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Cardiovascular and Renal Actions of Dopamine: Potential Clinical Applications[1]

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I. Introduction

The anatomical distribution, biochemistry and pharmacology of the third endogenous catecholamine, dopamine, has been extensively investigated and substantial evidence has accumulated supporting its physiological role and action on specific receptors in the central nervous system. These data and the relationship of dopamine to the etiology and treatment of Parkinson's disease were reviewed in this Journal by Hornykiewicz (99) in 1966 and more recently by Sandler (157) and Hornykiewicz (100). Parallel studies have demonstrated that dopamine exerts unusual cardiovascular and renal effects which also appear to be due in part to an action on a specific receptor. The present review will be primarily concerned with these unusual effects and their clinical significance. Actions on other organ systems and pathways of synthesis and metabolism will not be included unless pertinent to the principal objective.

II. Effects of Dopamine on Blood Pressure

A. Vasopressor effects

The synthesis of dopamine (3,4-dihydroxyphenylethylamine) was first reported in 1910, apparently independently by Mannich and Jacobsohn (134) and Barger and Ewins (13). For the next 30 years, cardiovascular research was essentially limited to comparisons of the action of dopamine with other sympathomimetic amines. In 1910 Barger and Dale (12) observed that dopamine had a pressor potency in the spinal cat $\frac{1}{35}$ that of *d,l*-epinephrine and $\frac{1}{50}$ that of *d,l*-norepinephrine. In 1930 Tainter (166) reported that the pressor effects of epinephrine and dopamine in the spinal cat were equally potentiated by cocaine and reversed by ergotoxine. In 1931 Hamet (82) observed that intravenous injections of 2 mg of dopamine hydrochloride markedly elevated the blood pres-

sure of the vagotomized, anesthetized dog and that this pressor effect was reversed by yohimbine and potentiated by cocaine. Hamet (82) also observed vasoconstriction in the perfused dog kidney. In 1937 Gurd (77) reported that the pressor potency of dopamine in the spinal cat was $\frac{1}{30}$ that of epinephrine. The potency of dopamine in increasing the amplitude of contraction of the perfused cat heart was $\frac{1}{14}$ that of epinephrine. Hence he concluded that the pressor effect of dopamine was due more to cardiac actions and less to vasoconstriction than the increase in blood pressure produced by epinephrine.

B. Vasodepressor effects

Reductions in blood pressure after administration of dopamine were observed in the ergotoxine-treated cat (166) and the yohimbine-treated dog (82), but these effects were considered to be the same as those produced by epinephrine. The first evidence that dopamine was qualitatively different from other sympathomimetic amines was presented in 1942. Holtz and Credner (94) reported that dopamine differed from epinephrine in decreasing the blood pressure of the guinea pig and rabbit. Increases in blood pressure were observed only with very large doses of dopamine (>1 mg, i.v.). The pressor potency of dopamine in these species ranged between $\frac{1}{500}$ and $\frac{1}{1000}$ that of epinephrine, whereas this ratio in the cat was $\frac{1}{25}$ to $\frac{1}{40}$ and in the dog, $\frac{1}{30}$ to $\frac{1}{40}$.

C. Possible mechanisms responsible for blood pressure changes

The results of the studies by Holtz and Credner (94) led to extensive investigations of the mechanisms responsible for the species differences and for the vasodepressor effects of dopamine. Subsequent investigators demonstrated that the depressor effect was not limited to the rabbit and guinea pig, for small doses of dopamine lowered blood pressure in the urethane-anesthetized cat (30, 56) but not in the spinal cat (30, 94), the vagotomized, pentobarbital-anesthetized dog (67, 123) and unanesthetized man (101, 125). Increases in blood pressure occurred when larger doses of dopamine were administered to these and other species (3, 22, 42, 45, 67, 79, 85, 123, 136, 147, 156a).

1. Effects of standard antagonists. The pressor effect of dopamine is antagonized or reversed in man (129, 131), dog (48, 82, 123, 132, 133), cat (42, 96, 129, 154, 155) and rat (20, 129) by *alpha*-adrenergic blocking agents. The depressor effect, however, is not blocked by atropine (123), antihistamines (123) or *beta*-adrenergic blocking agents (96, 97, 123, 175).

2. Generation of vasodilating substances. Holtz and Credner (94) suspected that the depressor effect was due to production of a vasodilating substance, and Holtz and his colleagues investigated this possibility for many years (92–97). Initially, Holtz and Credner (94) postulated that the depressor effect was due to formation of an aldehyde by action of monoamine oxidase. Hornykiewicz (98), however, later found that the monoamine oxidase inhibitor, iproniazid, prolonged rather than eliminated the depressor effect of dopamine in the guinea pig. Monoamine oxidase inhibitors also do not attenuate the depressor effects of dopamine in the dog (57, 67).

Holtz, Stock and Westermann (96, 97) later postulated that the vasodepressor effect was due to formation of a condensation product of dopamine, *i.e.*, tetrahydropapaveroline. Halushka and Hoffmann (80), however, found that insufficient quantities of tetrahydropapaveroline were generated to produce a depressor effect. In addition, the vasodilating effects of tetrahydropapaveroline, unlike those of dopamine are blocked by *beta*-adrenergic blocking agents (97).

3. Combination with alpha-adrenergic receptors. Burn and Rand (30) observed that prior administration of large doses of reserpine to rabbits and guinea pigs changed the depressor effects of dopamine to pressor effects, and that the depressor effect was reinstituted after intravenous infusions of norepinephrine. They also observed that dopamine caused relaxation of the rabbit aortic strip previously contracted by norepinephrine. Burn and Rand thus postulated that dopamine produced a depressor effect by combining with receptors ordinarily occupied by the more potent vasoconstrictor, norepinephrine. This phenomenon, however, cannot be solely responsible for the depressor effect, since it is accentuated and not blocked by *alpha*-adrenergic blocking agents. A more likely explanation is that reserpine prevented binding of dopamine in sympathetic nerves and thus increased the quantity of the amine combining with *alpha*-adrenergic receptors (96).

4. Neurogenic mechanisms. McDonald and Goldberg (123) observed that intravenous injections of dopamine caused vasodilation in the perfused limb of the dog, whereas intra-arterial injections of dopamine into the limb circulation resulted only in vasoconstriction. The vasodilation occurred simultaneously with the systemic depressor effect, despite a 2-min lag in the perfusion circuit and it was eliminated by denervation. Therefore, it was suggested that the vasodepressor effect was due to reflex or central nervous system actions, possibly mediated *via* the sympathetic nervous system.

Bogaert and deSchaepdryver (21) localized the site of neurogenic vasodilation to the autonomic ganglia, since the vasodilation in the hindlimb only occurred when dopamine was allowed to reach the lumbar sympathetic ganglia. Brody *et al.* (26) reported that tripelennamine antagonized the vasodilation produced by dopamine in the perfused hindlimb and on the basis of this and other data concluded that the phenomenon was due to release of histamine from nerve fibers distributed with the lumbar sympathetic nerves.

These investigations offer several hypotheses to explain vasodilation of the perfused limb after intravenous dopamine administration, but do not prove that the vasodepressor effect of dopamine is due solely to a neurogenic mechanism. Rather, evidence against this explanation is more prevailing for the following reasons: 1) Perfused limb vasodilation takes place with a number of sympathomimetic amines which do not evoke dopamine-like depressor effects (145). 2) The depressor effects of dopamine cannot be blocked by hexamethonium or antihistamines (123). 3) Imipramine abolishes neurogenic vasodilation in the perfused limb, and at the same time increases the depressor effects of dopamine (48).

III. Vasodilation by Action on Dopamine Receptors

Inability of conventional blocking agents to attenuate the vasodepressor effect of dopamine suggested that dopamine was acting on a unique vascular receptor. The existence of such a receptor, however, cannot be proven by measurement of blood pressure, since a vasodepressor effect can be caused by many factors reducing cardiac output and peripheral resistance.

The first evidence that dopamine caused vasodilation by an unusual mechanism was reported in 1963 by McDonald *et al.* (124, 125). Intravenous infusions of dopamine in normal human subjects resulted in marked reductions in renal arterial resistance. In the same year McNay *et al.* (132a, 133) reported that injections of dopamine into the renal artery of anesthetized dogs caused dose-related reductions in renal vascular resistance. Renal vasodilation was the sole response in doses ranging from 0.75 to 6 μg; transient initial vasoconstriction occurred in 45% of the animals when 12 μg were injected. The magnitude and duration of the vasoconstriction increased with larger doses, so that vasoconstriction was the predominant effect when doses of 96 to 192 μg were injected.

After administration of phenoxybenzamine, the vasoconstriction was eliminated and vasodilation was observed at all dose ranges, permitting construction of complete dose-response curves. Tachyphylaxis to the renal vasodilating actions of dopamine was not observed.

By use of appropriate specific antagonists and non-specific vasodilating agents, it was found that the renal vasodilation produced by dopamine was not attenuated by adequate blocking doses of the *beta*-adrenergic blocking agents, dichloroisoproterenol and nethalide (130, 132a, 133), atropine (132a, 133) or antihistamines (132a, 133), nor was it eliminated by prior treatment with reserpine (130), monoamine oxidase inhibitors (130) or compound 48/80 (62). Two metabolites of dopamine, 3-methoxy-4-hydroxyphenylethylamine and 3,4-dihydroxyphenylacetic acid, did not produce renal vasodilation (130). Tetrahydropapaveroline dilated the renal vascular bed, but this effect was blocked by *beta*-adrenergic blocking agents (130).

Although these studies suggested that dopamine was acting on a previously undescribed receptor, it was necessary to rule out non-selective vasodilation, as occurs with drugs such as papaverine or glyceryl trinitrate. This was accomplished by demonstrating that injections of dopamine in the femoral vascular bed resulted in vasoconstriction (132a, 133). After administration of phenoxybenzamine, vasodilation of the femoral vascular bed was observed, but only with doses of dopamine approximately 50 times those required to dilate the renal vascular bed. This vasodilation, unlike that in the kidney, was blocked by *beta*-adrenergic blocking agents (130).

Eble (48) confirmed the renal vasodilation produced by dopamine in the anesthetized dog and in addition found that similar vasodilation, not blocked by nathalide, also occurred in the superior mesenteric and celiac vascular beds. Eble also reported that the vasodepressor effects after intravenous injections of dopamine were markedly reduced after clamping the celiac, superior mesenteric

and renal arteries. On the basis of these experiments and his demonstration that imipramine prevented neurogenic vasodilation without blocking the vasodepressor effect, Eble concluded that the depressor effect of dopamine was primarily due to vasodilation in the celiac, renal and mesenteric vascular beds.

Renal vasodilation produced by dopamine in the dog has been confirmed by a number of investigators using electromagnetic flowmeters (127, 128, 139), clearances of *para*-aminohippurate (PAH) (28, 138, 140) and radiological techniques (23). Renal vasodilation in humans has now been observed by clearances of PAH (25, 125, 151), an indicator dilution technique (25) and by renal angiography (1).

Ross and Brown (153) did not observe consistent renal vasodilation in the cat. However, *alpha*-adrenergic blocking agents were not administered, and thus it is not known whether a renal vasodilating action of dopamine in this species was masked by *alpha*-adrenergic vasoconstriction. Mesenteric vasodilation, not blocked by *beta*-adrenergic blocking agents, was observed in the cat as in the dog.

More recently, Schuelke *et al.* (158) reported that dopamine caused vasodilation in the coronary vascular bed of the dog similar to that occurring in the renal and mesenteric vascular beds. This effect, unlike renal and mesenteric vasodilation, could only be detected after administration of large doses of both *alpha*- and *beta*-adrenergic blocking agents.

A. Dopamine blocking agents

The concept that dopamine causes renal, mesenteric and coronary vasodilation by acting on a specific receptor was strengthened by the discovery of specific dopamine blocking agents. Rossum (155) reported that administration of the butyrophenones, spiramide and haloperidol, antagonized the reduction in blood pressure caused by dopamine in the anesthetized rabbit and in the yohimbine-treated, anesthetized cat. In the single experiment presented, the reduction in blood pressure produced by 0.3 μmol of dopamine in the cat was attenuated after administration of 0.32 μmol of spiramide. Since only blood pressure was measured, this effect was not necessarily due to blockade of dopamine-induced vasodilation. Furthermore, evidence was not presented to demonstrate that the doses of spiramide used selectively antagonized the effects of dopamine. However, Yeh *et al.* (193) later reported that within a relatively narrow dose range, intra-arterial injections of haloperidol attenuated dopamine-induced renal and mesenteric vasodilation without affecting the vasodilation produced by isoproterenol or bradykinin. The blocking effects of haloperidol persisted for only about 2 min; thus, maximum antagonism was best demonstrated when haloperidol was injected simultaneously with dopamine. Schuelke *et al.* (159) reported that haloperidol also attenuated dopamine-induced coronary vasodilation.

Phenothiazines were found by Goldberg and Yeh (71, 72) and Brotzu (28) to exert similar dopamine blocking actions. Chlorpromazine, trifluoperazine, prochlorperazine and fluphenazine selectively attenuated dopamine-induced

renal vasodilation in the dog in doses approximately twice those required with haloperidol; thioridazine produced similar blocking effects with doses approximately four times those of haloperidol (72). More recently, Tseng and Walaszek (172) reported that bulbocapnine, which was first suggested as a dopamine blocking agent by Ernst (49, 50), antagonized the vasodepressor effects of dopamine in the rabbit, guinea pig and phenoxybenzamine-treated cat. Bulbocapnine also selectively attenuates renal vasodilation in the dog (66).

Apomorphine was considered by Ernst (49, 50) to act as a dopamine agonist, rather than an antagonist, since it produces compulsive gnawing behavior in the guinea pig similar to that produced by *l*-dopa. Simon and Van Maanen (164), however, considered that apomorphine was a dopamine blocking agent on the basis of experiments with the isolated rat vas deferens. Apomorphine apparently exerts both agonistic and antagonistic effects in the dog kidney, for it increases renal blood flow (68) and also attenuates dopamine-induced renal vasodilation when injected in combination with the amine (66).

Contrary results were reported by Dhasmana *et al.* (42), for they found that apomorphine, chlorpromazine and fluphenazine failed to antagonize dopamine-induced vasodepression in the phenoxybenzamine-treated cat. On the other hand, they reported that morphine or codeine was effective in reversing the depressor effect. In addition, these investigators observed that nalorphine antagonized the blocking effect of morphine and codeine and the depressor effect of dopamine reappeared. Many of these drugs have apparently not been investigated in the dog kidney, but the contrary results with apomorphine and the phenothiazines suggest that data obtained from blood pressure recordings in the phenoxybenzamine-treated cat do not necessarily correlate with attenuation of dopamine-induced vasodilation in the dog kidney.

B. Structure-activity relationships

Structural requirements for dopamine-induced renal vasodilation appear to be much stricter than those required for activity on standard *alpha-* and *beta-*adrenergic receptors. Of 44 sympathomimetic amines studied, only the N-methyl analog of dopamine, epinine, caused typical dopamine-induced renal and mesenteric vasodilation attenuated by haloperidol (68, 193). Epinine, however, differed from dopamine, in exerting more pronounced *alpha-* and *beta-*adrenergic actions. The former action may explain the initial pressor effect observed with epinine in the guinea pig (98).

As described above, apomorphine also appears to produce dopamine-like renal vasodilation (68). However, a much larger dose is required to evoke vasodilation and the maximum effect is much less than that produced by dopamine or epinine. Amphetamines, which Rossum and Hurkmans (156) considered as acting on dopamine receptors in the brain, do not cause dopamine-like vasodilation in the kidney (68).

There is good agreement between the structure-activity data obtained in the dog kidney and in the isolated brain of the snail, *Helix aspersa*. Woodruff and Walker (191) observed that dopamine and epinine were the most potent com-

pounds tested as inhibitors of spontaneous electrical activity of the snail neuron. Apomorphine and amphetamines were not active in this preparation.

The extreme specificity for activation of dopaminergic receptors is supported by molecular orbital calculations of Kier and Truitt (108) who reported that the preferred conformation of dopamine was distinctly different from that previously calculated for norepinephrine.

C. Summary of evidence for a specific vascular dopamine receptor

The research described above satisfies the following criteria required for identification of a specific receptor: 1) Vasodilation occurs in the renal, mesenteric and coronary vascular beds of the dog. The dose required to produce renal vasodilation is much less than that required to cause *beta*-adrenergic vasodilation. 2) The vasodilation is not blocked by *beta*-adrenergic blocking agents, atropine or antihistamines, and is not attenuated by previous administration of reserpine, monoamine oxidase inhibitors or compound 48/80. 3) Butyrophenone and phenothiazine neuroleptic agents, apomorphine and bulbocapnine selectively attenuate dopamine-induced vasodilation. 4) The chemical structural requirement for dopamine-induced vasodilation is extraordinarily specific and does not resemble the structural requirements for action on other known receptors. 5) There is considerable evidence that a similar receptor may exist in the central nervous system. In this regard, it is interesting that Parkinson-like symptoms are produced after dopamine depletion by drugs such as reserpine (31a) and by the same neuroleptic agents which attenuate dopamine-induced vasodilation (106).

The deficiencies in the concept of a specific dopamine vascular receptor are no greater than those which existed when *alpha*- and *beta*-adrenergic receptors were first proposed by Ahlquist (1a). First, small doses of the currently available antagonists do not completely block the effects of dopamine, and they are nonspecific antagonists when larger doses are administered. Secondly, release of other vasodilating agents such as bradykinin or a prostaglandin has not been ruled out. This possibility appears to be unlikely, however, because of the almost immediate onset of dopamine-induced vasodilation and the lack of tachyphlaxis (68). The availability of an isolated organ which responds specifically to dopamine would facilitate research in these areas.

IV. *Alpha*-Adrenergic Effects

The predominant effect of dopamine on most arterial vascular beds is vasoconstriction due to action on *alpha*-adrenergic receptors (2, 43, 48, 123, 133, 139, 158). Dose response studies indicate that with a sufficiently large dose, the vasoconstrictor effect of dopamine predominates over vasodilating effects (48, 133). Accordingly, it is not surprising that with the large doses of dopamine used in the early studies of Hamet (82) and in the more recent study by Glick (60), only the vasoconstrictor effects of dopamine were observed in the dog kidney. The difference in *alpha*-adrenergic activity of dopamine in different species and in different vascular beds in the same experiment makes it imperative that effective *alpha*-adrenergic block be instituted before it is definitively stated that vasodilating receptors are not present in the vascular beds under study.

Most investigations have demonstrated that the *alpha*-adrenergic vasoconstriction produced by dopamine is due to a direct action, since both vasoconstrictor and pressor effects of dopamine are either increased or unaffected by cocaine (12, 52, 77, 82, 166), desmethylimipramine (22), methylphenidate (61) or prior administration of reserpine (28a, 30, 96). In most studies, this potentiation is less than that which occurs when these drugs are administered before epinephrine or norepinephrine.

Enhancement of the vasoconstrictor action of dopamine by any of these drugs could mask the vasodilating actions of the amine, thus leading to the erroneous interpretation that the vasodilation is blocked at the receptor. Again, this error could be avoided by use of appropriate doses of *alpha*-adrenergic blocking agents.

Vasoconstriction is the only effect described in studies of the effects of dopamine on veins (75, 135). Mark *et al.* (135) found that dopamine constricted the perfused left colic and saphenous veins of the dog and that the vasoconstriction was blocked by phenoxybenzamine and phentolamine. Vasodilation was never observed. The vasoconstriction was not affected by cocaine or by reserpine pretreatment, indicating that it was due to direct action on *alpha*-adrenergic receptors. Dopamine was $\frac{1}{13}$ as potent a vasoconstrictor as norepinephrine in the left colic vein and $\frac{1}{25}$ as potent in the saphenous vein. Thus, dopamine exerts a relatively greater vasoconstrictor effect on veins than on arteries (norepinephrine/dopamine ratio in the dog femoral artery is 1/44 (133)). Venoconstriction also occurs in man. Wheeler *et al.* (182) demonstrated that intravenous infusions of dopamine at rates ranging from 2 to 6 μg/kg/min decreased mean venous capacitance as measured plethysmographically.

Dopamine causes vasoconstriction in the perfused pulmonary vascular bed of the dog. Waller (177) found that the vasoconstrictor potency of dopamine compared with norepinephrine in this vascular bed was $\frac{1}{25}$. On the other hand, dopamine failed to constrict bronchial vessels. Detailed studies with appropriate blocking agents were not carried out.

V. *Beta*-Adrenergic Effects

A. Vasodilation

Dopamine is an extremely weak peripheral *beta*-adrenergic agonist in experimental animals. In the femoral vascular bed of the dog, the *beta*-adrenergic potency of dopamine is less than $\frac{1}{1000}$ that of isoproterenol and about $\frac{1}{65}$ that of norepinephrine (130). Dopamine is less than $\frac{1}{10}$ as effective as norepinephrine in relaxing the rabbit aortic strip contracted with carbachol (109) and $\frac{1}{600}$ as potent as isoproterenol in causing *beta*-adrenergic induced coronary vasodilation in the dog (158).

Studies in man have not been definitive. Wheeler *et al.* (182) detected only vasoconstriction after intravenous infusions of dopamine at rates of 2 to 6 μg/kg/min, but Allwood and Ginsburg (3) and Whelan (183) demonstrated that intravenous infusions of dopamine at rates of 500 and 1000 μg/min increased forearm blood flow, while decreasing hand blood flow. Allwood and Ginsburg (3) also observed that intra-arterial administration of 50 μg/min of dopamine

increased both forearm and hand blood flow, after the administration of phenoxybenzamine, suggesting an action on *beta*-adrenergic receptors. However, the effects of *beta*-adrenergic blocking agents were not investigated.

B. Myocardial stimulation

1. Direct and indirect action. In his early investigations, Gurd (77) demonstrated that dopamine increased the amplitude of contraction of isolated rabbit, cat and dog hearts, and that this action was attenuated, but not blocked, by cocaine. On this basis, Gurd (77) considered that dopamine acted midway between tyramine and epinephrine. This conclusion has been supported by more recent investigations which have demonstrated that the positive inotropic and chronotropic actions of dopamine are reduced or not potentiated by cocaine (52, 171), desmethylimipramine (173) and reserpine (16, 52, 113, 171) pretreatment. Thus, dopamine is classified as a "mixed amine," which exerts cardiac effects both by acting directly on *beta*-adrenergic receptors and by releasing norepinephrine from sympathetic storage sites. An indirect component of dopamine's action is also suggested by data which indicate that the cardiac actions are potentiated and prolonged by monoamine oxidase inhibitors (57, 67).

The relative contributions of the direct and indirect actions of dopamine are difficult to evaluate because when dopamine enters the sympathetic storage sites, it replaces, prevents uptake and increases the synthesis of norepinephrine (34, 86, 171). Tsai *et al.* (171) investigated the effects of reserpine and cocaine on the action of dopamine in guinea pig atria and concluded that the prevention of uptake of norepinephrine increased the relative contribution of the indirect component. On the other hand, they considered, on the basis of experiments with the dopamine-β-oxidase inhibitor, disulfiram, that increased synthesis did not play a significant role in the cardiac actions.

2. Positive inotropic effects. Detailed studies of the isolated and intact dog heart with the Walton-Brody strain gauge arch (91, 123) and left ventricular hemodynamic techniques (18, 19, 85, 190) have demonstrated that dopamine increases cardiac contractility in a manner similar to that of other sympathomimetic amines and that this effect can be completely blocked by appropriate doses of *beta*-adrenergic blocking agents (19, 123). Dopamine appears to be about $\frac{1}{30}$ to $\frac{1}{40}$ as potent as epinephrine or norepinephrine in increasing cardiac contractility in the open chest, vagotomized, anesthetized dog (36, 123).

3. Positive chronotropic effects. In studies in the intact dog, dopamine was found to differ from other catecholamines in that it causes a smaller increase in heart rate at an equivalent increment in cardiac contractile force (18, 85, 123, 190). For example, when norepinephrine and epinephrine increase cardiac contractile force in the vagotomized, anesthetized dog by approximately 50%, heart rate is increased about 20 beats/min (36). When similar increments in contractile force are produced by dopamine, however, heart rate does not change (123). The disparity between rate and contractility is not due to lack of effect of dopamine on the SA node. Rolett and Black (149) infused norepinephrine and dopamine into the sinus node artery of the dog and found that both amines

produced a similar dose-dependent rate increase, but that dopamine was approximately $\frac{1}{10}$ as potent as norepinephrine. Similar findings were described by James *et al.* (105). A neurogenic mechanism was ruled out in the dog by Tuttle (173) since the differential positive inotropic:positive chronotropic effect occurred despite destruction of the brain and spinal cord. On the basis of experiments with reserpine and desmethylimipramine, Tuttle (173) concluded that the differential positive chronotropic:positive inotropic action was due to dopamine increasing contractility by release of norepinephrine at a smaller dose than necessary to increase heart rate by a predominantly direct action.

C. Potential for producing arrhythmias

Dopamine resembles other sympathomimetic amines in producing ventricular arrhythmias in the presence of cyclopropane or halothane anesthesia (107, 142, 143), and after extremely large doses even without sensitizing agents (2, 45). Katz *et al.* (107) reported that dopamine was about $\frac{1}{100}$ as potent as norepinephrine in causing arrhythmias under cyclopropane anesthesia. These investigators also observed that dopamine-induced arrhythmias during cyclopropane and halothane anesthesia could be completely prevented by administration of *beta*-adrenergic blocking agents.

VI. Hemodynamic Effects

A. Dog

The differential effects of small and large doses of dopamine on vascular resistance make a pronounced difference in the results of hemodynamic studies carried out at the different dose ranges. Thus, when dopamine is administered to the anesthetized dog intravenously at rates of 50 μg/kg/min or more, mean blood pressure is elevated, total peripheral resistance increases, and the hemodynamic effects resemble those produced by norepinephrine (18, 85, 136, 190). However, when 10 μg/kg/min or less are infused, cardiac output increases with little change or a decrease in total peripheral resistance and without change in the heart rate (18, 85, 190). Differential effects also occur in the pulmonary circulation. Large doses of dopamine (25–50 μg/kg) increase pulmonary pressure, but not pulmonary resistance in the anesthetized dog (85). Smaller doses do not affect pulmonary pressure (85).

B. Man

Horwitz *et al.* (101) and McDonald *et al.* (125) infused dopamine at rates ranging from 2.8 to 11.6 μg/kg/min to normal human subjects and observed that cardiac index increased, systemic vascular resistance decreased, and there was little or no change in heart rate or mean arterial blood pressure. This hemodynamic pattern does not occur with other catecholamines (2, 6). Norepinephrine increases systemic resistance and usually causes reflex bradycardia (73). Isoproterenol decreases systemic resistance and increases heart rate (150). Low rates of infusion of epinephrine produce hemodynamic patterns similar to those of isoproterenol; higher rates of infusion resemble norepinephrine (73).

Döring *et al.* (45) and Rosenblum *et al.* (151, 152) observed that similar rates of infusion of dopamine as used by Horwitz *et al.* (101) and McDonald *et al.* (125) increased left and right ventricular dp/dt (differential pressure/differential time).

Detailed hemodynamic studies have not been obtained in man with higher infusion rates of dopamine, but Allwood and Ginsburg (3) and Döring *et al.* (45) administered dopamine to normal subjects at rates of 750 and 1000 μg/min and observed elevations of systolic pressure above 200 mm Hg with only minimal increments in diastolic pressure. Heart rate decreased and premature ventricular contractions were recorded. Dopamine-induced increments in systolic and diastolic pressure were observed by Horwitz *et al.* (102) in hypertensive patients treated with monoamine oxidase inhibitors.

C. Coronary blood flow

Brooks *et al.* (27) reported that infusions of dopamine in the dog at rates ranging from 5 to 80 μg/kg/min resulted in progressive linear increments in coronary blood flow which were proportional to increments in oxygen consumption. Administration of propranolol eliminated both the positive inotropic action and the increment in coronary blood flow. Hence, it was concluded that coronary vasodilation occurred secondary to the increase in myocardial oxygen demands. Parallel increments in cardiac contractility and coronary blood flow were also noted by Schuelke *et al.* (158) and Nayler *et al.* (140a).

VII. Effects on the Kidney

A. Normal human subjects

McDonald *et al.* (125) reported that intravenous infusions of dopamine (2.6 to 7.1 μg/kg/min) to 7 normal subjects increased the average estimated renal plasma flow (C_{PAH}) from 507 to 798 ml/min, inulin clearance (C_{IN}) from 109 to 136 ml/min, and average sodium excretion ($U_{Na}V$) from 171 to 571 μEq/min. Simultaneous hemodynamic studies indicated that these changes were accompanied by pronounced increments in cardiac output but no significant changes in arterial blood pressure or heart rate. Similar increases in renal function have not been reported after administration of other sympathomimetic amines (6, 141, 150).

B. Experimental animals

Meyer *et al.* (138) demonstrated that intravenous infusions of dopamine (6 μg/kg/min) to anesthetized and unanesthetized dogs produced percentage increments in $U_{Na}V$ similar to these found in normal human subjects. However, glomerular filtration rate (GFR) increased an average of 11% in the dog as compared to 16% in man, and C_{PAH} increased only 25% in the dog as compared to 58% in man. These investigators also proved that the augmentation of renal function was not secondary to systemic hemodynamic changes, for administration of dopamine in one renal artery produced greater augmentation of GFR, C_{PAH} and $U_{Na}V$ in the infused kidney than on the contralateral side.

A number of studies have been directed toward determining whether the natriuresis results from a direct action of dopamine on the renal tubule or is secondary to renal vascular changes. This is a most difficult problem and has not yet been resolved. Davis *et al.* (39), Morimoto (139) and McGiff and Burns (127, 128) demonstrated that natriuresis could occur in anesthetized dogs despite reductions in renal blood flow and glomerular filtration rate. Davis *et al.* (39) presented evidence on the basis of lissamine-green injections that dopamine was acting on the distal convoluted tubule. Morimoto (140) came to a similar conclusion by using a stop-flow technique. Seely and Dirks (159), however, localized the site of action to the proximal convoluted tubule by means of a recollection micropuncture technique.

Dissociation between natriuresis and increments in renal blood flow was also observed by Brotzu (28), who reported that chlorpromazine reduced the increment in renal blood flow produced by dopamine by 20% without affecting the natriuresis, and by McGiff and Burns (127, 128), who observed that phentolamine and renal nerve stimulation abolished natriuresis without affecting the increase in renal blood flow.

Although renal blood flow and glomerular filtration rate may be unchanged or decreased when natriuresis is produced by dopamine, intrarenal vascular changes could still be the responsible mechanism (31b, 47). In this regard, dopamine (25, 138, 152) and other vasodilating agents which increase sodium excretion decrease the extraction of PAH, suggesting that a shunt may occur from cortical to medullary areas of the kidney. Evidence against a tubular mechanism was provided by May and Carter (137) who demonstrated that the injection of dopamine into the renal portal system of chickens does not result in natriuresis. Finally, Deis and Alonso (40) observed that dopamine increased urine volume in rats and suggested that the diuresis in these animals was related to blocking of the anti-diuretic hormone. However, studies of osmolar and electrolyte excretion will have to be carried out to confirm this hypothesis.

VIII. Clinical Applications

A. Congestive heart failure

The study of Horwitz *et al* (101) demonstrating that dopamine could increase cardiac output without significantly altering heart rate or blood pressure led Goldberg *et al.* (65) to investigate the effects of dopamine in patients with severe congestive heart failure. Consistent increments of sodium excretion occurred when dopamine was infused intravenously at rates which did not affect diastolic blood pressure (range 100–1000 μg/min). In a more detailed study, McDonald *et al.* (125) observed that C_{IN}, C_{PAH}, $U_{Na}V$, and U_KV increased in each of five patients with congestive heart failure. More recently, Rosenblum *et al.* (151, 152) observed similar improvements in renal function in a series of 19 patients with congestive heart failure. The latter investigators also performed detailed hemodynamic studies and found that cardiac index, stroke volume and left ventricular dp/dt increased; systemic and pulmonary vascular resistance decreased and heart rate did not change significantly.

1. Therapeutic potential. The above investigations demonstrate that intravenous infusions of dopamine can improve both cardiac and renal function in patients with congestive heart failure. Indeed, dopamine is the only sympathomimetic amine reported to consistently increase sodium excretion in these patients (6, 63). The use of dopamine for the treatment of chronic congestive heart failure, however, is currently limited to relatively short term intravenous infusions. Furthermore, the rate of the infusions must be carefully adjusted to avoid tachycardia and vasoconstriction which could occur with excessive doses. Adverse effects have included nausea and vomiting in a few patients and single episodes of ventricular arrhythmias and angina pectoris (65). The potential application of an oral analog of dopamine for the treatment of congestive heart failure has previously been discussed in greater detail (63).

B. Shock

1. Investigations in man. MacCannell *et al.* (121) first investigated the potential use of dopamine in 16 patients with hypotension or shock unresponsive to plasma volume expansion. The etiologies of the shock included myocardial infarction, infection, neurological injury and cardiac surgery. The infusion rate of dopamine ranged from 1 to 10 μg/kg/min and was adjusted according to response of blood pressure, heart rate and urine volume. Five patients received dopamine for less than 35 min. The remaining 11 patients received the drug from 2 to 51 hr and were studied more extensively. Peripheral circulation and urine output improved in five patients and one of these functions improved in five others. Although six patients excreted less than 15 ml of urine per hour while receiving norepinephrine, epinephrine or metaraminol, urine output of four of these patients increased to greater than 80 ml/hr during dopamine administration. Hemodynamic studies indicated that cardiac output increased in six of seven patients studied; total peripheral resistance decreased in five and increased in two. Two patients in this series experienced transient supraventricular tachycardia during dopamine infusions. MacCannell *et al.* (121) also investigated the combined use of dopamine and phenoxybenzamine in one patient with shock and oliguria following myocardial infarction. This patient had intense vasoconstriction, and the infusion of dopamine did not improve urine flow. After administration of phenoxybenzamine, however, the urine flow increased and this improvement was maintained and possibly augmented by subsequent administration of dopamine. The successful use of combined therapy with phenoxybenzamine and dopamine has also been reported by Goldberg *et al.* (69) in a patient in shock following cardiovascular surgery.

Talley *et al.* (168) compared the hemodynamic responses of dopamine and isoproterenol in 22 patients in shock of various etiologies. Dopamine was found to be superior to isoproterenol in seven patients with normal or low peripheral resistance. In these patients, isoproterenol lowered blood pressure to levels inconsistent with adequate organ perfusion. Isoproterenol was superior in three patients in whom dopamine did not increase cardiac output. Both dopamine and isoproterenol produced adequate clinical response in four patients and a

combination of these two drugs were necessary for adequate therapy in two others. Of interest, two patients survived the shock syndrome after receiving dopamine continuously for 68 and 72 hr respectively.

Loeb *et al.* (118) investigated the hemodynamic effects of dopamine in 62 patients. In 36 patients with infectious shock, mean arterial pressure was increased by 30% and cardiac output by 37%. Urine flow increased from 0.5 ml/min to 1.6 ml/min. Norepinephrine administered to 26 patients produced a higher mean arterial pressure, lower cardiac output and similar urine flow; administration of isoproterenol in 19 of the patients resulted in lower mean arterial pressure, higher cardiac output and significantly lower urine flow. In 13 patients with cardiogenic shock, dopamine increased mean arterial pressure by 6% and cardiac output by 40%. Urine flow increased from 0.6 ml/min to 1.1 ml/min. Norepinephrine administration resulted in a smaller increase in cardiac output than was produced by dopamine; isoproterenol resulted in a larger increase in cardiac output in five of eight patients. Dopamine was considered to be superior to isoproterenol because the latter amine did not raise arterial pressure to adequate levels. Dopamine was also considered to be superior to norepinephrine in patients in cardiogenic shock with increased systemic vascular resistance, since only dopamine increased cardiac output. Adverse effects reported by Loeb *et al.* (118) included one episode each of ventricular and supraventricular tachycardia. In addition, one patient experienced an atypical response during dopamine infusion manifested by moderate reductions in mean arterial pressure, central venous pressure, heart rate and systemic resistance, and a slight reduction in cardiac output. This patient later responded typically to isoproterenol and norepinephrine. In a separate study, these investigators (189) reported that dopamine caused less myocardial anerobiasis than norepinephrine or isoproterenol (as measured by transmyocardial lactate production).

Février *et al.* (53) reported the successful use of dopamine in 76 patients with shock or oliguria due to a variety of causes. Two detailed case reports were presented demonstrating improved cardiovascular and renal function. More recently, Rosenblum and Frieden (150a) reported that dopamine improved the hemodynamic and renal status of 10 of 15 patients in refractory shock following cardiac surgery. Maximum infusion rates ranged from 7 to 35 μg/kg/min and the duration of the infusions ranged from 3 to 332 hr.

2. Animal experiments. (A) ENDOTOXIN SHOCK. Lansing and Hinshaw (112) and Shanbour and Hinshaw (161) observed that intravenous infusions of dopamine (40–150 μg/min and 17–34 μg/kg/min, respectively) were effective in reversing the venous pooling, the low peripheral resistance and the bradycardia caused by endotoxin in dogs. Survival rate was improved. Shanbour and Hinshaw (162) reported that dopamine decreased the volume of the isolated dog liver which had markedly increased after administration of endotoxin and suggested that the reversal of venous pooling was related to this action of dopamine. More recently, Shanbour *et al.* (160) found that infusions of dopamine (30 μg/kg/min) did not reverse the decreased renal blood flow, glomerular filtration rate and urine flow produced by endotoxin in the dog unless the amine was

infused after administration of phenoxybenzamine (1 mg/kg) and dextran (20 ml/min). Guenter and Hinshaw (76) and Hinshaw *et al.* (89) observed that dopamine in doses ranging from 0.5 to 10.0 mg/min increased cardiac output of the endotoxin-treated rhesus monkey, but, unlike the dog, systemic resistance decreased despite the very large doses used. Increasing cardiac output above pre-shock levels did not reverse the metabolic acidosis, hyperventilation, or increased alveolar-arterial oxygen gradients.

(B) CORONARY SHOCK. MacCannell (120) reported that dopamine (0.4 to 32 μg/kg/min) increased cardiac output and renal blood flow in dogs following coronary-microsphere injections. Isoproterenol (0.1 to 0.64 μg/kg/min) also increased cardiac output, but renal blood flow was increased only at the lowest infusion rate. Dopamine was more effective in raising arterial blood pressure than isoproterenol. Wintroub *et al.* (190) observed that intravenous infusions of dopamine (8 μg/kg/min) decreased the elevated left atrial pressure and systemic vascular resistance, and increased the decreased cardiac output and left ventricular dp/dt which occurred after ligation of the coronary arteries in the dog. Heart rate and arterial pressure were not significantly affected. Carvalho *et al.* (32) reported that infusions of dopamine (8 μg/kg/min) increased heart rate, mean blood pressure, mean cardiac output, stroke volume, dp/dt, mean coronary blood flow, mean renal artery blood flow and mean superior mesenteric artery blood flow in dogs following either circumflex coronary artery ligation or coronary microsphere injections. Bagwell and Daniell (7) compared the effects of dopamine and norepinephrine on myocardial function and metabolism after cardiogenic shock produced by microsphere coronary embolization. Dopamine (2.5 to 10 μg/kg/min) and norepinephrine (0.5 to 1.0 μg/kg/min) produced equivalent improvement in aortic pressure, aortic coronary flow, stroke volume and myocardial function. These authors pointed out that the increase in aortic pressure observed with these doses of dopamine did not occur in previous studies of animals without myocardial infarction.

(C) HEMORRHAGIC SHOCK. Gifford *et al.* (59) reported that dopamine (6.0 μg/kg/min) and isoproterenol (0.06 μg/kg/min) increased thoracic, abdominal, aortic, splanchnic and renal blood flow in dogs in severe hemorrhagic shock. Cardiac output, as measured by the Fick principle, however, was increased only by isoproterenol. Dagher *et al.* (38) demonstrated that dopamine (10–30 μg/kg/min) had no effect on 48-hr survival in the splenectomized dog in severe hemorrhagic shock and suggested that the beneficial effects of dopamine were overcome by *alpha*-adrenergic vasoconstriction resulting from hypovolemia. In contrast to the above studies, Carvalho *et al.* (32) reported that intravenous infusions of 8 μg/kg/min of dopamine increased cardiac output, mean left anterior descending coronary artery blood flow, mean renal blood flow and mean superior mesenteric arterial blood flow. However, the animals were bled until blood pressure reached 70 mm Hg in the latter experiment whereas in the former studies, the blood pressure was reduced to 30 and 40 mm Hg.

3. Therapeutic potential. The use of dopamine for the treatment of shock is currently being evaluated at a number of clinical centers. The papers reviewed

above and unpublished data from these studies suggest that dopamine may be useful as part of the regimen for patients in shock unresponsive to plasma volume expansion. Dopamine appears to be most beneficial in oliguric patients with low or normal systemic resistance. Patients with high peripheral resistance may not experience increase in urine volume following dopamine administration because of excessive *alpha*-adrenergic vasoconstriction. Dopamine may be advantageously used in the latter patients in combination with isoproterenol, phenoxybenzamine or phentolamine. In addition to the possibility of improving renal blood flow, dopamine increases peripheral resistance more than does isoproterenol and less than does norepinephrine. Thus, dopamine may be used when isoproterenol does not adequately elevate blood pressure and the intense vasoconstriction produced by norepinephrine is not necessary. More detailed discussions of the potential use of dopamine for the treatment of shock and comparisons with the actions of other sympathomimetic amines are included in several recent reviews (9, 53, 55, 69, 78, 84, 165).

C. Hypertension

McNay *et al.* (131) infused dopamine (1 to 1.5 μg/kg/min) intravenously to six patients with severe essential hypertension treated with bethanidine or guanethidine and mean blood pressure increased an average of 10 mm Hg. However, after intravenous administration of phenoxybenzamine, 1 mg/kg, the same infusion rate of dopamine reduced mean arterial pressure in the supine position by an average of 37 mm Hg. Cardiac output increased an average of 2.6 liters/min, heart rate increased an average of 16 beats/min, and total peripheral resistance decreased by 50%. Creatinine clearance did not decrease despite the marked reduction in blood pressure. More recently, Breckenridge *et al.* (25) investigated the effects of dopamine (1 and 2 μg/kg/min) on renal blood flow (by a direct dye dilution technique), cardiac output and PAH extraction of nine patients with hypertension caused by unilateral renal disease. Most patients were being treated with bethanidine or methyldopa. Heart rate and mean blood pressure was not altered. Renal blood flow, however, increased an average of 73.1% above control values, and cardiac output an average of 16.7%. PAH extraction decreased in three patients and rose in three. Clearance studies were carried out in four additional patients. Urine flow, C_{PAH}, C_{IN} and $U_{Na}V$ were significantly increased.

1. Therapeutic potential. Progressive renal failure is a common sequela of essential hypertension (24, 90) and often occurs in spite of effective antihypertensive therapy. These studies suggest that an orally absorbed form of dopamine, preferably without *alpha*- or *beta*-adrenergic activity, might be useful in improving renal function in these patients.

D. Cirrhosis

Barnardo *et al.* (14) investigated the effects of intravenous infusions of dopamine (1.3 to 3 μg/kg/min) in 10 patients with renal failure due to cirrhosis. Average C_{PAH} significantly increased from 308 ml/min to 478 ml/min and aver-

age C_{IN} significantly increased from 58 to 73 ml/min. Average $U_{Na}V$ increased from 4.6 to 9.4 mEq/min. These patients experienced similar increments in C_{PAH} and C_{IN} as patients with congestive heart failure, but the increase in sodium excretion was neither clinically nor statistically significant. However, the patient who received the highest dose of dopamine experienced a 10-fold increase in sodium excretion. The lack of more pronounced natriuresis in the other patients may have been related to the extremely low initial sodium excretion values which are characteristic of these patients and indicate the extreme retention of sodium in this condition. In addition to augmenting renal function, administration of dopamine reduced elevated renin levels in 10 of 13 patients (15). Similar results were reported in a preliminary study by MacGaffey and Jick (122). Again, one patient experienced pronounced natriuresis when dopamine was infused at a rate of 10.6 μg/kg/min.

1. Therapeutic potential. Dopamine is the first drug reported to improve kidney function in patients with renal failure due to cirrhosis. This condition is usually fatal. Since occasional patients experienced both renal hemodynamic improvement and a marked diuretic response, further studies should be conducted to determine whether higher doses or a combination of dopamine with other drugs might produce a more consistent diuretic effect.

E. Acute renal failure

Talley *et al.* (167) investigated the effects of intravenous infusions of dopamine (4 μg/kg/min) alone and combined with diuretics in five patients with acute renal failure due to dehydration, injection of iodinated contrast materials, vigorous diuretic therapy, or major surgery. Neither dopamine nor diuretics alone were effective, but urine flow increased and blood urea nitrogen or serum creatinine levels were reduced toward preoliguric levels in all patients with combined therapy.

1. Therapeutic potential. Additional studies are necessary to determine whether dopamine can be used successfully as part of a regimen for the treatment of acute renal failure. It is possible that early combined treatment with dopamine and potent diuretics could obviate the necessity for dialysis in some of these patients.

F. Drug intoxication

Gifford *et al.* (58) compared the effects of dopamine and norepinephrine in dogs intoxicated with phenobarbital. Both amines increased mean blood pressure in these hypotensive animals to approximately the same extent, but only dopamine significantly increased urine flow and the clearance of phenobarbital. Dopamine was also effective in increasing the renal clearance of salicylates, but since hypotension is not a critical feature of salicylate poisoning the use of dopamine was not considered to be therapeutically useful. Silverman and Okun (163) observed that dopamine was also effective in increasing the excretion of meprobamate.

1. *Therapeutic potential.* These studies suggest that dopamine may be useful

in increasing the excretion of drugs by the kidney. Its greatest application appears to be in hypotensive patients in whom other drugs needed to elevate blood pressure might further reduce renal blood flow. Dopamine might also increase the metabolism of drugs by improving hepatic blood flow. Increased clearance of phenobarbital in one child poisoned with that drug (58a) suggests that additional clinical studies should be carried out.

G. Catecholamine repletion

It is possible that administration of dopamine or *l*-dopa could result in increased synthesis of norepinephrine and epinephrine when the latter amines are depleted in conditions such as congestive heart failure (33, 176), thermal burns (74) or shock (87, 111). Goodall and Alton (74) observed that administration of dopamine-2-^{14}C to patients with severe thermal burns caused a shift toward norepinephrine synthesis and utilization at the expense of dopamine metabolism. These investigators concluded that the infused dopamine was rapidly synthesized into norepinephrine and then released and metabolized. LaBrosse and Cowley (111) administered tritiated *l*-dopa and dopamine ^{14}C to patients with septic shock or undergoing surgery and observed that the norepinephrine excreted in the urine was derived to a greater extent from *l*-dopa than from dopamine. These data suggested that *l*-dopa was taken up more rapidly by the norepinephrine synthesizing cells than dopamine.

1. Therapeutic potential. Although the above studies have demonstrated increased synthesis of norepinephrine after administration of *l*-dopa and dopamine, additional investigations are necessary to determine whether beneficial repletion occurs. For example, Hashimoto (87) observed that administration of *l*-dopa to dogs with severe hemorrhagic shock resulted in increased norepinephrine content of the heart, but there was no evidence of improved myocardial function. Obviously, the extent of repletion depends upon many factors including condition of the sympathetic nerves and adrenal glands and their contained enzymes (176, 180). Furthermore, the location of replenishment may be critical since repletion of norepinephrine stores in the kidney might result in detrimental renal vasoconstriction, whereas repletion of norepinephrine stores in the heart might result in improved myocardial function. Finally, it will be necessary to separate the pharmacological effects of dopamine from those due to norepinephrine or epinephrine replenishment.

IX. Cardiovascular and Renal Effects of *L*-Dopa

A. l-Dopa as a source of dopamine

It was evident from the studies of Holtz and associates (94, 95) reported in 1938 and 1942 that dopa was decarboxylated *in vitro* and *in vivo* to dopamine. D-Dopa was not decarboxylated. In addition, these investigators emphasized the importance of dopamine in the cardiovascular actions of dopa, for they observed typical, prolonged depressor effects in the guinea pig and pressor effects in the cat after intravenous administration of the amino acid. Clark and

his associates (35) subsequently demonstrated that the effect of dopa on blood pressure was prevented by prior administration of decarboxylase inhibitors. Early studies of the cardiovascular actions of *l*-dopa and the proposed mechanisms responsible for these actions were reviewed by Holtz (92) and Clark (35) in this Journal in 1959. Further evidence that the cardiovascular effects of *l*-dopa resemble those of dopamine more than norepinephrine was provided by Goldberg *et al.* (64) and Goldberg and Whitsett (70). These investigators observed that intravenous administration of *l*-dopa to the dog resulted in prolonged increments in cardiac contractile force, which could be produced by either dopamine or norepinephrine. However, simultaneous reductions in renal vascular resistance were observed which occurs only with dopamine. Both cardiac and renal effects were prevented by prior administration of decarboxylase inhibitors.

B. Clinical significance

The availability of *l*-dopa increased the importance of the cardiovascular and renal effects of dopamine with regard to new therapeutic applications and potential adverse effects in patients being treated for Parkinson's disease. Unlike dopamine, *l*-dopa crosses the blood brain barrier (99), and thus cardiovascular effects could also result from a central action of the amino acid or one of its metabolites.

1. Hypertension. In early studies of *l*-dopa, relatively large doses of the amino acid were administered intravenously and hypertension was frequently produced (41, 146). Hypertension also occurs when *l*-dopa is administered orally to patients receiving monoamine oxidase inhibitors (103). Fortunately, hypertensive reactions are only rarely encountered in patients treated with therapeutic doses of *l*-dopa (37, 126).

The increase in blood pressure produced by *l*-dopa can be blocked or reversed by *alpha*-adrenergic blocking agents (70, 103, 148). Thus it appears that this reaction is due to excessive amounts of dopamine acting on *alpha*-adrenergic receptors.

2. Hypotension. Hypotension is a relatively common occurrence in the patient treated with *l*-dopa (8, 31, 37, 192). The greatest reduction in blood pressure is usually recorded in the standing position, but blood pressure in the recumbent position is also lowered in many patients. The occurrence of orthostatic hypotension suggests that *l*-dopa attenuates the function of the sympathetic nervous system. In support of this contention, Watanabe *et al.* (178) demonstrated that reflex forearm arteriolar constriction is reduced after oral administration of *l*-dopa.

Both central and peripheral neurogenic mechanisms have been proposed for the hypotension. Watanabe *et al.* (178) concluded that a central mechanism was responsible for the reduction in sympathetic nerve function because administration of the peripheral decarboxylase inhibitor MK-485 (*d*, *l-alpha*-methyldopa-hydrazine) exaggerated, rather than prevented, the hypotensive effect of *l*-dopa in patients. Supporting animal data was presented by Henning and

Rubenson (88) who demonstrated the hypotensive effect of *l*-dopa in the rat was not reversed by MK-485, and by Osborne *et al.* (144), who reported that venous pooling in the dog was not eliminated by the same inhibitor.

Burn (29) suggested that *l*-dopa was causing hypotension by replacing norepinephrine in the sympathetic nerves by the weaker vasoconstrictor, dopamine. In support of this concept Farmer (51), Whitsett *et al.* (188) and Whitnack *et al.* (184) demonstrated that administration of *l*-dopa to dogs and cats resulted in decreased responses to postganglionic sympathetic nerve stimulation. In addition, Liu *et al.* (117) and Breese and Prange (25a) observed that *l*-dopa reduced the norepinephrine content and increased the dopamine content of rat heart.

It is also possible that an action of dopamine on receptors could be responsible for the hypotensive effects. Blood pressure could be lowered by renal and mesenteric vasodilation or by loss of sodium (54). Duvoisin (46) observed that orthostatic hypotension produced by *l*-dopa could be attenuated by administration of *beta*-adrenergic blocking agents and suggested that activation of *beta*-adrenergic receptors might be responsible.

Despite the relatively common occurrence of orthostatic hypotension, therapy is not limited in most patients. Furthermore, tolerance apparently develops to this side effect in most patients (126, 192). Serious consequences however, could occur in patients with cerebral or coronary atherosclerosis.

3. Cardiac stimulation. Whitsett *et al.* (185, 187) reported that significant shortening of the externally recorded pre-ejection period (PEP) occurred in patients with Parkinson's disease after administration of 1 to 2 g of *l*-dopa. [PEP is derived from recordings of the carotid pulse contour, the second heart sound and the electrocardiogram (181).] Shortening of the PEP reflects positive inotropic effects and occurs after administration of *beta*-adrenergic agonists (83, 169). Maximal shortening of the PEP was recorded 30 to 60 min after administration of the drug and significant shortening persisted for approximately 120 min. This effect was not accompanied by significant alteration in heart rate or arterial blood pressure. Administration of 10 mg of propranolol, 45 min before ingestion of *l*-dopa, prevented the shortening of the PEP (186, 187).

Interestingly, the shortening of the PEP did not occur in patients treated with *l*-dopa for 3 months or longer (185, 187). Whitsett *et al.* (185, 187) demonstrated that the tolerance was not due to lack of responsiveness of the myocardium or to block of *beta*-adrenergic receptors, since both dopamine and epinephrine produced equivalent shortening of the PEP during initial weeks of therapy and after 3 months of continuous treatment. It is possible that the tolerance was related to decreased production of dopamine, for decreased activity of dopa decarboxylase has been demonstrated in rat liver (38a), mouse tissues and human erythrocytes (169a) after continuous *l*-dopa administration.

The action of *l*-dopa on the myocardium is not detrimental in most patients. However, increased episodes of arrhythmias have occurred in some individuals, most of whom had previous myocardial disease (104, 114, 192). More detailed

summaries of the adverse cardiovascular effects of *l*-dopa and suggestions for their prevention and treatment have been published (70, 104).

4. Effects on renal function. Finlay *et al.* (54) observed that after oral administration of 1 to 2 g of *l*-dopa to seven patients with Parkinson's disease, C_{PAH} increased from an average of 341.3 to 407.7 ml/min, C_{IN} from 78.7 to 85.7 ml/min, $U_{Na}V$ from 116 to 288.9 μEq/min, and U_KV from 50.9 to 71.4 μEq/min. Increase in $U_{Na}V$ also followed administration of *l*-dopa in three patients with congestive heart failure and one with hypertension. The natriuretic effect of *l*-dopa persisted for at least 150 min.

5. Potential new clinical applications of l-dopa. The above studies have clearly demonstrated that oral administration of *l*-dopa produces cardiac and renal actions similar to those resulting from intravenous infusions of dopamine. Accordingly, *l*-dopa is being investigated for the treatment of patients with congestive heart failure (54) and hypertension (9, 10, 11, 54, 170a). *l*-Dopa has also been studied experimentally in animals in shock (87, 119). In addition, as discussed in section VII G, *l*-dopa might find therapeutic application to replenish depleted norepinephrine stores.

Although *l*-dopa may have useful cardiovascular and renal actions, it is not an ideal means of administering dopamine orally. Extremely large doses are required, and the amount of dopamine generated is variable (170a). Furthermore, side effects such as anorexia, nausea and vomiting limit its use in many patients. Accordingly, investigations should be continued in hopes of finding a more suitable oral form of dopamine (17).

X. Possible Physiological Role of Dopamine Vascular Receptors

The discovery of vascular receptors which respond specifically to relatively small quantities of dopamine has led to numerous speculations concerning their possible physiological role. Dopamine has been found in relatively high concentration in the kidneys of several species (5, 81, 179) and it has been possible to demonstrate dopamine release from sympathetic nerves (170), the adrenal medulla (116) and carotid body tumor cells (115). Thus far, however, physiological dopamine-induced vasodilation has not been described. A recent attempt to produce renal vasodilation by sympathetic nerve stimulation was unsuccessful (44). Nevertheless, it is still possible that dopamine released within the kidney or mesenteric vascular beds might regulate local blood flow or be involved in the regulation of renin secretion as has been suggested by Barbeau *et al.* (9, 11) and Kuchel *et al.* (110).

Involvement of dopamine vascular receptors in a pathological process is also possible. Renal and mesenteric blood flow could be increased in patients with excessive dopamine levels (catecholamine-secreting tumors (4), *l*-dopa therapy). The opposite effect could occur in patients reported to excrete less dopamine than normal individuals [Parkinson's disease (9, 99, 100, 157), hypertension (159a)]. In this regard, lesions have been found in the sympathetic ganglia (174) of patients with Parkinson's disease and idiopathic orthostatic hypotension, but their relationship to dopamine has apparently not been explored.

XI. Conclusion

Cardiovascular and renal effects of dopamine result from actions on *alpha*- and *beta*-adrenergic receptors and on specific dopamine receptors in the renal and mesenteric vascular beds. In large doses, *alpha*-adrenergic vasoconstriction predominates and increased peripheral resistance and elevations of blood pressure result. In smaller doses, renal and mesenteric vasodilation predominate, and peripheral resistance and blood pressure decrease. Unique hemodynamic and renal effects are produced when dopamine is infused at low rates. Cardiac contractility and output increase, total peripheral resistance decreases and heart rate and blood pressure are not significantly changed. Renal blood flow, glomerular filtration rate and sodium excretion also increase. These hemodynamic and renal effects have led to clinical trials of dopamine for the treatment of shock, congestive heart failure, cirrhosis, oliguric renal failure and drug intoxication. Cardiovascular and renal effects of orally administered *l*-dopa are similar to those produced by intravenous infusion of dopamine, except that *l*-dopa may also exert a central hypotensive effect. Recognition of the cardiovascular and renal actions of *l*-dopa is important because of potential clinical applications and possible adverse effects in the parkinsonian patient.

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