Dopamine receptors: applications in clinical cardiology

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THE DISCOVERY of the renal vasodilating action of dopamine more than 20 years ago led to extensive research that demonstrated other unusual actions of this endogenous catecholamine. Investigators using traditional pharmacologic models and modern biochemical techniques have documented the existence of distinct dopamine receptor subtypes that mediate these responses. Appreciation of the structure-activity requirements of these receptors has led to the synthesis of drugs that may have a profound influence on the management of the patient with heart disease.

Taxonomy of dopamine receptors. Rigid criteria must be met to prove the existence of a new receptor by classical pharmacologic methods, including construction of a unique potency series of agonists and demonstration of specific antagonism. In contrast, biochemical techniques are applied to tissue homogenates, and different standards are frequently used to classify receptors.

After many years of research, two distinct dopamine receptor subtypes, DA₁ and DA₂, were identified conclusively by classical criteria in physiologic preparations. DA₁ receptors are located postsynaptically and subserve vasodilation in renal, mesenteric, coronary, and cerebral blood vessels (figure 1). DA₂-induced vasodilation can be observed in other vascular beds, but the response is less prominent, probably because of the lower density of dopamine receptors. The molecular structure required for activation of DA₂ receptors is very strict. Currently, all active compounds have two hydroxyl groups in positions analogous to the 3- and 4-positions on the benzene ring of the dopamine molecule, and a limited distance exists between the hydroxyl groups and the amino group.

DA₂ receptors are located on postganglionic sympathetic nerves and autonomic ganglia, and when these receptors are activated, norepinephrine release from sympathetic nerve endings is inhibited (figure 1). DA₂ receptors are also located in the emetic center of the area postrema and in the anterior lobe of the pituitary gland. Activation of these receptors results in emesis and inhibition of prolactin release, respectively. The structural requirements for DA₂ agonists are much less restrictive than those for DA₁ agonists. Indeed, the structures of DA₂ agonists are so diverse that it is difficult to determine molecular requirements for activity.

Major advances have been made in the synthesis of new dopamine agonists, and compounds are now available with spectra of receptor activity different from that of dopamine. Of significance, the benzazepine derivative, fenoldopam, proved to be a selective DA₁ agonist. Selective DA₂ agonists have been available for several years. Examples include piribedil and ergot derivatives, which are used for the treatment of Parkinson’s disease, and LY 17155, an ergoline derivative.

The first dopamine antagonists used to classify dopamine receptors were the neuroleptics, haloperidol and chlorpromazine. Although these agents made it possible to distinguish dopamine receptors from other receptors, the dose range in which they are specific antagonists for dopamine receptors is very narrow. Furthermore, these antagonists cannot be used to differentiate dopamine receptor subtypes. Recently, selective antagonists that discriminate between DA₁ and DA₂ receptors have been synthesized. An example of a selective DA₁ antagonist is the benzazepine, SCH 23390, which is chemically related to fenoldopam. Domperidone, a butyrophenone derivative related to haloperidol, is an example of a selective DA₂ antagonist.

Availability of selective dopamine agonists and antagonists has aided in the determination of whether dopamine subtypes classified on the basis of cardio-
vascular responses are similar to those receptors identified in brain and endocrine tissues by biochemical techniques. In one biochemical method, dopamine receptors are subdivided according to the effects of agonists on the enzyme, adenylate cyclase. Activation of D₁ receptors results in stimulation of adenylate cyclase; activation of D₂ receptors either results in inhibition of adenylate cyclase or has no effect on that enzyme.⁴ In a second biochemical method, dopamine receptors are subdivided according to the pattern of displacement of radioactive ligands by dopamine agonists or antagonists.⁷ The radioligand binding assays have been extremely controversial because of the many inconsistencies in the dopamine receptor subtypes “identified” by these assays.⁶ ⁷ It appears that many of the early ligand-binding investigations yielded increased numbers of receptor subtypes because the ligands used were not selective or because strict criteria required to characterize receptors were not fulfilled.⁴ ⁶ Recent studies conducted with more selective ligands have identified only two dopamine subtypes similar to D₁ and D₂.⁶ Comparison of the DA₁ and DA₂ classification with the revised D₁ and D₂ classification suggests that the same receptors are identified by the two methods. However, a few significant discrepancies in the potency series of agonists and antagonists remain, and further studies are needed to determine the reasons for these differences.⁴

**Pharmacologic actions of dopamine.** The activation of adrenoceptors and dopamine receptors by dopamine is the basis for its diverse clinical applications.² ³ Because of extreme individual variations in the infusion rates of dopamine required to activate the different receptors, patients must be monitored carefully to achieve the desired hemodynamic profile. DA₁ and DA₂ receptors are activated at the lowest infusion rates, resulting in a decline in peripheral vascular resistance and modest increments in renal blood flow, urine volume, and sodium excretion. At these low rates of infusion (usually 0.5 to 2 µg/kg/min) dopamine may initiate a diuresis in patients refractory to furosemide.¹¹ As the infusion rate is increased (usually above 2 µg/kg/min), β₁-adrenoceptors are activated and cardiac output begins to increase, typically with little change in heart rate. This is the hemodynamic response sought in the treatment of heart failure. The infusion rate may then be gradually increased until recruitment of α₁- and α₂-adrenoceptors occurs as manifested by an increase in vascular resistance or until excessive β₁-adrenoceptor activity leads to tachycardia or ventricular arrhythmias. Higher infusion rates can be used if the undesirable vasoconstriction is eliminated by simultaneous administration of a vasodilating agent.³ With such concurrent administration, caution must be exercised to avoid excessive reduction in arterial pressure. Indeed, unmasking of the vasodilating effects of dopamine in the presence of phenoxybenzamine was the first demonstration of its potential use in the treatment of hypertension.¹² A different hemodynamic pattern may be achieved by conjoint administration of dopamine and dobutamine. This combination provides greater β₁-adrenoceptor activity, maintenance of the beneficial renal effects of dopamine, and avoidance of α-adrenoceptor–mediated vasoconstriction seen with high doses of dopamine.³

**Orally active pro-drugs.** Poor oral bioavailability of
dopamine stimulated the development and investigation of orally active pro-drugs with dopamine activity. Two oral pro-drugs, levodopa and ibopamine, have been studied in the treatment of congestive heart failure.

After oral administration of the biochemical precursor of dopamine, levodopa, dopamine is generated by the action of aromatic amino acid decarboxylase in the liver and other tissues. Investigations in patients with Parkinson's disease demonstrated that oral administration of levodopa in doses of 1 to 1.5 g produces cardiac and natriuretic effects approximating the responses observed with intravenous infusions of dopamine at rates of 2 to 4 μg/kg/min. On this basis, levodopa was studied recently in patients with severe congestive heart failure. After ingestion of levodopa (1.5 to 2.0 g), significant improvement in cardiac performance was observed. Furthermore, the beneficial hemodynamic effects were sustained during long-term therapy for 3 or more months. The lack of tolerance to levodopa is in sharp contrast to the findings of previous studies conducted with pirbuterol, which was ineffective after sustained therapy. This difference could be explained by the partial agonist activity of pirbuterol and the full agonist activity of dopamine. Down-regulation of β2-adrenoceptors with continuous therapy should decrease activity of partial agonists to a much greater extent than that of full agonists.

No serious adverse effects were observed in this initial study with levodopa. However, levodopa can produce nausea and vomiting unless the dose is gradually increased. Accordingly, the dose was increased from 250 mg qid to 1.5 to 2.0 g qid over a 5 to 7 day period. In addition 50 mg of pyridoxine was administered daily, since previous studies have shown that this vitamin is required for the decarboxylation of levodopa.

In addition to the trial of levodopa in congestive heart failure, the pro-drug has also been used to help wean patients from long-term intravenous infusion of dopamine.

Ibopamine is the diisobutyric ester of N-methyl dopamine (epinephrine). When ibopamine is absorbed, it is acted upon by esterases in the plasma to release N-methyl dopamine (epinephrine). Epinephrine resembles dopamine pharmacologically. Several studies in Europe and the United States have shown that oral ingestion of 100 to 300 mg of ibopamine produces beneficial hemodynamic effects in patients with congestive heart failure. Ibopamine has recently been approved for clinical use in Italy.

New dopamine agonists. The possibility that several receptors may be responsible for the beneficial hemodynamic effects of dopamine, levodopa, and ibopamine is supported by the results of studies which demonstrate that dopamine agonists lacking β2-adrenergic activity elicit beneficial responses in patients with severe congestive heart failure. Propylbutyl dopamine (an agonist of DA1 and DA2 receptors) was administered intravenously to patients with severe congestive heart failure. Cardiac index increased while pulmonary capillary wedge pressure and systemic vascular resistance were significantly reduced. No change in heart rate was observed. Mean arterial pressure decreased in a dose-related manner, declining 20 mm Hg when infused at a rate of 20 μg/kg/min. Vasodilation caused by activation of DA1 and DA2 receptors by propylbutyl dopamine appeared to be responsible for the hemodynamic responses observed. Renal hemodynamics were not measured in these patients, but studies in normal subjects and hypertensive patients demonstrated that propylbutyl dopamine produces pronounced increments in renal blood flow.

Hemodynamic improvement was also observed in patients with severe congestive heart failure when the ergot derivative, bromocriptine, was administered orally in a dose of 2.5 mg. Bromocriptine has been shown to act as a DA1 agonist in peripheral nerves but also may decrease sympathetic activity via a central nervous system mechanism. Heart rate, mean arterial pressure, left ventricular end-diastolic pressure, and mean right atrial pressure decreased while stroke volume increased. Cardiac index did not increase, possibly because of the decrease in heart rate. A decline in plasma norepinephrine concentrations accompanied these hemodynamic changes.

Hemodynamic actions of the selective DA1 agonist, fenoldopam, were evaluated in a pilot study in patients with congestive heart failure. Oral administration of fenoldopam (200 mg) resulted in a decline in pulmonary capillary wedge pressure and systemic vascular resistance and an increase in cardiac index. Heart rate did not change. The renal effects of fenoldopam were not studied in these patients, but increments in renal blood flow and sodium excretion were observed when the drug was administered to normal subjects and hypertensive patients. The natriuresis induced by DA1 agonists is unusual for vasodilating agents.

The availability of orally effective dopamine congeners has greatly expanded the potential clinical indications for these agonists. Of particular significance, fenoldopam, propylbutyl dopamine, and bromocriptine have been found to be effective in lowering blood pressure in hypertensive patients. Another possible
new use for dopamine agonists is in the treatment of arrhythmias. A study in the anesthetized dog has shown that bromocriptine is effective in the prevention of digitalis-induced arrhythmias. The mechanism responsible for this antiarrhythmic effect appears to be decreased sympathetic activity.

In summary, the results of studies with orally effective dopamine agonists have suggested new approaches to the management of patients with cardiovascular disease. The safety and efficacy of these agents during long-term therapy remains to be established. Although the results of preliminary investigations are encouraging, only a limited number of patients have been observed for prolonged periods. Regardless of the results of these studies, future research will undoubtedly lead to the development of new dopamine agonists with greater bioavailability, different spectra of receptor activity, and fewer adverse effects. A new and exciting era of dopamine research has begun.

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