7}	< 2 (9)
Chlorpromazine	2.5×10^{-7}	< 2 (19)
Prochlorperazine	2.5×10^{-7}	< 2 (19)
Trifluoperazine	2.5×10^{-7}	< 2 (19)
Fluphenazine	2.5×10^{-7}	< 2 (19)
Thioridazine	5.0×10^{-7}	< 2 (19)
Bulbocapnine	4.7×10^{-8}	~ 8 (20)
Metoclopramide	1.5×10^{-6}	>10 (23)
Sulpiride	2.9×10^{-8}	>10 (23)

[a] Reference numbers are listed in parentheses.
[b] Dose to produce 3–4× shift in DA dose-response curves.
[c] $\frac{\text{(minimal dose attenuating vasodilating responses of bradykinin or isoproterenol)}}{\text{minimal dose attenuating vasodilating responses of DA}}$.

pointed out that metoclopramide enhances responses to various agonists such as acetylcholine, substance P, histamine, and barium chloride, and seems to enhance acetylcholine release. The authors expressed doubt that blockade of DA receptors was involved in the effects of metoclopramide on the gastrointestinal tract, but in neither paper were the effects of DA examined. Despite some apparent controversy with respect to the effects of metoclopramide, the available evidence indicates that there are specific DA inhibitory receptors in the gut and that activation of these receptors decreases intestinal motility; blockade by metoclopramide stimulates gastric emptying and intestinal motility in man (31–33) and in the rat (34). The putative gut DA receptor is similar to the vascular DA receptor in terms of an equal response to DA and epinine and antagonism by haloperidol, bulbocapnine, and metoclopramide. Antagonism of the gut receptor by pimozide is a possible discrepancy. A detailed structure-activity study of DA agonists on the gut has not been reported.

An early report of the effects of sympathomimetic amines on canine pancreatic secretion (35) showed that DA and epinine, as well as metatyramine stimulated pancreatic secretion. Hashimoto et al (36) reported that *l*-dopa or DA, injected intraarterially, increased secretion from the isolated, blood-perfused, canine pancreas, an effect not blocked by atropine, phentolamine, propranolol, guanethidine, or tetrodotoxin. Isoproterenol and norepinephrine did not increase pancreatic secretion. The secretory response to DA was attenuated by haloperidol in dogs pretreated with phentolamine and propranolol (37). Apomorphine apparently acted as a partial DA agonist in this system (38). A recent report by Bastie et al (39) confirmed the above results. Thus, there is some support for stimulatory DA receptors on pancreatic exocrine cells, in terms of equal responsiveness to DA and epinine, the partial agonist character of apomorphine, and block by haloperidol. Apparently, further work needs to be done before this DA receptor may be compared to the receptors

in other systems. The possibility of a specific DA receptor influencing guinea pig submandibular gland amylase secretion has been proposed on the basis of the secretory response to DA, but not to norepinephrine and its inhibition by apomorphine, haloperidol, pimozide, and fluspirilene (40). The presence of such a receptor would be consistent with a DA receptor stimulating pancreatic amylase secretion, but again, the characterization of this receptor is, as yet, fragmentary.

In summary, there are indications for the presence of specific, apparently postsynaptic, receptors for DA in the esophagus, stomach, and small intestine, as well as the pancreas and submandibular glands. To the limited extent that structure-activity studies have been done, these DA receptors appear similar to the renal vascular DA receptors, in responsiveness to DA, epinine, apomorphine, haloperidol, bulbocapnine, and metoclopramide. These tissues may represent useful systems on which to study potential new DA agonists or antagonists.

PERIPHERAL NERVOUS SYSTEM DA RECEPTORS

Postganglionic Sympathetic Nerve

Norepinephrine and other α-adrenergic agonists have been shown repeatedly to inhibit release of tritiated norepinephrine from postganglionic sympathetic nerve preparations made from a variety of organs in different species, leading to the view that perineuronal norepinephrine (exogenous or released from the neurons) acts on the presynaptic inhibitory α-adrenergic receptor to inhibit the release of norepinephrine following nerve stimulation (41–44). Comparisons of the relative activities of α-receptor agonists demonstrated differences in activity at the presynaptic versus postsynaptic sites (45–47). Based on these observations, Langer (46) proposed that α-receptors at the two sites may be different and may be subclassified as α_1 at the postsynaptic and α_2 at the presynaptic sites. Other investigators provided support for this hypothesis (48–53).

Using similar techniques, Langer and his colleagues postulated (46, 47) that the postganglionic sympathetic nerve also contained DA receptors. First, DA and norepinephrine were found to be equipotent at presynaptic sites, whereas, DA is one fiftieth to one one-hundredth as potent as norepinephrine at postsynaptic sites. Second, apomorphine was at least as potent as DA at the presynaptic sites. Third, phentolamine antagonized the presynaptic effects of norepinephrine in concentrations that did not affect DA and apomorphine; in contrast, chlorpromazine and pimozide antagonized DA and apomorphine in concentrations that did not affect norepinephrine (54).

There is, however, considerable controversy concerning the existence of separate DA and α-presynaptic receptors and concerning the possible physiological role of DA at this site. In support of their concept, Enero & Langer (54) reported that chlorpromazine and pimozide, unlike phentolamine and POB, did not increase transmitter release and on this basis concluded that DA presynaptic receptor had a different location and function than the presynaptic α-receptor. However, results in other species are not consistent with such an assumption (55–57).

Of importance to the present review, the equivalent potency of apomorphine and DA in many of the above studies suggests that the vascular DA receptor and the presynaptic receptor are different. Furthermore, Long and his colleagues demonstrated that DA analogues, inactive as vascular DA receptor agonists, acted at the presynaptic nerve to inhibit the effect of nerve stimulation on several effector organs (58–61). Ilhan et al reported that N,N-dimethyl DA (60), apomorphine, and 5,6-dihydroxy-2-dimethylaminotetralin (59, 61) were similar to DA in inhibiting the increase in heart rate resulting from stimulation of the postganglionic cardioaccelerator nerve in the cat. Comparison of the effects of α-adrenergic antagonists (phentolamine and POB) and DA antagonists (bulbocapnine, pimozide, and chlorpromazine) suggested to these authors that the analogues were acting on a specific DA presynaptic receptor (58–62). More recently, however, Kitzen et al (63) were unable to confirm this hypothesis in similar experiments utilizing N,N-dimethyl DA in the dog and concluded that N,N-dimethyl DA may inhibit the sympathetic postganglionic nerve by acting on either α- or DA-presynaptic receptors.

Sympathetic Ganglia

DA, epinephrine, and norepinephrine inhibit transmission in the sympathetic ganglia (64, 65). Two mechanisms may be involved. First, presynaptic stimulation may release a catecholamine (DA or NE, depending on the species) (66–67a) from the small intensely fluorescent (SIF) cells, mediating the slow inhibitory postsynaptic potential (S-IPSP) (68, 68a). Second, the catecholamine may block the presynaptic release of acetylcholine, thus effectively blocking ganglionic transmission (68b). However, neither the catecholamine involved endogenously nor the type of receptor subserving this function in the ganglia has been clearly identified.

Although the release of DA or its metabolites was not demonstrated, Libet (68, 68c) and Libet & Tosaka (69) concluded in electrophysiological studies that DA was involved in the mediation of the slow inhibitory postsynaptic potential (S-IPSP) and was by far the most, if not the only, effective catecholamine involved in facilitation of the slow excitatory postsynaptic (S-EPSP). Based on the relative activities of DA, norepinephrine, epinephrine, bulbocapnine, and phenoxybenzamine, the authors suggested that in the rabbit superior cervical ganglion (SCG) "the α-type adrenergic receptor for the facilitatory effect (on S-EPSP) is apparently more specialized for DA and is presumably different from the receptors that mediate the S-IPSP." Measuring adenosine 3',5'-monophosphate (cAMP) levels in response to exogenous catecholamines, Kababian & Greengard found DA to be equipotent to or more potent than norepinephrine in activating adenylate cyclase in the bovine SCG (70), providing support for a DA receptor in the rabbit SCG (71). However, their findings with antagonists were not consistent with this hypothesis. Haloperidol and chlorpromazine were weaker antagonists than phentolamine and POB (72). Furthermore, Greengard & Kababian (72a) suggested that the S-IPSP is actually generated by an effect of DA on cAMP and resultant effect on the membrane protein kinase; this view has been challenged recently (72b).

In view of the indirect evidence advanced in support of DA as the transmitter in the rabbit SCG in the above investigations, it is important to note that Noon et al

(73) failed to detect the release of DA or its metabolites from the rabbit SCG following stimulation of the cervical sympathetic nerve.

Another independent line of investigation that lent support to the hypothesis of DA receptors in the sympathetic ganglia came from experiments directed toward explaining DA-induced neurogenic vasodilation in the isolated canine hind limb (14). Bogaert & De Schaepdryver (74) suggested that inhibition of ganglionic transmission by DA may be the basis of the DA-induced femoral vasodilation. This was confirmed by Willems (75) by recording the postganglionic activity in response to preganglionic stimulation of the lumbar sympathetic trunk of the dog before and after intraaortic administration of DA and DA agonists and antagonists. It was found that DA, norepinephrine, epinine, and apomorphine were equipotent in this preparation. Moreover, it was noted that phentolamine preferentially blocked the effects of norepinephrine while haloperidol, pimozide, and chlorpromazine were more effective against DA than against norepinephrine. These results have since been confirmed by measurements of perfusion pressure changes in isolated vascular beds (76) and, thus, provide evidence that there are specific DA receptors in the dog sympathetic ganglia.

To summarize this section on sympathetic ganglia, the available evidence supports the presence of specific DA receptors. However, in view of the observation that apomorphine is equipotent to DA and that DA effects are antagonized by pimozide suggest that the receptor in ganglia may be different from the renal vascular DA receptor. Additional studies with agonists and antagonists would provide further clarification.

CENTRAL NERVOUS SYSTEM DA RECEPTORS

DA-Sensitive Adenylate Cyclase

Stimulation of cAMP production in response to DA and putative DA agonists, and the blockade of this response in brain homogenates is widely used as a model system for testing agonist and antagonist interactions with DA receptor sites (3,77). Most structure-activity investigations have utilized homogenates of rat basal ganglia. Kebabian, Petzold & Greengard (78) reported that DA and apomorphine stimulated cAMP formation in these homogenates and that the stimulation was blocked by haloperidol and chlorpromazine, as well as by high doses of phentolamine. Several lines of evidence indicated that the striatal DA sensitive adenylate cyclase is in a postsynaptic location. First, the cyclase is apparently enriched in subcellular fractions containing synaptic membranes, an appropriate location for the postulated synaptic function (79). Second, the response to DA is maintained after administration of 6-hydroxydopamine or surgical lesion of the substantia nigra (80). Denervation supersensitivity in terms of increased response to DA was observed by Mishra et al (81), but not by Von Voigtlander et al (80). Intrastriatal injection of kainic acid, which destroys striatal neurons while leaving intact dopaminergic terminals (81a, 81b), destroys the DA-sensitive adenylate cyclase (81c).

There are marked similarities in the potencies of DA agonists to increase adenylate cyclase activity and to produce renal vasodilation. DA, epinine, and A-6,7-DTN

are approximately equipotent in these two systems. In both systems the catechol group and a 2-carbon side chain in an extended position are required for activation. Increase in nitrogen substitution and α- or β-carbon substitution decreases activity. The semi-rigid analogue of the β-rotameric conformation of DA, A-6,7-DTN, was active in both systems, whereas, the analogue of the α-rotameric form, A-5,6-DTN, was essentially inactive (13, 82, 82a). The requirements for stimulation of the renal vascular DA receptor seem to be more specific, in that N,N-dimethyl DA, N,N,N-trimethyl DA, *l*-norepinephrine, α-methyl DA, 6,7-dihydroxytetrahydroisoquinoline, and S-584 [*l*-(3,4-dihydroxybenzyl)-4-(2-pyrimidinyl) piperizine] all produce increases in striatal adenylate cyclase activity, but they are inactive in the renal artery. Many of the compounds that stimulate striatal cyclase activity but not renal vasodilation have significant α-adrenergic activity (83, 84). As mentioned, norepinephrine produces some stimulation of the striatal adenylate cyclase, and phentolamine attenuates this response, as well as the response to DA. It is thus possible that discrepancies noted may be related to action on α-adrenergic receptors. This difficulty is virtually eliminated in the DA vascular receptor model by the administration of a large dose of POB, but as noted, this could not be done with striatal cyclase because of effects on the DA response. Interestingly, it has been found (85) that A-6,7-DTN has greater α-adrenergic potency than A-5,6-DTN, suggesting that a similar conformation of the DA molecule is required for stimulation of both DA and α-receptors. This factor further underscores the importance of eliminating α-adrenergic influences in studies of the potency of DA agonists and antagonists.

Discrepancies have also been noted in relative antagonist potencies in the two systems. Haloperidol and several phenothiazines are active antagonists of both systems, but the order of potency is considerably different. The fluorinated phenothiazines, fluphenazine and trifluoperazine, are more active than haloperidol in inhibiting the effects of DA on striatal adenylate cyclase (86), but these agents are only 50% as active as haloperidol in antagonizing renal vasodilation (19). A more striking difference involves the effects of metoclopramide and sulpiride, which are active as antagonists of DA-induced renal vasodilation, but do not inhibit DA-induced stimulation of striatal adenylate cyclase (87–89). Also, as mentioned, pimozide blocks the DA-induced stimulation of striatal cyclase, but is apparently inactive as an antagonist of DA-induced vasodilation (21, 24).

In summary, striatal DA-sensitive adenylate cyclase and the renal vascular bed exhibit considerable similarity in their response to agonists and antagonists. The discrepancies between the two systems may involve the inherent difficulties in obtaining a relatively pure receptor preparation from brain homogenates. When allowances are made for possible interference of the effects of α-adrenergic receptors, the responses of the striatal cyclase to DA agonists appear quite similar to those of the renal artery. However, the complete inactivity of sulpiride and metoclopramide in the striatum, in contrast to their ability to antagonize DA-induced renal vasodilation, indicates that there may be fundamental differences in these receptors. Additional studies comparing the effects of DA agonists and antagonists on adenylate cyclase homogenates prepared from brain and renal arteries could be helpful in resolving this problem (90).

Receptor Binding Assays

In the past few years numerous reports have appeared in which the displacement of tritiated DA and tritiated apomorphine from striatal homogenates has been correlated with agonist potency on the central nervous system DA receptors (91–93). In comparing the results obtained with the receptor binding assays to those obtained with agonists in the renal artery system, the major points of similarity involve the equipotency of DA, epinine, and A-6,7-DTN. The discrepancies, however, are quite marked. Apomorphine appears to be somewhat more potent than DA in the displacement of tritiated DA, but in the production of renal vasodilation apomorphine is a partial agonist. Apomorphine is several times more potent in its ability to displace tritiated DA than 6-*n*-propyl norapomorphine, which is more potent than apomorphine in producing renal vasodilation. Several other compounds can displace tritiated DA, but are inactive in the renal artery, including N,N-dimethyl DA, N-ethyl DA, N-methyl-A-5,6-DTN, N,N-dimethyl-A-5,6-DTN, and N,N-dimethyl-A-6,7-DTN (94). Interestingly, most of the above compounds are potent agonists at peripheral presynaptic sites (see section on postganglionic sympathetic nerve), and it is possible that they are binding at presynaptic sites in the central nervous system.

The ability of neuroleptic agents to displace tritiated haloperidol from striatal homogenates has been reported to correlate with clinical antipsychotic potency and, presumably, with potency in blocking central nervous system DA receptors (95), although this assertion has been challenged (96, 97). The greater potency of agonists to displace tritiated DA than tritiated haloperidol and the greater potency of neuroleptics to displace tritiated haloperidol than tritiated DA was considered to involve the interconversion of the DA receptor between agonist and antagonist states (92). However, Seeman et al (93) have detected no difference between the DA and haloperidol binding sites. In comparing the ability of neuroleptics to displace tritiated haloperidol with their ability to block DA-induced renal vasodilation, pimozide is again seen to be a major discrepancy, being quite potent in the binding assay, but apparently inactive in the renal artery. Fluphenazine is somewhat more potent than haloperidol in the binding assay, but about 50% as potent as haloperidol in the renal artery as is chlorpromazine. The latter drug, however, is about sevenfold weaker than haloperidol in the displacement of tritiated haloperidol (94).

In summary, the results obtained with the various receptor binding assays do not correlate well with the characteristics of the vascular DA receptor with respect to either agonist or antagonist potency. There has, however, been serious question concerning the identity of binding sites with the pharmacological receptors, as summarized by Rocha e Silva (98): "In the absence of information that a labelled agonist or antagonist has produced or blocked a biological effect, there is no guarantee that the observed site of fixation actually is the specific receptor." With regard to the DA receptor, it has been pointed out (99) that the DA agonist A-6,7-DTN would be expected to bind to catechol-*o*-methyltransferase, which can exist in a membrane-bound form (100), and possibly also to combine with synaptosomal

transport sites for DA (101). The relatively nonspecific binding of various physiologically inactive catechols to COMT could explain the above-noted discrepancies in agonist potency.

Behavioral Responses As Central Nervous System DA-Receptor Models

Various behavioral parameters have been monitored in laboratory animals as indications of the stimulation of central nervous system DA receptors, including apomorphine or amphetamine-induced hyperactivity, apomorphine or amphetamine-induced stereotyped behavior, or asymmetric rotatory behavior after unilateral lesions of the substantia nigra (77, 102). Very few systematic structure-activity relationship studies have been performed with any of these behavioral models, but a few points of comparison with the vascular DA receptor may be made. A-6,7-DTN stimulated locomotor activity upon intraventricular injection in conscious rats (103) and produced contralateral turning in unilaterally nigral lesioned rats (104), effects similar to DA and apomorphine. 6-Propylnorapomorphine is a more potent vasodilator than apomorphine (12) and is more effective than apomorphine in eliciting stereotyped behavior in rats (105, 106), although the two derivatives are apparently equipotent in ability to stimulate locomotor activity (107).

In a study of the ability of various phenylethylamines to produce asymmetric body posturing and hyperactivity or stereotyped behavior (108), it was found that DA and epinine were active while any of the following alterations in the molecule markedly reduced or abolished activity: alteration of length of the ethylamine side chain, α-methylation (α-methyl DA), β-hydroxylation (norepinephrine), either 3- or 4-hydroxylation instead of the catechol moiety (tyramine or metatyramine). Apomorphine was active but isoapomorphine was found inactive. These results are consistent with the requirements for the production of renal vasodilation by phenylethylamines (15). However, many compounds inactive in the production of renal vasodilation have been found active in various behavioral models including various 2-amino-5,6-dihydroxytetralins (109, 110, 110a); piribedil and S-584 (111); lergotrile, bromocryptine, ergometrine, and LSD (111); and *d*-amphetamine. 3,4-Dihydroxyphenylamino-2-imidazoline (DPI), a compound reported to specifically activate inhibitory DA receptors (112), is inactive in the renal artery (H. Struyker Boudier, personal communication).

The agonist potency of many of the above compounds could be explained if the relevant DA receptors within the caudate and mesolimbic system were of distinct types (113) with characteristics different from the vascular DA receptor. However, these compounds could affect noradrenergic, serotonergic, or cholinergic neurons or receptors to produce behaviors indistinguishable from "classic" DA responses. For example, unilateral lesions of the locus coeruleus decreased cortical norepinephrine levels with minimal effects on striatal DA; these rats showed contralateral rotation after injection of apomorphine, a phenomenon thought to be a manifestation of supersensitive DA receptors (114). The central α-adrenergic agonist clonidine potentiated the locomotor and contralateral turning behaviors induced by apomorphine (115). Furthermore, effects on serotonin neurons influence DA func-

tion (115–118), and it is well known that the functional state of the striatum depends on the balance of cholinergic and DA influences (102, 119–124). Thus, the use of the various behavioral models may provide useful insights into the central effects of known DA agonists, but use of these methods does not appear to be a reliable way to define agonist potencies at specific receptors.

Emesis and DA Receptors

The induction of emesis by *l*-dopa and apomorphine and its inhibition by DA antagonists have suggested to many investigators that a specific DA receptor mediating emesis is located in the chemoreceptor trigger zone of the medulla (125).

Cannon and colleagues carried out a systematic study to determine the emetic pharmacophore of apomorphine and reported that N,N-dimethyl derivative of A-5,6-DTN (Figure 2) was an extremely potent emetic drug (126). Cannon (127) proposed that "the biologically significant rotamer of the DA molecule for central emetic effects ... is represented by structure α, rather than the other possibility, structure β" (Figure 2). As discussed previously, this conformation is diametrically opposed to the structure-activity relationship required for activation of the vascular DA receptor. Furthermore, the N,N-dimethyl derivatives of either conformation are totally inactive in the renal system while the N,N-dimethyl A-5,6-DTN is the most potent emetic reported by Cannon et al (126). Accordingly, emesis by these compounds is either related to a different DA receptor (perhaps a type of apomorphine receptor) or to some other mechanism.

DA RECEPTORS INVOLVED IN PROLACTIN RELEASE

The release of prolactin from the anterior pituitary is considered to be regulated by an inhibitory DA receptor (128–130). Since the anterior pituitary is not protected by the blood-brain barrier, and since effects of DA are demonstrable on anterior pituitary explants, this receptor appears to be a peripheral, postsynaptic receptor. This section compares the characteristics of the anterior pituitary DA receptor with the vascular DA receptor.

Considering first the potency of DA agonists, DA has been found to inhibit prolactin release in vitro in concentrations of 10^{-9}M (131). Norepinephrine and epinephrine were also found to be active, at somewhat higher concentrations, and the effects of all three catecholamines on prolactin release could be blocked by the combination of phentolamine and propranolol (130). The above findings differ from the renal artery, in which norepinephrine and epinephrine are inactive, and the effects of DA are unaffected by combined α- and β-adrenergic blockade. Apomorphine is approximately equipotent to DA in prolactin release inhibition (132), although much weaker than DA at vascular receptors (15, 12). A-6,7-DTN is active in the renal vascular bed and is a potent inhibitor of prolactin release (132a). In contrast, A-5,6-DTN, N,N-dimethyl-A-5,6-DTN, and N,N-dimethyl-A-5,8-DTN are inactive as DA vascular agonists (133), but are active in inhibiting prolactin release (134). Piribedil (135) and various ergot derivatives such as lergotrile (136)

and bromocryptine (137) inhibit prolactin release by apparently direct actions on the pituitary, but these compounds are inactive in the renal artery (133).

With respect to antagonists in the two systems, haloperidol, chlorpromazine, fluphenazine, metoclopramide (138, 139), and sulpiride (140, 141) raise prolactin levels, presumably by blocking the effects of DA, and block DA-induced renal vasodilation. However, the order of potency of the antagonists in the two systems does not correspond (96).

In summary, there appears to be a DA receptor in the anterior pituitary which regulates prolactin release, in terms of responses to DA, A-6,7-DTN, and apomorphine, and blockade of these responses by neuroleptic drugs. However, the anterior pituitary receptor is much less specific than the vascular DA receptor in structural requirements for agonist activity. As mentioned, the influence of α-adrenergic receptors cannot be eliminated without appreciably blocking responses to DA, a factor that complicates interpretation of the agonist experiments. Furthermore, serotonin stimulates prolactin release, and serotonin antagonists decrease prolactin release (128, 129). Thus, serotonin antagonists act like DA agonists in this system. It, therefore, seems likely that difficulty in obtaining a pharmacologically pure receptor preparation has contributed to the lack of specificity of the prolactin response.

CONCLUSIONS

Characterization of receptors by classical physiological techniques requires demonstration of certain criteria established by many years of research (142). In brief, the responses observed must not be influenced by opposite or identical responses due to action on other receptors or by neurogenic, hormonal, or other extraneous influences. Specific antagonism must be demonstrated, and the order of potency of a series of agonists and antagonists must be the same in all tissues or organs considered to have the same receptor. For precise quantitation, the responses being measured must reach a steady state and the concentration of the agent at the active site must be in equilibrium with the bathing medium. It is clear that all these conditions have not been fulfilled in studies of the DA receptor, primarily because they require a suitable isolated organ system. Canine renal, coronary, mesenteric, and cerebral arteries (143, 144); aortic strips from young rats (145); and strips containing gastrointestinal smooth muscle (25) respond to DA agonists, but quantitative studies with specific antagonists have not yet been accomplished.

Although precise quantitation of agonist and antagonist ratios can only be obtained in vitro, in vivo experiments can provide valid evidence for differentiation of receptors. This conclusion is especially true for intraarterial injections since, as stated by Furchgott (142), "If injections are made into the arteries directly supplying blood to a responding tissue, control of the doses of agonists reaching the tissues can be fairly accurate." On this basis, we have restricted our studies to rapid intraarterial injections of agonists dissolved in small volumes, even though this mode of administration precludes investigation of poorly soluble drugs.

Through use of renal artery vasodilation following intraarterial injections of DA and a series of agonists, the following criteria have been met: (*a*) opposing vasoconstricting actions of DA and most DA agonists can be blocked by POB; (*b*) specific antagonism can be demonstrated with a dose of antagonist that does not affect other vasodilators; (*c*) β-adrenergic, cholinergic, histaminergic, serotonergic, and neurogenic influences can be eliminated; (*d*) the same order of potency of agonists and antagonists has been demonstrated in both the renal and mesenteric vascular beds.

If structural requirements for action on the vascular DA receptor are accepted as valid, an explanation must be found for the marked qualitative and quantitative discrepancies found when comparing results obtained with the canine renal artery to other organs and tissues. One possibility is that different DA receptors with distinct characteristics exist, as recently demonstrated with β-adrenergic and histamine receptors. However, the chemical heterogeneity of agonists reported to be active and the quality of evidence presented in many of the studies reviewed makes it equally possible that many responses described were due to mechanisms other than action on DA receptors. Certainly, similarity of a response to that produced by DA or apomorphine and antagonism of this response by "specific" antagonists does not prove the existence of a DA receptor since DA, apomorphine, and the antagonists exert many other actions.

This review delineates the many problems involved in attributing diverse physiological, biochemical, and behavioral responses to actions on DA receptors. Despite these difficulties, additional studies using more rigid pharmacological criteria to compare the same agonists and antagonists in the various preparations could be of great importance. More precise characterization of DA receptors would not only help determine the role of DA in a variety of pathological processes, but could also lead to the development of more specific drugs.

Acknowledgments

The data presented in this review could not have been obtained without the cooperation of many investigators who donated compounds for study. In particular, we are indebted to Dr. Joseph G. Cannon and Dr. Roger M. Pinder. We also wish to thank Dr. Alvin N. Kotake for stimulating discussions. Research was supported by USPHS grants from NIH, GM-22220 and NS-12324. Dr. Volkman was supported by NIH training grant GM-07019.

Literature Cited

1. Goldberg, L. I. 1972. Cardiovascular and renal actions of dopamine: Potential clinical applications. *Pharmacol. Rev.* 24:1–29
2. Calne, D., Chase, T. N., Barbeau, A., eds. 1975. *Dopaminergic Mechanisms. Adv. Neurol.*, Vol. 9
3. Iversen, L. L. 1975. Dopamine receptors in the brain. *Science* 188:1084–89
4. Costa, E., Gessa, G. L., eds. 1977. *Nonstriatal Dopaminergic Neurons. Adv. Biochem. Psychopharmacol.*, Vol. 16
5. Goldberg, L. I. 1975. The dopamine vascular receptor. *Biochem. Pharmacol.* 24:651–53
6. Pendleton, R. G., Setler, P. E. 1977. Peripheral cardiovascular dopamine receptors. *Gen. Pharmacol.* 8:1–5
7. Goldberg, L. I., Hsieh, Y. Y., Resnekov, L. 1977. Newer catecholamines for treatment of heart failure and shock: An update on dopamine and a first look at dobutamine. *Prog. Cardiovasc. Dis.* 19:327–40
8. McNay, J. L., Goldberg, L. I. 1966. Comparison of the effects of dopamine, isoproterenol, norepinephrine, and bradykinin on canine renal and femoral blood flow. *J. Pharmacol. Exp. Ther.* 151:23–31
9. Yeh, B. K., McNay, J. L., Goldberg, L. I. 1969. Attenuation of dopamine renal and mesenteric vasodilation by haloperidol: Evidence for a specific dopamine receptor. *J. Pharmacol. Exp. Ther.* 168:303–9
10. Bell, C., Conway, E. L., Lang, W. J., Padanyi, R. 1975. Vascular dopamine receptors in the canine hindlimb. *Br. J. Pharmacol.* 55:167–72
11. Gooding, J. M., Karp, R. B., Appelbaum, A., Tracy, W. G. 1977. Hemodynamic responses to dopamine infusion at controlled normal and low cardiac output states in the anesthetized dog. *J. Thorac. Cardiovasc. Surg.* 73:758–62
12. Crumly, H. J., Hinshaw, W. B., Pinder, R. M., Goldberg, L. I. 1976. Dopamine-like renal and mesenteric vasodilation caused by apomorphine, 6-propyl-norapomorphine and 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene. *Nature* 259:584–87
13. Volkman, P. H., Kohli, J. D., Goldberg, L. I., Cannon, J. G., Lee, T. 1977. Conformational requirements for dopamine-induced vasodilation. *Proc. Natl. Acad. Sci. USA* 74:3602–6
14. McDonald, R. H. Jr., Goldberg, L. I. 1963. Analysis of the cardiovascular effects of dopamine in the dog. *J. Pharmacol. Exp. Ther.* 140:60–66
15. Goldberg, L. I., Sonneville, P. F., McNay, J. L. 1968. An investigation of the structural requirements for dopamine-like renal vasodilation: Phenylethylamines and apomorphine. *J. Pharmacol. Exp. Ther.* 163:188–97
16. Volkman, P. H., Kohli, J. D., Goldberg, L. I., Cannon, J. G. 1977. Dipropyldopamine, a qualitatively different dopamine (DA) agonist. *Fed. Proc.* 36:1049
17. Bell, C., Conway, E. L., Lang, W. J. 1974. Ergometrine and apomorphine as selective antagonists of dopamine in the canine renal vasculature. *Br. J. Pharmacol.* 52:591–95
18. Volkman, P. H., Kohli, J. D., Goldberg, L. I. 1977. Apomorphine, a partial agonist of the vascular dopamine receptor. *6th Int. Meet.: Int. Soc. Neurochem., Satellite Symp. on DA, Univ. Southampton,* Aug. 30-Sept. 1, 1977
19. Goldberg, L. I., Yeh, B. K. 1971. Attenuation of dopamine-induced renal vasodilation in the dog by phenothiazines. *Eur. J. Pharmacol.* 15:36–40
20. Goldberg, L. I., Musgrave, G. 1971. Selective attenuation of dopamine-induced renal vasodilation by bulbocapnine and apomorphine. *Pharmacologist* 13(2):227
21. Setler, P. E., Pendleton, R. G., Finlay, E. 1975. The cardiovascular actions of dopamine and the effects of central and peripheral catecholaminergic receptor blocking drugs. *J. Pharmacol. Exp. Ther.* 192:702–12
22. Day, M. D., Blower, P. R. 1975. Cardiovascular dopamine receptor stimulation antagonized by metoclopramide. *J. Pharm. Pharmacol.* 27:276–78
23. Kohli, J. D., Volkman, P. H., Glock, D., Goldberg, L. I. 1978. Metoclopramide and sulpiride: Antagonists of the vascular dopamine receptor. *Fed. Proc.* In press
24. Imbs, J. L., Schmidt, M., Velly, J., Schwartz, J. 1976. Effects of apomorphine and of pimozide on renin secretion in the anesthetized dog. *Eur. J. Pharmacol.* 38:175–78
25. DeCarle, D. J., Christensen, J. 1976. A dopamine receptor in esophageal smooth muscle of the opossum. *Gastroenterology* 70:216–19

26. Rattan, S., Goyal, R. K. 1976. Effect of dopamine on the esophageal smooth muscle in vivo. *Gastroenterology* 70: 377–81
27. Mukhopadhyay, A. K., Weisbrodt, N. 1977. Effect of dopamine on esophageal motor function. *Am. J. Physiol.* 232(1): E19–E24
28. Valenzuela, J. E. 1976. Dopamine as a possible neurotransmitter in gastric relaxation. *Gastroenterology* 71:1019–22
29. Bury, R. W., Mashford, M. L. 1976. The effects of metoclopramide in modifying the response of isolated guinea-pig ileum to various agonists. *J. Pharmacol. Exp. Ther.* 197:641–46
30. Hay, A. M. 1977. Pharmacological analysis of the effects of metoclopramide on the guinea-pig isolated stomach. *Gastroenterology* 72:864–69
31. Justin-Besançon, L., Laville, C., Thominet, M. 1964. Le métoclopramide et ses homolôgues. Introduction à leur étude biologique. *C. R. Acad. Sci.* 258:4384–88
32. Justin-Besançon, L., Grivaux, M., Wattez, E. 1964. L'épreuvre au métoclopramide en radiologie digestive. *Bull. Soc. Med. Hop. Paris* 115:721–26
33. Chevrot, L., Roux, G., Menard, J. C. 1965. Métoclopramide et routine radiologique digestive. *Sem. Hop.* 41: 1803–7
34. Guerrin, F., Milbled, G., Merveille, P., Hequet, B. 1967. Effets du métoclopramide sur la motricité gastrique du rat. *C. R. Soc. Biol.* 161:1318–25
35. Greengard, H., Roback, R. A., Ivy, A. C. 1942. The effect of sympathomimetic amines on pancreatic secretion. *J. Pharmacol. Exp. Ther.* 74:309–31
36. Hashimoto, K., Satoh, S., Takeuchi, O. 1971. Effect of dopamine on pancreatic secretion in the dog. *Br. J. Pharmacol.* 43:739–46
37. Furuta, Y., Hashimoto, K., Iwatsuki, K., Takeuchi, O. 1973. Effects of enzyme inhibitors of catecholamine metabolism and of haloperidol on the pancreatic secretion induced by L-dopa and by dopamine in dogs. *Br. J. Pharmacol.* 47:77–84
38. Furuta, Y., Hashimoto, K., Ishii, Y., Iwatsuki, K. 1974. Modification by drugs of the secretagogue effect of dopamine on the pancreas. *Br. J. Pharmacol.* 51:225–30
39. Bastie, M. J., Vaysse, N., Brenac, B., Pascal, J. P., Ribet, A. 1977. Effects of catecholamines and their inhibitors on the isolated canine pancreas. *Gastroenterology* 72:719–23
40. Bloom, G. D., Carlsöö, B., Danielsson, Å. 1975. Dopamine-induced amylase secretion from guinea-pig submandibular gland. *Br. J. Pharmacol.* 54:523–28
41. Starke, K. 1972. Influence of extracellular noradrenaline on the stimulation-evoked secretion of noradrenaline from sympathetic nerves: Evidence for an α-receptor-mediated feed-back inhibition of noradrenaline release. *Naunyn-Schmiedberg's Arch. Pharmacol.* 275: 11–23
42. McCulloch, M. W., Rand, M. J., Story, D. F. 1972. Inhibition of ^{3}H-noradrenaline release from sympathetic nerves of guinea-pig atria by a presynaptic α-adrenoceptor mechanism. *Br. J. Pharmacol.* 46:523P–24P
43. Enero, M. A., Langer, S. Z. 1973. Influence of reserpine-induced depletion of noradrenaline on the negative feed-back mechanism for transmitter release during nerve stimulation. *Br. J. Pharmacol.* 49:214–25
44. Kirpekar, S. M., Furchgott, R. F., Wakade, A. R., Prat, J. C. 1973. Inhibition by sympathomimetic amines of the release of norepinephrine evoked by nerve stimulation in the cat spleen. *J. Pharmacol. Exp. Ther.* 187:529–38
45. Langer, S. Z. 1973. The regulation of transmitter release elicited by nerve stimulation through a pre-synaptic feed-back mechanism. In *Frontiers in Catecholamine Research*, ed. E. Usdin, S. H. Snyder, pp. 543–49. Oxford, England: Pergamon
46. Langer, S. Z. 1974. Presynaptic regulation of catecholamine release. *Biochem. Pharmacol.* 23:1793–1800
47. Dubocovich, M. L., Langer, S. Z. 1974. Negative feed-back regulation of noradrenaline release by nerve stimulation in the perfused cat's spleen: Differences in potency of phenoxybenzamine in blocking the pre- and post-synaptic adrenergic receptors. *J. Physiol.* 237: 505–19
48. Starke, K., Endo, T., Taube, H. D. 1975. Pre- and post-synaptic components in effect of drugs with α-adrenoceptor affinity. *Nature* 254:440–41
49. Starke, K., Borowski, E., Endo, T. 1975. Preferential blockade of presynaptic α-adrenoceptors by yohimbine. *Eur. J. Pharmacol.* 34:385–88
50. Drew, G. M. 1976. Effects of α-adrenoceptor agonists and antagonists on pre- and post-synaptically located

α-adrenoceptors. *Eur. J. Pharmacol.* 36:313–20
51. Lokhandwala, M. F., Coats, J. T., Buckley, J. P. 1977. Effects of several catecholamines on sympathetic transmission to the myocardium: Role of pre-synaptic α-adrenoceptors. *Eur. J. Pharmacol.* 42:257–65
52. Drew, G. M. 1977. Pharmacological characterization of the presynaptic α-adrenoceptor in the rat vas deferens. *Eur. J. Pharmacol.* 42:123–30
53. Cambridge, D., Davey, M. J., Massingham, R. 1977. Prazosin, a selective antagonist of post-synaptic α-adrenoceptors. *Br. J. Pharmacol.* 59:514P–15P
54. Enero, M. A., Langer, S. Z. 1975. Inhibition by dopamine of ^{3}H-noradrenaline release elicited by nerve stimulation in the isolated cat's nictitating membrane. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 289:179–203
55. Tayo, F. M. 1977. Further evidence for dopaminoceptors in the vas deferens. *Br. J. Pharmacol.* 59:511P–12P
56. Simon, A., Van Maanen, E. F. 1976. Dopamine receptors and dopaminergic nerves in the vas deferens of the rat. *Arch. Int. Pharmacodyn.* 222:4–15
57. Stjärne, L. 1975. Selectivity for catecholamines of pre-synaptic α-receptors involved in feed-back control of sympathetic neurotransmitter secretion in guinea-pig vas deferens. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 288: 296–303
58. Long, J. P., Heintz, S., Cannon, J. G., Kim, J. 1975. Inhibition of the sympathetic nervous system by 5,6-dihydroxy-2-dimethylamino tetralin (M-7), apomorphine, and dopamine. *J. Pharmacol. Exp. Ther.* 192:336–42
59. Ilhan, M., Long, J. P., Cannon, J. G. 1974. Inhibition of responses to stimulation of the cardioaccelerator nerves of the cat by N,N-dimethyldopamine and apomorphine. *Arch. Int. Pharmacodyn.* 212:247–54
60. Ilhan, M., Nichols, D. E., Long, J. P., Cannon, J. G. 1975. Apomorphine-like effect of an aminotetralin on the linguomandibular reflex of the cat. *Eur. J. Pharmacol.* 33:61–64
61. Ilhan, M., Long, J. P., Cannon, J. G. 1975. Bulb capnine's ability to antagonize the adrenergic inhibitory action of dopamine and analogs. *Eur. J. Pharmacol.* 33:13–18
62. Ilhan, M., Long, J. P., Cannon, J. G. 1976. The ability of pimozide to prevent inhibition by dopamine analogs of cardioaccelerator nerves in cat hearts. *Arch. Int. Pharmacodyn.* 222:70–80
63. Kitzen, J. M., Ilhan, M., Cannon, J. G., Long, J. P. 1976. α-Adrenergic activity of N,N-dimethyldopamine (DMDA). *Eur. J. Pharmacol.* 38:365–72
64. McIssac, R. J. 1966. Ganglionic blocking properties of epinephrine and other related amines. *Int. J. Neuropharmacol.* 5:15–26
65. Kadzielawa, K., Gawecka, I., Kadzielawa, R. 1968. The potentiating influence of imipramine on ganglionic effects of catecholamines. *Int. J. Neuropharmacol.* 7:517–21
66. Schümann, H. J. 1956. Nachweis von oxytyramin (dopamin) in sympathischen nerven und ganglien. *Arch. Exp. Path. Pharmakol.* 227:566–73
67. Björklund, A., Cegrell, L., Falck, B., Ritzén, M., Rosengren, E. 1970. Dopamine-containing cells in sympathetic ganglia. *Acta Physiol. Scand.* 78:334–38
67a. Elfvin, L. G., Hokfelt, T., Goldstein, M. 1975. Fluorescence, microscopical, immunohistochemical, and ultrastructural studies on sympathetic ganglia of the guinea pig, with special reference to the SIF cells and their catecholamine content. *J. Ultrastruct. Res.* 51:377–96
68. Libet, B. 1970. Generation of slow inhibitory and excitatory post-synaptic potentials. *Fed. Proc.* 29(6):1945–56
68a. Nishi, S. 1974. Ganglionic transmission. In *The Peripheral Nervous System*, ed. J. I. Hubbard, pp. 225–55. New York: Plenum
68b. Dun, N., Karczmar, A. G. 1977. The presynaptic site of action of norepinephrine in the superior cervical ganglion of the guinea pig. *J. Pharmacol. Exp. Ther.* 200:328–35
68c. Libet, B. 1977. Role of intra-ganglionic catecholamines and slow synaptic action. *Proc. Int. Union Physiol. Sci., Paris* 12:558
69. Libet, B., Tosaka, T. 1970. Dopamine as a synaptic transmitter and modulator in sympathetic ganglia: A different mode of synaptic action. *Proc. Natl. Acad. Sci. USA* 67:667–73
70. Kebabian, J. W., Greengard, P. 1971. Dopamine-sensitive adenyl cyclase: Possible role in synaptic transmission. *Science* 174:1346–49
71. Kalix, P., McAfee, D. A., Schorderet, M., Greengard, P. 1974. Pharmacological analysis of synaptically mediated increase in cyclic adenosine monophosphate in rabbit superior cervical gan-

glion. *J. Pharmacol. Exp. Ther.* 188: 676–87

72. Kalix, P., Kebabian, J. W., McAfee, D. A., Greengard, P. 1974. Quoted in *J. Pharmacol. Exp. Ther.* 188:676–87

72a. Greengard, P., Kababian, J. W. 1974. Role of cyclic AMP in synaptic transmission in the mammalian peripheral nervous system. *Fed. Proc.* 33:1059–67

72b. Dun, N. J., Kaibara, K., Karczmar, A. G. 1977. Dopamine and adenosine 3',5'-monophosphate responses of single mammalian sympathetic neurons. *Science* 197:778–79

73. Noon, J. P., McAfee, D. A., Roth, R. H. 1975. Norepinephrine release from nerve terminals within the rabbit superior cervical ganglion. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 291: 139–62

74. Bogaert, M. G., De Schaepdryver, A. F. 1967. Dopamine-induced neurogenic vasodilation in the hindleg of the dog. *Arch. Int. Pharmacodyn.* 166:203–7

75. Willems, J. L. 1973. Dopamine-induced inhibition of synaptic transmission in lumbar paravertebral ganglia of the dog. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 279:115–26

76. Willems, J. L., Bogaert, M. G. 1975. Dopamine-induced neurogenic vasodilation in isolated perfused muscle preparation of the dog. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 286: 413–28

77. Iversen, L. L., Horn, A. S., Miller, R. J. 1975. Actions of dopaminergic agonists on cyclic AMP production in rat brain homogenates. *Adv. Neurol.* 9:197–212

78. Kebabian, J. W., Petzold, G. L., Greengard, P. 1972. Dopamine sensitive adenylate cyclase in the caudate nucleus of rat brain and its similarity to the "dopamine receptor." *Proc. Natl. Acad. Sci. USA* 69:2145–49

79. Greengard, P. 1976. The action of antipsychotic drugs on dopamine-stimulated adenylate cyclase activity. In *Antipsychotic Drugs: Pharmacodynamics and Pharmacokinetics,* ed. G. Sedvall, pp. 271–83. New York: Pergamon

80. Von Voigtlander, P. F., Boukma, S. J., Johnson, G. A. 1973. Dopaminergic denervation supersensitivity and dopamine-stimulated adenyl cyclase activity. *Neuropharmacology* 12:1081–86

81. Mishra, R. K., Gardner, E. L., Katzman, R., Makman, M. H. 1974. Enhancement of dopamine-stimulated adenylate cyclase activity in rat caudate after lesions in substantia nigra: Evidence for denervation supersensitivity. *Proc. Natl. Acad. Sci. USA* 71:3883–87

81a. Coyle, J. T., Schwartz, R. 1976. Lesion of striatal neurons with kainic acid provides a model for Huntington's chorea. *Nature* 263:244–46

81b. McGeer, E. G., McGeer, P. L. 1976. Duplication of biochemical changes of Huntington's chorea by intrastriatal injection of glutamic and kainic acids. *Nature* 263:517–19

81c. DiChiara, G., Porceddu, M. L., Spano, P. F., Gessa, G. L. 1977. Haloperidol increases and apomorphine decreases striatal dopamine metabolism after destruction of striatal dopamine-sensitive adenylate cyclase by kainic acid. *Brain Res.* 130:374–82

82. Kotake, C., Goldberg, L. I., Hoffmann, P. C., Cannon, J. G. 1977. Effects of 2-aminotetralins on rat striatal adenylate cyclase. *Pharmacologist* 19:222

82a. Woodruff, G. N., Watling, K. J., Andrews, C. D., Poat, J. A., McDermed, J. D. 1977. Dopamine receptors in rat striatum and nucleus accumbens; conformational studies using rigid analogues of dopamine. *J. Pharm. Pharmacol.* 29:422–27

83. Fassett, D. W., Hjort, A. M. 1938. Some tetrahydroisoquinolines II. Their action on blood pressure, respiration, and smooth muscle. *J. Pharmacol. Exp. Ther.* 62:253–72

84. Ahlquist, R. P. 1948. A study of adrenotropic receptors. *Am. J. Physiol.* 153:586–600

85. Kohli, J. D., Volkman, P. H., Goldberg, L. I., Lee, T., Cannon, J. G. 1976. Conformational requirements in dopamine analogs for vascular smooth muscle excitatory activity. *Pharmacologist* 18:228

86. Miller, R. J., Horn, A. S., Iversen, L. L. 1974. The action of neuroleptic drugs on dopamine-stimulated adenosine-3'5'-monophosphate production in rat neostriatum and limbic forebrain. *Mol. Pharmacol.* 10:759–66

87. Trabucci, M., Longoni, R., Fresia, P., Spano, P. F. 1976. Sulpiride: A study of the effects on dopamine receptors in rat neostriatum and limbic forebrain. *Life Sci.* 17:1551–56

88. Roufogalis, B. D., Thornton, M., Wade, D. N. 1976. Specificity of the dopamine sensitive adenylate cyclase for antipsychotic antagonists. *Life Sci.* 19:927–34

89. Donaldson, I. M., Jenner, P., Marsden, C. D., Miller, R., Peringer, E. 1976. Is metoclopramide a directly acting dopa-

mine receptor antagonist? *Br. J. Pharmacol.* 56:373P

90. Murthy, V. V., Gilbert, J. C., Goldberg, L. I., Kuo, J. F. 1976. Dopamine sensitive adenylate cyclase in canine renal artery. *J. Pharm. Pharmacol.* 28: 567–71
91. Burt, D. R., Enna, S. J., Creese, I., Snyder, S. H. 1975. Dopamine receptor binding in the corpus striatum of mammalian brain. *Proc. Natl. Acad. Sci. USA* 72:4655–59
92. Creese, I., Burt, D. R., Snyder, S. H. 1975. Dopamine receptor binding: Differentiation of agonist and antagonist states with ^{3}H-dopamine and ^{3}H-haloperidol. *Life Sci.* 17:993–1002
93. Seeman, P., Lee, T., Chau-Wong, M., Tedesco, J., Wong, K. 1976. Dopamine receptors in human and calf brains using ^{3}H-apomorphine and an antipsychotic drug. *Proc. Natl. Acad. Sci. USA* 73:4354–58
94. Seeman, P., Tedesco, J. L., Lee, T., Chau-Wong, M., Muller, P., Bowles, J., Whitaker, P. M., McManus, C., Tittler, M., Weinrich, P., Friend, W. C., Brown, G. M. 1978. Dopamine receptors in the central nervous system. *Fed. Proc.* In press
95. Creese, I., Burt, D. R., Snyder, S. H. 1976. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science* 192:481–83
96. Meltzer, H. 1976. Dopamine receptors and average clinical doses. *Science* 194:545–46
97. Crow, T. J., Deakin, J. W. F., Johnstone, E. C. 1977. Stereospecificity and clinical potency of neuroleptics. *Nature* 267:183–84
98. Rocha e Silva, M. 1976. Pharmacological ways to study pharmacological receptors. *Gen. Pharmacol.* 7:87–91
99. Roberts, P. J., Woodruff, G. N., Poat, J. A. 1977. Binding of a conformationally restricted dopamine analogue, 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene, to receptors on rat brain synaptic membranes. *Mol. Pharmacol.* 13: 541–47
100. Traiger, G. J., Calvert, D. N. 1969. O-methylation of ^{3}H-norepinephrine by epididymal adipose tissue. *Biochem. Pharmacol.* 18:109–18
101. Horn, A. S. 1974. Further evidence for the stimulation of rat brain dopamine receptors by a cyclic analogue of dopamine. *J. Pharm. Pharmacol.* 26:740–44
102. Klawans, H. L., Weiner, W. J. 1974. Animal models of human extrapyramidal disorders. In *Models of Human Neurological Diseases,* ed. H. L. Klawans, pp. 5–38. Amsterdam: Excerpta Med.
103. Woodruff, G. N., Elkhawad, A. O., Pinder, R. M. 1974. Long-lasting stimulation of locomotor activity produced by the intraventricular injection of a cyclic analogue of dopamine into conscious mice. *Eur. J. Pharmacol.* 25: 80–86
104. Kelly, P. H., Miller, R. J. 1975. Quoted in Actions of dopaminergic agonists on cyclic AMP production in rat brain homogenates. *Adv. Neurol.* 9:197–212
105. Costall, B., Naylor, R. J., Neumeyer, J. L. 1975. Differences in the nature of the stereotyped behavior induced by aporphine derivatives in the rat and in their actions in extrapyramidal and mesolimbic areas. *Eur. J. Pharmacol.* 31:1–16
106. Schoenfeld, R. I., Neumeyer, J. L., Dafeldecker, W., Roffler-Tarlov, S. 1975. Comparison of structural and stereoisomers of apomorphine on stereotyped sniffing behavior of the rat. *Eur. J. Pharmacol.* 30:63–68
107. Menon, M. K., Clark, W. G., Cannon, J. G. 1976. Comparison of the dopaminergic effects of N-substituted aporphines. *J. Pharm. Pharmacol.* 28: 778–81
108. Costall, B., Naylor, R. J., Pinder, R. M. 1974. Design of agents for stimulation of neostriatal dopaminergic mechanisms. *J. Pharm. Pharmacol.* 26:753–62
109. McDermed, J. D., McKenzie, G. M., Phillips, A. P. 1975. Synthesis and pharmacology of some 2-aminotetralins. Dopamine receptor agonists. *J. Med. Chem.* 18:362–67
110. Costall, B., Naylor, R. J., Cannon, J. G., Lee, T. 1977. Differential activation by some 2-aminotetralin derivatives of the receptor mechanisms in the nucleus accumbens of rat which mediate hyperactivity and stereotyped biting. *Eur. J. Pharmacol.* 41:307–19

110a. Cannon, J. G., Lee, T., Goldman, H. D., Costall, B., Naylor, R. J. 1977. Cerebral dopamine agonist properties of some 2-aminotetralin derivatives after peripheral and intracerebral administration. *J. Med. Chem.* 20:1111–16

111. Fuxe, K., Agnati, L. F., Corrodi, H., Everitt, B. J., Hökfelt, T., Löfström, A., Ungerstedt, U. 1975. Action of dopamine receptor agonists in forebrain and hypothalamus: Rotational behavior,

ovulation, and dopamine turnover. *Adv. Neurol.* 9:223–42

112. Struyker Boudier, H. A. J., Teppema, L., Cools, A. R., Van Rossum, J. M. 1975. (3,4-Dihydroxyphenylamino)-2-imidazoline (DPI): A new potent stimulant at dopamine receptors mediating neuronal inhibition. *J. Pharm. Pharmacol.* 27:882–85
113. Cools, A. R., Struyker Boudier, H. A. J., Van Rossum, J. M. 1976. Dopamine receptors: Selective agonists and antagonists of functionally distinct types within the feline brain. *Eur. J. Pharmacol.* 37:283–93
114. Donaldson, I. M., Dolphin, A., Jenner, P., Marsden, C. D., Pycock, C. 1976. The involvement of noradrenaline in motor activity as shown by rotational behavior after unilateral lesions of the locus coeruleus. *Brain* 99:427–46
115. Pycock, C. J., Jenner, P. G., Marsden, C. D. 1977. The interaction of clonidine with dopamine-dependent behavior in rats. *Arch. Pharmacol.* 297:133–41
116. Milson, J. A., Pycock, C. J. 1976. Effect of drugs acting on cerebral 5-hydroxytryptamine mechanisms on dopamine-dependent turning behavior in mice. *Br. J. Pharmacol.* 56:77–85
117. Costall, B., Naylor, R. J., Marsden, C. D., Pycock, C. J. 1976. Serotonergic modulation of the dopamine response from the nucleus accumbens. *J. Pharm. Pharmacol.* 28:523–26
118. Weiner, W. J., Goetz, C., Klawans, H. L. 1975. Serotonergic and anti-serotonergic influences on apomorphine-induced stereotyped behavior. *Acta Pharmacol. Toxicol.* 36:155–60
119. Ladinsky, H., Consolo, S., Bianchi, S., Samanin, R., Ghezzi, D. 1975. Cholinergic-dopaminergic interaction in the striatum: The effect of 6-hydroxydopamine or pimozide treatment on the increased striatal acetylcholine levels induced by apomorphine, piribedil, and d-amphetamine. *Brain Res.* 84:221–26
120. Guyenet, P. G., Agid, Y., Javoy, F., Beaujouan, J. C., Rossier, J., Glowinski, J. 1975. Effects of dopaminergic receptor agonists and antagonists on the activity of the neostriatal cholinergic system. *Brain Res.* 84:227–44
121. Giorgueiff, M. F., LeFloc'h, M. L., Westfall, T. C., Glowinski, J., Besson, M. J. 1976. Nicotinic effect of acetylcholine on the release of newly synthesized ^{3}H-dopamine in rat striatal slices and cat caudate nucleus. *Brain Res.* 106:117–31
122. Giorgueiff, M. F., LeFloc'h, M. L., Glowinski, J., Besson, M. J. 1977. Involvement of cholinergic pre-synaptic receptors of nicotinic and muscarinic types in the control of the spontaneous release of dopamine from striatal dopaminergic terminals in the rat. *J. Pharmacol. Exp. Ther.* 200:535–44
123. Simke, J. P., Saelens, J. K. 1977. Evidence for a cholinergic fiber tract connecting the thalamus with the head of the striatum of the rat. *Brain Res.* 126:487–95
124. Miller, R. J., Hiley, C. R. 1976. Anti-dopaminergic and antimuscarinic effects of dibensodiazepines. Relationship to drug-induced Parkinsonism. *Naunyn-Schmeideberg's Arch. Pharmacol.* 292:289–93
125. Goodman, L. S., Gilman, A., eds. 1975. *The Pharmacological Basis of Therapeutics.* New York: Macmillan. 229 pp.
126. Cannon, J. G., Kim, J. C., Aleem, M. A., Long, J. P. 1972. Centrally acting emetics.6.Derivatives of β-naphthylamine and 2-indanamine. *J. Med. Chem.* 15:348–50
127. Cannon, J. G. 1975. Chemistry of dopaminergic agonists. *Adv. Neurol.* 9:177–83
128. MacLeod, R. M. 1976. Regulation of prolactin secretion. In *Frontiers of Neuroendocrinology,* ed. L. Martini, W. F. Ganong, pp. 169–94. New York: Raven
129. MacLeod, R. M., Login, I. S. 1977. Regulation of prolactin secretion through dopamine, serotonin, and the cerebrospinal fluid. *Adv. Biochem. Psychopharmacol.* 16:147–57
130. Meites, J. 1977. Catecholamines and prolactin secretion. *Adv. Biochem. Psychopharmacol.* 16:139–46
131. Shaar, C. J., Smalstig, E. B., Clemens, J. A. 1973. The effect of catecholamines, apomorphine, and monoamine oxidase on rat anterior pituitary prolactin release in vitro. *Pharmacologist* 15:256
132. Hill, M. K., MacLeod, R. M., Orcutt, P. 1976. Dibutyryl cyclic AMP, adenosine and guanosine blockade of the dopamine, ergocryptine, and apomorphine inhibition of prolactin release in vitro. *Endocrinology* 99:1612–17

132a. Rick, J., Payne, P., Cannon, J., Frohman, L. 1977. Evidence for differences in pituitary dopamine (DA) receptors from those in the kidney based on the prolactin (PRL)-supersensitive effects of 2-aminotetralin analogs. *Clin. Res.* 25(4):566A

133. Volkman, P. H., Goldberg, L. I. 1976. Lack of correlation between inhibition of prolactin release and stimulation of dopaminergic renal vasodilation. *Pharmacologist* 18:130
134. Rusterholz, D. B., Barfknecht, C. F., Clemens, J. A. 1976. Ergoline congeners as potential inhibitors of prolactin release. *J. Med. Chem.* 19:99–102
135. Chase, T. N., Shoulson, I. 1975. Dopaminergic mechanisms in patients with extrapyramidal disease. *Adv. Neurol.* 9:359–66
136. Clemens, J. A., Smalstig, E. B., Shaar, C. J. 1975. Inhibition of prolactin secretion by lergotrile mesylate: Mechanism of action. *Acta Endocrinol.* 79:230–37
137. Pasteels, J. L., Dariguy, A., Frerotte, M., Ectors, F. 1971. Inhibition de la secretion de prolactine par l'ergocormine et la 2-brome-α-ergocryptine. Action direct sur l'hypophyse en culture. *Ann. Endocrinol.* 32:188–211
138. McCallum, R. W., Sowers, J. R., Hershman, J. M., Sturdevant, R. A. 1976. Metoclopramide stimulates prolactin secretion in man. *J. Clin. Endocrinol. Metab.* 42:1148–52
139. Carlson, H. E., Briggs, J. E., McCallum, R. W. 1977. Stimulation of prolactin secretion by metoclopramide in the rat. *Proc. Soc. Exp. Biol. Med.* 154: 475–78
140. Iwasaki, Y., Kato, Y., Chihara, K., Ohgo, S., Maeda, K., Imura, H. 1976. Effect of sulpiride on plasma prolactin in rats. *Neuroendocrinology* 21:267–74
141. MacLeod, R. M., Robyn, C. 1977. Mechanism of increased prolactin secretion by sulpiride. *J. Endocrinol.* 72:273–77
142. Furchgott, R. F. 1972. The classification of adrenoceptors (adrenergic receptors). An evaluation from the standpoint of receptor theory. In *Handbook of Experimental Pharmacology*, ed. H. J. Blaschko, E. Muscholl, pp. 283–335. New York: Springer
143. Goldberg, L. I., Toda, N. 1975. Dopamine induced relaxation of isolated canine renal, mesenteric, and femoral arteries contracted with prostaglandin $F_{2\alpha}$. *Circ. Res.* 36:I–97–I–102
144. Toda, N., Goldberg, L. I. 1975. Effects of dopamine on isolated canine coronary arteries. *Cardiovasc. Res.* 9:384–89
145. Murakami, W., Shibata, S. 1976. Evidence for a dopamine sensitive receptor in the young rat aorta. *Res. Commun. Chem. Pathol. Pharmacol.* 13:349–54