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COMMENTARY

THE DOPAMINE VASCULAR RECEPTOR*

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Dopamine has come of age. Until relatively recently, dopamine was known only as the precursor of norepinephrine. Today, it commands at least as much attention as its beta-hydroxylated analog. Indeed, the unusual distribution of dopamine and the identification of specific dopaminergic tracts suggest the likelihood of unique physiological roles. Research and speculation have linked dopamine to the involvement of many diverse activities including growth, secretion of milk, excretion of sodium, vomiting, sexual function and neurotransmission [1, 2]. Pathological implications are equally broad and range from schizophrenia to hypertension. Obviously, much solid research remains to be carried out before true functions can be separated from imposters. It is not too early, however, to ask: Which dopamine effects are due to action on a specific dopamine receptor, and which are manifestations of actions on previously described receptors? These questions are pertinent, as physiological and biochemical studies have shown that dopamine can act on many different receptors. The structure of dopamine is consistent with this multi-receptor potential; the catecholamine head and the flexible side chain should fit many receptors.

The cardiovascular actions of dopamine provide a good example of its diverse effects and also illustrate the difficulty of receptor differentiation [2].

Heart. Dopamine increases cardiac contractility and heart rate. These effects are due both to direct action on receptors and to release of norepinephrine from adrenergic nerve terminals in the myocardium. The third possible mechanism, increased synthesis of norepinephrine, does not appear to be involved. All cardiac actions are antagonized by propranolol, indicating that they are due to a typical beta-adrenergic mechanism. (Recent studies have suggested that there are two classes of beta-adrenergic receptors in the cardiovascular system. Beta$_1$-adrenergic receptors subserve cardiac actions and coronary artery vasodilation; beta$_2$ receptors subserve vasodilation in other blood vessels [3–5]).

Blood vessels. The actions of dopamine on the blood vessels are at least as complex as on the heart. In addition, classification of potential agonist–receptor interactions is confounded by the opposing effects of contraction and relaxation [2].

Dopamine-induced contraction has been demonstrated in arteries and veins, and this phenomenon must be eliminated before relaxing effects can be quantitatively assessed. Both contraction of isolated blood vessels and vasoconstriction in intact vascular beds can be blocked by phenoxybenzamine and other alpha-adrenergic blocking agents. Therefore, these responses appear to be due, at least in part, to action on alpha-adrenergic receptors. However, extremely large doses of phenoxybenzamine are required to completely eliminate contracting effects, and since these concentrations of phenoxybenzamine also block other receptors, additional mechanisms must be considered [2, 6]. One possibility is an action on serotonin or tryptamine receptors. Preliminary studies have shown that the selective serotonin antagonist, cyproheptadine, can specifically attenuate dopamine-induced vasoconstriction.‡ Such an action is supported by studies in other organ systems [7, 8].

Several mechanisms are also involved in the relaxing action of dopamine, and these must be taken into account in investigations of "specific dopamine receptors". First, dopamine can cause vasodilation by both reflex and neurogenic mechanisms [2]. Second, there is a possibility that dopamine acts on beta-adrenergic receptors. After administration of phenoxybenzamine, dopamine causes vasodilation in the skeletal muscle vascular bed of the dog [9], and relaxation of the isolated aortic strip [10]. These phenomena are antagonized by propranolol, suggesting action on beta$_2$-adrenergic receptors. However, because of the extremely large dose used, it is possible that this antagonism is not due to blockade of beta-adrenergic receptors, but to return of alpha-adrenergic vasoconstricting activity [11]. This latter contention is strengthened by the observation that relaxation induced by dopamine in isolated canine renal, mesenteric, coronary or femoral arteries is not affected by concentrations of propranolol sufficient to markedly shift the dose–response curve of isoproterenol [6, 12].

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The third possible mechanism, action on a specific dopamine vascular receptor, was first suggested by investigations in man which demonstrated that intravenous infusions of dopamine decreased renal vascular resistance [13]. Most subsequent investigations attempting to classify the postulated receptor were carried out in the anesthetized dog. After administration of phenoxybenzamine, dose-related vasodilation occurs in the renal and mesenteric vascular beds after intra-arterial injections of dopamine. This vasodilation is not attenuated by propranolol, atropine, antihistamines or by pretreatment with reserpine, 48/80 or monoamine oxidase inhibitors [2]. Similar vasodilation has been demonstrated in the coronary [14] and intracerebral vascular beds [15], but not in the skeletal muscle vascular bed of the anesthetized dog [9].

Such selective vasodilation certainly suggests the existence of a dopamine "receptor". However, two as yet unsolved problems have prevented removal of the quotation marks according to current criteria [3, 4]. First, the order of potency of a series of closely related analogs must be determined and found to be similar in all tissues whose responses are considered to be due to action on the receptor. Unfortunately, despite intensive structure activity studies, only the *N*-methyl derivative of dopamine, epinine, produces similar renal and mesenteric vasodilation [16]. Other substitutions on either the catechol moiety or the side chain have resulted in complete loss of activity. More recently, however, a breakthrough in this impasse may have been accomplished. First, apomorphine was found to exert weak dopamine-like vasodilating activity, and also to possess slight antagonistic properties [16]. Second, the *n*-propyl derivative of apomorphine, 6-propylnoraporphine-10,11-diol, was found to be a more potent renal vasodilator than apomorphine, but less effective than epinine and dopamine [17]. Thus, a potency series, dopamine = epinine > 6-propylnoraporphine-10,11-diol > apomorphine, has been generated. Preliminary studies with other apomorphine analogs suggest that this potency series may be further expanded.

The second criterion required for removal of the quotation marks is that specific antagonism must be demonstrated. Selective antagonism of dopamine-induced renal and mesenteric vasodilation has been demonstrated with haloperidol, and other butyrophenones, several phenothiazines, and bulbocapnine [2]. The problem is that all of these agents have a very narrow range of selectivity, and thus only partial antagonism can be demonstrated without affecting the vasodilation caused by other drugs. In addition, all of these antagonists have a very short duration of action, and in order to demonstrate maximum effects, they must be administered simultaneously with dopamine. Discovery of a more potent antagonist is clearly desirable and possibly necessary.

Finally, precise quantitation of agonist and antagonist relationships requires an isolated organ system [4], since other mechanisms could be involved in the vasodilation in the intact animal. This obstacle has now been partially overcome and may be amenable to complete solution. Recent studies have shown that when isolated canine, renal, mesenteric, coronary and intracerebral arteries are exposed to phenoxybenzamine, and contracted with potassium or prostaglandin $F_{2\alpha}$, dopamine causes dose-related relaxation. Similar relaxation occurs with epinine, but not with other dopamine analogs [12]. The relaxation is not antagonized by propranolol. Dopamine-induced relaxation does not occur in large (>1 mm, outside diameter) femoral arteries, but relaxation does occur in smaller femoral arteries [12]. These observations are in partial agreement with results obtained in the intact animal. Such differential actions now make it possible to separate dopamine-like effects from those produced by nonselective vasodilators. The final step in establishing the identity of a dopamine "receptor", however, has not yet been accomplished. All the selective dopamine antagonists, active *in vivo*, cannot be used in sufficiently high concentrations *in vitro*, since each of them causes relaxation of isolated canine vessels [12].

Lack of a potent antagonist and a sufficiently long series of agonists has also hampered attempts to classify a dopamine "receptor" by biochemical techniques. Biochemical studies of dopamine–receptor interactions are often weakened by two fundamental flaws [3]. First, most such studies utilize a biochemical marker, such as cyclic AMP, but there is no proof that changes in level of such a marker is a necessary step in the expression of a physiological or pharmacological response. Second, in many biochemical studies sufficiently strict criteria are not used to prove that a chemical change is the result of action on a specific dopamine "receptor", and not due to action on previously described receptors. As an example of this difficulty, the change in cyclic AMP and electrical activity produced by dopamine in the superior cervical ganglion has been shown to be more typical of actions on alpha-adrenergic receptors than on a specific dopamine "receptor" [18].

More recently, however, evidence has been accumulating which suggests that specific dopamine "receptors" are involved in the elevation of cyclic AMP occurring after addition of dopamine to homogenates of mammalian brain and retina [19–23]. Such increments of cyclic AMP are not attenuated by propranolol, and fluorinated phenothiazines are better antagonists than phenoxybenzamine [19–23]. Furthermore, epinine is equal to dopamine as an agonist [23]; other catecholamines including norepinephrine are much less potent; and apomorphine is a weak agonist [19–23]. These biochemical results are in remarkable agreement with the physiological data obtained in blood vessels. However, a few discrepancies must be explained before the "receptors" in these areas can be considered identical [24].

The time appears to be approaching when crucial experiments will be conducted to convince even the most demanding critic that a dopamine receptor exists.

Furthermore, it is now becoming feasible to simultaneously measure physiological and biochemical changes in one tissue. Recently, preliminary studies have shown that dopamine increases levels of cyclic AMP in canine renal arteries, and as in the brain and retina, this effect is antagonized by haloperidol, but not by propranolol [25]. Thus, the dopamine "receptor" subserving relaxation in blood vessels may serve as a fertile arena for combined physiological and biochemical studies. Hopefully, such investigations will contribute to the ultimate goal—chemical characterization of the dopamine "receptor" molecule.

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