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Neuronal Dopamine Receptors on Autonomic Ganglia and Sympathetic Nerves and Dopamine Receptors in the Gastrointestinal System*

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I. Introduction

In 1972, Goldberg (180) wrote the first extensive review on peripheral dopamine receptors in the mammalian organism. The peripheral dopamine receptors which had been identified up to then were located on the smooth muscle cells of renal and mesenteric arterial beds and mediated vasodilatation. The evolution since 1972 of the knowledge of peripheral dopamine receptors has been discussed in several reviews (54, 100, 110, 117, 185, 188, 322, 390, 412). Peripheral dopamine receptors have now been described in the mammalian organism at many sites other than the vascular smooth muscle, i.e., on autonomic nerve endings in the cardiovascular system, the nictitating membrane, the spleen, the vas deferens and other organs, on autonomic ganglia, in the gastrointestinal system, the retina, the carotid body, endocrine cells, and the kidney.

The study of peripheral dopamine receptors should be considered together with the functional role of dopamine (DA) and dopamine receptors in the central nervous system (CNS), since it is to be expected that a better knowledge of the peripheral dopamine receptor will improve the understanding of the central dopaminergic mechanisms and vice versa. We now have a better understanding of the peripheral pharmacological effects of dopamine, dopamine receptor agonists, and antagonists, and we have new therapeutic uses for these agents.

In contrast to central dopamine receptors which have been extensively studied with radioligand binding techniques, peripheral dopamine receptors have been mainly characterized by the pharmacological effects of agonists and antagonists upon them. Some of these effects have been ascribed to interaction with dopamine receptors situated on the efferent autonomic innervation of the cardiovascular and gastrointestinal systems. Our interest in these dopamine receptors, and in the effects they mediate on ganglionic transmission, heart rate and vascular tone, and gastric motility, led to the choice of the three main parts of this review. Chapter II, in which the dopamine receptors on sympathetic nerve endings in the cardiovascular system are discussed, has been extended to describe the presynaptic receptors on sympathetic nerve endings at other places, e.g., nictitating membrane and vas deferens. The dopamine receptors in autonomic ganglia are dealt with in chapter III. Chapter IV starts with the discussion of the receptor mediating the inhibitory effects of dopamine on gastrointestinal motility and is extended to a discussion of the receptors mediating the excitatory effects of dopamine on gastrointestinal motility and the inhibitory and excitatory effects on gastrointestinal exocrine secretory processes.

We do not discuss the postsynaptic dopamine receptor on vascular smooth muscle cells, nor the dopamine receptors involved with natriuresis, regulation of renin release, response of the carotid body to CO_2, electrical coupling between cells in the retina, and secretion of various hormones. These dopamine receptors and the effects they mediate have been reviewed extensively by others (4, 161, 184, 188, 189, 255, 256, 271, 306, 322, 355, 365, 381, 449, 492).

We included within the different chapters of this review all literature data available to us at the end of 1984—mainly full papers and symposia proceedings, but also abstracts providing some interesting details or new information. Most emphasis is put on original work suggesting the presence of dopamine receptors in the different systems. These experimental observations are discussed in detail to explain why we do or do not accept the authors' interpretation of the data.

In this introductory chapter, some aspects of pharmacological receptor characterization and the different classifications for dopamine receptors used in the literature are briefly discussed.

A. Pharmacological Receptor Characterization

Pharmacological receptor characterization is based on the determination of relative potencies of a number of agonists and antagonists. These relative potencies, however, are an estimate of the relative affinities for the receptor only if some conditions are met (see refs. 168 and 169). The most important shortcomings in *in vivo* experiments are the lack of knowledge of the drug concentration at the receptor and the absence of equilibrium in the drug-receptor interaction. Furthermore, in both *in vivo* and *in vitro* experiments, interaction of the drug with other receptors can often not be avoided or excluded. For example, when studying the presynaptic effect of dopamine receptor agonists in heart and blood vessels, their influence on postsynaptic α- and β-adrenoceptors and presynaptic α_2-adrenoceptors can modify their apparent potency on the presynaptic dopamine receptor. Furthermore, in most of the experiments that will be discussed, the final effect depends not only upon the drug-receptor interaction, but also upon the interplay of decreased transmitter release with other neurohumoral determinants of vascular tone and cardiac rate. For these reasons, the presence or absence of an effect and the relative potencies of agonists and antagonists do not necessarily reflect the efficacy and the affinity at the receptor site. Although some of these drawbacks can be minimized, they probably explain in part the lack of consistency of pharmacological SAR-studies.

B. Classification of Dopamine Receptors

Dopamine receptors in the CNS and in the periphery do not seem to constitute a homogenous group, and several classification systems have been proposed.

Central dopamine receptors have been classified in different ways, depending upon the identification technique used.

A first classification has been proposed by Cools and Van Rossum (114) and is based on the behavioral effects of dopamine receptor agonists and antagonists; it distinguishes an excitation-mediating dopamine receptor (DAe) and an inhibition-mediating dopamine receptor (DAi). This classification is further linked to differences in potency of agonists and antagonists: the DAe receptor is preferentially stimulated by agonists showing the α-rotamer configuration (see fig. 2 and chapter II) and preferentially blocked by butyrophenones, whereas the DAi receptor shows selectivity for agonists with the β-rotamer configuration (see fig. 2 and chapter II) and for antagonists such as benzamides. Finally, these two dopamine receptor types also have different anatomical localizations (114). This classification is similar to that proposed in molluscan neurons where dopamine has been described as producing specific excitatory (depolarization) or inhibitory (hyperpolarization) effects in different kinds of neurons (501). A modification of the classification, including also a mixed DAe/i receptor, was later introduced to explain some aberrant observations (113).

A second classification has been proposed by Kebabian and Calne (272). It distinguishes two types of receptors, based on the difference in the biochemical effect they mediate: a D-1 receptor linked to a cyclic AMP system and stimulating a dopamine-specific adenylate cyclase; and a D-2 receptor not linked to adenylate cyclase. This difference is parallelled by differences in agonist and antagonist potencies, where, for example, apomorphine, the butyrophenones, and the benzamides preferentially react with the D-2 receptor (271, 272). The behavioral effects of neuroleptic agents and the characteristics of agonists and antagonists in displacing [^{3}H]haloperidol binding in the striatum (see below) are related to the D-2 receptor characteristics. The D-1 adenylate cyclase was first found in the striatum, but its physiological or pharmacological significance there is not known. An adenylate cyclase linked D-1 receptor is also found in bovine parathyroid gland, where its stimulation is accompanied by the release of parathyroid hormone, and in the external horizontal cells of the carp retina, where its stimulation causes the electrical coupling between cells (271, 272). The D-2 receptor is found in the mammotrophs of the anterior pituitary, where it mediates inhibition of prolactin secretion (271, 272, 449). It has also been described in the melanotrophs of the intermediate lobe of the pituitary, where it inhibits the release of melanocyte stimulating hormone. It is now known that the D-2 receptor in the pituitary is negatively linked to the cyclic AMP system and inhibits adenylate cyclase. The potency of agonists for inhibition of adenylate cyclase and of hormone secretion parallels their potency for inhibition of [^{3}H]haloperidol binding in the pituitary (271, 449). Finally, besides differences in biochemical effects and in relative potencies of agonists and antagonists, there is also a difference in absolute potency of the agonists for the two receptors: agonists are active in μM range for the D-1 and in nM range for the D-2 receptor (271, 272).

A third classification, originating from studies using radioligand binding techniques, is mainly based on differences in absolute potency (122, 424–426, 436). Seeman (425, 426) describes four different dopamine receptive sites: D_1 (sensitive to agonists and antagonists in μM concentrations); D_2 (sensitive to agonists in μM and antagonists in nM); D_3 (sensitive to agonists in nM and antagonists in μM); and D_4 (sensitive to agonists and antagonists in nM concentrations). Variants of this classification are those of Creese and coworkers (122) which describe, besides the D_1 receptor, two receptive sites, a low and high affinity state of the D_2 receptive site and a D_3 site, and that of Schwartz and coworkers (424, 436) for which the D_2 site presents high agonist affinity and the D_4 site, low agonist affinity. A further characteristic of this classification system is that different ligands have to be used, *cis*-[^{3}H]flupenthixol for the study of the D_1

site, and [^{3}H]haloperidol for the study of the D_2, D_3, and D_4 sites. Interestingly, the relative potency of the agonists in displacing these ligands on the four sites is the same (425, 426). The question can be asked whether these receptive sites are equivalent to pharmacological receptors mediating an effect. According to Seeman (425, 426), the D_2 site corresponds to the central neuroleptic receptor, and the D_4 site corresponds to the receptor in the anterior and intermediary lobes of the pituitary. The D_3 site is an autoreceptor on central dopaminergic neurons (122, 424–426, 436). According to Langer (300), the D_2 site is a D_2 receptor inhibiting the release of various neurotransmitters in the brain (they are presynaptic receptors), the D_2 receptor situated on dopaminergic nerves being an autoreceptor. Recently, Creese and coworkers suggested that the ^{3}H-labeled agonist binding to the D_3 site or autoreceptor is, in fact, labeling a high-affinity agonist-binding state of a D_1 site (123). According to Laduron (289, 290, 313), only one dopamine receptor exists which is not linked to an adenylate cyclase and which is not an autoreceptor.

From these attempts at classification, the concept of the existence of two dopamine receptors emerges, now indicated as the D_1 and D_2 receptor (449). The D_2 receptor mediates the central effects of dopamine receptor agonists and dopamine receptor antagonists, the relative binding affinities being similar to the relative potencies in behavioral tests and in therapeutic efficacy, particularly for the butyrophenones and the benzamides. This D_2 receptor is the same as the D-2 receptor described in the anterior and intermediate part of the pituitary. It remains possible that this receptor can exist in different affinity states in function of the presence or absence of guanyl nucleotides or other cofactors (122, 425). At some places at least, this receptor is negatively linked to adenylate cyclase. The pituitary seems to be the most suitable preparation to study the different steps between D_2 receptor activation and pharmacological effect. The D_1 receptor seems different from the D_2 receptor, particularly because there is no relationship between the affinity of the butyrophenones and benzamides for this receptor and their behavioral and therapeutic potency. The activation of the D_1 receptor stimulates a dopamine sensitive adenylate cyclase. Besides a possible role in the bovine parathyroid gland, no receptor role for the D_1 site linked to striatal adenylate cyclase is known in the CNS (271, 272, 425, 426, 449). This could, however, change, as the selective D_1 antagonist SCH 23390 was found to resemble many neuroleptics in its pharmacological profile (106, 257).

As far as *peripheral dopamine receptors* are concerned, it has already been mentioned that, in 1972, only a postsynaptic dopamine receptor was known (180). After the first descriptions, however, of a specific dopamine receptor on sympathetic ganglia (497), on the accelerator nerves of the heart (334), on the sympathetic nerve endings of the nictitating membrane (152), the ear artery (238), and the femoral vascular bed (68), and with further observations on the postsynaptic receptor (188), it became clear that the pharmacological characteristics of all peripheral dopamine receptors were not identical.

The first suggestion of two types of receptors was made by us in 1978, based on the parallellism between some effects of dopamine and the α- and β-effects of noradrenaline (500). Noradrenaline and dopamine inhibit ganglionic transmission and decrease the release of noradrenaline from sympathetic nerve endings; although the receptors involved are different, the effects of both noradrenaline and dopamine are prevented by phenoxybenzamine (152, 238, 497). On the other hand, both noradrenaline and dopamine produce renal vasodilatation and, although the receptors involved are different, for both, the vasodilatation is only observed in the presence of phenoxybenzamine (180, 188). Hence, it appeared that phenoxybenzamine blocks the dopamine receptor located on the neuronal system, without affecting the dopamine receptor located on vascular smooth muscle. This difference between a "neuronal" and a "vascular" dopamine receptor was further strengthened by the differences in relative potencies of the dopamine receptor agonist apomorphine and the antagonist haloperidol, apomorphine being a full agonist and haloperidol a potent antagonist on the neuronal, but not on the vascular, receptor (500).

Goldberg and Kohli (183) confirmed the existence of two classes of peripheral dopamine receptors and proposed the terminology of a DA_1 receptor, subserving vascular relaxation, and a DA_2 receptor, subserving inhibition of noradrenaline release from postganglionic sympathetic nerves. They used the canine femoral vascular bed as a model for the presynaptic receptor and the canine renal vascular bed for the postsynaptic receptor and studied systematically several dopamine receptor agonists and antagonists. This terminology, chosen in accordance with the α_1-α_2, β_1-β_2, and H_1-H_2 terminology used for other neurotransmitter systems, was on purpose different from the D-1, D-2 terminology proposed around the same time by Kebabian and Calne for the central dopamine receptors (see above). Indeed, the relative potencies of different agonists and antagonists on DA_1 and D-1, and on DA_2 and D-2 receptors are different (183, 188). More recently, the terms "postsynaptic" or "vascular" for the DA_1 receptor and "presynaptic" for the DA_2 receptor have been abandoned, since these receptor types may also be located at other sites in and outside the vascular system.

Lokhandwala and Barrett (322) introduced the term "neurotropic" dopamine or δ_2 receptor for dopamine receptors located on sympathetic ganglia and sympathetic nerve endings, and "postsynaptic" dopamine or δ_1 receptor for the vascular musculotropic dopamine receptors and dopamine receptors in adrenal cortex, juxtaglomerular cells, and renal tubules.

In this review, we will use the DA_1-DA_2 terminology. The distinction between DA_1 and DA_2 receptors and the comparison between DA_1, DA_2, and D_1, D_2 dopamine receptors will be discussed in more detail in chapter II, B.

II. Presynaptic Dopamine Receptors

In the past decade, it has become apparent that endogenous and exogenous substances can modify the release of transmitter from postganglionic sympathetic nerve endings through an effect on receptors located on these nerve endings, the so-called presynaptic receptors. As pointed out by Haeusler (205), the term "prejunctional" would be more appropriate, as the junctions between the sympathetic nerve endings and smooth muscle cells are morphologically different from a synapse. However, the term presynaptic is generally accepted and will also be used in this review.

As far as adrenergic substances are concerned, inhibitory α-adrenoceptors and facilitatory β-adrenoceptors have been described on sympathetic nerve endings in several organs, and the presynaptic regulation of noradrenaline release has been extensively reviewed (297–299, 387, 442, 443, 494). Some sympathetic nerve endings are also endowed with an inhibitory receptor selective for dopamine. In contrast to the presynaptic α-adrenoceptor, which is distributed over all organs in all species, the distribution of the presynaptic dopamine receptor is limited with regard to different organs as well as to different species (341).

The organs in which presynaptic dopamine receptors have been described are discussed in detail in the following sections. For part of them, the experimental observations are listed in tables 1 to 3. The tables are subdivided according to the experimental technique used, and information is given on the agonists and antagonists studied. In the tables, the doses of the agonists which showed the effect described are given. The great variety of doses used and the difficulty in constructing potency ratios *in vivo* and *in vitro* are apparent. For each organ, we first focus in the text on the principal observations which support the presence of dopamine receptors mediating the inhibition of the release of noradrenaline and/or the inhibition of the end organ response to sympathetic simulation. This is then followed by a discussion of the observations made with a large number of dopamine analogues. The fact that a large series of compounds, structurally related to dopamine, mimic the presynaptic effect of dopamine is indeed an argument in favour of the presence of a dopamine receptor. The dopamine analogues mentioned in tables 1 to 3 are those producing a presynaptic inhibitory effect, whether or not this effect is mediated via a dopamine receptor. Dopamine analogues studied, but not showing this presynaptic effect, are referred to in the text but are not mentioned in the tables.

Detailed discussions of the structural characteristics of dopamine analogues and of their relationship with activity have been presented by others (77, 78, 268, 425). We want to comment briefly on these structural characteristics, as this terminology will be used in the further discussions.

The basic structure of the different subgroups of dopamine agonists used is shown in fig. 1.

The phenethylamines are directly derived from dopamine, with substitutions on the nitrogen atom, the side-chain, or the ring structure of the molecule.

Three-dimensional structural analysis shows that the dopamine molecule can exist in different structural conformations. Since it appeared that, for the different types of dopamine receptors, the preferred dopamine conformation might be different, these conformations were frozen in more rigid analogues. Most interest turned to the conformation in which the catechol ring is coplanar with the plane of the ethylamine side chain (see the Newman projections, fig. 2). This conformation exists either as the α-conformer or as the β-conformer. The α-conformer was then fixed, and the influence of different substitutions was further explored in the 5,6-dihydroxy-2-aminotetralins (5,6-ADTN) and the 4,5-aminoindans; the β-conformer was fixed in the 6,7-dihydroxy-2-aminotetralins (6,7-ADTN).

The ergot alkaloids constituted another starting point for chemical synthesis, as it was recognized that some of these compounds were either agonists or antagonists at the dopamine receptor. Their structure was simplified in the ergolines and the indoles.

The octahydrobenzoquinolines constitute, in part, a structural bridge between the 2-aminotetralins (ATN) and the ergolines or are further variations of the ring structure in which the dopamine moiety is fixed in one of its configurations. The α-conformer of dopamine is found in the 7,8-dihydroxyoctahydrobenzo(*f*)quinolines, the 6,7-dihydroxyoctahydrobenzo(*g*)quinolines, and the 8,9-dihydroxyoctahydrobenzo(*h*)quinolines. The β-conformer of dopamine is found in the 8,9-dihydroxy(*f*)-, the 7,8-dihydroxy(*g*)-, and the 7,8-dihydroxy(*h*)benzoquinolines. The terms *cis* and *trans* refer to the hydrogen atoms associated with the B and C ring, the *trans* form being a highly rigid coplanar extended structure, whereas the *cis* form is less rigid, existing in more than one conformation.

Finally, a number of miscellaneous structures have been studied, e.g., the benzazepines.

A. Presynaptic Dopamine Receptors in Different Organs

1. *Nictitating membrane (table 1).* The first indication for the existence of a peripheral presynaptic dopamine receptor came from the experiments of Langer and coworkers (152, 296) in the *in vitro* nictitating membrane preparation of the cat. In the presence of cocaine, dopamine was equipotent with noradrenaline in inhibiting

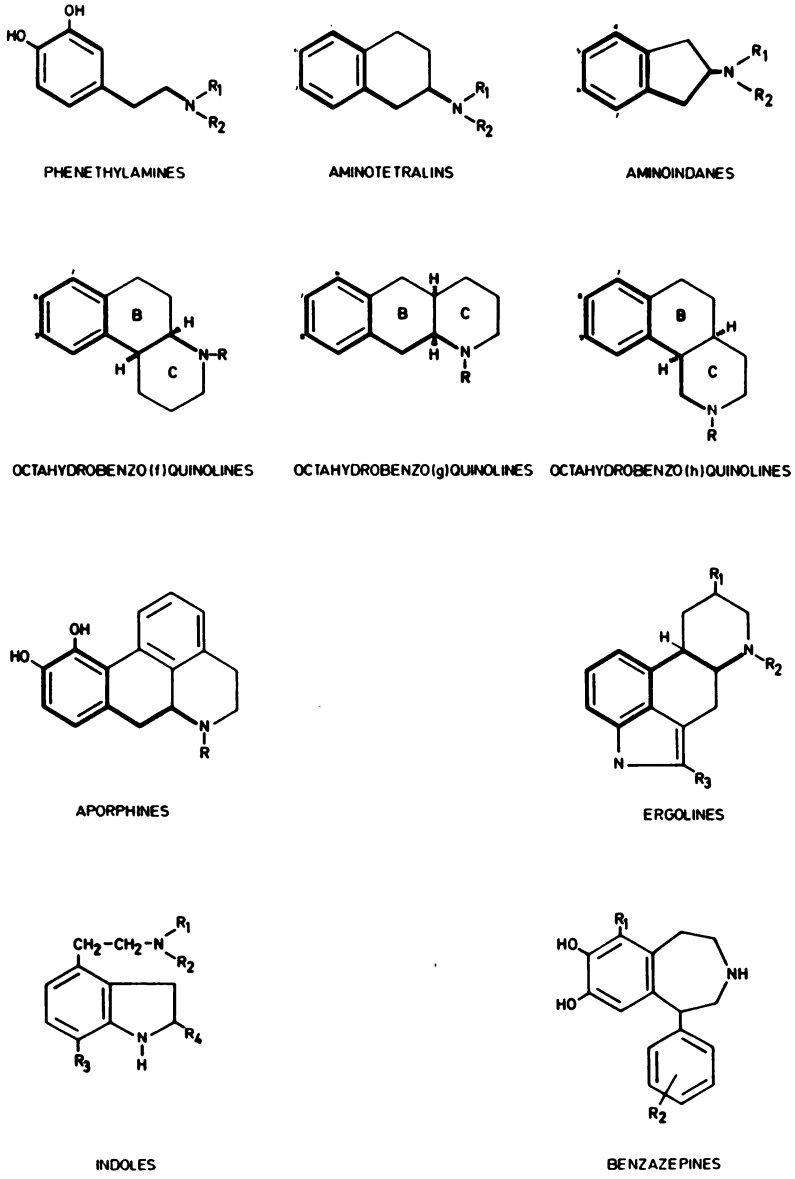

FIG. 1. Basic structures of the different groups of dopamine receptor agonists studied for their presynaptic inhibitory dopaminergic activity. The dopamine moiety within each structure is indicated.

the nerve stimulation-evoked release of [^{3}H]noradrenaline. Since dopamine is 40 times less potent that (−)-noradrenaline at postsynaptic α-adrenoceptors, Langer (296) first suggested that both noradrenaline and dopamine interacted with a presynaptic α-adrenoceptor which was different from the postsynaptic α-adrenoceptor (see also ref. 446). However, apomorphine mimicked the effect of dopamine, and the effect of dopamine and apomorphine was antagonized by chlorpromazine and pimozide in concentrations that did not affect the inhibitory effect of noradrenaline. Phentolamine, on the other hand, blocked the effect of noradrenaline, but much less that of dopamine. Phenoxybenzamine antagonized the effects of noradrenaline, dopamine, and apomorphine (152, 296). On the basis of these findings, it was concluded that dopamine inhibits the release of noradrenaline via a dopamine receptor. In contrast to its clear effect on transmitter overflow, dopamine only partially inhibited the stimulation-induced contraction of the nictitating membrane (152). This illustrates that the end organ response, even under *in vitro* conditions, does not always clearly reflect what happens at the presynaptic level (139).

Observations in the cat confirmed that known dopaminergic agents also interfered *in vivo* with nerve stimulation-induced contractions of the nictitating membrane via a dopamine receptor. Dopamine in the presence of cocaine (199), apomorphine (199, 201), bromocriptine, and piribedil (201) inhibited these contractions. The effect of dopamine was antagonized by haloperidol (199), the effect of piribedil by sulpiride (201), the effect of apomorphine by haloperidol (199) and sulpiride (201), but not by phentolamine (199). The effect of bromocriptine was long lasting, and haloperidol and sulpiride were only effective as antagonists when given before bromocriptine (200) (see also chapter II.A.3.).

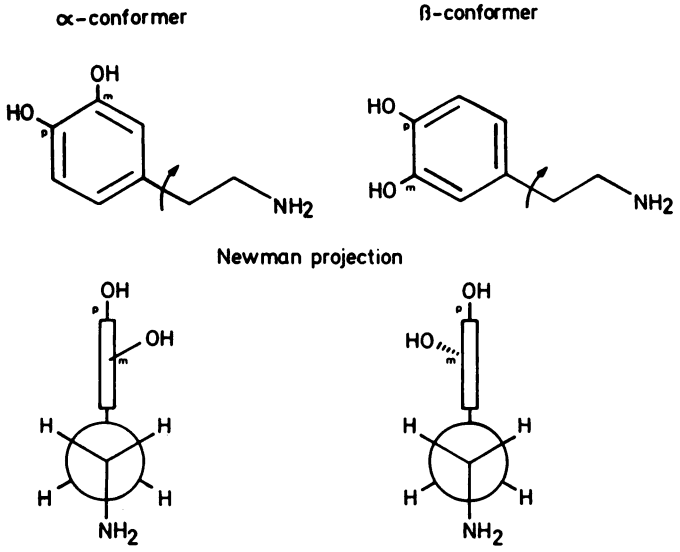

FIG. 2. α- and β-conformers of dopamine with their respective Newman projection.

Other structural analogues of dopamine were then tested on the *in vivo* nictitating membrane preparations of the cat and the dog. It was accepted that these agonists inhibited the stimulation-evoked contractions by interaction with the dopamine receptor, because their effect was antagonized by haloperidol, sulpiride, and (+)-butaclamol. The results obtained in the dog by Shepperson and coworkers (430) with the different antagonists listed in table 1, mainly with *R*- and *S*-sulpiride, form one of the bases used to distinguish DA_2 from DA_1 receptors (see chapter II.B): it was shown that *S*-sulpiride but not *R*-sulpiride is a specific antagonist against the presynaptic effect of *N*,*N*-di-*n*-propyl-DA.

It should be added that, in several of the experiments listed in table 1, preganglionic nerve stimulation was applied so that a ganglionic inhibitory effect of the agents studied cannot be excluded (12, 199–201, 428, 430). As far as the observations of Shepperson *et al.* are concerned, the authors argue that their results in the nicti-

TABLE 1

Presynaptic dopamine receptors in the nictitating membrane. The experimental observations whereby dopamine and dopamine receptor agonists produced a presynaptic inhibitory effect in the nictitating membrane are listed.

Agonist	Species	Reference	Dose or concentration*	Antagonized by	Not antagonized by
Inhibition of ^{3}H-noradrenaline overflow elicited by sympathetic stimulation in vitro					
Dopamine (DA)	Cat	152	200–650	Chlorpromazine Phenoxybenzamine	Phentolamine
Apomorphine	Cat	152	30–100	Chlorpromazine Pimozide Phenoxybenzamine	Phentolamine
Inhibition of the contractions of the nictitating membrane elicited by sympathetic nerve stimulation in vivo					
Phenethylamines					
Dopamine (DA)	Cat	199	160–1600/kg i.v.	Haloperidol	
N,*N*-di-*n*-propyl-DA	Cat	350	623/kg/min i.v.	*RS*-Sulpiride	
	Dog	12, 430	78.5–628/kg/min i.v. 316–2528/kg i.v.	Haloperidol *S*-Sulpiride (+)-Butaclamol	Yohimbine *R*-Sulpiride Bulbocapnine (−)-Butaclamol
Aporphines					
Apomorphine	Cat	199, 201	66–165/kg i.v. 10–26 i.a.	Haloperidol Sulpiride	Phentolamine
2-Aminotetralins (ATN)					
N,*N*-di-*n*-propyl-5-hydroxy-6-methyl-ATN (DK118)	Cat	485	96–290/kg intrad.		
Octahydrobenzo (*f*)quinolines					
GJH-166 (*N*-methyl-7,8-diOH, *trans*)	Dog	428	1.6–6.4/kg i.v.	Haloperidol	
Ergotalkaloids					
Bromocriptine	Cat	200, 201	27–40/kg i.v. 1.5–12.2 i.a.	Haloperidol Sulpiride	
Miscellaneous					
Piribedil	Cat	200, 201	0.9–1400/kg i.v. 330–500 i.a.	Haloperidol Sulpiride	
355/1057 (2 (*R*,*S*)-Cyano-3-(6-methylergolin-8β-yl)propionamide)	Cat	405	300-3000/kg intrad.		
LY 141865 (*N*-*n*-propyl-2 H-octahydro-pyrasolo (*g*)quinoline, *trans*)	Dog	12	35–280/kg i.v.	Sulpiride	

* Doses given i.v., intraarterially (i.a.), or intraduodenally (intrad.) in nmol, or concentrations in vitro in nM; ranges of active doses (concentrations) for which a dose (concentration)-effect relationship existed are given.

tating membrane with preganglionic stimulation are identical to those obtained in the heart where postganglionic nerve stimulation is applied (430). The ganglionic inhibitory effect of dopamine is discussed in chapter III.

2. The heart (table 2). a. BASIC OBSERVATIONS. Soon after the demonstration that a dopamine receptor mediates the presynaptic effects of dopamine in the nictitating membrane, similar observations were made in the heart. Experiments *in vivo* in the cat by Long, Cannon, and coworkers showed that dopamine (after cocaine administration) and the structurally related agents, apomorphine and *N,N*-dimethyl-5,6-dihydroxyamino-

TABLE 2

Presynaptic dopamine receptors in the heart. The experimental observations whereby dopamine and dopamine receptor agonists produced a presynaptic inhibitory effect in the heart are listed.

Agonist	Species	Reference	Dose or concentration*	Antagonized by	Not antagonized by
Inhibition of the chronotropic response to postganglionic cardioaccelerator nerve stimulation in vivo					
Phenethylamines					
Dopamine (DA)	Cat	87, 247 250, 334, 341	105/kg i.v. (ID_{50})	Haloperidol Bulbocapnine	Phenoxybenzamine
	Dog	325, 326	26–52/kg/min	Haloperidol Pimozide	Phentolamine
α-Methyl-DA	Dog	325	47/kg/min	Phentolamine	
N-Methyl-DA	Dog	325	24/kg/min	Haloperidol	
N,N-Dimethyl-DA	Cat	82, 249 250, 252	24/kg i.v. (ID_{50})	Haloperidol Pimozide Bulbocapnine	Phenoxybenzamine
N,N-Diethyl-DA	Dog	333	3.8–38/kg/min i.v.		
	Cat	82	41/kg i.v. (ID_{50})	Haloperidol	Phentolamine
N,N-di-*n*-propyl-DA	Dog	333	10–103/kg/min i.v.		
	Cat	82	68/kg i.v. (ID_{50})	Haloperidol	Phentolamine
	Dog	12, 97	134/kg i.v. (ID_{50})	*RS*-Sulpiride	Phentolamine
		279, 286 320, 333 430	31–628/kg/min i.v.	Metoclopramide Clebopride Domperidone *S*-Sulpiride Haloperidol (+)-Butaclamol	*l*-Bulbocapnine *R*-Sulpiride Yohimbine
N-*n*-Propyl-*N*-*n*-butyl-DA	Rat	97	314/kg/min i.v.	Phentolamine	Haloperidol
	Dog	216		Sulpiride	
Aminotetralins (ATN)					
2-Aminotetralins (ATN) (ADTN)					
N,N-di-*n*-propyl-ATN (TL-68)	Cat	253	350/kg (ID_{50})	Haloperidol	Yohimbine
2-Amino-5,6-dihydroxytetralins (5,6-ADTN)					
N,N-Dimethyl-5,6-ADTN (M7)	Cat	250, 252 334, 341	2–80/kg i.v.	Haloperidol Chlorpromazine Bulbocapnine Pimozide	Phentolamine
	Dog	334	2–270/kg i.v.		
	Rat	81, 108 109, 227	10–173/kg i.v. 3500/kg s.c.	Yohimbine Sulpiride Piperoxan	Haloperidol Pimozide Metoclopramide Fluphenazine
N,N-Diethyl-5,6-ADTN (TL-259)	Rat	81, 227	0.8–40/kg i.v.	Phentolamine Yohimbine	Haloperidol Pimozide Perphenazine
N,N-di-*n*-propyl-5,6-ADTN (TL-102)	Cat	341	8.2/kg i.v. (ID_{50})	Haloperidol	
	Rat	81, 208 227	1.5–36/kg i.v.	Yohimbine	Haloperidol Pimozide Fluphenazine
2-Amino-6,7-dihydroxytetralins (6,7-ADTN)					
N,N-Dimethyl-6,7-ADTN (TL-99)	Cat	275, 341	0.31/kg i.v. (ID_{50})	Haloperidol	Phentolamine
	Dog	275	4–12.5/kg i.v.	Phentolamine	Haloperidol
N,N-di-*n*-propyl-6,7-ADTN (TL-232)	Cat	341	1/kg i.v. (ID_{50})	Haloperidol	

TABLE 2—Continued

Agonist	Species	Reference	Dose or concentration*	Antagonized by	Not antagonized by
2-Amino-5,7-dihydroxytetralins (5,7-ADTN)					
N,N-Dimethyl-5,7-ADTN	Cat	79	21/kg i.v. (ID_{50})	Haloperidol	
N-Ethyl-5,7-ADTN	Cat	79	40/kg i.v. (ID_{50})	Haloperidol	
N,N-Diethyl-5,7-ADTN	Cat	79	24/kg i.v. (ID_{50})	Haloperidol	
N,N-di-*n*-propyl-5,7-ADTN	Cat	79	35/kg i.v. (ID_{50})	Haloperidol	
2-Amino-5,6-substituted tetralins					
N,N-Diethyl-5-OH,6-methyl-ATN (DK121)	Cat	83, 485	480/kg i.v. (ID_{50})	Haloperidol	
N,N-di-*n*-propyl-5-OH,6-methyl-ATN (DK118)	Cat	83, 485	25/kg i.v. (ID_{50})	Haloperidol	Phentolamine
	Dog	485	145–290/kg i.v.	Haloperidol	Phentolamine
N,N-di-*n*-propyl-5-OH-ATN (JGC-174)	Cat	341	5.9/kg i.v. (ID_{50})	Haloperidol	
N,N-di-*n*-propyl-6-OH-ATN (JMB-249)	Cat	341	150/kg i.v. (ID_{50})	Haloperidol	
Aminoindan					
N,N-Diethyl-4,5-dihydroxy-aminoindan	Cat	87	50/kg i.v. (ID_{50})	Haloperidol	
N,N-di-*n*-propyl-4,5-dihydroxy-aminoindan	Cat	87	20/kg i.v. (ID_{50})	Haloperidol	
N,N-di-*n*-propyl-4,7-dimethoxy-aminoindane (RDS-127)	Cat	433	107/kg i.v. (ID_{50})	Haloperidol	
Aporphines					
Apomorphine	Cat	79, 82 83, 85 86, 87 249, 250 252, 334 335, 341 433	19–103/kg i.v. (ID_{50})	Haloperidol Bulbocapnine Pimozide	Phentolamine Phenoxybenzamine
Octahydrobenzoquinolines					
TL-224 (*N*-H-7,8-diOH(*f*),*cis*)	Cat	335, 341	27/kg i.v. (ID_{50})	Phentolamine	Haloperidol
TL-137 (*N*-H-7,8-diOH(*f*),*trans*)	Cat	335, 341	0.7/kg i.v. (ID_{50})	Haloperidol	Phentolamine
GJH-171 (*N*-methyl-7,8-diOH(*f*),*cis*)	Cat	335, 429	620/kg i.v. (ID_{50})	Haloperidol	Phentolamine
GJH-166 (*N*-methyl-7,8-diOH(*f*),*trans*)	Cat	335, 429	5.2/kg i.v. (ID_{50})	Haloperidol	Phentolamine
TL-121 (*N*-ethyl-7,8-diOH (*f*),*trans*)	Cat	335	0.47/kg i.v. (ID_{50})	Haloperidol	Phentolamine
TL-140 (*N*-*n*-propyl-7,8-diOH(*f*),*trans*)	Cat	335, 341	0.3/kg i.v. (ID_{50})	Haloperidol	Phentolamine
Substance 3b (*N*-methyl-8,9-diOH(*f*),*trans*)	Cat	85	5.5/kg i.v. (ID_{50})	Haloperidol	
Substance 23 (*N*-methyl-8,9-diOH(f),*cis*)	Cat	85	310/kg i.v. (ID_{50})	Phentolamine	
Substance 3c (*N*-ethyl-8,9-diOH(*f*),*trans*)	Cat	85	0.9/kg i.v. (ID_{50})	Haloperidol	
Substance 24 (*N*-ethyl-8,9-diOH(*f*),*cis*)	Cat	85	450/kg i.v. (ID_{50})	Haloperidol	
TL-308 (*N*-*n*-propyl-8,9-diOH(*f*),*trans*)	Cat	85, 341	1.3/kg i.v. (ID_{50})	Haloperidol	
TL-312 (*N*-*n*-propyl-8,9-diOH(*f*),*cis*)	Cat	85, 341	260/kg i.v. (ID_{50})	Haloperidol	
TL-332 (*N*-methyl-6,7-diOH(*g*),*trans*)	Cat	341	9.4/kg i.v. (ID_{50})	Haloperidol	
TL-333 (*N*-ethyl-6,7-diOH(*g*),*trans*)	Cat	341	0.23/kg i.v. (ID_{50})	Haloperidol	
TL-334 (*N*-*n*-propyl-6,7-diOH(*g*),*trans*)	Cat	341	0.32/kg i.v. (ID_{50})	Haloperidol	
Substance 21 (*N*-H-8,9-diOH(*h*),*cis*)	Cat	86	310/kg i.v. (ID_{50})	Haloperidol	
Substance 3a (*N*-H-8,9-diOH(*h*),*trans*)	Cat	86	800/kg i.v. (ID_{50})	Haloperidol	

TABLE 2—Continued

Agonist	Species	Reference	Dose or concentration*	Antagonized by	Not antagonized by
Substance 3b (*N*-methyl-8,9-diOH(*h*),*trans*)	Cat	86	520/kg i.v. (ID_{50})	Haloperidol	
Substance 3c (*N*-ethyl-8,9-diOH(*h*),*trans*)	Cat	86	810/kg i.v. (ID_{50})	Haloperidol	
Substance 22 (*N*-*n*-propyl-8,9-diOH(*h*),*cis*)	Cat	86	900/kg i.v. (ID_{50})	Haloperidol	
Substance 3d (*N*-*n*-propyl-8,9-diOH(*h*),*trans*)	Cat	86	800/kg i.v. (ID_{50})	Haloperidol	
Ergotalkaloids					
Bromocriptine	Cat	413, 414 415	22/kg i.v. (ID_{50})	Haloperidol Chlorpromazine Sulpiride Chlorprothixene Clozapine	Pizotifen
	Dog	321	1.5/kg/min i.v.	Pimozide	
Dihydroergotoxine	Cat	414	0.7 μg/kg i.v. (ID_{50})	Phentolamine	Haloperidol
Ergotamine	Cat	414	2.9 μg/kg i.v. (ID_{50})		Haloperidol Phentolamine
Ergolines					
Lergotrile	Cat	80, 87 415	270/kg i.v. (ID_{50})	Haloperidol	
	Rat	502	1700/kg i.v.		
Lisuride	Cat	415	1.5/kg i.v. (ID_{50})		
Pergolide	Cat	80	20/kg i.v. (ID_{50})	Haloperidol	
	Dog	21	3/kg/min i.v.	Sulpiride	Yohimbine
	Rat	93, 502	28.6–143/kg i.v. (ID_{50})	Sulpiride	
Indoles					
4-[2-(di-*n*-propylamino)ethyl]indole	Cat	80	220/kg i.v. (ID_{50})	Haloperidol	
TL-350 (6-OH-4-[2-(di-*n*-propylamino)ethyl]indole)	Cat	248	19/kg i.v. (ID_{50})	Sulpiride Haloperidol	Yohimbine
Indolones					
SKF 88827 (4-[2-aminoethyl]-7-OH-2(3H)indolone)	Dog	286	40.6/kg i.v. (ID_{50})		
SKF 89124 (*N*,*N*-di-*n*-propyl SKF88827)	Dog	286	3.3/kg i.v. (ID_{50})		
Miscellaneous					
Piribedil	Dog	303	6000/kg i.v.	Haloperidol	
LY 141865 (*N*-*n*-propyl-2H-octahydro-pyrasolo (*g*)quinoline, *trans*)	Dog	12	35–280/kg i.v.	Sulpiride	
Inhibition of the chronotropic response to field stimulation in vitro					
Phenetylamines					
Dopamine (DA)	Rabbit	486	$3–30.10^3$	*cis*-Flupenthixol	Phentolamine
N,*N*-Dimethyl-DA	Cat	82, 251 252	70 (IC_{50})	Haloperidol Pimozide	
	Guinea pig	445		Phentolamine	
N,*N*-Diethyl-DA	Cat	82	340 (IC_{50})		
N,*N*-di-*n*-propyl-DA	Cat	82	420 (IC_{50})		
2-Aminotetralins					
N,*N*-di-*n*-propyl-ATN (TL-68)	Cat	253	120 (IC_{50})	Haloperidol	Yohimbine
N,*N*-Dimethyl-5,6-ADTN (M7)	Cat	251, 252 334, 450	10–412	Haloperidol Pimozide	Phentolamine

TABLE 2—Continued

Agonist	Species	Reference	Dose or concentration*	Antagonized by	Not antagonized by
Aporphines					
Apomorphine	Cat	82, 251 252, 258 335	8, 43, 580 (IC_{50})	Haloperidol Pimozide *RS*-Sulpiride Phentolamine Yohimbine	Phentolamine
	Rabbit	486	10,000	*cis*-Flupenthixol	
Octahydrobenzo(*f*)quinolines					
TL-224 (*N*-H-7,8-di OH, *cis*)	Cat	335	80 (IC_{50})		
TL-137 (*N*-H-7,8-di OH, *trans*)	Cat	335	64 (IC_{50})		
GJH-171 (*N*-methyl-7,8-di OH, *cis*)	Cat	335, 429	45 (IC_{50})	Haloperidol	
GJH-166 (*N*-methyl-7,8-di OH, *trans*)	Cat	335, 429	2.6 (IC_{50})	Haloperidol	
GJH-172 (*N*-methyl-7-OH, *trans*)	Cat	429	33–330		
TL-121 (*N*-ethyl-7,8-di OH, *trans*)	Cat	335	3.5 (IC_{50})		
TL-140 (*N*-*n*-propyl-7,8-di OH, *trans*)	Cat	335	4.6 (IC_{50})		
CS-265 (*N*-*n*-propyl *trans*)	Cat	254	1070 (IC_{50})	Haloperidol	
Indoles					
TL-350 (6-OH-9-[di-*n*-propylamino)ethyl]indole)	Cat	248	26 (IC_{50})	Haloperidol Sulpiride	
Inhibition of stimulus-induced noradrenaline release from sympathetic nerves in vitro					
Dopamine (DA)	Rabbit	165	0.2–2000	Flupenthixol	
N,*N*-Dimethyl-5,6-ADTN (M7)	Cat	450	10		

* Doses given i.v., intraarterially (i.a.), or s.c. in nM, or concentrations *in vitro* in nM; ranges of active doses (concentrations) for which a dose (concentration)-effect relationship existed are given.

tetralin (M7), inhibit the increase in heart rate evoked by cardioaccelerator nerve stimulation; this effect was most marked at lower stimulation frequencies (334). The doses of dopamine studied had no influence on the tachycardia induced by noradrenaline (247); haloperidol antagonized the effects of dopamine and M7, and chlorpromazine antagonized the effect of M7 (334); the effect of dopamine was also antagonized by bulbocapnine (250); high doses of phentolamine were needed to block the dopamine and M7 effects, and phenoxybenzamine in the dose used did not block them (247, 249). However, in these experiments, no α-adrenoceptor agonist was used, so that one cannot be sure that the dose of phenoxybenzamine administered was sufficient to block the presynaptic α-adrenoceptor. The results obtained in the canine heart (325, 326, 334) are similar to those obtained in the cat heart. Phentolamine, in doses that block α-methyldopamine, also partially antagonized dopamine (325), and pimozide blocked dopamine in doses that are without effect on postsynaptic α- and β-adrenoceptors (326). *l*-Dopa also shows a presynaptic inhibitory effect, probably through conversion to dopamine (326).

Direct evidence that dopamine indeed inhibits endogenous transmitter release from cardiac sympathetic nerve endings was found in the rabbit heart *in vitro* (165). A low concentration of dopamine (2×10^{-7} M) produced a small inhibition of the rise in noradrenaline-overflow evoked by sympathetic nerve stimulation. Higher concentrations produced an increase in overflow which was reversed by cocaine to an inhibition. Flupenthixol antagonized the effect of dopamine but not the inhibitory effect of the α-adrenoceptor agonist oxymetazoline. *In vitro* experiments where heart rate was measured gave similar results (486).

b. STRUCTURE-ACTIVITY RELATIONSHIP. After the first evidence for the presence of presynaptic dopamine receptors on the sympathetic nerve endings in the cat heart had been presented, the *in vivo* cat accelerans nerve-heart preparation was used to screen many dopamine analogues for their selectivity for these receptors, a prop-

erty of potential pharmacological and therapeutical interest (see chapter II.C). The dopamine analogues which are active and the experimental observations are listed in table 2. The data gathered constitute good evidence that indeed presynaptic dopamine receptors are present in the heart. The fact that several substances, which are dopamine receptor antagonists in the central nervous system, also block the presynaptic effects of dopamine and of most of these dopamine analogues is also strongly in favour of the presence of a dopamine receptor. The different subgroups of agonists studied are here discussed separately.

i. PHENETHYLAMINES. The *N*-substituted dopamine analogues, particularly *N*,*N*-di-*n*-propyl-DA, produce a selective presynaptic effect in cat and dog which is antagonized by dopamine receptor antagonists and not by α-adrenoceptor antagonists. *N*,*N*-dimethyl-DA probably stimulates both presynaptic dopamine receptors and α-adrenoceptors (82, 249, 333).

N,*N*-dibutyl-DA, α- or β-carbon-substituted dopamines, and their *N*-alkyl derivatives did not show presynaptic activity in the heart (82, 89). *N*-*n*-propyl-*N*-*n*-butyl-DA acts on presynaptic dopamine receptors and α-adrenoceptors (216).

ii. AMINOTETRALINS AND AMINOINDANS. *N*-alkylated derivatives of 5,6-dihydroxy-2-aminotetralins (5,6-ADTN) (α-conformer) inhibit the nerve stimulation-evoked increase in heart rate in the cat, and this effect is antagonized by haloperidol (250, 252, 334, 341). The same, however, occurs with a series of *N*-alkyl derivatives of 6,7-ADTN (β-conformer) and of 5,7-ADTN (79, 275, 341). In the dog heart, the effect of *N*,*N*-dimethyl-6,7-ADTN is not antagonized by the usual dose of haloperidol (2.43×10^{-7} mol/kg i.v.), but by phentolamine (275).

N-alkyl substitution, mainly *N*,*N*-di-alkyl substitution (e.g., diethyl and di-*n*-propyl), also generated presynaptic dopamine-like activity in 5- and in 6-hydroxy-2-aminotetralin (5-OH-ATN, 6-OH-ATN), in 4,5-dihydroxyaminoindan, and in 4,7-dimethoxyaminoindan (87, 341, 433). 5,7-ADTN and nonsubstituted or single *N*-alkyl-substituted derivatives of these molecules are inactive as dopamine receptor agonists. All the active dopamine receptor agonists mentioned have at least one OH group or a substituted OH group on the catechol ring. *N*-alkyl derivatives of 2-ATN are inactive (341), except *N*,*N*-di-*n*-propyl-ATN (253).

Some *N*-alkyl-substituted 5-OH,6-methylaminotetralins also inhibit the effect of *in vivo* sympathetic stimulation of the heart (83, 485). Since *N*,*N*-di-*n*-propyl-5-OH,6-methyl-ATN (DK 118) is ineffective *in vitro* (84), it has been suggested that these compounds behave as prodrugs and are metabolized to the active 5,6-dihydroxy derivatives. Derivatives of r-amino- 6,7-dihydroxytetralin are inactive (88).

iii. OCTAHYDROBENZOQUINOLINES. Some octahydrobenzo(*f*)quinolines, as well the 7,8-dihydroxy derivatives (α-conformer) as the 8,9-dihydroxy derivatives (β-conformer), are potent inhibitors of the increase in heart rate induced in the cat by postganglionic sympathetic nerve stimulation (85, 335, 341, 429), and their effect is selectively antagonized by haloperidol but not by phentolamine. It was accepted that the two OH functions are essential for dopaminergic activity and that the *trans*-isomers, the rigid extended forms, are more potent than the *cis*-isomers. *N*-alkyl substitution increases the potency (85). Recent observations have shown that *N*-propyl substitution in a nonhydroxylated octahydrobenzo(*f*)quinoline (CS-265) induces presynaptic dopamine agonist properties, provided the molecule is in the *trans* form (254).

Among the octahydrobenzo(*g*)quinolines, the 7,8-di-OH derivatives (β-conformer) are inactive, but the *N*-alkyl-6,7-di-OH derivatives (α-conformer) are active (341).

Some octahydrobenzo(*h*)quinolines, e.g., 8,9-di-OH-derivatives (α-conformer) also produce a haloperidol-sensitive inhibition of the effect of cardioaccelerator nerve stimulation, but they are less potent than the (*f*)quinolines. The *cis*- and *trans*-isomers of this series were equally effective, and *N*-alkyl substitution did not increase their potency. It should be added that it is not clear from the literature whether the antagonistic effect of phentolamine was studied against all octahydrobenzoquinolines (see table 2).

iv. OTHER SUBSTANCES. Several ergot alkaloid derivatives produce a presynaptic inhibitory effect on the sympathetic innervation of the heart similar to that of dopamine, e.g., bromocriptine (321, 413–415), lergotrile (80), pergolide (21, 80), and lisuride (415). The fact that 4-[2-(di-*n*-propylamino)ethyl]indole and its hydroxylated derivative, TL-350, also inhibit the effect of cardioaccelerator nerve stimulation, without influencing direct postsynaptic stimulation (80, 248), indicated that this indole is the active pharmacophore of the ergot alkaloids (80).

Dihydroergotoxine and ergotamine give presynaptic inhibition of the sympathetic tone in the cat heart, but their effect seems to be mediated by α-adrenoceptors (414).

Piribedil also inhibits the sympathetic tone in the dog heart, an effect which is antagonized by pimozide and haloperidol in doses that do not antagonize the presynaptic effects of clonidine (303).

For some of the compounds mentioned, *in vitro* data are also available (see table 2), confirming that the effect occurs via a presynaptic dopamine receptor. M7 has been shown to decrease the [^{3}H]noradrenaline overflow from isolated cat hearts stimulated at low frequency (450).

c. CONCLUSION. The data mentioned above constitute good evidence that presynaptic dopamine receptors are present in the heart, at least in cat and dog.

For other species, the data are less convincing or give rise to a different conclusion. As far as the rabbit is concerned, the evidence in favour of a presynaptic dopamine receptor is based on experiments where high doses of apomorphine were used (10 μM; ref. 486); others,

TABLE 3

Presynaptic dopamine receptors in the vascular system. The experimental observations whereby dopamine and dopamine receptor agonists produced a presynaptic inhibitory effect in the vascular system are listed.

Agonist	Blood vessel, species	Reference	Dose or concentration*	Antagonized by	Not antagonized by
Dilatation of the innervated blood vessel (A) or inhibition of nerve stimulation-induced vasoconstriction (B) in vivo					
Phenethylamines					
Dopamine (DA)	(B) Renal dog	324	53/kg/min	Pimozide	
	(B) Mesenteric dog	399			
	(B) Mesenteric cat	406	211/min i.a.		
N,N-Diethyl-DA	(B) Hindlimb cat	333	1–10/kg i.a. 10–100/kg i.v.	Haloperidol	
N,N-di-*n*-propyl-DA	(A) Femoral dog	69, 136	3–750 i.a.	Haloperidol	*R*-Sulpiride
		179, 279	8.4/kg/min (ID_{50})	Metoclopramide	(−)-Butaclamol
		281, 282		*S*-Sulpiride	
		286, 489		Domperidone	
				Fluphenazine	
				RS-Sulpiride	
				(+)-Butaclamol	
	(B) Hindlimb cat	333	0.1–3/kg i.a., 3–30/kg i.v.	Haloperidol	
	(B) Renal dog	140	23/kg/min i.a.	*RS*-Sulpiride	
	(A) Renal dog				
	(B) Renal dog	350	22/kg/min i.a.	*RS*-Sulpiride	
N-*n*-propyl-*N*-ethyl-DA	(A) Femoral dog	282	3–190 i.a.		
N-*n*-propyl-*N*-*n*-butyl-DA	(A) Femoral dog	179, 282	3–190 i.a.		
N-*n*-propyl-*N*-*n*-isobutyl-DA	(A) Femoral dog	179, 282	3–190 i.a.		
N-*n*-propyl-*N*-*n*-pentyl-DA	(A) Femoral dog	179, 282	3–190 i.a.		
N-*n*-propyl-*N*-*n*-phenethyl-DA	(A) Femoral dog	179, 282	3–190 i.a.		
2-Aminotetralins (ATN)					
2-amino-5,6-dihydroxytetralins (5,6-ADTN)					
N-Methyl-5,6-ADTN (M8)	(A) Femoral dog	343	3.10^{-3}–3/kg i.a.	Propranolol	
N,N-Dimethyl-5,6-ADTN (M7)	(A) Femoral dog	69, 280	0.6 i.a.	Haloperidol	
N,N-di-*n*-propyl-5,6-ADTN	(A) Femoral dog	69, 280	0.04–0.15 i.a.	Haloperidol (+)-Butaclamol	(−)-Butaclamol
2-Amino-6,7-dihydroxytetralins (6,7-ADTN)					
N,N-Dimethyl-6,7-ADTN (TL-99)	(A) Femoral dog	280	4/kg i.v.		
2-Amino-5,6-substituted tetralins					
N,N-di-*n*-propyl-5-OH, 6-methyl-ATN (DK118)	(B) Hindlimb cat	485	36–145/kg i.v.	Haloperidol	
Aporphines					
Apomorphine	(A) Femoral dog	65, 67, 68	0.6–50 i.a.	Haloperidol	Bulbocapnine
		69, 136		Phenoxybenzamine	*trans*-Flupenthixol
		304, 363		Pimozide	(−)-Butaclamol
		499		Thioridazine	
				Metoclopramide	
				cis-Flupenthixol	
				(+)-Butaclamol	
				Domperidone	
				Fluphenazine	
				Metopimazine	
				Sulpiride	
				Dihydroergotoxine	
	(B) Hindquarters rat	145	3.7/kg/min i.a.	Haloperidol	Rauwolscine
	(B) Renal rabbit	103	0.3–33/min i.a.	Haloperidol	
	(A) Bone dog	463, 464	3.3–16.5/min i.a.		Haloperidol Phentolamine

TABLE 3—Continued

Agonist	Blood vessel, species	Reference	Dose or concentration*	Antagonized by	Not antagonized by
	(B) Carotid cat	201	79/kg i.v. (ID_{50})	Sulpiride	
N,-*n*-Propylnorapomorphine	(A) Femoral dog	69	0.1–0.3 i.a.	Haloperidol (+)-Butaclamol	(−)-Butaclamol
Octahydrobenzo(*f*)quinolines					
GJH-166 (*N*-methyl-7,8-diOH, *trans*)	(B) Hindlimb dog	428	0.8–3/kg i.v.	Haloperidol	
	(B) Gracilis dog	428	13/kg i.v.	Haloperidol	
Ergotalkaloids					
Bromocriptine	(A) Femoral dog	49, 70	10–40 i.a.	Haloperidol	
	(B) Renal dog	330	1.5/kg/min i.v.	Pimozide	
	(B) Carotid cat	201	24/kg i.v.		
Ergolines					
Elymoclavine	(A) Femoral dog	500	1–5 i.a.	Haloperidol	
N-Ethyl-*N*-norelymoclavine	(A) Femoral dog	500	5–20 i.a.	Haloperidol	
N-Propyl-*N*-norelymoclavine	(A) Femoral dog	500	1–5 i.a.	Haloperidol	
N-Benzyl-*N*-norelymoclavine	(A) Femoral dog	500	80–320 i.a.	Haloperidol	
Elymonitrile	(A) Femoral dog	500	0.3–1 i.a.	Haloperidol	
Elymoacetamide	(A) Femoral dog	500	0.6–2.5 i.a.	Haloperidol	
Pergolide	(A) Femoral dog	22	40/kg i.v.	Sulpiride	
	(B) Renal dog	22	40/kg i.v.	Sulpiride	
	(B) Hindquarters rat	145	3/kg/min	Haloperidol	Rauwolscine
Indolones					
SKF 88827 (4-[2-aminoethyl]-7-OH-2(3H)-indolone)	(A) Femoral dog	286	0.60/kg/min i.v. (ID_{50})		
SKF 89124 (*N*,*N*-di-N-propyl-SKF88827)	(A) Femoral dog	286	0.03/kg/min i.v. (ID_{50})		
Benzazepines					
Fenoldopam	(A) Hindlimb dog	331, 332	160–640 i.a.	Sulpiride	
	(A) Forelimb dog	194	80–320/min i.a.	Sulpiride	
SKF 85174 (3-(2-propen-1-yl-fenoldopam	(B) Renal dog	47			
Miscellaneous					
Piribedil	(A) Femoral dog	64, 304	2.5–10 i.a.	Haloperidol Pimozide	
	(B) Hindleg dog	303	3000/kg i.v.	Haloperidol	
	(B) Renal dog	303	3000/kg i.v.	Pimozide	
	(B) Renal rabbit	103	0.3–30/min i.a. (+ desipramine)	Haloperidol	
	(B) Mesenteric dog	303	3.10^3/kg i.v.	Pimozide Haloperidol	
	(B) Carotid cat	201	77/kg i.v.	Sulpiride	
Inhibition of nerve stimulation-induced (field stimulation) vasoconstriction in vitro					
Phenethylamines					
Dopamine (DA)	Ear artery rabbit	39, 58 229, 444 445, 446	1.2, 37 (IC_{50})	Haloperidol Spiroperidol Droperidol Pimozide Penfluridol Perphenazine (+)-Butaclamol Metoclopramide	Phentolamine (−)-Butaclamol
	Mesenteric rabbit	11	100–1000	Haloperidol	Yohimbine
	Mesenteric rat	10, 11	100–1000	Haloperidol	Yohimbine
	Mesenteric mouse	11	100–1000	Yohimbine	Haloperidol
2-Methyl-DA	Ear artery rabbit	229, 445	43 (IC_{50})		Haloperidol

TABLE 3—Continued

Agonist	Blood vessel, species	Reference	Dose or concentration*	Antagonized by	Not antagonized by
					Spiroperidol Pimozide
6-OH-DA	Ear artery rabbit	229, 445	420 (IC_{50})	Haloperidol	
6-Methyl-DA	Ear artery rabbit	445	1700 (IC_{50})	Haloperidol	
S(+)-α-methyl-DA	Ear artery rabbit	229, 445	180 (IC_{50})		Haloperidol Spiroperidol Pimozide
R(−)-α-methyl-DA	Ear artery rabbit	229, 445	1200 (IC_{50})		Haloperidol Spiroperidol Pimozide
2-α-Dimethyl-DA	Ear artery rabbit	229			Haloperidol Spiroperidol Pimozide
α-Ethyl-DA	Ear artery rabbit	229			Haloperidol Spiroperidol Pimozide
N-Methyl-DA (Epinine)	Ear artery rabbit	229, 445	16 (IC_{50})		Haloperidol Spiroperidol Pimozide
N,*N*-Dimethyl-DA	Ear artery rabbit	229, 445	28 (IC_{50})	Haloperidol (noncompetitive)	Haloperidol Spiroperidol Pimozide
N,*N*-di-*n*-propyl-DA	Ear artery rabbit	228, 245, 445	80 (IC_{50})	Haloperidol *S*-Sulpiride	
2-Aminotetralins (ATN)					
5,6-ADTN	Ear artery rabbit	58, 59	4, 290 (IC_{50})	Metoclopramide	
N,*N*-Dimethyl-5,6-ADTN (M7)	Ear artery rabbit	58	0.1 (IC_{50})	Metoclopramide	
N,*N*-di-*n*-propyl-5,6-ADTN-	Ear artery rabbit	59	9 (IC_{50})	Metoclopramide	
(TL-102) 6,7-ADTN	Ear artery rabbit	58, 61	0.1 (IC_{50})	(−)-Sulpiride	(+)-Sulpiride
N,*N*-di-*n*-propyl-5-OH-ATN- (JGC-174)	Ear artery rabbit	59	10 (IC_{50})	Metoclopramide	
N,*N*-di-*n*-propyl-6-OH-ATN (JMB-249)	Ear artery rabbit	59	750 (IC_{50})	Metoclopramide	
Aporphines					
Apomorphine	Ear artery rabbit	59, 229 444	0.2 (IC_{50})	Haloperidol Spiroperidol Droperidol Pimozide Penfluridol Perphenazine (+)-Butaclamol Metoclopramide	(−)-Butaclamol
	Mesenteric rabbit	11	0.5–5000	Haloperidol	Yohimbine
	Mesenteric rat	11	0.5–5000	Haloperidol	Yohimbine
	Mesenteric mouse	11	0.5–5000	Yohimbine	Haloperidol
	Saphenous dog	66	100		
Ergotalkaloids					
Bromocriptine	Ear artery rabbit	505	40		
Indolones					
SKF 88827 (4-[2-aminoethyl]-7-OH-2 (3H)indolone)	Ear artery rabbit	228, 245	120 (IC_{50})		
SKF 89124 (*n*,*N*-di-*n*-popyl SKF 88827)	Ear artery rabbit	228, 245	1.8 (IC_{50})	*l*-Sulpiride	
Miscellaneous					
DPI ((3,4-dihydroxyphenyl-amino)2-imidazoline)	Ear artery rabbit	58	0.1		Metoclopramide

TABLE 3—Continued

Agonist	Blood vessel, species	Reference	Dose or concentration*	Antagonized by	Not antagonized by
Inhibition of stimulus-evoked ^{3}H-noradrenaline (A) or endogenous noradrenaline (B) release					
Phenethylamines					
Dopamine (DA)	(A) Ear artery rabbit	235, 238 239, 352 396	50–5000	Metoclopramide Pimozide Haloperidol Ergometrine Phenoxybenzamine	Phentolamine
	(A) Gracilis muscle dog	48	1.2/min i.a.	Haloperidol	Phentolamine
	(A) Renal cattle	269	3000	Metoclopramide Pimozide	
	(A) Renal rat	329	10–1000	Sulpiride Phentolamine	
	(A) Pulmonary rabbit	150	1000		
	(A) Saphenous dog	66	5600		
	(A) Saphenous dog	18	10–1000	Sulpiride	Yohimbine
	(A) Omental vein human	448	200–1000		
	Mesenteric guinea pig	167	$10–10^4$	Haloperidol Sulpiride	Phentolamine
N-Methyl-DA	(A) Ear artery rabbit	235	500		
Aporphines					
Apomorphine	(A) Ear artery rabbit	396	1.10^5		
	(B) Gracilis muscle dog	48	1.2/min i.a.		Phentolamine
	(A) Portal vein rat	151	300–1000	Pimozide	
	(A) Renal rat	329	1–1000	Sulpiride	Phentolamine
Ergotalkaloids					
Bromocriptine	(B) Ear artery rabbit	505	40		
Indolones					
SKF 88827 (4-[2-aminoethyl]-7-OH-2(3H)-indolone	(A) Ear artery rabbit	228			
SKF 89124 (*N*,*N*-di-*n*-propyl SKF 88827)	(A) Ear artery rabbit	228			
Miscellaneous					
LY 141865 (*N*-*n*-propyl-2H-octahydro-pyrazolo(*g*)quinoline, *trans*)	(A) Renal rat	329	10–300	Sulpiride	Phentolamine
DPI ((3,4-dihydroxylphenylamino)2-imidazoline	(A) Ear artery rabbit	356	100	Metoclopramide	
Piribedil	(B) Renal artery	103	0.3–30/min i.a.	Haloperidol	

* Doses given i.v. or intraarterially (i.a.) in nmol, or concentrations *in vitro* in nM; ranges of active doses (concentrations) for which a dose (concentration)-effect relationship existed are given.

using lower doses (300 nM; ref. 191), did not confirm these observations. The data obtained in rat (81, 93, 97, 227, 487, 496) and guinea pig (445) seem to indicate that dopamine and dopamine analogues inhibit neurotransmitter release from sympathetic nerves in the heart by interaction with presynaptic α_2-adrenoceptors. The fact that these findings in the rat were obtained in the presence of *d*-tubocurarine (93, 97, 227), which inhibits presynaptic dopamine receptors in the rabbit ear artery (377), does not explain the negative findings with regard to a presynaptic dopamine receptor in the rat heart. Indeed, presynaptic dopamine receptors have been described in the systemic circulation of the rat in the presence of *d*-tubocurarine (see chapter II.C).

3. The vascular system (table 3). a. RABBIT EAR ARTERY. Rand and coworkers found that dopamine is equipotent

with noradrenaline in inhibiting the [^{3}H]noradrenaline release from sympathetic nerve endings in the isolated rabbit ear artery (352). In the rabbit ear artery, dopamine also inhibited the vasoconstrictor responses induced by low frequency field stimulation without affecting vasoconstrictor responses produced by exogenous noradrenaline (352, 396). On the basis of these observations, it was suggested that these dopamine effects were mediated via a presynaptic dopamine receptor. The relationship between the two phenomena, inhibition of transmitter release and of vascular constriction, is, however, not simple. When dopamine is left in contact with the rabbit ear artery for a prolonged period, the inhibition of the vasoconstriction gradually decreases and sometimes reverses to a potentiation, whereas the inhibition of the transmitter release persists (352). This has been explained by the fact that the 3-methoxy metabolite of dopamine may inhibit extraneuronal uptake of noradrenaline and thereby increase smooth muscle contraction (352).

The hypothesis that a presynaptic dopamine receptor was involved in this inhibitory effect on sympathetic nerve-evoked responses was further tested with selective antagonists and some known dopamine receptor agonists. Measuring field stimulation-induced release of [^{3}H]noradrenaline, it was found that the inhibitory effect of dopamine was blocked by metoclopramide and pimozide in concentrations (10^{-7} M) that did not antagonize the presynaptic effect of noradrenaline. Concentrations of pimozide of 10^{-6} M, however, no longer showed selectivity and antagonized the inhibitory effect of both dopamine and noradrenaline (239). Other selective dopamine receptor antagonists were haloperidol and ergometrine, whereas phentolamine in low concentrations (2.10^{-7} M) was selective for noradrenaline but antagonized both noradrenaline and dopamine at higher concentrations (10^{-6} M) (208). Phenoxybenzamine antagonized both dopamine and noradrenaline (238).

N-Methyldopamine (235), apomorphine (396), and bromocriptine (505) also inhibit the stimulation induced-transmitter outflow in the rabbit ear artery; antagonists were not studied against these agonists. It is important to note that the concentration of apomorphine needed to inhibit the transmitter overflow was at least 20 times higher than that of dopamine. This is in contrast with the fact that apomorphine is equipotent with dopamine in inhibiting field stimulation-induced vasoconstriction in the rabbit ear artery (396).

The dopamine-induced inhibition of the vasoconstrictor responses in the rabbit ear artery is markedly reduced by haloperidol but not by phentolamine (39). More detailed studies by Steinsland and coworkers (444, 445) showed that haloperidol, spiroperidol, droperidol, pimozide, penfluridol, perphenazine, and (+)-butaclamol, but not (−)-butaclamol, produced a concentration-dependent parallel shift to the right of the concentration-inhibition curve of dopamine, allowing the calculation of K_B values. Even at a concentration of 70 times its K_B value against dopamine, haloperidol did not antagonize the inhibition by clonidine and tolazoline (444). However, the K_B value for yohimbine against dopamine was only about twice that against clonidine (302). It should be added that two groups of investigators found different potencies for dopamine with regard to its presynaptic inhibitory effects in the rabbit ear artery (396, 444), which might be due to differences in stimulation characteristics. The potency of the antagonists, on the other hand, is dependent on the duration of the incubation period; after an incubation time of 1 h, they are effective in the nanomolar concentration range (444). The K_B values of the antagonists are the same against apomorphine as against dopamine (444).

b. HINDLEG VASCULATURE. The first indication that inhibition of transmitter release from sympathetic nerve endings via a presynaptic dopamine receptor might indeed have a significant effect on vascular resistance came from experiments in the canine hindleg vasculature. Apomorphine, injected into the femoral artery, produced a marked but transient vasodilatation (68, 304), not antagonized by β-adrenoceptor blocking drugs (68, 304), atropine (68, 304), or the combination of mepyramine and metiamide (67), in doses sufficient to block the vasodilatory effects of the respective agonists. The femoral vasodilatation produced by apomorphine was antagonized by haloperidol in doses that did not influence the responses to isoprenaline, acetylcholine, histamine, and nitroglycerine (68). That this vasodilatation was due to interference with the sympathetic vasoconstrictor tone was shown by the fact that it disappeared after transsection of the lumbar sympathetic chain (68), of the spinal cord or the femoral and sciatic nerves (304), and after administration of α-adrenoceptor antagonists (68, 304), guanethidine and hexamethonium (304). Moreover, after sympathetic denervation, the vasodilator effect of apomorphine was restored when vascular tone was raised by electrical stimulation of the sympathetic innervation, but not when tone was increased by noradrenaline infusion (68).

These observations were interpreted as evidence for the presence of a presynaptic dopamine receptor, although dopamine did not produce a similar effect, presumably because of its α-adrenoceptor-mediated vasoconstrictor properties. In some dogs, however, dopamine produced vasodilatation (68), which has been ascribed to stimulation of postsynaptic dopamine receptors in the distal femoral vasculature (319). Like haloperidol, other dopamine receptor antagonists, pimozide (69), metopimazine (363), thioridazine (69), fluphenazine (136), metoclopramide (363), *cis*-flupenthixol (69), (+)-butaclamol (69), domperidone (363, 499), and sulpiride (363), also antagonized the femoral vasodilatation by apomorphine. For flupenthixol and butaclamol, the an-

tagonism is stereospecific, as *trans*-flupenthixol and (−)-butaclamol are inactive (69). In the isolated perfused gracilis muscle, dopamine and apomorphine inhibit the release of [^{3}H]noradrenaline induced by low frequency lumbar sympathetic nerve stimulation. This inhibition is observed in the presence of phentolamine but does not occur after haloperidol pretreatment (48).

As far as the hindleg vasculature in other species is concerned, *N*-alkylated dopamine derivatives and *N*,*N*-di-*n*-propyl-5-OH,6-methyl-ATN produce a haloperidol-sensitive decrease in vascular resistance in the cat autoperfused hindlimb and hindquarter preparations (333, 485). In the cat, as in the dog, dopamine in contrast elicits vasoconstriction (205). Apomorphine and pergolide (145) inhibit, in the rat autoperfused hindquarters, the vasoconstriction elicited by stimulation of the paravertebral lumbar chain. Their effect is antagonized by haloperidol in a dose without effect on presynaptic α_2-adrenoceptors but not by rauwolscine in a dose that blocked the presynaptic effect of the α_2-adrenoceptor agonist 5-bromo-6-(2-imidazolin-2-ylamino)quinoxaline (UK-14304) (145).

c. RENAL AND MESENTERIC VASCULATURE. As far as other blood vessels are concerned, special attention has been paid to the renal and mesenteric vasculature, since postsynaptic dopamine receptors have first been described in these blood vessels in the dog (180). It was, therefore, of interest to know whether a presynaptic mechanism also plays a role in the dopamine-induced vasodilatation in these vessels when sympathetic tone is present.

In the dog renal vasculature, a presynaptic inhibitory effect has been described for dopamine, which was antagonized by pimozide (324) and mimicked by *N*,*N*-di-*n*-propyl-DA (140, 350). The inhibition by *N*,*N*-di-*n*-propyl-DA was partially antagonized by *RS*-sulpiride (140, 350). Bromocriptine and piribedil also had a presynaptic inhibitory effect antagonized by pimozide (303, 330), the effect of bromocriptine also being antagonized by bulbocapnine (330).

In the isolated, saline-perfused kidney of the rabbit, apomorphine reduced the increase in perfusion pressure evoked by renal nerve stimulation, mainly at lower frequencies, without influencing perfusion pressure responses to exogenous noradrenaline. Apomorphine also reduced the increase in venous outflow of endogenous noradrenaline. Both inhibitory effects were antagonized by haloperidol (103). Piribedil produces a more complex effect in this preparation: the nerve stimulation-induced vasoconstriction is inhibited, but the noradrenaline outflow is increased. In the presence of desipramine, however, both phenomena are inhibited by piribedil, and this inhibition is antagonized by haloperidol in doses that do not affect the responses to exogenous noradrenaline. The authors concluded that, in this preparation, presynaptic dopamine receptors are present but that piribedil also possesses indirect, amphetamine-like, and α_1-adrenoceptor blocking effects (103).

Dopamine reduces the [^{3}H]noradrenaline outflow induced by field stimulation from isolated bovine renal artery, and this effect is antagonized by metoclopramide and pimozide, the latter in a concentration without effect on noradrenaline-induced vasoconstriction. Dopamine also inhibited the nerve stimulation-induced vasoconstriction, without effect on the noradrenaline-evoked response, but higher concentrations were needed than those which inhibit [^{3}H]noradrenaline outflow (269). In the perfused rat kidney, dopamine, apomorphine, and LY 141865 inhibit the neurogenic release of [^{3}H]noradrenaline; sulpiride, but not phentolamine, antagonized this effect (329).

As far as the mesenteric vasculature is concerned, dopamine has been shown to inhibit the nerve stimulation-induced mesenteric vasoconstriction in the dog (399), the cat (406), the rat (10, 11), the rabbit (11), and the mouse (11). In the cat, the rat, and the rabbit, this occurs without influencing the vasoconstrictor response to noradrenaline; in the dog and the mouse, this was not studied. In the rat (10, 11) and the rabbit (11), the effect was mimicked by apomorphine and antagonized by haloperidol but not by yohimbine. In the dog, the effect was mimicked by piribedil, and this inhibition was antagonized by pimozide (303). This suggests the presence of presynaptic dopamine receptors in the mesenteric vasculature of rat, rabbit, and dog. In the cat, dopamine is about 20 times less potent than noradrenaline in inhibiting nerve stimulation-induced vasoconstriction (406), and in the mouse, the effects of dopamine and apomorphine are antagonized by yohimbine but not by haloperidol (11), suggesting that, in these two species, the presynaptic effect is mediated by α_2-adrenoceptors.

d. OTHER BLOOD VESSELS. Other blood vessels in which inhibitory presynaptic dopamine receptors have been suggested are the rat portal vein (151) and the human omental vein (448). A presynaptic inhibitory effect of dopamine has further been described in the dog saphenous vein, where it is mimicked by apomorphine (66, 124, 125), and in the rabbit pulmonary circulation, where it is not mimicked by apomorphine (150). As noradrenaline was much more potent than dopamine (124, 125, 150), and phentolamine antagonized the effect of dopamine (124, 125), these effects are presumably mediated via an α-adrenoceptor. In the vasculature of the tibia of the dog, apomorphine reduces perfusion pressure, but this is not antagonized by haloperidol (463, 464).

e. STRUCTURE-ACTIVITY RELATIONSHIP. The study of the structure-activity relationship of agonists for the presynaptic dopamine receptor in blood vessels has mainly been performed in the rabbit ear artery preparation *in vitro* and in the canine femoral vasculature *in vivo*.

i. Phenethylamines. Ring and side-chain substituted dopamine analogues were studied in the rabbit ear artery. 6-Methyl-DA and 6-OH-DA produced a haloperidol-sensitive inhibition of the nerve stimulation-induced vasoconstriction; the K_B value for haloperidol against both agents was the same as that against dopamine (229). The inhibition by side-chain substituted analogues was not antagonized by dopamine receptor antagonists (229, 445).

Among the *N*-alkylated dopamine derivatives, epinine and *N*,*N*-dimethyl-DA produced inhibition in the rabbit ear artery; however, the inhibition by epinine was not antagonized by haloperidol and, in the case of *N*,*N*-dimethyl-DA, haloperidol produced a noncompetitive type of antagonism (229, 445). *N*,*N*-di-*n*-propyl-DA produced a haloperidol-sensitive inhibition in the rabbit ear artery, but the K_B value of haloperidol was about 3 times higher than against dopamine (445). This led the authors to postulate that another type of presynaptic dopamine receptor might be involved in the response to this agonist; this has also been suggested for some CNS effects of *N*,*N*-di-*n*-propyl-DA (425).

In the dog hindlimb, *N*,*N*-di-*n*-propyl-DA produces an apomorphine-like femoral vasodilatation (69, 136, 281, 489), antagonized by haloperidol (69, 489), metoclopramide (489), sulpiride (136), and fluphenazine (136), but not by atropine or propranolol (489). The antagonism by sulpiride resides in its S-isomer (186). Some other *N*-alkylated dopamine derivatives have been shown to produce femoral vasodilatation abolished by hexamethonium or phenoxybenzamine (179, 282), but the effect of dopamine receptor antagonists was not studied.

ii. Aminotetralins. The aminotetralins 5,6-ADTN, *N*,*N*-dimethyl-5,6-ADTN, and 6,7-ADTN produce a metoclopramide-sensitive inhibition of the nerve stimulation-induced vasoconstriction in the rabbit ear artery; 5,6-dimethoxy-ATN was ineffective (58, 131). *S*-sulpiride antagonized the presynaptic effect of 6,7-ADTN without influencing pre- or postsynaptic α-adrenoceptors; *R*-sulpiride was much less effective (61).

The femoral vasodilatation by *N*-methyl-5,6-ADTN is antagonized by propranolol (343); the dilatation by *N*,*N*-dimethyl-5,6-ADTN and *N*,*N*-di-*n*-propyl-5,6-ADTN is antagonized by haloperidol (69).

iii. Aporphines. *N*-*n*-propylnorapomorphine produces a haloperidol-sensitive vasodilatation in the dog hindlimb; dimethoxy-apomorphine is ineffective (69).

iv. Octahydrobenzoquinolines. Among the octahydrobenzoquinolines, only GJH-166 has been studied in the dog hindlimb vasculature; when injected i.v., it caused an inhibition of the increase in perfusion pressure evoked by lumbar sympathetic chain stimulation in doses that did not influence the resistance increase by i.v. infusion of noradrenaline; this inhibitory effect was antagonized by haloperidol (428). GJH-166 produced a similar presynaptic inhibition in the perfused gracilis muscle preparation when postganglionic nerve stimulation was applied (428).

v. Ergot alkaloids. Bromocriptine was shown to produce presynaptic inhibition in the rabbit ear artery, but no antagonists were studied (505). In the dog hindlimb, it produces vasodilatation which is prevented by haloperidol pretreatment; this femoral vasodilatation is long lasting and, once it is present, haloperidol does not reverse it (49, 70) (see also chapter II.A.2); this might be explained by assuming that the dissociation of bromocriptine from the receptor is very slow.

The ergolines—elymoclavine, *N*-ethyl-*N*-norelymoclavine, *N*-propyl-*N*-norelymoclavine, *N*-benzyl-*N*-norelymoclavine, elymoacetamide, and elymonitrile—produce, like apomorphine, a short-lasting and haloperidol-sensitive femoral vasodilatation (500). The ergolines, chanoclavine-I and *N*-propionylelymoclavine, do not produce an apomorphine-like femoral vasodilatation (500).

On local injection into the femoral artery, piribedil produces dilatation that is antagonized by haloperidol and pimozide and is not mediated by its catechol metabolite S584 (64). It also inhibits the increase in perfusion pressure in the perfused hindlimb evoked by low frequency stimulation of the lumbar sympathetic chain without changing the resistance increase by local noradrenaline; this inhibition is antagonized by haloperidol (304).

vi. Other substances. Substances that produce a presynaptic inhibitory effect in the vasculature presumably via a dopamine receptor are DPI (52), the indolones SKF 89124 and SKF 88827 (228, 245, 246), and the benzazepine SKF 85174 (47). The benzazepine, fenoldopam also produces a vasodilatation in the canine hindleg (331, 332), but since this substance is devoid of any effect on the tachycardia by accelerans nerve stimulation (400), this vasodilatation is ascribed to an inhibition of sympathetic tone at the ganglionic level.

f. CONCLUSION. Presynaptic dopamine receptors, mediating inhibition of neurotransmitter release from sympathetic nerve endings in blood vessels, have first been demonstrated in the rabbit ear artery and the canine hindleg vasculature. These preparations have been used extensively to characterize the presynaptic dopamine receptor and to perform structure-activity relationship studies of dopamine receptor agonists and antagonists. Presynaptic dopamine receptors have also been described in the cat and rat hindleg vasculature; in the canine, bovine, rat, and rabbit renal vascular bed; and in the mesenteric vasculature of rat, rabbit and dog.

4. Other organs. The presence in mammalian organs of selective dopamine receptors, mediating presynaptic inhibitory effects, has been further postulated at several sites other than the nictitating membrane and the cardiovascular system.

a. SPLEEN. Some evidence for the presence of presyn-

aptic dopamine receptors has been found in the spleen of cat and dog. Dopamine and apomorphine inhibit the rise in perfusion pressure of the spleen induced by nerve stimulation (138) and reduce the stimulation-induced outflow of [^{3}H]noradrenaline (138, 296), dopamine being equipotent with noradrenaline (296). The effects of dopamine and apomorphine were selectively blocked by *S*-sulpiride (138), in a concentration that had no effect on presynaptic α_2-adrenoceptors, whereas they were not antagonized by phentolamine in a concentration sufficient to block α_2-adrenoceptors. The effect of dopamine on [^{3}H]noradrenaline outflow is mimicked by *N,N*-di-*n*-propyl-DA, but the effect of this agonist, which is completely blocked by *RS*-sulpiride, is partially antagonized by phentolamine (140, 350). In the dog spleen *N*-methyl-7,8-dihydroxy-*trans*-octahydrobenzo(*f*)quinoline (GJH-166) inhibits the increase in perfusion pressure elicited by splenic nerve stimulation, without influencing the constrictor responses to exogenous noradrenaline, and this effect is prevented by haloperidol (428).

b. VAS DEFERENS. In the isolated vas deferens of the rat, dopamine inhibits the contractions induced by hypogastric nerve stimulation (458) or field stimulation (203, 459, 460) without influencing the contractions evoked by exogenous noradrenaline (203). Dopamine was more potent than noradrenaline at this presynaptic site (459, 460), and its effect was mimicked by apomorphine (203, 459, 460) and bromocriptine (203). Pimozide antagonized dopamine (458) and apomorphine (459, 460) in concentrations that did not antagonize noradrenaline (459, 460); its pA_2 value against dopamine and apomorphine was greater than that against clonidine, noradrenaline, and oxymetazoline (459). Haloperidol antagonized dopamine (203, 458) and apomorphine (203) but also noradrenaline (458); it did not antagonize bromocriptine (203). Sulpiride antagonized the effect of dopamine but not that of apomorphine or of bromocriptine (203). The pA_2 value of yohimbine against dopamine and apomorphine was lower than against clonidine, noradrenaline, and oxymetazoline (459, 460). These conflicting observations notwithstanding, it was assumed until recently that presynaptic dopamine receptors were present in the vas deferens of the rat. More recent experiments, however, done under more carefully controlled conditions, with blockade of β-adrenoceptors and of uptake of catecholamines at neuronal and extraneuronal sites, showed that noradrenaline was 40 times more potent than dopamine in inhibiting twitches induced by electrical field stimulation and that noradrenaline and dopamine were antagonized to the same extent by yohimbine (307). It can therefore be concluded that, in the rat vas deferens, the presynaptic effect of dopamine is mediated via α_2-adrenoceptors. Results with sulpiride and with tolazoline (17), showing for both a similar pA_2 value against clonidine and apomorphine, confirm this. The same applies to the vas deferens of the mouse (178, 246) and the guinea pig (33, 39): the presynaptic effect of dopamine on nerve stimulation-evoked twitch contractions is blocked by yohimbine (178, 246) and phentolamine (33, 39) but not by *cis*-flupenthixol (246), pimozide (178, 246), and haloperidol (33, 39, 178). Bromocriptine in the mouse (178) and dopamine in the guinea pig (447) reduced the nerve-induced outflow of [^{3}H]noradrenaline, but dopamine was 25 times less potent than noradrenaline, and the effect of bromocriptine was antagonized by yohimbine.

c. VARIOUS. A presynaptic effect of bromocriptine has been described in the anococcygeus muscle of the rat, but no antagonists were studied (177). In the human bladder, dopamine does not produce a specific effect (224), and metoclopramide does not modify bladder function (472).

The presynaptic inhibitory effects of dopamine and dopamine analogues discussed so far are all related to the autonomic sympathetic innervation of the different systems. A few comments have to be made about inhibitory effects of dopamine on the cholinergic transmission in the neuromuscular end plate. Dopamine inhibits the neuronally evoked release of acetylcholine from the rat phrenic nerve and its release by oxotremorine, and both effects are inhibited by pimozide; no comparison with other agonists and antagonists was made (175). Inhibitory effects of dopamine have also been described for the nerve stimulation-induced contractions of the cat anterior tibialis (46) and gastrocnemius (159) muscles and of the same muscles in the rat (90). In the rat, the effect was antagonized by haloperidol and chlorpromazine (90). In the cat gastrocnemius muscle, the effect was antagonized by phentolamine and phenoxybenzamine (159). It is clear that more studies are needed to identify whether these effects of dopamine on the cholinergic neuromuscular transmission are presynaptic or postsynaptic, and that more agonists and antagonists have to be compared in the same preparations before it can be concluded that a dopamine receptor is involved.

B. Characteristics of the Presynaptic Dopamine Receptor

1. Presynaptic dopamine receptor versus presynaptic α_2-adrenoceptor. It appears from previous sections that the presence of a presynaptic dopamine receptor on sympathetic nerve endings in different organs has been accepted because the presynaptic effects of dopamine agonists and antagonists cannot be explained by an interaction with an α_2-adrenoceptor. In most cases, it was possible to block selectively the presynaptic effects of noradrenaline with doses of phentolamine or other α-adrenoceptor antagonists that did not interfere with the presynaptic effects of dopamine or dopamine receptor agonists. Conversely, it was possible to block the presynaptic effect of dopamine with dopamine receptor antagonists without antagonizing the α_2-adrenoceptor mediated presynaptic inhibition. Furthermore, substances

such as dopamine, aminotetralins, apomorphine, ergot alkaloids, and their derivatives, which are agonists for the presynaptic dopamine receptor, behave quite differently on the α-adrenoceptor, either as agonists, partial agonists, or antagonists.

However, for each organ, the selectivity of the antagonism of the dopamine and the noradrenaline effects has to be assessed carefully, and several groups have addressed this problem in more detail. Indeed, most dopamine receptor agonists also have α-mimetic effects, and most dopamine receptor antagonists have α-lytic properties, although they are more potent on α_1- than on α_2-adrenoceptors (111, 191, 277, 932). Likewise, α-adrenoceptor antagonists show dopamine antagonistic properties when applied in higher doses. Very recently, it has been suggested, on the basis of pA_2 calculations against apomorphine and clonidine, that phentolamine and yohimbine are not the ideal agents to discriminate between dopamine receptor and α_2-adrenoceptors, since in isolated cat atria, their selectivity for the α_2-adrenoceptor is not very high (285, 302). It has been shown also that sulpiride (19) and pimozide (239) in higher doses interact with α_2-adrenoceptors. Domperidone has been said to be 30 times more potent on DA_2 receptors than on α_2-adrenoceptors and to be a good agent to discriminate between both (279). This is, however, probably not true for all preparations (see chapter IV.A.1.). Phenoxybenzamine blocks both α_2-adrenoceptors and presynaptic dopamine receptors. The similarity of the peripheral presynaptic dopamine receptor with the α_2-adrenoceptor is also stressed by Seeman (425), when he says that the relative potency of different agonists on the DA_2 receptor is similar to their relative potency in interfering with the ^{3}H-clonidine binding to central sites. Maixner and coworkers (341) addressed the problem of discriminating between presynaptic dopamine receptors and presynaptic α_2-adrenoceptor by identifying selective agonists for both receptors. They compared the presynaptic effects of a series of dopamine receptor agonists on the *in vivo* cat cardioaccelerator nerve (containing dopamine receptors) and the *in vitro* guinea pig ileum (containing α_2-adrenoceptors). A series of dopamine analogues, e.g., *N*-alkyl derivatives of 5,6-ADTN and 6,7-ADTN, 7,8-dihydroxyoctahydrobenzo(*f*)quinolines, and 6,7-dihydroxyoctahydrobenzo(*g*) quinolines, were active both on the dopamine receptor and the α_2-adrenoceptor. Their relative order of potency on the two receptors is different. The finding of a difference in relative potencies is, however, of limited value, since on the cat cardioaccelerator nerve α_2-adrenoceptors are present in addition to the dopamine receptors, and the agonists interact with both receptors. As has been said in chapter I, the fact that more than one receptor might be involved implies that the potency with regard to the effect does not reflect the affinity at the receptor. More clearcut differences were, however, found for the *N*,*N*-di-*n*-propyl derivatives of 5-OH-ATN and 6-OH-ATN, which were only active on the dopamine receptor, and for clonidine, *N*-alkyl derivatives of 2-ATN, *N*-*H*-8,9-dihydroxyoctahydrobenzo(*f*)quinoline, and *N*,*H*-6,7-dihydroxyoctahydrobenzo(*g*) quinoline which were selective for the α_2-adrenoceptor. Other observations have shown that, among the ethylenamines, the *N*-alkylderivatives still retain α_2-adrenoceptor activity which is, however, largely lost in *N*,*N*-di-*n*-propyl-DA that acts preferentially on the dopamine receptor (281) and is frequently used as the reference presynaptic dopamine receptor agonist. The indole TL-350 acts on presynaptic dopamine receptors but is without effect on α_2-adrenoceptors (248). LY 141865 preferentially acts on presynaptic dopamine receptors (212, 329). Of particular interest is the *trans*-isomer of the nonhydroxylated *N*-*n*-propyloctahydrobenzo(*f*)quinoline (CS-265), which is an agonist at the presynaptic dopamine receptor and an antagonist at α_2- and α_1-adrenoceptors (254).

It can be concluded that dopamine receptors on sympathetic nerve endings are different from α_2-adrenoceptors. An agonist reacts optimally with the dopamine receptor if it contains the dopamine moiety in the fully extended coplanar conformation; interaction with the α_2-adrenoceptor is also possible with less rigid structures. Furthermore, the α_2-adrenoceptor optimally interacts with agonists containing two OH groups on the benzene ring, wheras some monohydroxylated and even nonhydroxylated derivatives still react with the dopamine receptor (341).

2. Presynaptic dopamine receptor versus postsynaptic dopamine receptor. As mentioned in the introductory chapter, the presynaptic dopamine receptor has been shown to be different from the postsynaptic dopamine receptor. This difference will now be discussed in more detail.

a. THE POSTSYNAPTIC DOPAMINE RECEPTOR:DA_1. This review does not cover the extensive literature describing the postsynaptic DA_1 receptor located on vascular smooth muscle. Its characteristics have been described by others (132, 183–185, 188, 207, 278). For the purpose of our discussion, a short summary from these references follows.

i. Agonists. The structure-activity relationship for agonists of the DA_1 receptor is very limited. Hydroxyl groups on the 3 and 4 position of the catechol ring are necessary; further substitution (except fluorine) inactivates the molecule, as do substitutions on the α or β carbon atom of the ethylamine side-chain. Among the compounds with a single *N*-substitution, only *N*-methyldopamine (epinine) is active; among the *N*,*N*-bisubstituted substances, at least one substituting group must be *n*-propyl, except for *N*-ethyl-*N*-butyl-DA. Among the more complex molecules, some containing the dopamine moiety in the β-conformer structure react with the DA_1 receptor, e.g., 6,7-ADTN and a few of its derivatives. The benzazepines, SKF 38393 and fenoldopam, are selective

agonists for the DA_1 receptor. Most α-conformers do not interact, but exceptions are apomorphine, which is a partial agonist, and *N,N*-di-*n*-propyl-5,6-ADTN, which is a full agonist at the DA_1 receptor. It has, however, been suggested recently that, in the canine mesenteric vascular bed, apomorphine does not interact with the same postsynaptic receptor as *N,N*-di-*n*-propyl-DA (230).

ii. Antagonists. Among the DA_1 receptor antagonists, the compound SCH 23390, which is the 3-methyl-7-chloro analogue of 2,3,4,5-tetrahydro-7,8-diOH-r-phenyl-r H-3-benzazepine (SKF 38393), seems at least 10 to 100 times more potent on the DA_1 receptor than on the DA_2 receptor or other catecholamine receptors, suggesting it is a selective DA_1 receptor antagonist useful in characterizing dopamine receptors (182, 231). Another selective DA_1 receptor antagonist is SKF 83566, the 7-bromo analogue of SCH 23390 (41). The DA_1 receptor is not antagonized by phenoxybenzamine even in concentrations of 10^{-5} M (187, 410, 462). Most other antagonists are less selective and react with the DA_1 and DA_2 receptor. As far as their affinity for the DA_1 receptor is concerned, two different orders of potencies have been described. Studies in the canine mesenteric vascular bed, where the antagonists were given 10 min before the agonist, gave: (+)-butaclamol > haloperidol = bulbocapnine > *S*- or *R*-sulpiride > (−)-butaclamol (430). In the canine renal bed where the antagonists were administered simultaneously with the agonist, the order of potency was: sulpiride > bulbocapnine > haloperidol (184). It is generally said that *R*-sulpiride is more potent than or equipotent with *S*-sulpiride on the DA_1 receptor (24, 184, 411, 430). However, in the guinea pig renal vasculature, *S*-sulpiride has been reported to be 6 to 10 times more potent than *R*-sulpiride (346). Bulbocapnine is approximately 30 times more potent on the DA_1 receptor than on the DA_2 receptor (100, 300).

As far as stereoselectivity is concerned, (+)-butaclamol is much more potent than (−)-butaclamol (410), and *cis*-flupenthixol is more potent than *trans*-flupenthixol (411).

b. DA_2 RECEPTOR *VERSUS* DA_1 RECEPTOR. Tables 1 to 3 list the large series of structural analogues of dopamine that produce a presynaptic inhibitory effect which, with a few exceptions, is antagonized selectively by haloperidol. This large number of DA_2 receptor agonists is in contrast with the rather limited number of agonists at the DA_1 receptor. Others have speculated about the structural requirements for optimal activity at the different dopamine receptors (77, 78, 268, 425). We would like to mention only two particular aspects: the rotamer conformation of the dopamine moiety and the *N*-alkyl substitution.

Apomorphine, a full agonist on the DA_2 receptor, contains the dopamine moiety in the α-conformer. The α-conformer is also present in 5,6-ADTN which is active on the DA_2 but not on the DA_1 receptor, and in 6,7-dihydroxyoctahydrobenzo(*g*)quinolines active on the DA_2 receptor. The 7,8-dihydroxyoctahydrobenzo(*g*)-quinolines contain the β-conformer and are inactive at the DA_2 receptor. This might indicate that, in contrast to the DA_1 receptor, for the DA_2 receptor the α-conformer is preferred. That this structure is not the determinant for DA_2 agonist activity is, however, shown by drugs such as 6,7-ADTN and the 8,9-dihydroxyoctahydrobenzo(*f*)quinolines which contain the β-conformer and are also active on the DA_2 receptor.

A second structural property which seems to be important is the role of alkyl substituents in the amino group. *N*-Alkyl substitution, mainly *N,N*-di-*n*-propyl substitution, seems to increase the potency at the DA_2 receptor. This is particularly true for the non- or monohydroxylated aminotetralins, 5,7-dihydroxyaminotetralins, 4,5-amino indans, and 4,7-amino indans which are not active without this *N*-alkyl substitution. Nevertheless, the *in vivo* and *in vitro* potencies of a series of *N*-alkyl derivatives of a particular compound decrease with the length of the *N*-substituent (see tables 1 to 3). Furthermore, *N,N*-di-*n*-propyl substitution in 5,6-ADTN makes this molecule also active at the DA_1 receptor (280) indicating that, although this substitution is important for dopamine receptor agonist activity (see chapter II.B.1), it is not typical for DA_2 activity. Table 4 summarizes the potency of some of the agonists in different experimental set-ups typical for either the DA_2 or the DA_1 receptor. We selected agonists which were studied in the *in vitro* rabbit ear artery preparation and for which data on DA_1 potency were available; furthermore, agonists were chosen that are said to be selective for the DA_2 receptor. A first difference which appears from this comparison is that agonists are active in μM concentrations at the DA_1 receptor but in nM concentrations at the DA_2 receptor. Relative potencies are different from one preparation to the other but are not very useful to distinguish between the DA_1 and DA_2 receptor except for substances as LY 141865, pergolide, and piribedil which are selective DA_2 receptor agonists. LY 141865, which is a racemic mixture, owes its activity to its *l*-isomer LY 171555 (207). LY 141865 still produces a vasodilatation after α- and β-adrenoceptor blockade in coronary vessels, but this is not due to an interaction with DA_1 receptors but with histamine-2 receptors (12). Other substances which show a rather good selectivity for the DA_2 receptor are bromocriptine (and other ergot alkaloids), DPI, and pergolide (and other ergolines). As far as the agonists are concerned, the DA_1 and DA_2 receptors show a similar stereoselectivity (60).

The differences seen between the DA_2 and the DA_1 receptor are somewhat more consistent when antagonists are studied. Within their systematic study, Shepperson et al. (430) found the following order of antagonist potency for the DA_2 receptor in the cat nictitating mem-

brane and heart: haloperidol > (*S*)-sulpiride = (+)-butaclamol > *R*-sulpiride > (−)butaclamol > bulbocapnine; *S*-sulpiride was almost 100 times more potent than *R*-sulpiride (59, 430). Steinsland and coworkers (444) found in the rabbit ear artery the following order of antagonist potency: (+)-butaclamol > pimozide > haloperidol > (−)-butaclamol. These values are clearly different from those for the DA_1 receptor discussed above. If one looks at the published data (430), it can even be said that *R*-sulpiride, (−)-butaclamol, and bulbocapnine in the doses studied hardly modify the presynaptic effect of the dopamine agonist *N,N*-di-*n*-propyl-DA. *S*-Sulpiride has been reported to be 100 times more potent on the DA_2 than on the DA_1 receptor (24, 100). More recent observations suggest that domperidone (279), clebopride (320), and 5-(aminosulfonyl)-*N*-(1-cyclohexyl-3-pyrrolidinyl)-2-methoxybenzamide (AHR 6092) (278) are also selective DA_2 receptor antagonists. Domperidone is at least 1000 times more potent on DA_2 than on DA_1 receptors (279). Phenoxybenzamine blocks that DA_2 receptor at a concentration of 200 to 290 nM (152, 238). DA_2 receptors are also antagonized by *d*-tubocurarine (377) and verapamil (265).

It can be concluded that there is, for a limited number of agonists and antagonists, a clear difference between their activity on the DA_1 and the DA_2 receptor, but, for a large number of compounds, there is not. The existence of several antagonists which show a rather high selectivity for either the DA_2 or the DA_1 receptor is the main argument for accepting the existence of both subtypes.

In order to clearly characterize both dopamine receptor types, one should study them under similar, well-controlled *in vitro* conditions. Another approach is the simultaneous study *in vivo* in the dog of the DA_1 receptor—in the renal or mesenteric artery—and of the DA_2 receptor—in the femoral artery—provided the agonists are injected locally and the antagonists i.v. in order to obtain similar distributions in both arterial beds. However, neither *in vitro* nor *in vivo*, interaction with other receptors playing a role in the effect recorded can be excluded. More specifically, with regard to the presynaptic DA_2 receptor, the presence of presynaptic α_2-adrenoceptors can modify the apparent affinities of the agonists. Radioligand binding techniques for the study of the DA_2 receptor are not commonly available.

3. Comparison between the DA_1-DA_2 and the D_1-D_2 classifications. As discussed in chapter I, dopamine receptors in the central nervous system, pituitary, and parathyroid glands can be subdivided in two types, the D_1 and D_2 receptor. This D_1-D_2 classification is very similar, although not identical, to the DA_1-DA_2 classification.

There are no striking differences between the DA_2 and D_2 receptors (at least the high affinity state of the D_2 receptor) (271, 449). Both are sensitive to nanomolar concentrations of agonists and antagonists. The agonists which are active on the DA_2 receptor are active on the D_2 receptor and vice versa (271, 272, 426). A typical example is the parallelism between the activities of a series of ergolines on both receptors (500); the same applies for LY 141865 (449). The selective DA_2 receptor antagonist domperidone is also selective at the D_2 receptor (279, 449). A further similarity resides in the ability

TABLE 4

Comparison of the potency of some dopamine receptor agonists at the presynaptic DA_2 and the postsynaptic DA_1 receptor, in vivo and in vitro. The values for the doses or concentrations, having 50% effect at the presynaptic DA_2 receptor, are taken from tables 2 and 3. For references where this value is not given, an approximate value is calculated from the available experimental data; if this is not possible, the active dose range (within brackets) is given. The values for the doses or concentrations, having 50% effect at the postsynaptic DA_1 receptor, are from references 188, 256, 411, 425, and 426.

Agonist	In vitro			In vivo		
	Presynaptic DA_2 receptor[cat heart (1) or rabbit heart (2)] (IC_{50}, nM)	Presynaptic DA_2 receptor [rabbit ear artery] (IC_{50}, nM)	Postsynaptic DA_1 receptor [rabbit mesenteric artery (3) or rat kidney (4)] (EC_{50}, μM)	Presynaptic DA_2 receptor [femoral vascular bed dog] (ED_{50}, nmol i.a.)	Presynaptic DA_2 receptor [chronotropic response in cat heart] (ID_{50}, nmol/kg i.v.)	Postsynaptic DA_1 receptor [renal artery dog] (ED_{50}, nmol i.a.)
Dopamine	1000 (2)	1.2	20 (3) 2.5 (4)		105	
N,N-di-*n*-propyl-DA	420 (1)	80	16 (4)	5.5	68	377
5,6-ADTN		4	Inactive			
6,7-ADTN		0.1	3 (3)			(10–22)
Apomorphine	8 (1)	0.2	0.3 (3) 0.1 (4)	1	19	1000
Bromocriptine		40	9 (3) 1.3 (4)	(10–40)	22	Inactive
DPI		0.1	1400 (4)			
Piribedil		140		(2.5–10)	6000	Inactive
Pergolide				(40/kg i.v.)	20	Inactive
LY 141865					(35–280)	Inactive

of phenoxybenzamine to block both the D_2 receptor (271, 312) and the DA_2 receptor (152, 238) in micromolar concentrations. It would be of interest to also test on a DA_2 receptor newer specific D_2 receptor agonists and antagonists (449).

There are also many similarities between the DA_1 and D_1 receptors; they are, e.g., both sensitive to micromolar concentrations of agonists and antagonists. However, the main obstacle to accept their identity, as put forward by Goldberg and coworkers (188), was that sulpiride and metoclopramide are antagonists of the DA_1 receptor but are without effect on the D_1 receptor. As pointed out by Kebabian (271), this discrepancy might be less important than originally thought, as it was shown that *S*-sulpiride is a weak antagonist *in vitro* on the DA_1 receptor and also on the D_1 receptor. The selective D_1 receptor agonists, SKF 38393 and fenoldopam, and the selective D_1 receptor antagonists, (−)-bulbocapnine and SCH 23390, also act on the DA_1 receptor (182, 207, 257, 271, 449).

Although it is not our aim to fully discuss in this review the DA_1 receptor, we want to mention some other discrepancies between the DA_1 and the D_1 systems. Phenoxybenzamine, for example, blocks the D_1 receptor in the same concentrations as the D_2 receptor (2 μM) (491), but, even in concentrations of 10 μM, it has no effect on the DA_1 receptor (187, 410, 462). Furthermore, the link between the D_1 receptor and an adenylate cyclase is less certain in the case of the DA_1 receptor (373, 375); at least some authors did not find a correlation between DA_1 receptor stimulation and cyclic AMP increase, sulpiride antagonizing the former but not the latter (346).

C. Physiological and Pharmacological Significance of Presynaptic Dopamine Receptors

1. Physiological role. In contrast to the almost general acceptance of a physiological function of the presynaptic α_2-adrenoceptors on sympathetic nerve endings in the negative feedback regulation of noradrenaline release, most observations argue against a physiological role of the presynaptic DA_2 receptor on sympathetic nerve endings. Dopamine receptor antagonists do not potentiate the nerve stimulation-evoked responses in dog hindlimb (303), dog renal vascular bed (324), dog heart (325), rabbit heart (165), cat spleen (138), and nictitating membrane (152). They do not potentiate the nerve stimulated [^{3}H]noradrenaline release in the rat kidney (329) and dog saphenous vein (18) nor do they have a lasting influence on resting blood flow or reflex vasodilatation in the canine hindlimb vasculature (65).

Other observations, however, suggest a possible physiological function for the presynaptic DA_2 receptor. Haloperidol and pimozide potentiate the responses of the cat atrium to nerve stimulation (251, 252) and the vasoconstriction and [^{3}H]noradrenaline outflow induced by nerve stimulation in the rabbit ear artery (238). It should be added that blockade of presynaptic α_2-adrenoceptors might play a role in the observations made in the rabbit ear artery but, in the cat atrium, haloperidol and pimozide were effective in concentrations that did not interfere with the presynaptic inhibitory effect of clonidine (251, 252).

It has been suggested that dopamine and presynaptic DA_2 receptors participate in the negative feedback of noradrenaline release in situations of prolonged nerve activity. It was proposed that, under these conditions, dopamine is released from noradrenergic nerves and acts on presynaptic DA_2 receptors to decrease the noradrenaline release in order to save transmitter (223, 236, 237). This has been observed in the rabbit ear artery where, after pretreatment with a dopamine-β-hydroxylase inhibitor and loading with [^{3}H]dopamine, [^{3}H]dopamine is released by nerve stimulation, and this release is enhanced by metoclopramide and ergometrine, although not by haloperidol (236, 237). Metoclopramide diminishes the decrease of tritiated transmitter release which normally occurs during prolonged stimulation, but metoclopramide had no effect during short stimulation periods (344).

The presynaptic DA_2 receptors we discussed in this review are located on noradrenergic nerve terminals. It has been suggested that dopaminergic nerves exist in the periphery liberating dopamine as their neurotransmitter; they have been described mainly in the kidney in several species and in the canine hindpaw (34–38, 53, 102, 130, 322). It has not been investigated whether or not presynaptic DA_2 receptors are present on these dopaminergic nerve terminals nor whether they mediate a negative feedback on dopamine release. Their role seems to be to regulate local blood flow and natriuresis via postsynaptic DA_1 receptors (35, 322). It remains possible that the dopamine released from these nerves also acts on DA_2 receptors on noradrenergic nerve endings and inhibits noradrenaline release.

2. Pharmacological role. Although it is not clear whether presynaptic DA_2 receptors play a physiological role in the regulation of sympathetic nerve transmitter release, they are of interest from a pharmacological point of view. Presynaptic inhibition of sympathetic tone, with reduction of peripheral vascular resistance and heart rate, might be useful in the treatment of hypertension, while the afterload reduction might be useful in heart failure and shock. It has been suggested that an alteration of the negative feedback control mechanism of noradrenaline release plays a role in the increased peripheral resistance observed in hypertension (327).

For several of the dopamine analogues mentioned in tables 2 and 3 and studied *in vivo* for a particular presynaptic effect, it was shown that they decrease heart rate and/or blood pressure in the anaesthetized or conscious animal when administered systemically. This has been studied in more detail for pergolide (23, 98, 328), lergotrile (20), LY 141865 (211, 212), bromocriptine (217,

364), *N*-*n*-propyl-*N*-*n*-butyl-DA (158), and *N*,*N*-di-*n*-propyl-DA (209, 211, 242, 342, 350, 383). For *l*-dopa, it has been shown that a presynaptic effect, probably after conversion to dopamine, partially explains the hypotension observed as a side effect (326). 1-*N*-Methyl-8-α-[sulfa(*N*,*N*-dimethylamido)]aminoergoline (Cu 32-085), which inhibits prolactin secretion, decreases blood pressure in the rat (366). These observations in the intact animal after systemic administration do not, however, by themselves prove the role of the presynaptic DA_2 receptors: when given systemically, the agents can also act centrally at the ganglionic level and on postsynaptic DA_1 receptors (20, 101, 132, 184, 322, 323). This has been discussed mainly for dopamine (205), pergolide (23, 98, 328), and *N*,*N*-di-*n*-propyl-4,7-dimethoxy-amino-indan (RDS-127) (13). In the rat, pergolide and RDS-127 stimulate the parasympathetic tone on the heart via central dopamine receptors (13, 97, 98). For apomorphine, however, it has been shown that its hypotensive effect in rat and dog is mainly due to stimulation of peripheral presynaptic dopamine receptors (50, 368).

The influence of DA_2 receptor agonists on peripheral vascular resistance has been studied more extensively in the pithed rat with spinal cord electrical stimulation. Bromocriptine (487), pergolide (93, 98), M7 (109), *N*,*N*-di-*n*-propyl-DA (96, 109, 496), and *N*,*N*-di-*n*-propyl-6,7-ADTN (496) antagonize the electrically induced pressor responses by interacting with presynaptic DA_2 receptors, but the antagonism of the increase in heart rate seems to be mediated via α_2-adrenoceptors (93, 97, 98) (see also chapter II.A.2). LY 141865 inhibited the blood pressure increase but not the evoked tachycardia; the inhibition was antagonized by sulpiride (94). For pergolide, it has further been shown that the inhibition of the evoked blood pressure response is accompanied by a decrease in noradrenaline plasma levels (99).

The potential clinical use of DA_2 receptor agonists has been studied in some disease models in animals. Dopamine itself has a hypotensive effect in the spontaneously hypertensive rat (SHR), but this effect is mainly due to β-adrenoceptor stimulation (129). In the SHR, *N*,*N*-di-*n*-propyl-DA (96, 311), bromocriptine (354), lergotrile (208, 453, 454), ergoline derivatives (43, 405), and pergolide (95, 503) have been shown to decrease blood pressure. The effect of lergotrile is antagonized by haloperidol but not by yohimbine (208); since it is also antagonized by domperidone (454), the effect of lergotrile is at least partially peripheral. However, the interpretation of the observations in the SHR is not always straightforward; bromocriptine, for example, was shown to decrease cardiac output in the SHR without concomitant change in peripheral vascular resistance or heart rate, which seems to negate the hypothesis that the hypotensive effect is due to presynaptic inhibition of noradrenaline release (451). In neurogenic hypertensive dogs, bromocriptine (364) and pergolide (23) produce hypotension by decreasing vascular resistance; for pergolide, a central mechanism is also involved (23).

It has already been mentioned that afterload reduction by decreasing vascular resistance is useful in shock. When it was tested in the dog with acute hemorrhagic shock whether or not dopamine receptor agonists are suitable for this purpose, only dopamine improved renal hemodynamics, probably because of its blood pressure-raising effects; bromocriptine and *N*,*N*-di-*n*-propyl-DA, which did not increase blood pressure, did not improve renal hemodynamics (215). The latter might be related to the experimental observation, made by many authors, that the presynaptic inhibitory effect of DA_2 receptor agonists greatly decreases when the sympathetic nerves are stimulated at high frequencies (more than 10 Hz).

In primates, including man, a few data are available on the use of DA_2 receptor agonists to reduce vascular resistance (see refs. 101, 132, 181, 207). In the anesthetized rhesus monkey, LY 171555, the levo-isomer of LY 141865, and *N*,*N*-di-*n*-propyl-DA decrease peripheral vascular resistance and blood pressure (210). In patients with heart failure, *l*-dopa decreased vascular resistance; this effect could be due to activation of DA_1 and DA_2 receptors (394). This observation is of interest as L-dopa was administered orally. *N*-*n*-propyl-*N*-*n*-butyl-DA was shown to decrease vascular resistance and increase renal blood flow in normal volunteers (157) and to reduce afterload in patients suffering from congestive heart failure (157, 158). Bromocriptine lowers blood pressure in man by venous and arteriolar dilatation due to suppression of sympathetic tone (264, 438), and it lowers blood pressure in hypertensive patients (283, 439, 440, 452). The suppression of sympathetic tone was demonstrated in normal volunteers and in hypertensive patients by measuring basal and stimulated noradrenergic activities (91, 345, 439, 440).

Finally, it should be added that the use of DA_2 receptor agonists in human therapy will probably be hampered by drug-induced emesis, via the chemoreceptor trigger zone (135, 188, 347), and by inhibition of prolactin release, as the receptor mediating these effects is the D_2-receptor which is very similar to the DA_2 receptor. DA_1 receptor agonists, which are also clinically tested, are devoid of these side effects (3).

III. Ganglionic Dopamine Receptors

A. Effects of Dopamine on Ganglionic Transmission

Exogenous dopamine has inhibitory and facilitatory effects on ganglionic transmission. On the basis of the ganglionic effects of some dopamine receptor antagonists, it was suggested that endogenous dopamine plays a physiological modulatory role in ganglionic transmission. Before discussing the receptors involved, we will describe the effects in more detail.

1. Dopamine-induced ganglionic inhibition. Dopamine

decreases vascular resistance in the hindleg of the dog when injected into the blood supply of the paravertebral lumbar ganglia (51), an effect which had already been described in the cat and the dog for adrenaline and noradrenaline (63, 218, 266). Injected close to the superior cervical ganglion, dopamine, as the other catecholamines, inhibits the contraction of the nictitating membrane elicited by preganglionic stimulation (for refs., see 204, 465, 490). These observations provide indirect evidence that dopamine—and other catecholamines—inhibit ganglionic transmission. Direct electrophysiological evidence for such an effect of dopamine was provided for the cat, rabbit, and rat superior cervical ganglion (144, 353, 376, 392), the canine paravertebral lumbar ganglia (52, 497), the vesical parasympathetic ganglia of the cat (127), the inferior mesenteric ganglion of the cat and dog (318, 353), and the neurons of the submucosal plexuses of the guinea pig small intestine (233).

Two different mechanisms have been suggested to explain the ganglionic inhibitory effect of catecholamines, including dopamine: one via the postsynaptic ganglionic neuron; the other via the presynaptic preganglionic nerve ending.

Concomitantly with their inhibitory effect on ganglionic transmission, adrenaline and noradrenaline produce ganglionic hyperpolarization, and the changes in action potential configuration observed are similar to those produced by hyperpolarizing pulses (128, 147). Both the hyperpolarization and the ganglionic inhibition are blocked by dihydroergotamine (128), suggesting that the ganglionic inhibition by exogenous catecholamines is due to *postsynaptic hyperpolarization*. Other observations also point to a postsynaptic effect: in the nicotinized superior cervical ganglion, a slow inhibitory postsynaptic potential (s.i.p.s.p.) is recorded on preganglionic stimulation; this hyperpolarization is mimicked by catecholamines, including dopamine (147, 314). Similar results were obtained in the submucosal plexus of the guinea pig intestine (233). On the basis of several observations, using different experimental approaches, it was hypothesized that the s.i.p.s.p. registered during preganglionic stimulation is produced by a disynaptic process, whereby preganglionically released acetylcholine acts on an interneuron, a small, intensely fluorescent cell (SIF-cell), and stimulates the release of a catecholamine, presumably dopamine. The dopamine released would then interact with the postganglionic neuron producing the s.i.p.s.p. (147, 241, 314, 316, 317). It was suggested that the hyperpolarization was mediated by the second messenger cyclic AMP, via the stimulation of a membrane-bound dopamine sensitive adenylate cyclase (193). Not all observations, however, are compatible with this relation between adenylate cyclase stimulation and ganglionic inhibition (392).

On the basis of the cyclic AMP hyperpolarization hypothesis, one could expect that dopamine plays a physiological role in modulating ganglionic transmission and that the postsynaptic hyperpolarization also explains the inhibitory effect of exogenous dopamine. The disynaptic hypothesis of a physiological inhibitory modulator role for dopamine, which is based on circumstantial electrophysiological, pharmacological, and histochemical evidence, has been strongly criticized and is no longer generally accepted (164, 174, 219, 240, 351, 490, 493).

As an alternative hypothesis, a *presynaptic effect* of dopamine and catecholamines was proposed, with inhibition of the release of the neurotransmitter acetylcholine from preganglionic nerve endings. In the superior cervical ganglion of the rabbit and the guinea pig, dopamine and other catecholamines, in concentrations that block ganglionic transmission, reduce the quantal content of the excitatory postsynaptic potential (e.p.s.p.), without changing postsynaptic membrane potential or membrane resistance and without interfering with the excitatory potential elicited by iontophoretically applied acetylcholine (105, 142, 144, 382). In the intestinal submucosal plexus, too, the excitatory potential of part of the neurons is inhibited by dopamine, presumably via a presynaptic mechanism (233).

2. Dopamine-induced ganglionic facilitation. Attention has also been drawn to a facilitatory effect of dopamine, acting via cyclic AMP, on the slow excitatory postsynaptic potential (s.e.p.s.p.) (14, 315, 317). A potentiation of ganglionic transmission, presumably via β-adrenoceptors, has been described for exogenously administered catecholamines (490). This facilitatory effect, presumably via a postsynaptic mechanism, has, however, attracted much less attention than the inhibitory effect.

B. The Receptor Mediating the Ganglionic Effects of Dopamine

1. Dopamine-induced ganglionic inhibition. Adrenaline and noradrenaline are thought to inhibit ganglionic transmission via an α-adrenoceptor (105, 127, 128, 147, 204, 353, 465, 490). Several experimental observations suggest that, at least in some ganglia, dopamine acts on a receptor different from the α-adrenoceptor. In this discussion, we will distinguish between the different techniques used to record ganglionic transmission.

a. RECORDING OF POSTGANGLIONIC NERVE ACTIVITY OR END-ORGAN RESPONSE. In experiments where the inhibition of the postganglionic compound action potential was studied, dopamine was first found to be less potent and less effective than noradrenaline in the cat superior cervical ganglion (267, 353), in the intramural ganglia of the cat bladder (127), and in the canine stellate ganglion (287). In the bladder preparation, the effects of adrenaline, noradrenaline, and dopamine are blocked by dihydroergotamine and phentolamine. Bulbocapnine, a dopamine antagonist (388), blocked the effects of dopamine in this preparation but also those of noradrenaline and of sympathetic stimulation (409). These observations suggested that dopamine acts via an α-adrenoceptor. Later on, however, an observation in dog paraverte-

bral ganglia suggested that, in that ganglion, dopamine inhibits ganglionic transmission via a receptor different from the α-adrenoceptor. Dopamine was equipotent with (−)-noradrenaline and 20 times more potent than (+)-noradrenaline (497), where, according to the Easson-Stedman hypothesis, dopamine should be equipotent with (+)-noradrenaline for the interaction with an α-adrenoceptor (389).

In the same preparation, different dopamine receptor agonists and antagonists were studied. The agonists apomorphine, epinine, and piribedil also produce ganglionic inhibition, apomorphine and epinine being equipotent with dopamine and piribedil being 2 times less potent (497, 498, 500). S584 (the catechol metabolite of piribedil) was without effect (498).

The dopamine effect was selectively antagonized, in decreasing order of potency, by (+)-butaclamol, haloperidol, pimozide, aceperone, and chlorpromazine, applied in doses that hardly influenced the effect of (−)-noradrenaline. (−)-Butaclamol was without effect. Phentolamine, on the other hand, selectively blocked the (−)-noradrenaline effect. Haloperidol also antagonized the inhibitory effect of epinine, apomorphine, and piribedil in doses which were without influence on (−)- and (+)-noradrenaline. Phenoxybenzamine antagonized both (−)-noradrenaline and dopamine (497, 498, 500). The dopamine effect was also blocked by domperidone (499). Ergometrine, an antagonist of dopamine receptors in molluscan neurons (501), had no effect in the dog paravertebral ganglion (497). On the basis of these results, it was concluded that dopamine inhibits the transmission in the paravertebral ganglia of the dog via a selective dopamine receptor. Similar conclusions were drawn from observations in the inferior mesenteric ganglion and the superior cervical ganglion of the cat (318, 466). Other dopamine receptor agonists that have been shown to inhibit ganglionic transmission are *N,N*-dimethyl-6,7-ADTN (TL-99) and *N,N*-dimethyl-5,6-ADTN (M7) (275, 276), fenoldopam (6, 194, 332, 400), and LY 171555 (5, 6). The ganglia studied were the dog paravertebral ganglia, the cat superior cervical ganglion and lumbar ganglia, and the rat superior cervical ganglion. In the studies with TL-99 and M7, end organ responses to preganglionic stimulation were measured as an index of ganglionic transmission. TL-99 does not depress transmission in the stellate ganglion of the dog, phentolamine antagonized the effect of TL-99 on the canine cardiac ganglia, whereas haloperidol is an antagonist in the cat but not in the dog (276). Since, however, selective α-adrenoceptor agonists were not used in these experiments, no firm conclusions can be drawn with regard to the receptor involved. When the dopamine-induced inhibition in the stellate ganglion of the dog was studied by recording stimulation-evoked tachycardia, it was found that the dopamine effect was antagonized by both α-adrenoceptor and dopamine receptor antagonists, whereas the effect of noradrenaline was antagonized only by α-adrenoceptor antagonists (287). Here, too, no attempt was made to test the selectivity of the different antagonists used, so that no clear conclusions can be drawn.

It is difficult to say whether the dopamine receptor involved in the inhibition of the synaptic process in some ganglia is a DA_1 or a DA_2 receptor. Some results point to the presence of a DA_2 receptor: the equipotency of apomorphine with dopamine (497); the potent and long-lasting blockade by haloperidol and by the DA_2 selective antagonist, domperidone (497, 499); the activity of piribedil (498); and the antagonistic activity of phenoxybenzamine (497). The DA_1 selective agonist, fenoldopam, however, inhibits ganglionic transmission in dog paravertebral ganglia (332, 400) and in rat superior cervical ganglion, in which case the effect is blocked by *R*-sulpiride (5, 6). The DA_2 selective agonist, LY 171555, is less potent in the rat, and its effect is antagonized by *S*-sulpiride (5, 6). Furthermore, *R*-sulpiride specifically antagonized the dopamine-induced ganglionic inhibition, whereas *S*-sulpiride antagonized the noradrenaline effect (241). It would be of interest to repeat the electrophysiological experiments using in the same series of experiments the selective DA_1 and DA_2 receptor agonists and antagonists that are now available and to determine their relative potencies.

b. RECORDING OF POSTSYNAPTIC NEURONAL HYPERPOLARIZATION. In order to characterize the receptor mediating the postsynaptic neuronal hyperpolarization by dopamine or the receptor involved in the s.i.p.s.p., the postsynaptic ganglionic effect was measured directly by electrophysiological recordings.

Dopamine is less potent than (−)-noradrenaline in producing postganglionic hyperpolarization in rabbit and rat superior cervical ganglia (57, 112). Haloperidol antagonizes the dopamine-induced hyperpolarization in the rabbit superior cervical ganglion (141), but no comparison was made with its effect on α-adrenoceptor agonists. Others found that the dopamine receptor antagonists, chlorpromazine, haloperidol, and pimozide, had no effect on the dopamine-induced hyperpolarization (57, 112, 376). A careful *in vitro* study, using (−)-noradrenaline, dopamine, apomorphine, oxymetazoline, clonidine, methoxamine, phentolamine, haloperidol, methysergide, fluphenazine, *cis*-flupenthixol, yohimbine, and prazosin, led Brown and Caulfield (57) to conclude that the postsynaptic hyperpolarization by dopamine in the rat superior cervical ganglion is mediated by an α_2-adrenoceptor. Similar results were obtained by Cole and Shinnick-Gallagher (112). The dopamine-induced hyperpolarization in neurons of the submucosal plexus of the guinea pig intestine was blocked by methysergide, but this was also true for the noradrenaline-induced hyperpolarization (233).

The s.i.p.s.p. in nicotinized ganglia is blocked by dibenamine and phenoxybenzamine (147, 174, 314). Chlorpromazine, haloperidol, and pimozide inhibited the slow

hyperpolarization (P wave) but also the rapid and slow depolarizations (N and LN waves) in amphibian ganglia (376). Haloperidol blocks the hyperpolarizing effect of iontophoretically applied acetylcholine to the rabbit superior cervical ganglion (143), but other authors found that haloperidol had a nonselective action, and chlorpromazine, pimozide, and sulpiride had no effect on the s.i.p.s.p. induced by preganglionic stimulation of the superior cervical ganglion of the rabbit (112, 376). The increase of cyclic AMP in bovine ganglia produced by dopamine is antagonized by phenoxybenzamine and phentolamine, whereas the increase by noradrenaline is antagonized by propranolol (273). These observations do not allow a clear characterization of the receptor involved in the s.i.p.s.p. The contradictory results and the lack of evidence that the dopamine hyperpolarization and the s.i.p.s.p. are mediated via the same receptor are part of the evidence against the disynaptic hypothesis of the origin of the s.i.p.s.p.

One could argue that most dopamine receptor antagonists used in the studies mentioned are more or less selective for the DA_2 receptor and are therefore not suitable for characterization of the postsynaptic ganglionic receptor if it would be a DA_1 receptor. However, in both the studies of Gallagher and coworkers (174) and of Brown and Caulfield (57), racemic sulpiride, which blocks the DA_1 receptor leaving the effect of dopamine intact, and specific α_2-adrenoceptor antagonists, which block the dopamine effect, were used. The conclusion is that the postsynaptic hyperpolarization is not mediated via a specific dopamine receptor.

c. MEASUREMENT OF PRESYNAPTIC TRANSMITTER RELEASE. We already mentioned the presynaptic effect of catecholamines, inhibition of transmitter release, which is more likely to explain their transient inhibitory effect on ganglionic transmission. Less work has been done with regard to the receptor involved in this presynaptic effect. (−)-Noradrenaline is thought to act presynaptically on an α-adrenoceptor, as the relative potency of agonists is adrenaline > noradrenaline > isoprenaline, and as this effect is blocked by phenoxybenzamine and dihydroergotoxine but not by propranolol (105). As the effect of dopamine is also blocked by phenoxybenzamine, but not by propranolol, it was concluded that dopamine also acts via a presynaptic α-adrenoceptor (144). However, as we have already pointed out, phenoxybenzamine blocks both α-adrenoceptors and DA_2 receptors. The only direct search for a presynaptic ganglionic dopamine receptor has been done by Nakamura (376), who was unable to block in the isolated rabbit superior cervical ganglia the inhibitory effect of dopamine on the excitatory postsynaptic potential with haloperidol, chlorpromazine, or pimozide. As mentioned before, these agents antagonize the dopamine-induced ganglionic inhibition in the dog paravertebral lumbar ganglia. It has been suggested that study of the dopamine-induced phosphorylation of protein I in ganglia might be useful for the characterization of the presynaptic dopamine receptor; phentolamine antagonizes this effect, but no other antagonists or agonists were studied (378).

2. *Dopamine-induced ganglionic facilitation.* For the potentiating effect of dopamine on ganglionic transmission, Libet (315) proposed that the increase in cyclic AMP and the potentiation of the s.e.p.s.p. are mediated via a specific M (modulator) receptor, which, because of a possible link with cyclic AMP, was classified as a D_1 receptor (15). The same authors had classified this receptor previously as a DA_1 receptor (14), as it was blocked by spiroperidol, (+)-butaclamol, and bromocriptine. The latter agents, however, cannot be accepted as selective DA_1 or D_1 antagonists (184, 272). Furthermore, sulpiride, which antagonizes DA_1 receptors, was without effect, and (−)-butaclamol produced the same results as (+)-butaclamol. Others described potentiation of ganglionic transmission by apomorphine and inhibition of transmission by haloperidol in the superior cervical cat ganglion under nicotinic blockade, leaving only the muscarinic pathway available (176). These authors explain their observations within the disynaptic SIF-cell hypothesis, assuming that dopaminergic agents inhibit the release of dopamine from the SIF-interneuron via a presynaptic autoreceptor and that this receptor is blocked by haloperidol. This hypothesis, as well as the existence of a dopamine autoreceptor on the SIF-cell, is offered as an explanation for the observations, but proof is not available.

C. Conclusion

In some mammalian ganglia, a dopamine receptor has been described, mediating inhibition of the synaptic process. The observations with DA_1 and DA_2 receptor agonists and antagonists do not allow identification of the dopamine receptor subtype involved, and further experiments to determine the relative potency of these agents in the same experimental preparation are needed to clarify this problem.

In contrast, the experiments designed to study the mechanism of the ganglionic inhibition, either postsynaptic hyperpolarization or preganglionic inhibition of transmitter release, showed that these dopamine effects are mediated via an α-adrenoceptor. An exact localisation of the ganglionic dopamine receptor is, therefore, not yet possible.

IV. Dopamine Receptors in the Gastrointestinal System

Dopamine has inhibitory and excitatory effects on smooth muscle activity and exocrine gland secretion in the gastrointestinal tract. For some of these effects, interaction with a specific dopamine receptor has been suggested. It has also been suggested that endogenous dopamine plays a physiological role in the regulation of some aspects of gastrointestinal motility and exocrine secretion. Significant amounts of dopamine have indeed

TABLE 5

The effect of dopamine and dopamine receptor agonists on gastrointestinal motility. For each experimental preparation, the effect described is that of dopamine or the dopamine receptor agonist used; the agonists and antagonists listed indicate whether an effort has been made to characterize the receptor involved.

Part of the G.I. tract, species, and experimental preparation	Reference	Effect of dopamine or dopamine receptor agonist	Agonists studied	Antagonists of the following receptors studied
Esophageal body				
Guinea pig				
In vitro, longitudinal muscularis mucosae strip	270	Inhibition of electrically induced contractions Weak contractions in the presence of propranolol Relaxation of carbachol-contracted strips in the presence of phentolamine	Dopamine Noradrenaline Adrenaline Isoprenaline	DA α, β Muscarinic
Opossum				
In vitro, transverse strip	126	Inhibition of contractile off-response Contractions at high concentrations	Dopamine Epinine Noradrenaline Isoprenaline	DA α, β
In vivo, intraluminal pressure	397	Contraction	Dopamine Isoprenaline Phenylephrine	DA α, β
In vivo, intraluminal pressure	369	Contraction	Dopamine	DA α, β Muscarinic
Lower esophageal sphincter				
Guinea pig				
In vitro, longitudinal strip	121	Relaxation	Dopamine Noradrenaline Phenylephrine Isoprenaline Clonidine Acetylcholine Tyramine 5-HT	DA α, β 5-HT
In vitro, circular strip	402	Relaxation followed by contraction	Dopamine Noradrenaline Phenylephrine Isoprenaline	DA α, β
Opossum				
In vitro, transverse strip	126	Relaxation followed by repetitive contractions at high concentrations	Dopamine Epinine Noradrenaline Isoprenaline	DA α, β
In vivo, intraluminal pressure	397	Relaxation frequently interrupted by contractions	Dopamine Isoprenaline Phenylephrine	DA α, β
In vivo, intraluminal pressure	369	Relaxation followed by repetitive contractions	Dopamine	DA α, β Muscarinic
Dog				
In vivo	258	Inhibition of interdigestive contractions	Dopamine	DA
Man				
In vivo, intraluminal pressure	29	Relaxation Inhibition of increase in pressure by metoclopramide, not of increase by bethanechol	*l*-Dopa Bethanechol	DA
In vivo, intraluminal pressure	40	No effect on basal pressure	Dopamine	
Stomach				
Rat				
In vitro, fundus strip	437	Contraction	Dopamine (only 10^{-7} M was used)	α, β 5-HT

TABLE 5—Continued

Part of the G.I. tract, species, and experimental preparation	Reference	Effect of dopamine or dopamine receptor agonist	Agonists studied	Antagonists of the following receptors studied
			5-HT Noradrenaline Isoprenaline	
In vitro, fundus strip	284	Contraction (low concentrations) Relaxation (high concentrations) Contraction at all concentrations	Dopamine Phenylephrine Apomorphine	DA α, β
In vitro, fundus strip	308	Inhibition of electrically and methacholine-induced contractions	Dopamine Noradrenaline Phenylephrine Clonidine	DA α, β
In vitro, whole stomach	104, 384	Inhibition of antral motility	Dopamine	DA
Guinea pig				
In vitro, stomach-duodenal bulb preparation	417–421 423 479–481	Relaxation Inhibition of phasic activity Inhibition of antroduodenal coordination	Dopamine Noradrenaline Secretin 5-HT Substance P ATP Phenylephrine	DA α, β Muscarinic
In vitro, fundic and antral pouches	467	Inhibition of the physostigmine-induced contractile response in the antral pouch	Dopamine Adrenaline Isoprenaline Phenylephrine	
In vitro, circular strip corpus	115, 401 403, 404	Contraction (low concentrations) Relaxation (high concentrations)	Dopamine Noradrenaline Isoprenaline Phenylephrine Clonidine Apomorphine Acetylcholine	DA α, β Muscarinic 5-HT
In vivo, gastric emptying	120	Inhibition	Apomorphine	DA
In vivo, gastric emptying	116	Inhibition	Apomorphine	DA α, β Muscarinic
Rabbit				
In vitro, transverse strip	156	Contraction	Dopamine Noradrenaline Adrenaline	α, β
Chick				
In vivo, proventriculus strip	427	Contraction Inhibition of electrically induced contractions	Dopamine Adrenaline Noradrenaline Clonidine Phenylephrine Isoprenaline	α, β
Cat				
In vivo, intragastric volume	2	Relaxation	Apomorphine	Muscarinic
Dog				
In vitro, fundus strip	310	Inhibition of electrically induced contractions	Dopamine Noradrenaline	DA α, β
In vivo, intragastric pressure	473	Relaxation	Dopamine Noradrenaline	DA α, β
In vivo, intragastric pressure	431	Relaxation	Dopamine	DA, α, β
In vivo motor activity	258	Inhibition of postprandial motor activity and interdigestive contractions	Dopamine	DA
In vivo, intraantral pressure	30, 31	Inhibition of pentagastrin- and bethanechol-stimulated antral activity	Dopamine	DA α, β
In vivo, intragastric pressure	44, 309	Relaxation	Apomorphine Morphine Fentanyl	DA Opiate

TABLE 5—Continued

Part of the G.I. tract, species, and experimental preparation	Reference	Effect of dopamine or dopamine receptor agonist	Agonists studied	Antagonists of the following receptors studied
Goat				
In vitro, ruminal strip	336, 478	Contraction *in vitro*	Dopamine	DA
In vivo, intraruminal pressure		Inhibition of ruminal contractions *in vivo*	Apomorphine Noradrenaline Adrenaline Isoprenaline Acetylcholine	α, β Muscarinic Opiate
Man				
In vitro, longitudinal and circular strip	434, 435	Inhibition of electrically and acetylcholine-induced contractions	Dopamine Noradrenaline Isoprenaline	DA α, β
In vitro, longitudinal and circular strip	461	Inhibition of spontaneous activity	Dopamine Isoprenaline Acetylcholine	DA α, β Muscarinic
In vivo, intraantral pressure	294	Inhibition of antral activity	Dopamine	DA
In vivo, intragastric pressure	475	Relaxation	*l*-Dopa	DA
In vivo, intragastric pressure and gastric empyting	477	Relaxation Delay in gastric emptying	Dopamine	DA
In vivo, gastric emptying	263	Prolongation stationary phase	Dopamine Pentagastrin	DA
In vivo, gastric emptying	26	Delay	Dopamine	
In vivo, gastric emptying	42	Delay	*l*-Dopa	DA
In vivo, gastric emptying	56	Delay	Apomorphine	DA
In vivo, gastric emptying	391	Delay	Apomorphine	DA
In vivo, gastric emptying	395	Delay	Apomorphine	DA
Pyloric sphincter				
Guinea pig				
In vitro, strip	155	Relaxation	Dopamine Noradrenaline	DA α, β
In vitro, circular strip	402	Relaxation followed by contraction	Dopamine Noradrenaline Phenylephrine Isoprenaline	DA α, β
Dog				
In vivo, motility measurement via strain gauge transducers	148, 149	Retroperistaltism	Apomorphine	DA
In vivo, duodenogastric reflux	371	Increase of reflux rate	Apomorphine	
Small intestine				
Rat				
In vitro, whole duodenum	357–361	Contraction (low concentrations) Relaxation (highest concentration)	Dopamine Dopa Adrenaline Noradrenaline 3-0 Me DOPA DOPAC 3-Methoxylyramine HVA MN NMN MHPG VMA Serotonine	DA α, β 5-HT Muscarinic H
Guinea pig				
In vitro, whole ileum strip	370	Inhibition of electrically and carbachol-induced contractions	Dopamine	DA
In vitro, longitudinal muscle strip	488	Inhibition of electrically induced contractions	Dopamine	α
In vitro, longitudinal muscle strip	160	Inhibition of electrically induced contractions	Dopamine Apomorphine Morphine	α, β Opiate
In vitro, longitudinal muscle strip	128, 504	Inhibition of electrically induced contractions, potentiation un-	Dopamine	DA α

TABLE 5—Continued

Part of the G.I. tract, species, and experimental preparation	Reference	Effect of dopamine or dopamine receptor agonist	Agonists studied	Antagonists of the following receptors studied
		der phentolamine		
		Inhibition of electrically and acetylcholine-induced contractions	Bromocriptine	DA α
In vitro, whole ileum strip	495	Inhibition of electrically induced contractions In the terminal ileum weak contractions in the presence of atropine and sotalol	Dopamine Noradrenaline Adrenaline Phenylephrine Oxymetazoline Clonidine	DA α, β Muscarinic H
In vitro, whole ileum (terminal) strip	362	Contractions	Dopamine + 11 other adrenergic agonists	DA α Muscarinic H
In vitro, whole ileum strip	154	Inhibition of electrically and acetylcholine-induced contractions	Dopamine Apomorphine Noradrenaline Isoprenaline Clonidine Phenylephrine	DA α, β
In vitro, whole ileum strip	459	Inhibition of electrically induced contractions	Dopamine Apomorphine Noradrenaline Clonidine Oxymetazoline	DA α, β
In vitro, whole ileum strip	441	Inhibition of electrically induced contractions	Dopamine Noradrenaline Clonidine 2-Chloroadenosine	DA β
In vitro, whole ileum strip	190	Inhibition of electrically induced contractions	Dopamine Noradrenaline Clonidine Apomorphine	DA α, β
In vitro, whole ileum strip	340	Inhibition of electrically induced contractions	2-Aminotetralins Benzo(*f*)quinolines Clonidine Noradrenaline	α
Opossum				
In vitro, longitudinal and circular duodenum strip	9	Contraction	Dopamine	DA α, β Muscarinic
Rabbit				
In vitro, whole jejunum strip	225	Relaxation	Dopamine Noradrenaline Methoxamine Isoprenaline	α, β
In vitro, whole ileum strip	202	Antagonism of relaxation induced by sympathetic nerve stimulation	Dopamine Apomorphine Bromocriptine Piribedil Noradrenaline Nomifensine	DA α
Cat				
In vitro, small intestine strip	385	Inhibition of spontaneous electrical and mechanical activity, and inhibition of acetylcholine-induced contractions	Dopamine Dopa Noradrenaline Adrenaline Metanephrine Normetanephrine Phenylephrine Isoprenaline Salbutamol	α, β
Man				
In vivo, duodenum, intraluminal pressure and electrical activity	348	Stimulatory effect for 8 to 12 min followed by inhibitory effect	Dopamine	DA

TABLE 5—Continued

Part of the G.I. tract, species, and experimental preparation	Reference	Effect of dopamine or dopamine receptor agonist	Agonists studied	Antagonists of the following receptors studied
Colon				
Mouse				
In vitro, longitudinal strip distal colon	162	Contraction (low concentrations) Relaxation (high concentrations)	Dopamine Apomorphine Noradrenaline Adrenaline Phenylephrine Clonidine Isoprenaline	DA α, β Muscarinic Opiate H 5-HT
Guinea pig				
In vitro, taenia caecum	456	Relaxation	Dopamine Noradrenaline Isoprenaline Dopamine derivatives Papaverine Nicotine	α, β Muscarinic
Dog				
In vitro, longitudinal strip distal colon	195	Relaxation	Dopamine Noradrenaline Adrenaline Isoprenaline	DA α, β
In vivo, motility (circular muscle) measurement via strain gauge transducers	62	Inhibition of the ascending and transverse colon, stimulation of the descending colon Stimulation of the whole colon	Dopamine Clonidine Phenylephrine Bromocriptine	DA α, β
Man				
In vivo, sigmoid colon, intraluminal pressure	293	Stimulatory effect	Dopamine	α, β Muscarinic
In vitro, right and left colon	398			
longitudinal strip		Relaxation	Dopamine	DA
Circular strip		Inhibition of off-response	Dopamine	DA
Rectum				
Rat				
In vitro, rectum segments	380	Contraction (low concentrations) Relaxation (high concentrations)	Dopamine Apomorphine Phenylephrine Endorphins	DA
Rabbit				
In vitro, isolated rectococcygeus muscle	137	Inhibition of electrically induced contractions	Dopamine Noradrenaline + several other dopamine receptors and α-adrenoceptor agonists	DA, α

been found in the gastrointestinal wall of several mammalian species (234) and in human gastric juice (107, 206).

In this chapter, we will discuss the experimental evidence for the presence of dopamine receptors in the gastrointestinal tract with regard to motility and exocrine secretion. We will not discuss the effect of dopamine on gastrointestinal hormones, except when there could be a relation with the effects discussed, as, for example, the influence of dopamine on gastrin and gastric acid secretion.

A. Dopamine Receptors Influencing Gastrointestinal Motility

Like noradrenaline and other sympathomimetic agents, dopamine and dopamine receptor agonists produce inhibitory and excitatory effects on gastrointestinal motility. These effects in different parts of the gastrointestinal tract are summarized in table 5. *Inhibitory effects*—relaxation or inhibition of induced contractions or of spontaneous activity—are observed in several species in lower esophageal body, lower esophageal sphincter, stomach, small intestine, and colon. *Excitatory effects*—contraction or potentiation of induced contractions—have been less frequently observed but also occur in all parts of the gastrointestinal system. In most instances, excitatory effects are seen together with the inhibitory effect as a biphasic response, or as excitation at concentrations of the agonists lower than those producing inhibition.

1. The receptor mediating the inhibitory effects of dopamine. The inhibitory effect of dopamine on motility

seen in some gastrointestinal preparations has been explained by interaction with a specific dopamine receptor. The best evidence for the presence of an inhibitory dopamine receptor has been obtained in the opossum lower esophageal sphincter. We will describe, in order of decreasing experimental evidence, the results which have been interpreted by the respective authors as proof of the presence of a dopamine receptor. This will be followed by a discussion of results of studies, where the inhibitory effect of dopamine was explained by interaction with α- and/or β-adrenoceptors.

a. EXPERIMENTAL OBSERVATIONS EXPLAINED BY INTERACTION WITH A DOPAMINE RECEPTOR. **i. Opossum lower esophageal sphincter.** In the opossum lower esophageal sphincter, in both *in vivo* experiments, where lower esophageal sphincter pressure is measured, and *in vitro* experiments with transverse strips, dopamine produces a dose-dependent relaxation, antagonized by haloperidol and bulbocapnine, but not by phenoxybenzamine, phentolamine, or propranolol (126, 369, 397). *In vitro*, the relaxation by noradrenaline and isoprenaline was not influenced by haloperidol and bulbocapnine but was completely abolished by propranolol. Similar results as for dopamine were obtained for epinine (126). As tetrodotoxin does not modify the dopamine effect (126, 397), dopamine probably acts on the smooth muscle cells, and the receptor involved is not located on neuronal structures.

ii. Guinea pig stomach. Much work has been done on the receptor mediating the inhibitory effect of dopamine on guinea pig gastric motility. The idea that a specific dopamine receptor is involved was put forward by Van Nueten and coworkers (417–423, 479–481). Based on the observation that the dopamine-induced relaxation in the isolated guinea pig stomach is antagonized by haloperidol and domperidone, reduced by tetrodotoxin, and blocked by phenoxybenzamine and phentolamine, Van Nueten and Janssen suggested that dopamine acts on a dopamine receptor to release noradrenaline, which inhibits gastric motility by acting on an α-adrenoceptor (480). Later results of the same group, however, showed that, in contrast to phenoxybenzamine and phentolamine, the α_1-adrenoceptor antagonist prazosin was much more effective against noradrenaline than against dopamine (419). Moreover, where, in the original paper (480), domperidone antagonized the dopamine effect in concentrations not affecting the noradrenaline-induced response, in later experiments, domperidone was found to antagonize the relaxation induced by phenylephrine almost as effectively as the relaxation by dopamine (418). Nevertheless, the original hypothesis was maintained, and it was suggested that, besides α_2-adrenoceptors, dopamine receptors are involved in the relaxation of the guinea pig stomach induced by periarterial (left gastric artery) stimulation, as the relaxation was antagonized by domperidone, pimozide, yohimbine, piperoxan, and tolazolin, but not by prasozin or propranolol (422).

The same group found also that dopamine reduces the amplitude of gastric phasic activity and that domperidone increases phasic amplitude (479, 480). Therefore, it was hypothesized that dopamine has a functional role in gastric motility and that domperidone produces its effects by interacting with endogenous dopamine. However, dopamine does not influence the frequency of phasic activity, whereas domperidone does (419), an effect which is not blocked by tetrodotoxin (421). Moreover, there is no relationship between the antagonism of the dopamine effect and the effect on phasic activity of some antagonists; phentolamine and phenoxybenzamine, for example, clearly antagonize the relaxatory effect of exogenous dopamine, but they do not influence spontaneous phasic activity (480). These discrepancies were explained by assuming that domperidone stimulates gastric phasic activity by antagonism of endogenous dopamine at receptor sites different from those on which exogenous dopamine acts, thus not involving the release of noradrenaline (480).

More recently, the same group put more emphasis on the inhibitory effect of dopamine on antroduodenal coordination and the opposite effect of domperidone (417, 419–421, 423). The effect of dopamine was antagonized by domperidone but not by prazosin and does not occur when antroduodenal coordination is inhibited by tetrodotoxin but restored by bethanechol. The stimulatory effect of domperidone disappeared after tetrodotoxin and atropine but not after hexamethonium. These observations suggest that dopamine interferes with the cholinergic innervation in the gastric wall and that the receptor involved is located on nervous structures (423). It was further observed that pretreatment with 6-hydroxydopamine also completely prevented the effect of domperidone, suggesting that the stimulatory effect of domperidone on antroduodenal coordination is dependent on the presence of postganglionic noradrenergic nerve endings, thus implicating an intermediary role of noradrenaline (421). This is in contrast with Van Nueten's explanation for the stimulatory effect of domperidone on gastric phasic activity; moreover, neither the α_1-adrenoceptor antagonist prazosin, nor the α_2-adrenoceptor antagonist rauwolscine, nor the β-adrenoceptor antagonist propranolol influences antroduodenal coordination; moreover, after pretreatment with the α_1-adrenoceptor antagonist prazosin, domperidone still increases antroduodenal coordination (420).

It is difficult to explain all the results obtained by Van Nueten and coworkers in the guinea pig stomach-duodenum preparation by one inhibitory mechanism, involving dopamine and a neuronal dopamine receptor. Moreover, studying circular and longitudinal muscle preparations of the different regions of the guinea pig stomach, Costall and coworkers did not find evidence for the involvement of a specific dopamine receptor in field stimulation-induced responses (118, 119). Others expressed doubts about the selectivity of domperidone for

the dopamine receptor (153). The suggestion that dopamine is involved in the inhibitory effects on the stomach of, for example, secretin, 5HT, and substance P (479, 481), has thus to be viewed with caution, since it is only based on the antagonistic properties of domperidone on these substances.

iii. Other gastrointestinal preparations. Observations in other gastrointestinal preparations have also been interpreted as pointing to the presence of an inhibitory dopamine receptor. In longitudinal and circular human gastric smooth muscle preparations, dopamine produces a dose-dependent inhibition of acetylcholine-induced contractions. As the effect of dopamine was completely antagonized by combined α- and β-adrenoceptor blockade and by domperidone, while the effects of noradrenaline and isoprenaline were not influenced by domperidone, it was concluded that, as in the guinea pig stomach, dopamine acts on specific receptors, leading to activation of an inhibitory noradrenergic mechanism (434, 435). In the rabbit ileum, dopamine and dopamine receptor agonists inhibit the relaxation induced by sympathetic nerve stimulation. It was proposed that these substances act on α-adrenoceptors and on dopamine receptors on the sympathetic nerve endings, so inhibiting the release of noradrenaline (202). In the guinea pig ileum, presynaptic dopamine receptors on the intramural cholinergic neurons have been proposed to be involved in the inhibitory effect of dopamine on contractions induced by transmural electrical stimulation, but dopamine also interacts with presynaptic α-adrenoceptors and with postsynaptic β-adrenoceptors (154). The presence of dopamine receptors is suggested because phentolamine is more potent against clonidine than against apomorphine, while the opposite is true for pimozide; however, phentolamine and pimozide are both equally active against noradrenaline and dopamine (154). Using yohimbine as α-adrenoceptor antagonist, Tayo (459) made similar observations, except that yohimbine was less potent in antagonizing dopamine than noradrenaline. Various 2-aminotetralins and benzo[*f*]quinolines also produce a presynaptic inhibition of cholinergic transmission in guinea pig ileum. The effect of the hydroxylated aminotetralins and of the benzo[*f*]quinolines was antagonized by phentolamine, but that of the non-hydroxylated aminotetralins was not; no other antagonists were tested (340). The ergot alkaloids ergosinine, dihydroergosine, and dihydroergotamine also inhibit cholinergic transmission at a presynaptic level, but in these experiments, no antagonists were used (393). For the presynaptic inhibitory effect of dopamine on intramural cholinergic neurons in the rabbit rectococcygeus muscle, a more complete analysis has been done. The effect of dopamine is antagonized by haloperidol and sulpiride, but not by phentolamine and yohimbine; it is concluded that presynaptic dopamine receptors are present on the cholinergic nerves (137).

Finally, we should mention experimental observations with dopamine, dopamine receptor agonists, and/or dopamine receptor antagonists in the canine lower esophageal sphincter (258), the rat stomach (104, 384), the canine stomach (30, 31, 258, 431, 473), the goat rumen (336), the human stomach (26, 42, 56, 263, 294, 391, 395, 475, 477), the canine gastroduodenal region (148, 149, 371), the guinea pig taenia caeci (456), the canine proximal colon (62), and the human colon (398). Most of these results have been explained by assuming that inhibitory dopamine receptors are involved, but the evidence presented in these papers is not convincing. Indeed, in several studies, only dopamine and dopamine receptor antagonists were used, while it is well known that these agents lack specificity and also react with other adrenoceptors. Moreover, most of these studies are performed *in vivo*, and an influence on gastrointestinal motility via receptors outside the gastrointestinal system cannot be excluded.

b. EXPERIMENTAL OBSERVATIONS EXPLAINED BY INTERACTION WITH α-AND β-ADRENOCEPTORS. In contrast to the papers mentioned previously, in a large series of studies, the authors came to the conclusion that there are no dopamine receptors present in the gastrointestinal wall. In these *in vitro* studies on isolated strips, α- and β-adrenoceptor agonists and antagonists as well as dopamine receptor agonists and antagonists were used in well-controlled conditions. The conclusion is that the inhibitory activity of dopamine and dopamine receptor agonists can be satisfactorily explained by interaction with α- and/or β-adrenoceptors. This applies to the guinea pig esophageal longitudinal muscularis mucosae (270), the guinea pig lower esophageal sphincter (121, 402), the rat gastric fundus (284, 308), the guinea pig cardia, fundus, corpus, and antrum (115, 401, 403, 404), the chicken proventriculus (427), the canine gastric fundus (310), the human stomach (461), the guinea pig pyloric sphincter (155, 402), the rat duodenum (360), the guinea pig ileum (146, 160, 190, 370, 441, 488, 495, 504), the rabbit jejunum (225), the mouse distal colon (162), and the dog distal colon (195). The β-adrenoceptors involved are located postsynaptically on the smooth muscle cells; the α-adrenoceptors are located postsynaptically and/or presynaptically on the intramural cholinergic neurons. Both α_1- and α_2-adrenoceptors have been described, but this will not be discussed in this review.

The results of the studies mentioned above illustrate that all available dopamine receptor antagonists, including domperidone and sulpiride, lack specificity, so that their effect in itself is no proof for the presence of dopamine receptors. In some of these studies, the effect observed with apomorphine or bromocriptine was different from that of dopamine (146, 162, 284, 504). In myenteric plexus-longitudinal muscle strips of the guinea pig ileum, bromocriptine inhibited the electrically evoked twitch responses, as did dopamine, but it also inhibited acetylcholine-induced contractions. As the effect of bromocriptine was not antagonized by the α-adrenocep-

tor antagonist phentolamine nor by the dopamine receptor antagonists haloperidol, metoclopramide, and pimozide, it is probably due to nonspecific properties (146, 504). In the rat gastric fundus, apomorphine induced contractions at all concentrations tested, while dopamine had a relaxatory effect in the higher concentrations; the influence of the antagonists against apomorphine was not studied (284). In the mouse distal colon, apomorphine in high concentrations, produced relaxation but in contrast to dopamine, this relaxation was not antagonized by α- and β-adrenoceptor blockade. As this effect was likewise not antagonized by dopamine receptor antagonists nor by neuronal blockade, it was suggested that apomorphine in high doses directly inhibits smooth muscle (162).

2. The receptor mediating the excitatory effects of dopamine. It has been suggested that dopamine receptors mediate excitatory effects of dopamine or dopamine receptor agonists, such as the potentiation of the electrically induced contractions of the guinea pig ileum in the presence of phentolamine (146), the stimulatory motor effect on the human duodenum (348) and on the descending colon of the dog (62), and the contractions of the human sigmoid colon (293). The experimental evidence for these suggestions is, however, not strong, as in most of these studies, no pharmacological characterization was attempted, and, in these *in vivo* studies, extragastrointestinal sites could also be involved. In the dog, the stimulatory effect of dopamine on the descending colon and of bromocriptine on the whole colon was not influenced by α- and β-adrenoceptor antagonists but was abolished by haloperidol and domperidone, suggesting the presence of excitatory dopamine receptors (62). Dopamine receptors were also said to mediate the repetitive contractions induced by dopamine in the opossum esophageal body (397). This effect of dopamine was antagonized by haloperidol but not by phentolamine or propranolol. Similar results were obtained in another study, where it was, however, suggested that the dopamine-induced contractions could be due to a rebound phenomenon, secondary to the inhibitory response induced by dopamine in the lower esophageal sphincter via the inhibitory dopamine receptor described earlier (369).

In the goat rumen, dopamine increases smooth muscle tone *in vitro*. Using α-adrenoceptor agonists and α- and β-adrenoceptor antagonists, it was shown that this excitatory effect is due to interaction with α-adrenoceptors (478). Apomorphine has a similar effect that was antagonized by domperidone; the influence of α-adrenoceptor antagonists was not studied (336).

The contractile effect of dopamine on opossum duodenum strips can be explained by interaction with α-adrenoceptors, as it is completely blocked by phenoxybenzamine or phentolamine (9). The existence of excitatory dopamine receptors in that preparation cannot be excluded, however, as high concentrations of bulbocapnine and haloperidol had a small antagonistic activity in some strips; the author adds that these high concentrations have α-lytic properties (9). The contractile effect of dopamine in the chicken proventriculus is blocked by phenoxybenzamine but not by phentolamine. No further receptor analysis was performed (427). Contractile responses to dopamine were also observed in lower esophageal sphincter, gastric corpus, and pyloric sphincter of the guinea pig. A detailed pharmacological investigation showed that the contractions by dopamine in the guinea pig lower esophageal and pyloric sphincter are mediated via α_1-adrenoceptors (402), while the contractile effect of low concentrations of dopamine and apomorphine in the guinea pig gastric corpus is mediated by interaction with α_2-adrenoceptors (115, 403). The contractile effect of low doses of dopamine and apomorphine on the mouse distal colon is also mediated by α_2-adrenoceptors, as shown in a study with a large series of antagonists (162).

In the guinea pig terminal ileum, high concentrations of dopamine induced weak contractions (362, 495). In the first study, where the contractions were obtained in the presence of atropine and sotalol, antagonists were not tested against dopamine, but the contractions induced by noradrenaline were antagonized by α-adrenoceptor antagonists and were ascribed to interaction with postsynaptic excitatory α-adrenoceptors (495). In the second study, the dopamine effect was not antagonized by α-adrenoceptor antagonists but decreased by haloperidol. Haloperidol, however, in the concentrations used, also decreased the contractile effect of barium chloride, which indicates that the antagonism of the dopamine effect is not specific and that the conclusion of the authors that the effect of dopamine is partly mediated by activation of dopamine receptors is probably not correct (362).

In the guinea pig esophageal longitudinal muscularis mucosae, high concentrations of dopamine induced weak contractions in the presence of propranolol. No antagonist was tested against dopamine, while the contractions induced by noradrenaline and adrenaline in similar conditions were abolished by phentolamine (270).

Finally, an indirect action of dopamine on 5HT-receptors, via the release of endogenous serotonin, has been proposed to explain its excitatory effects on the rat fundus (437). A direct action on 5HT-receptors has been proposed for the contractile effect of low concentrations of dopamine in the rat duodenum (357, 360, 361). This interpretation was later modified by the same authors, who suggested that an excitatory dopamine receptor, resembling the 5HT-receptor and blocked by sulpiride and metoclopramide but not by haloperidol, could be involved (358, 359). This should be interpreted with caution as sulpiride and metoclopramide are not specific as dopamine antagonists.

3. Do dopamine and dopamine receptors play a role in the regulation of gastrointestinal motility? The evidence that endogenous dopamine interacting with excitatory dopamine receptors participates in man in the regulation

of duodenal motility (348) or distal colon motility (292, 295, 305) is weak. Much more has been published about the possibility that endogenous dopamine regulates gastrointestinal motility by interaction with inhibitory dopamine receptors. Such a role has been proposed for the regulation of lower esophageal sphincter pressure in man (28, 29), gastric motility and antroduodenal coordination in guinea pig (417, 419), the relaxation induced by stimulation of the inhibitory vagus in canine stomach (473), and gastric emptying in man (26, 27, 42, 263). As well for the studies proposing an excitatory role as for those proposing an inhibitory role of endogenous dopamine in the regulation of gastrointestinal motility, two major comments can be made.

First, conclusions are mostly based on the effect of one dopamine receptor antagonist and the assumption that this antagonist is specific. However, the facilitatory effect of metoclopramide on twitch height and evoked acetylcholine release in the guinea pig ileum, for example, is probably serotoninergic in origin (274), and in the same preparation, metoclopramide antagonizes the inhibitory effect of acetylcholine as well as morphine on twitch responses (163). The suggestion that a dopaminergic inhibitory mechanism exists at the level of the lower esophageal sphincter in man was based on the results with metoclopramide (28, 29). Berges et al. (40), however, were unable to induce lower esophageal sphincter relaxation with dopamine infusions in man. Furthermore, in the opossum lower esophageal sphincter, where there is evidence for the presence of a muscular dopamine receptor, the lower esophageal sphincter relaxations induced *in vitro* by field stimulation (126) or *in vivo* by vagal stimulation (397) or by esophageal distension (369) were not antagonized by dopamine receptor antagonists.

Moreover, most of these studies were done *in vivo* so that involvement of sites of action outside the gastrointestinal system cannot be excluded. Indeed, apomorphine, for example, induces gastric relaxation in the dog by interaction with a site in the central nervous system, probably the dopamine receptor in the chemoreceptor trigger zone (44, 309). The pathway leading to the stomach is probably the nonadrenergic noncholinergic relaxatory vagal system, since vagotomy in the cat prevents the apomorphine-induced gastric relaxation (2). In the dog, apomorphine markedly increases the venous plasma levels of vasoactive intestinal polypeptide (VIP), a gastrointestinal hormone, that relaxes the stomach (468). Since this effect of apomorphine was blocked by haloperidol, it was ascribed to interaction with dopamine receptors, although no other antagonists were tested. The possibility was suggested that the apomorphine-induced gastric relaxation is caused by activation of dopamine receptors in the chemoreceptor trigger zone, which results in a vagally mediated release of gastric VIP (468). Vagotomy in the dog partially abolishes the gastrokinetic effect of domperidone (166, 431), and the remaining effect is probably due to stimulation of intramural cholinergic neurons (166). Still in the dog, domperidone did not influence pentagastrin- and bethanechol-stimulated gastric antral motility (32). In contrast to the observations with domperidone in vagotomized dogs, dopamine decreases intragastric pressure and delays gastric emptying equally in vagotomized human patients and in healthy volunteers, and in both, the effect is antagonized by domperidone (477). This is compatible with a site of action distal to the vagotomy but allows no conclusions as far as the receptor concerned. Apomorphine also delays gastric emptying in the guinea pig by interaction with a central nervous system site; whether these receptors lie within or outside the blood brain barrier is not clear, since in one study domperidone antagonized the effect of apomorphine (116), while in another it did not (120).

4. Conclusion. Dopamine and dopamine receptor agonists produce inhibitory and excitatory effects on smooth muscle activity in the gastrointestinal tract by a direct action on the smooth muscle cells and/or by interacting with the intrinsic and extrinsic nervous control systems.

For most parts of the gastrointestinal tract, detailed pharmacological analysis of the effects of dopamine and dopamine receptor agonists on motility has been done; the conclusion is that these effects are due to interaction of dopamine with α- and β-adrenoceptors. The evidence that dopamine receptors are present within the gastrointestinal tract is limited; it is best for the lower esophageal sphincter of the opossum. The hypothesis that dopamine, present in the gastrointestinal tract, might play a role in gastrointestinal motility is not firmly founded; it is nearly completely based on the effects of dopamine receptor antagonists which, however, also interact with other receptor systems.

B. Dopamine Receptors Influencing Gastrointestinal Exocrine Secretions

Inhibitory and excitatory effects on gastrointestinal exocrine secretions have been observed for dopamine and dopamine receptor agonists. Table 6 summarizes these experimental observations. For some effects, no particular receptor has been proposed, but for others, the involvement of dopamine receptors has been postulated; this will be discussed in the following sections. We only mention here briefly that dopamine stimulates sodium and chloride absorption in the rabbit ileum (133) and that dopamine and bromocriptine stimulate water absorption in the rat ileum and colon (134). Since the effects of dopamine were antagonized by haloperidol and by the α_2-adrenoceptor antagonist yohimbine, but not by propranolol and by the α_1-adrenoceptor antagonist prazosine, it was suggested that the effect of dopamine is due to interaction with both α_2-adrenoceptors and dopamine receptors. The effect of bromocriptine on rat ileal and colonic water transport was also antagonized by haloperidol and yohimbine.

1. The receptor mediating the inhibitory effects of do-

TABLE 6

The effect of dopamine and dopamine receptor agonists on gastrointestinal exocrine secretory processes. For each experimental preparation, the effect described is that of dopamine or the dopamine receptor agonist used; the agonists and antagonists listed indicate whether an effort has been made to characterize the receptor involved.

Part of the G.I. tract, species, and experimental preparation	Reference	Effect of dopamine or dopamine receptor agonist	Agonists studied	Antagonists of the following receptors studied
Salivary gland				
Rat				
In vivo, parotid gland	1	Increase of volume and protein amount	Dopamine Noradrenaline	DA, α, β, muscarinic
In vivo, submandibular gland	1	Increase of volume and protein amount	Dopamine Noradrenaline	DA, α, β, muscarinic
Guinea pig				
In vitro, submandibular gland slices	45, 92	Stimulation of peroxidase and amylase secretion	Dopamine Noradrenaline Adrenaline 5-HT Dibutyryl cyclic AMP + theophylline *l*-Dopa *l*-5-HTP 5-Hydroxydopamine Apomorphine	DA, α, β
Rabbit				
In vivo, parotid gland	372	Stimulation of parotid saliva	Dopamine	DA, α, β
Stomach, acid secretion				
Rat				
In vivo	213	Inhibition of acid secretion	Dopamine Histamine 5-HT 5-Hydroxyindole-acetic acid *l*-Dopa *l*-5-HTP *l*-Histidine	
In vivo	455	Inhibition of cysteamine-induced acid secretion	Bromocriptine Lergotrile Apomorphine	DA
In vivo	338	Inhibition of thyrotropin-releasing hormone-induced acid secretion	Apomorphine Bromocriptine Methamphetamine	DA
In vivo	339	Inhibition of 2-deoxy-D-glucose-stimulated acid secretion	Apomorphine Bromocriptine	DA
Cat				
In vivo	232	No effect on submaximal pentagastrin-stimulated acid secretion	Dopamine	
		Increase of submaximal pentagastrin-stimulated acid secretion	Bromocriptine	
Dog				
In vivo	476	Inhibition of pentagastrin-stimulated acid secretion	Dopamine	
In vivo	243, 244	Inhibition of pentagastrin-stimulated acid secretion Inhibition of bethanechol-stimulated acid secretion (high concentration) Enhancement of stimulatory effect of low doses of be-	Dopamine	DA, α, β

TABLE 6—Continued

Part of the G.I. tract, species, and experimental preparation	Reference	Effect of dopamine or dopamine receptor agonist	Agonists studied	Antagonists of the following receptors studied
		thanechol (low concentration)		
In vivo	196	Inhibition of food-stimulated acid secretion in vagally innervated gastric pouches, not in vagally denervated pouches	Dopamine	DA, α, β
Man				
In vivo	72	Inhibition of basal and pentagastrin-stimulated acid secretion	Dopamine	DA
In vivo	474	Inhibition of pentagastrin-stimulated acid secretion	Dopamine	DA
In vivo	73	Increase of submaximal pentagastrin-stimulated acid secretion	Bromocriptine	
Pancreas, exocrine secretion				
Rat				
In vitro, slices	483	Increase of cyclic AMP	Dopamine Secretin	DA
In vivo	172	Increase of pancreatic secretion	Dopamine Secretin Acetylcholine Noradrenaline Adrenaline Isoprenaline *l*-Dopa	DA, α, β, muscarinic
In vivo	367	Increase of pancreatic secretion	Dopamine Apomorphine *l*-Dopa 5-HT *l*-5-HTP Secretin Acetylcholine Carbamylcholine Phenylephrine Clonidine Histamine Isoprenaline	DA, α, β, muscarinic, 5-HT
Guinea pig				
In vitro, slices	7	No effect on amylase secretion	Dopamine Carbamylcholine *l*-5-HTP 5-HT *l*-Dopa Noradrenaline	
Rabbit				
In vivo	220	Depression of spontaneous pancreatic secretion at high doses	Dopamine *l*-Dopa Noradrenaline Adrenaline Isoprenaline	
Cat				
In vivo	220	Depression of secretin-induced increase in pancreatic secretion	Dopamine *l*-Dopa Adrenaline Isoprenaline	
Dog				
In vitro, dispersed acini	484	Increase of cyclic AMP	Dopamine Secretin VIP	DA
In vivo, perfused pancreas	25	Increase of pancreatic secre-	Dopamine	DA, α, β, muscarinic

TABLE 6—Continued

Part of the G.I. tract, species, and experimental preparation	Reference	Effect of dopamine or dopamine receptor agonist	Agonists studied	Antagonists of the following receptors studied
		tion	Apomorphine Noradrenaline Secretin Caerulein	
In vivo	192	Increase of pancreatic secretion	Dopamine and 26 other sympathomimetic amines	
In vivo	170, 171 173, 221 260, 261 262, 457	Increase of pancreatic secretion	Dopamine Noradrenaline Adrenaline Isoprenaline *l*-Dopa Secretin Pancreozymin Apomorphine Bromocriptine 6-OH-dopamine	DA, α, β, muscarinic, H_1
In vivo	476	Increase of bicarbonate and protein output	Dopamine	DA
In vivo	408	Increase of pancreatic secretion	Dopamine Histamine Acetylcholine Secretin Adrenaline Noradrenaline Isoprenaline 5-HT	DA, α, β, muscarinic, H_1, H_2
In vivo	259	Increase of pancreatic secretion	Dopamine, secretin, and 7 amino acid-conjugated dopamine derivatives	
Man				
In vivo	72	No significant influence on basal and secretin-CCK-stimulated pancreatic juice volume or amylase and bicarbonate output	Dopamine	
In vivo	301	No influence on pancreatic juice volume or bicarbonate and enzyme output	Dopamine	
In vivo	474	Decrease of amylase and lipase output under secretin-CCK infusion	Dopamine	DA

pamine. An inhibitory effect of dopamine on gastrointestinal exocrine secretion has only been described for gastric acid secretion. Since dopamine inhibits the pentagastrin-stimulated acid secretion in dog (476) and man (72, 474), it was postulated that dopamine receptors are involved in gastric acid secretion in these species. The evidence is poor, however. In the study in dogs, no antagonist was tested, and in the studies in man, only one antagonist, either metoclopramide (72) or haloperidol (474), was used. Moreover, a site of action for dopamine outside the gastrointestinal tract again cannot be excluded in these *in vivo* studies. Guldvog et al. (196), for example, showed in dogs that dopamine inhibits the acid response to food in vagally innervated gastric pouches but not in vagally denervated pouches. This inhibitory effect was not antagonized by sulpiride. An extensive investigation in dogs with α-, β-, and dopamine receptor antagonists led to the conclusion that the inhibitory action of dopamine on pentagastrin-stimulated gastric acid secretion is due to interaction with β_1-adrenoceptors (244). This was also concluded for the inhibitory action of high doses of dopamine on bethanechol-stimulated gastric acid secretion in dogs, although a combination of practolol and domperidone was needed to re-

verse this effect (243). For the dopamine analogue ibopamine, no inhibitory effect on gastric acid secretion in man was observed (74).

In rat gastric fistula, dopamine decreases acid secretion (213). Also in the rat, bromocriptine and lergotrile decrease cysteamine-induced gastric secretion, which possibly contributes to their protective effect against cysteamine-induced duodenal ulcers in these rats (455). Low doses of apomorphine also had an antiulcerogenic effect, while the dopamine receptor antagonists, haloperidol and pimozide, had a proulcerogenic effect (455). A protective effect against cysteamine-induced duodenal ulcers in rats was also shown for the dopamine receptor agonist, (−)-10,11-methylendioxy-*N*-*n*-propylnorapomorphine, and a proulcerogenic effect for the dopamine receptor antagonist, butaclamol (379). Prolonged pretreatment with bromocriptine, in contrast to a single injection, also had a marked protective effect against aspirin-, phenylbutazon-, and reserpine-induced gastric ulcers in the rat (386). Apomorphine and the indirect dopamine receptor agonists *d*-amphetamine, methylphenidate, and threo-*dl*-*p*-hydroxymethylphenidate protect rats against gastric ulceration induced by cold and restraint stress. This protective effect is blocked by domperidone (226). Dopamine had no protective effect against cold- or restraint stress-induced gastric ulcers in rats when administered intracerebroventricularly (198). These observations point to a peripheral site of action via inhibition of acid secretion. A specific binding site for dopamine was found in rat gastric and duodenal mucosa (407), and a dopamine-sensitive adenylate cyclase was found in the rat duodenal mucosa (374). Hence, the presence of a dopamine receptor was suggested. Other authors observed in the rat an inhibitory effect of bromocriptine, apomorphine, and methamphetamine on 2-deoxy-D-glucose-induced and/or thyrotropin-releasing hormone-induced gastric acid secretion; here it was suggested that this effect is due to central dopamine receptor stimulation (338, 339).

2. The receptor mediating the excitatory effects of dopamine. a. GASTRIC ACID SECRETION. Low doses of dopamine increase the bethanechol-induced acid secretion in the dog. As this effect was antagonized by domperidone and practolol as well as by propranolol, it was suggested that more than one receptor is involved (243). In contrast to the inhibitory effect of dopamine on pentagastrin-stimulated acid secretion in dog and man and the inhibitory effect of bromocriptine on cysteamine-induced acid secretion in rats (see B.1), bromocriptine potentiates the submaximal pentagastrin-stimulated acid secretion in man (73) and in cat (232); in the latter species, dopamine is without effect (232). It was suggested that this effect of bromocriptine is due to its α-adrenergic and/or serotoninergic antagonistic properties (73, 232). In the perfused rat stomach, basal gastric acid secretion is stimulated by ergotalkaloids, such as ergometrine but not by bromocriptine. The stimulatory effect was explained by a central mechanism without the involvement of dopamine receptors (337).

In the dog, high doses of apomorphine increase plasma gastrin levels (469), and in the cat, apomorphine induces the release of gastrin from an antral pouch (471). The effect in the dog was antagonized by haloperidol and, although no other antagonists were tested, the authors suggested that dopamine receptors are involved. As apomorphine fails to stimulate the release of gastrin from the isolated perfused stomach, central dopamine receptors are probably involved (470). It is difficult to understand the stimulatory effect of apomorphine on gastrin release within the overall inhibitory action of dopamine on gastric acid secretion. The effect could, of course, be specific for apomorphine. Indeed, neither dopamine nor bromocriptine modifies serum gastrin concentrations in man (72, 73, 416). In contrast, dopamine receptor antagonists have been shown to reduce the gastrin response to appropriate stimuli in both healthy volunteers (71, 75) and duodenal ulcer patients (76, 291). This is not the case for domperidone, and it was therefore suggested that agonists and antagonists have to reach a central dopamine receptor involved in the regulation of gastrin release (349). A large dose of haloperidol significantly enhanced meal-induced secretion of gastrin in healthy volunteers (416); sulpiride had an inhibitory effect on pentagastrin-stimulated gastric secretion in duodenal ulcer patients (16).

The influence of dopamine, dopamine receptor agonists, and dopamine receptor antagonists on gastric acid and gastrin secretion is thus quite variable. It remains to be determined, therefore, whether a dopamine receptor is involved, where it is situated, and whether dopamine has a physiological role in gastrin and gastric acid secretion or in the protection against ulcers.

b. PANCREATIC SECRETION. **i. Dog.** Dopamine stimulates exocrine pancreatic secretions in the dog, and it has been suggested that this is mediated by dopamine receptors. This stimulatory effect is probably not due to an effect on blood flow, as dopamine certainly decreases pancreatic blood flow when used in higher doses (25, 221, 457). Noradrenaline is reported to have either no influence on canine pancreatic secretion (408, 457), an inhibitory influence (221), (or a biphasic effect) inhibition followed by stimulation (192, 482). The precursor of dopamine, *l*-dopa, also has a stimulatory effect on secretion of canine pancreatic juice without any effect on pancreatic blood flow (221, 457). The stimulatory effect of *l*-dopa is reduced by DOPA-decarboxylase inhibition, while the stimulatory effect of dopamine is enhanced by dopamine-β-hydroxylase and monoamine oxidase inhibition (171, 261). The stimulatory effect of dopamine on canine pancreas secretion is not influenced by pretreatment with reserpine, phentolamine, phenoxybenzamine, propranolol, atropine, cimetidine, guanethidine, tetro-

dotoxin, and penthamethonium (25, 221, 408). It is, however, antagonized by haloperidol (25, 171, 408), chlorpromazine, and sulpiride (262, 408). Apomorphine increases the secretion of the dog pancreas, but to a lesser degree than dopamine (25, 170), and it inhibits the response to dopamine (170), which is compatible with a partial agonist activity. Bromocriptine also increases canine pancreatic secretion, the secretory response being inhibited by sulpiride but not by phentolamine, propranolol, atropine, metiamide, indomethacin, or tetrodotoxin (262). Seven amino acid-conjugated dopamine derivatives had a similar effect as dopamine. The duration of their effect was longer, but their potency was lower, decreasing with the number of conjugated amino acids (259). In dog pancreatic acini, it has been shown that dopamine stimulates cyclic AMP production and that this is inhibited by haloperidol. High affinity binding sites for dopamine have been demonstrated in the same tissue (484). These results suggest the presence of a dopamine receptor on exocrine cells in the dog pancreas, whose activation leads to increased secretion of pancreatic juice. Bastie et al. (25) observed that, after phenoxybenzamine, noradrenaline stimulated pancreatic secretion in the dog. As this effect was not influenced by propranolol or atropine, but abolished by haloperidol, they raised the hypothesis that noradrenaline acts as a partial agonist of the pancreatic dopamine receptors (25, 482). Iwatsuki et al. (262) classify this dopamine receptor as a D_2 receptor (i.e., similar to the DA_2; see chapter II.B) on the basis of the antagonism of the effect of bromocriptine by sulpiride.

However, the partial agonistic activity of apomorphine, the absence of phenoxybenzamine blockade, the rather high doses of haloperidol needed, and the stimulation of cyclic AMP point to the presence of a dopamine receptor belonging to the D_1 or DA_1 class. Further experiments using more selective antagonists, for example, domperidone and SCH 23390, might clarify this point.

A physiological role for dopamine in the regulation of canine pancreatic secretion is not established. As the different components in the pancreatic juice changed similarly upon stimulation with secretin and dopamine (173), and as secretin treatment increased the dopamine content of the dog pancreas without altering the noradrenaline content (170), it was suggested that dopamine is a physiological secretagogue, possibly participating in the secretion of pancreatic juice induced by secretin. Apomorphine pretreatment, however, inhibits the secretory effect of dopamine without influencing the effect of secretin (170); PGF_2 inhibited the effect of secretin but not that of dopamine (260); metoclopramide antagonized the increase in bicarbonate output and protein output by dopamine but not that by secretin (476). Furthermore, haloperidol has been reported not to antagonize the secretory influence of secretin (25) and to be less potent in inhibiting secretin than dopamine (408).

ii. Rat. Dopamine also stimulates the exocrine secretion of the rat pancreas, but its potency is clearly less than in dogs (172, 367). Since the effect of dopamine in the rat was not influenced by haloperidol, phenoxybenzamine, or atropine but is completely antagonized by propranolol, it was suggested that, in that species, a β-adrenoceptor is involved (172). Mori et al. (367) suggested a dopaminergic mechanism for protein secretion in the rat pancreas, but this suggestion was only based on a slight stimulatory effect of *l*-dopa on pancreatic protein concentration, which could be blocked by sulpiride. In rat pancreas slices, dopamine and secretin increase the cyclic AMP content; the effect of dopamine is antagonized by haloperidol, while that of secretin is not (483).

iii. Man. In man, dopamine has no stimulatory effect on basal pancreatic juice volume and output of bicarbonate and enzymes (72, 301, 474). Dopamine decreases the secretion of amylase and lipase induced by secretin-cholecystokinin, but haloperidol did not antagonize this effect, neither did it stimulate these secretions by itself (474). In contrast to haloperidol, sulpiride stimulates the secretin-cholecystokinin-induced secretion of pancreatic juice, bicarbonate, and enzymes; the interpretation that this indicates the presence of inhibitory dopamine receptors in human pancreas seems premature (197).

c. SALIVARY SECRETION. The presence of a specific dopamine receptor in the guinea pig submandibular gland was suggested to explain the stimulatory effect of dopamine on amylase secretion. Dopamine stimulates the secretion of peroxidase and amylase in guinea pig submandibular gland slices, an effect which is inhibited by propranolol, as is the stimulatory effect of adrenaline and noradrenaline; phenoxybenzamine has no influence on the effect of noradrenaline and adrenaline but markedly inhibited the secretory response to dopamine (92). The stimulatory effect of dopamine on the amylase secretion in submandibular gland slices is not influenced by dopamine-β-hydroxylase inhibition or by reserpine pretreatment (45). Haloperidol and fluspirilene antagonized the effect of dopamine without influencing the secretion elicited by noradrenaline, whereas pimozide inhibited both; apomorphine has a slight stimulatory effect on amylase secretion (45). In the conscious rabbit, dopamine stimulates dose dependently the secretion of parotid saliva; as this effect is blocked by the dopamine receptor antagonists haloperidol and chlorpromazine, but not by an α- or a β-adrenoceptor antagonist, the authors suggested that dopamine receptors may be present in the rabbit parotid gland, although this is difficult to ascertain in this *in vivo* study (372). In the anesthetized rat, dopamine increases volume and protein content of parotid and submandibular gland secretions. Since α-, β-, and dopamine receptor antagonists all influenced the dopamine-induced responses, the authors conclude that the action of dopamine is due to activation of α-, β-, and dopamine receptors (1).

3. Conclusion. Dopamine and dopamine receptor ago-

nists have inhibitory and excitatory effects on gastrointestinal exocrine secretions. Clear evidence for the involvement of specific dopamine receptors is only present for the stimulatory action of dopamine on pancreatic secretion in the dog. The evidence for a physiological role of dopamine in regard to gastrointestinal secretion is poor.

V. Conclusions

We have discussed, on the basis of the results of pharmacological characterization experiments, the arguments for the presence of dopamine receptors: (*a*) on the sympathetic nerve endings to the nictitating membrane, the heart, blood vessels, and other organs; (*b*) in the autonomic sympathetic ganglia; and, (*c*) in the gastrointestinal tract.

There is convincing evidence for the presence of presynaptic dopamine receptors on the sympathetic nerve endings of the nictitating membrane, the heart, and a number of blood vessels in several species. Stimulation of these presynaptic dopamine receptors inhibits the release of the neurotransmitter noradrenaline. Striking species differences do exist, where, for example, the influence of dopamine on cardiac sympathetic nerve endings is mediated via presynaptic dopamine receptors in cat, dog, and rabbit, but via presynaptic α-adrenoceptors in rat and guinea pig.

There is also good evidence for the presence of dopamine receptors in the sympathetic ganglia, where they are involved in the inhibition of ganglionic transmission by dopamine and dopamine analogues, e.g., in dog and cat. The exact localisation of these receptors, preganglionic or postganglionic, is still unknown.

For the gastrointestinal tract, arguments in favour of the presence of peripheral dopamine receptors are scarce. The best evidence for the presence of dopamine receptors has been obtained in the opossum lower esophageal sphincter, where their stimulation induces relaxation, and in the canine exocrine pancreas, where their stimulation increases secretion. The evidence for the presence of dopamine receptors elsewhere is weak; in most papers where the presence of dopamine receptors is suggested, the involvement of receptors localized outside the gastrointestinal tract and of adrenoceptors other than the dopamine receptor cannot be excluded.

As in the central nervous system, peripheral dopamine receptors belong to at least two classes. Based on the relative potency of dopamine receptor agonists and antagonists, a classification into DA_1 and DA_2 receptors was proposed for the cardiovascular system. The postsynaptic dopamine receptors on the vascular smooth muscle cells are DA_1 receptors, while the dopamine receptors located presynaptically, on sympathetic nerve endings, are DA_2 receptors. The dopamine receptors in the autonomic ganglia and in the gastrointestinal system cannot yet be classified on the basis of the information available.

The presence of dopamine receptors in different organs and different systems has led to the search for their possible physiological role. For the systems discussed in this review, the evidence for such a physiological role is poor. Therapeutic uses of drugs interacting with the peripheral dopamine receptors in the cardiovascular system have attracted much interest. Selective agonists for the presynaptic DA_2 receptor could be used to lower peripheral vascular resistance in the treatment of hypertension or heart failure. These potential therapeutic applications have generated an intense search for DA_2-selective dopamine receptor agonists.

Although there is a wealth of information on peripheral dopamine receptors, as is apparent from this review, much work has still to be done. Further pharmacological characterization of neuronal dopamine receptors, located on sympathetic ganglia and postganglionic nerve endings, and of vascular dopamine receptors and comparison of these receptors with dopamine receptors located in the kidney, the endocrine system, and the central nervous system is of particular interest. This might result in the design of new compounds with defined therapeutic indications and minimal side effects.

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