Activation of Peripheral Dopamine Presynaptic Receptors
Lowers Blood Pressure and Heart Rate in Dogs

ADDISON A. TAYLOR, M.D., PH.D., WILLIAM H. FENNELL, M.D.,
MITCHELL B. FELDMAN, M.D., TEDD A. BRANDON, B.S.,
JAMES Z. GINOS, PH.D., AND JERRY R. MITCHELL, M.D., PH.D.

SUMMARY Previous studies have identified several N,N-dialkyl substituted analogs of dopamine that lower blood pressure and cause renal and femoral vasodilation by activation of noradrenergic neuronal dopaminergic receptors that inhibit further release of norepinephrine (presynaptic DA2) or of vasodilatory dopaminergic receptors located in vascular beds (postsynaptic DA1). Unlike dopamine itself, these analogs demonstrate minimal β1-adrenergic receptor activation and α1-vasoconstrictor effect. In the present study, we have compared the relative hemodynamic, renal and emetic properties of four of these dopamine analogs in anesthetized and/or conscious dogs. The purposes of the studies were: 1) determination of the relative contribution of central versus peripheral nervous system sites of action of these analogs to their effects on cardiovascular function; 2) assessment of the importance of activation of DA2 versus DA1 receptors for the observed hemodynamic effects; and 3) investigation of the relative efficacy of dopamine antagonists for DA2 versus DA1 receptors. The reduction in blood pressure, increase in renal blood flow, and decrease in renal vascular resistance produced by propylbutyl-(PBDA), ethylbutyl-(EBDA), or propylpentyl-(PPDA) dopamine was similar to that reported previously for dipropyldopamine (DPDA). All analogs except PPDA also lowered heart rate. Doses of either the peripheral dopamine receptor antagonist, domperidone, or the peripheral and central dopamine receptor antagonist, metoclopramide, which attenuated PBDA-induced reductions in mean arterial pressure and heart rate did not antagonize the increase in renal blood flow produced by this analog. Following electrical stimulation of the cardioaccelerator nerve, all four dopamine analogs reduced the heart rate of spinal transected, vagotomized, anesthetized dogs. In addition, (-)-sulpiride but not phentolamine antagonized the reduction in both heart rate and coronary sinus norepinephrine secretion produced by PBDA during cardioaccelerator nerve stimulation. In conscious dogs, the emetic potency was: DPDA > PPDA = PBDA > EBDA. The dopamine receptor antagonist, (-)-sulpiride, completely abolished the emesis induced by PBDA administration. These results indicate that PBDA and other N,N-dialkyl substituted dopamine derivatives can lower blood pressure primarily through agonism of presynaptic DA2 receptors rather than postsynaptic DA1 vascular receptors. (Hypertension 5: 226–234, 1983)

KEY WORDS • propylbutyldopamine • dopamine analogs • sulpiride • domperidone 
dopamine antagonists • postsynaptic dopamine receptors • renal blood flow
Limited structure activity studies, however, have indicated that N,N-dialkyl substitution of dopamine greatly changes the relative receptor activity of the analogs. Six of 17 N,N-disubstituted analogs given directly into the renal artery caused renal vasodilation that was antagonized by metoclopramide or sulpiride but not by propranolol; the six also produced femoral vasodilation that was inhibited by hexamethonium but not by propranolol after i.a. injection. However, they differed from dopamine in that they lacked \( \alpha \)-adrenergic activity and exerted weaker \( \beta \)-vasoconstrictor effects.

As a prelude to our administration of one of these agents to patients, additional studies with four of the six dopamine analogs were carried out in anesthetized and conscious dogs. We report herein a comparison of their relative hemodynamic, renal and emetic properties during continuous intravenous infusion; an examination of their peripheral versus central nervous system site and mechanism of action on cardiovascular function; an analysis of the relative importance of DA \( _2 \) versus DA \( _1 \) receptor activation for the hemodynamic effects; and an investigation of the preferential blockade of their effects on DA \( _2 \) versus DA \( _1 \) receptors by three dopamine antagonists.

**Materials and Methods**

**Hemodynamic Comparisons of N-Alkyl Substituted Dopamine Analogs in Anesthetized Dogs**

Adult mongrel dogs of both sexes weighing 8 to 18 kg were used in these studies. Animals were anesthetized with sodium pentobarbital, 30 mg/kg, i.v., intubated with a balloon-cuffed endotracheal tube and artificially ventilated on room air by a large animal respirator. A carotid artery was cannulated with silastic tubing and the tubing connected to a Statham P231D pressure transducer and Gould 200 series recorder for measurement of arterial pressure. An external jugular vein was cannulated for administration of fluids and drugs. Needle electrodes were placed on the limbs for continuous electrocardiographic monitoring of heart rate. Through a left flank incision a pulsed Doppler flow probe was placed snugly but without constriction around the left renal artery for measurement of renal blood flow by the technique described by Hartley et al. After obtaining control values for mean arterial pressure, heart rate, and renal blood flow, N-n-propyl-N-n-butyl (PBDA)-, N-n-ethyl-N-n-butyl (EBDA)-, or N-n-propyl-N-n-pentyl (PPDA)-dopamine was infused progressively at doses of 10, 20, and 40 \( \mu \)g/kg.

![Schematic diagram of a postganglionic sympathetic neuroeffector junction illustrating the pharmacologic distribution of \( \alpha \), \( \beta \), and dopamine receptors on sympathetic nerve terminals and selected effector organs outside the brain. DA \( _2 \) postsynaptic receptors that mediate vasodilation are not distributed ubiquitously but are located primarily on vessels in the renal and mesenteric beds. In contrast, the distribution of DA \( _2 \) presynaptic receptors on sympathetic nerve terminals is more widespread. Activation of DA \( _2 \) receptors, like \( \alpha \) receptors, inhibits subsequent exocytotic release of norepinephrine (NE) in response to propagation of an action potential along the nerve. Dopamine itself activates vascular \( \alpha \) receptors and cardiac \( \beta \) receptors as well as DA \( _1 \) and DA \( _2 \) receptors, whereas the N.N-dialkyl substituted analogs of dopamine used in the present studies (DPDA, PBDA, PPDA, and EBDA) appear to activate primarily DA \( _1 \) and DA \( _2 \) receptors. Agonist-antagonist interactions examined in the present and previous (see refs. 7–14) studies suggest that \(-\)-sulpiride antagonizes primarily DA \( _2 \) receptors whereas \(+\)-sulpiride (see ref. 25) antagonizes DA \( _1 \) receptors. Domperidone at doses of 0.5 mg/kg antagonizes DA \( _2 \) but not DA \( _1 \) receptors without significant penetration of the blood-brain barrier (see ref. 27). Metoclopramide, a dopamine receptor antagonist known to have central nervous system effects, antagonizes primarily DA \( _2 \) receptors at doses up to 40 \( \mu \)g/kg and both DA \( _1 \) and DA \( _2 \) receptors at doses \( \geq 145 \) \( \mu \)g/kg.**

![Diagram of sympathetic nerve varicosity, neuroeffector junction, and effector cell](http://hyper.ahajournals.org/)

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**Figure 1.** Schematic diagram of a postganglionic sympathetic neuroeffector junction illustrating the pharmacologic distribution of \( \alpha \), \( \beta \), and dopamine receptors on sympathetic nerve terminals and selected effector organs outside the brain. DA \( _2 \) postsynaptic receptors that mediate vasodilation are not distributed ubiquitously but are located primarily on vessels in the renal and mesenteric beds. In contrast, the distribution of DA \( _2 \) presynaptic receptors on sympathetic nerve terminals is more widespread. Activation of DA \( _2 \) receptors, like \( \alpha \) receptors, inhibits subsequent exocytotic release of norepinephrine (NE) in response to propagation of an action potential along the nerve. Dopamine itself activates vascular \( \alpha \) receptors and cardiac \( \beta \) receptors as well as DA \( _1 \) and DA \( _2 \) receptors, whereas the N.N-dialkyl substituted analogs of dopamine used in the present studies (DPDA, PBDA, PPDA, and EBDA) appear to activate primarily DA \( _1 \) and DA \( _2 \) receptors. Agonist-antagonist interactions examined in the present and previous (see refs. 7–14) studies suggest that \(-\)-sulpiride antagonizes primarily DA \( _2 \) receptors whereas \(+\)-sulpiride (see ref. 25) antagonizes DA \( _1 \) receptors. Domperidone at doses of 0.5 mg/kg antagonizes DA \( _2 \) but not DA \( _1 \) receptors without significant penetration of the blood-brain barrier (see ref. 27). Metoclopramide, a dopamine receptor antagonist known to have central nervous system effects, antagonizes primarily DA \( _2 \) receptors at doses up to 40 \( \mu \)g/kg and both DA \( _1 \) and DA \( _2 \) receptors at doses \( \geq 145 \) \( \mu \)g/kg.
min. Each dose was infused for 5 to 7 minutes before obtaining hemodynamic measurements although hemodynamic changes had usually stabilized within 2 to 3 minutes of increasing the dose. Renal vascular resistance was calculated by the following formula:

\[
\text{Renal vascular resistance (mm Hg} \cdot \text{ml}^{-1} \cdot \text{min}^{-1}) = \frac{\text{mean arterial pressure (mm Hg)}}{\text{renal blood flow (ml} \cdot \text{min}^{-1})}
\]

**Effects of Metoclopramide and Domperidone on PBDA- and EBDA-Induced Changes in Mean Arterial Pressure and Renal Blood Flow**

Adult mongrel dogs were anesthetized and prepared for experimentation as described above. Two different groups of experiments were performed. In each, measurements of arterial pressure, heart rate, and renal blood flow were made before and during the continuous infusion of either PBDA or EBDA in doses of 10, then 20, and finally 40 μg/kg/min for 5 to 7 minutes at each dose. The dopamine analog infusion was then discontinued and hemodynamic measurements repeated 10 minutes later. In one group of experiments, dogs were then given domperidone, 0.5 mg/kg by i.v. bolus, and the dose-hemodynamic response curve to the appropriate dopamine analog repeated 60 minutes later. In the second group of experiments, the hemodynamic response curve to the appropriate dopamine analog was repeated starting 5 minutes after i.v. bolus administration of the following doses of metoclopramide: 8, 40, 145, and 290 μg/kg.

**Effects of N-alkyl Substituted Dopamine Analogs on Cardiovascular Hemodynamics and Coronary Sinus Norepinephrine Secretion during Electrical Stimulation of the Cardioaccelerator Nerve**

Following pentobarbital anesthesia and endotracheal intubation of adult mongrel dogs as described above, the spinal cord was transected between the second and third cervical vertebrae. The vagus nerves were identified in the carotid sheath and transected. Both carotid arteries were occluded by double ligatures. A silastic catheter was placed in one carotid artery proximal to the occlusion for monitoring of arterial pressure. Another catheter was inserted into one external jugular vein for administration of drugs and fluids. In one subgroup of experiments, a National Institutes of Health (NIH) performed catheter was inserted into the other external jugular vein and, following a median sternotomy incision, was advanced through the right atrium and, under direct visualization, positioned deep in the coronary sinus. A pulsed Doppler flow probe was placed around the circumflex coronary artery for measurement of coronary blood flow. The right stellate ganglion was identified in the second intercostal space, freed of its rostral and caudal connections, and a bipolar platinum electrode attached to the cardioaccelerator nerve. Needle electrocardiographic leads were inserted in the four limbs for continuous recording of heart rate.

After a 30-minute stabilization period, during which extracellular fluid volume was expanded with 0.9% saline i.v. to prevent hypotension, control measurements of heart rate, mean and phasic arterial pressure and circumflex coronary blood flow were made. Coronary sinus blood was collected by timed gravity flow into chilled tubes containing 60 mg EGTA and 90 mg/ml reduced glutathione for subsequent determination of plasma norepinephrine. The cardioaccelerator nerve was then stimulated electrically by a Grass S-5 stimulator with a continuous train of 1.5 msec pulses of supramaximal voltage (usually 10 V) at a frequency of 2 to 5 Hz. This stimulus frequency was adjusted to produce an increase in heart rate above control values of 80 to 90 bpm. Preliminary experiments demonstrated no deterioration in the cardioaccelerator nerve-induced increase in heart rate during periods of continuous electrical stimulation for as long as 45 minutes. In one series of experiments, only hemodynamic parameters were monitored during the control period and during continuous electrical stimulation of the cardioaccelerator nerve before, during and after recovery from intravenous infusion of β-n-dipropyladrenaline (DPDA), PBDA, EBDA and PPDA each infused for 5 minutes at a dose of 20 and then 40 μg/kg/min.

In another series of experiments, the effects of PBDA at doses of 20 and 40 μg/kg/min on hemodynamics and on coronary sinus norepinephrine secretion were evaluated during continuous cardioaccelerator nerve stimulation. These studies were performed first with no pretreatment, then 5 minutes following pretreatment with phentolamine, 0.3 mg/kg i.v., and finally 5 minutes after pretreatment with an i.v. bolus of (-)-sulpiride, 0.1 mg/kg. Coronary sinus blood was kept on ice until the plasma could be separated by centrifugation and stored at −80°C until norepinephrine analysis was performed. Plasma norepinephrine was measured by the radioenzymatic method of DaPrada and Zurcher with only minor modifications. Coronary sinus norepinephrine secretion rates were calculated by multiplying the timed coronary sinus blood flow by the coronary sinus norepinephrine concentration.

**Emetic Potency of N-Alkyl Substituted Dopamine Analogs In Conscious Dogs**

Dogs used in these studies were trained to lie quietly on a mat on the floor of the laboratory. On the day of an experiment, food was withheld until the completion of the study. A polyethylene catheter was inserted into the greater saphenous vein via percutaneous needle puncture for administration of fluids and drugs. One of the four dopamine analogs to be tested (PBDA, EBDA, PPDA or DPDA) was dissolved in sterile 5% dextrose in water and infused continuously at progressively higher doses (10, 20 and 40 μg/kg/min) for 5 to 7 minutes at each dose or until emesis was observed. Each dog was allowed at least 30 minutes to recover...
from the effects of one analog before receiving another. In one subgroup of experiments, animals were pretreated with the dopamine receptor antagonist, (−)-sulpiride hydrochloride (dissolved in 0.9% saline), as an intravenous bolus 5 minutes before the i.v. infusion of PBDA in progressively larger doses up to 40 μg/kg/min.

Drug Preparation

N-n-propyl-N-n-butyl dopamine hydrochloride, N-n-propyl-N-n-pentyl dopamine hydroiodide, N-n-ethyl-N-n-butyl-dopamine hydrochloride and N,N-n-dipropylpamino dopamine hydrochloride were synthesized by methods described previously.20 All analogs were dissolved in 5% dextrose in water for administration. Domperidone hydrochloride (generously supplied by Janssen Pharmaceuticals, New Brunswick, New Jersey) was dissolved in ethylene glycol, 0.1 mg/ml by stirring, and further diluted in warm (50°C) 0.9% saline to a concentration of 0.5 mg/ml before administration. (−)-Sulpiride hydrochloride (generously provided by Laboratories DeLagrange, Paris, France) was dissolved in warm 0.9% saline before administration.21 Metoclopramide hydrochloride (Reglan®) was obtained commercially in a solution of 2 mg/ml and was diluted with 0.9% saline before administration.

Statistical Analysis

Group or paired data were analyzed by standard parametric or nonparametric statistical tests as appropriate using a modification of the SPSS statistical package available on the PROPHET computer network.

Results

Hemodynamic Comparisons of N-Alkyl Substituted Dopamine Analogs in Anesthetized Dogs

The hemodynamic effects of PBDA, EBDA, and PPDA on mean arterial pressure, heart rate, renal blood flow, and renal vascular resistance in anesthetized dogs (fig. 2) were qualitatively similar to those reported previously by Fennell et al.9 for DPDA. Blood pressure was lowered similar amounts by the same doses of PBDA in the present study and by DPDA in a previous study9 (−13% ± 3.4% and −12% ± 2.3% respectively, at infusion rates of 40 μg/kg/min) whereas PPDA produced a consistently greater and EBDA a smaller hypotensive response at each dose than did PBDA or DPDA. All dopamine analogs except PPDA lowered heart rate in a dose-dependent manner. Each of the four analogs increased renal blood flow and decreased renal vascular resistance in a dose-dependent manner (fig. 2).9

![Figure 2](https://hyper.ahajournals.org/)

**Figure 2.** Effect of propylbutyldopamine (PBDA, n = 6), ethylbutyldopamine (EBDA, n = 5), and propylpentyldopamine (PPDA, n = 4) infused at 0 (C), 10, 20, and 40 μg/kg/min on heart rate, mean arterial pressure, renal blood flow, and renal vascular resistance in anesthetized dogs. Values are means ± SEM.
TABLE 1. Effect of Domperidone on PBDA- and EBDA-Induced Changes in Cardiovascular Hemodynamics in Anesthetized Dogs (n = 6)

<table>
<thead>
<tr>
<th>Analog dose (μg/kg/min)</th>
<th>Control</th>
<th>Domperidone*</th>
<th>Control</th>
<th>Domperidone</th>
<th>Control</th>
<th>Domperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>112 ± 16.7</td>
<td>95 ± 13.6</td>
<td>100 ± 16.7</td>
<td>155 ± 17.4</td>
<td>151 ± 5.9</td>
<td></td>
</tr>
<tr>
<td>Renal blood flow (ml/min)</td>
<td>124 ± 8.2</td>
<td>71 ± 10.5</td>
<td>72 ± 8.0</td>
<td>155 ± 20.6</td>
<td>143 ± 18.3</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>155 ± 17.4</td>
<td>152 ± 19.4</td>
<td>153 ± 9.8</td>
<td>124 ± 14.1</td>
<td>128 ± 24.1</td>
<td></td>
</tr>
</tbody>
</table>

*Domperidone dose = 0.5 mg/kg i.v.

Effects of Domperidone and Metoclopramide on Dopamine Analog-Induced Changes in Mean Arterial Pressure, Renal Blood Flow, and Heart Rate

Domperidone at doses of 2.5 mg/kg or less acts primarily as an antagonist of peripheral dopamine receptors since i.v. or oral administration of the drug at these low doses does not lead to significant accumulation in the brain. Domperidone at a dose of 0.5 mg/kg i.v. appeared to antagonize the reduction in mean arterial pressure (p < 0.07) and heart rate (p < 0.08) produced by infusions of PBDA when the changes from control to 40 μg/kg/min before and after domperidone were compared. Similar effects of domperidone on EBDA-induced changes in mean arterial pressure (p < 0.01) and heart rate (p < 0.06) were observed. In contrast, this dose of domperidone had much less antagonistic effect on the dose-related increase in renal blood flow associated with infusion of either PBDA (p > 0.4) or EBDA (p > 0.8) (table 1).

Pretreatment of anesthetized dogs with metoclopramide at doses of 40 μg/kg or greater (table 2) resulted in attenuation of the dose-dependent reduction in mean arterial pressure and heart rate.

TABLE 2. Effect of Metoclopramide on PBDA-Induced Changes in Cardiovascular Hemodynamics in Anesthetized Dogs (n = 5)

<table>
<thead>
<tr>
<th>PBDA dose (μg/kg/min)</th>
<th>Control</th>
<th>8 μg/kg</th>
<th>40 μg/kg</th>
<th>145 μg/kg</th>
<th>290 μg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>133 ± 6.1</td>
<td>132 ± 5.3</td>
<td>133 ± 8.8</td>
<td>132 ± 8.0</td>
<td>145 ± 9.8</td>
</tr>
<tr>
<td>Renal blood flow (ml/min)</td>
<td>75 ± 5.6</td>
<td>80 ± 9.5</td>
<td>82 ± 15.2</td>
<td>85 ± 14.1</td>
<td>98 ± 24.2</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>183 ± 9.6</td>
<td>184 ± 6.0</td>
<td>180 ± 7.2</td>
<td>173 ± 13.0</td>
<td>161 ± 10.8</td>
</tr>
</tbody>
</table>

Values are group means ± SEM.

*p < 0.05 for paired data compared to corresponding 0 μg/kg/min dose.
arterial pressure (p < 0.09) and, to a lesser extent, heart rate (p = 0.18) produced by infusion of PBDA, whereas metoclopramide doses of 290 μg/kg were required to even partially antagonize (p = 0.12) PBDA-induced increases in renal blood flow (table 2).

Effects of N-Alkyl Substituted Dopamine Analogs on Cardiovascular Hemodynamics and Coronary Sinus Norepinephrine Secretion during Electrical Stimulation of the Cardioaccelerator Nerve

Figure 3 illustrates the effect of dopamine analog infusion on heart rate increased by 48% to 58% above control values during continuous electrical stimulation of the cardiovascular nerve in spinally transected, vagotomized dogs. Each of the four dopamine analogs had qualitatively and quantitatively similar effects in this preparation. The heart rate was reduced 10% to 14% during infusion of each of the analogs at 20 μg/kg/min, whereas a dose of 40 μg/kg/min reduced the heart rate 18% to 24% compared to values during nerve stimulation alone. These dose-dependent reductions in heart rate were all statistically significant (p < 0.05). Within 5 minutes of discontinuing infusion of the dopamine analog, the heart rates returned to preinfusion nerve-stimulated values (fig. 3).

The effects of PBDA infusion at 20 and 40 μg/kg/min on cardioaccelerator nerve-stimulated heart rate in a second group of five dogs (fig. 4) were similar to those obtained during the first series of experiments (fig. 3). Phentolamine, 0.3 mg/kg i.v., increased heart rate slightly above values observed during cardioaccelerator nerve stimulation alone (fig 4) but did not significantly affect the dose-dependent reduction in heart rate produced by PBDA. In contrast, (−)-sulpiride itself had no significant effect on nerve-stimulated heart rate but markedly attenuated the reduction in heart rate produced by PBDA infusion (fig. 4).

Changes in coronary sinus norepinephrine secretion (fig. 5, top panel) induced by PBDA infusion during cardioaccelerator nerve stimulation before and after pretreatment with either phentolamine or (−)-sulpiride paralleled the observed changes in heart rate during these manipulations (fig. 5, middle panel). In the spinally transected, vagotomized dog preparation the changes in both heart rate and coronary sinus norepinephrine secretion were largely independent of changes in mean aortic pressure (fig. 5, bottom panel).

![Figure 3](http://hyper.ahajournals.org/)

**Figure 3.** Heart rate of anesthetized dogs in the control state (C) compared to values obtained during continuous electrical stimulation of the cardioaccelerator nerve (N) before, during (D20 and D40), and after infusion of 4 N,N-dialkyl substituted dopamine analogs at rates of 20 and 40 μg/kg/min. Values are means ± sem. PBDA = propylbutyldopamine (n = 6); DPDA = dipropylldopamine (n = 5); PPDA = propylpentyldopamine (n = 4); EBDA = ethylbutyldopamine (n = 4).
Emetic Potency of N-Alkyl Substituted Dopamine Analogs in Conscious Dogs

The emetic properties of different infusion rates of each of the four N-alkyl substituted dopamine analogs were examined in the conscious dog (table 3). None of the four analogs caused emesis at an infusion rate of 10 μg/kg/min. At a dose of 20 μg/kg/min, emesis was observed in 56% of the dogs receiving DPDA but only 9% of the dogs given PBDA. Emesis occurred in 83% of dogs given DPDA at a dose of 40 μg/kg/min, whereas emesis was observed in 55% of dogs at this same dose of PBDA. Chi-Square analysis revealed a significantly greater incidence of emesis during DPDA than PBDA administration (p < 0.05). No emesis was observed in dogs receiving PPDA or EBDA at a dose of 20 μg/kg/min, whereas a dose of 40 μg/kg/min was

<table>
<thead>
<tr>
<th>Dose (μg/kg/min)</th>
<th>PBDA</th>
<th>DPDA</th>
<th>PPDA</th>
<th>EBDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0/22*</td>
<td>0/9</td>
<td>0/6</td>
<td>0/10</td>
</tr>
<tr>
<td>10</td>
<td>0/20</td>
<td>0/6</td>
<td>0/6</td>
<td>0/8</td>
</tr>
<tr>
<td>20</td>
<td>2/22 (9%)*</td>
<td>5/9 (56%)</td>
<td>0/6</td>
<td>0/10</td>
</tr>
<tr>
<td>40</td>
<td>6/11 (55%)</td>
<td>5/6 (83%)</td>
<td>4/6 (66%)</td>
<td>3/10 (33%)</td>
</tr>
<tr>
<td>10 + (-) - Sulpiride‡</td>
<td>0/6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 + (-) - Sulpiride‡</td>
<td>0/6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 + (-) - Sulpiride‡</td>
<td>0/4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values represent number of dogs with emesis/all dogs who received that dose.
†Significantly different from DPDA at p < 0.05 by chi square analysis.
‡Pretreatment of the dog with (-) - sulpiride, 0.05 mg/kg i.v., 5 minutes prior to starting the dopamine analog infusion.
§Significantly different from emetic effect of PBDA, 40 μg/kg/min, alone: p < 0.05 by Fisher Exact Test.
(%)Percentage of dogs given the analog in which emesis occurred.
PERIPHERAL DOPAMINE PRESYNAPTIC RECEPTORS/Taylor et al.

FIGURE 5. Coronary sinus norepinephrine secretion (top panel), heart rate (middle panel), and mean arterial pressure (bottom panel) during continuous electrical stimulation of the cardioacceleratory nerve (N) of anesthetized dogs before, during, and after infusion of PBDA at 20 (D20) and 40 (D40) μg/kg/min. Values are means ± SEM.

emetic in 66% and 30% respectively, of the dogs given these two analogs. Pretreatment of six dogs with emesis at 40 μg/kg/min PBDA with the dopamine receptor antagonist, (−)-sulpiride, at a dose of 0.05 mg/kg completely abolished the emesis when the dogs were rechallenged with the same dose of PBDA (p < 0.04, by Fisher Exact Test).

Discussion

Recent investigation of the structure activity relationships of dopamine has led to the identification of a group of N,N-dialkyl derivatives of dopamine with relatively little β,-adrenergic agonist action and no α1- adrenoreceptor stimulation. 7-10, 22, 23 These compounds have appeal both as pharmacologic probes for identifying those dopamine receptors that participate in the normal and abnormal control of cardiovascular function and as potential therapeutic agents for the treatment of hypertension and congestive heart failure. 15, 16

In previous studies administration to anesthetized dogs or cats of N,N-dialkyl dopamine analogs containing alkyl moieties larger than methyl substituents 9-12 resulted in a lowering of blood pressure which was not antagonized by propranolol or by phenoxbenzamine but which was inhibited by prior ganglionic blockade or by sulpiride and haloperidol, dopamine receptor antagonists with prominent peripheral and central nervous system effects. 24 In the present study the blood pressure-lowering effects of PBDA were also antagonized by metoclopramide, a central and peripheral dopamine receptor antagonist 25, 26 as well as by domperidone, a compound that antagonizes principally peripheral dopamine receptors in vivo in the doses used in this study. 27, 28 probably due to poor penetration of the blood-brain barrier. This finding indicates that the hypotensive effect of PBDA occurs mainly through activation of peripheral dopamine receptors.

Unlike direct-acting vasodilators such as nitroprusside and hydralazine, the N,N-dialkyl-substituted dopamine analogs lower blood pressure without producing reflex tachycardia; in fact, several of these compounds reduce heart rate (fig. 2). 9-12 They share with dopamine the characteristic of increasing renal blood flow and reducing renal vascular resistance (fig. 2). 6, 9, 10

The demonstration in spinally transected, vagotomized dogs that each of the dopamine analogs (PBDA, DPDA, EBDA, and PPDA) is approximately equipotent in reducing the cardioacceleratory nerve-stimulated increases in heart rate, supports the view that the peripheral nervous system site of action is the presynaptic DA2 adrenergic receptor. Additional studies (fig. 4) demonstrate that the PBDA-induced decreases in heart rate and coronary sinus norepinephrine secretion during continuous cardioacceleratory nerve stimulation are antagonized by (−)-sulpiride but not by phentolamine. These data therefore provide further physiologic, biochemical and pharmacologic support, respectively, for the existence of inhibitory presynaptic DA2 receptors on peripheral noradrenergic neurons in the dog heart and for their activation by PBDA. The failure of vagotomy to alter the bradycardic effect of PBDA (fig. 2)12 indicates that these analogs do not decrease heart rate by activation of cardiac parasympathetic nerves in the dog.

The absence of inhibition of the PBDA-induced increase in renal blood flow by either domperidone or metoclopramide at doses which blocked PBDA-induced decreases in blood pressure, excludes the possibility that DA2-mediated renal vasodilation plays a significant role in the fall in blood pressure produced by PBDA administration. The lack of antagonism of DA1 receptors by doses of metoclopramide up to 145 μg/kg in the present study is not inconsistent with reports that metoclopramide does antagonize DA1 receptors on peripheral noradrenergic neurons when given in comparable doses directly into the renal artery 7 or when given intravenously, but in much higher doses (1000–10,000 μg/kg). 29 The finding of a dose-dependent antagonism of DA1 versus DA2 receptors by metoclopramide suggests that the affinity of this dopamine antagonist for the DA2 receptor is greater than that for the DA1 receptor.
The results of the present study differ somewhat from those reported by Hamed et al., for PBDA. In dogs in which heart rate was increased by cardioaccelerator nerve stimulation, the bradycardic action of PBDA was partially antagonized by both phenolamine and yohimbine. The two studies are not entirely comparable since Hamed and colleagues examined the effects of PBDA on heart rate in the dog not only at a dose (20 µg/kg) comparable to those used in the present studies but also at 80 µg/kg/min, a dose associated with significant α-adrenergic agonist action (Fennell and Taylor, unpublished observations). Thus, it is not surprising that a portion of the bradycardic effect of this large dose of PBDA might result from α₁-agonism and therefore be antagonized by phenolamine. In addition, their report of partial antagonism by yohimbine of the PBDA-induced reduction in cardioaccelerator nerve stimulated increases in heart rate might be explained by the antidopaminergic activity of yohimbine rather than by α₁-adrenoceptor antagonism.

Finally, an important prerequisite to the testing of any dopamine analog in man is its potency in producing vomiting. The mechanism of the emesis induced by the dopamine analogs apparently is the same as that seen with apomorphine, since the emesis is induced by specific dopamine receptor antagonists. The order of emetic potency with the analogs is: DPDA > PPDA = PBDA > EBDA (table 3). However, the hemodynamic effects of EBDA and PPDA (fig. 1) were less optimal than those for PBDA or DPDA. Because the doses of DPDA that resulted in significant reductions in blood pressure and heart rate and increases in renal blood flow in the anesthetized dog were associated with a substantial incidence of emesis (table 3), PBDA would appear to be the optimal choice among these dopamine analogs for further testing in man.

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