

# Depression of Ventilation by Dopamine in Man

## EVIDENCE FOR AN EFFECT ON THE CHEMORECEPTOR REFLEX

MICHAEL J. WELSH, DONALD D. HEISTAD, and FRANCOIS M. ABOUD, *Cardiovascular Division and the Department of Internal Medicine, Cardiovascular Center, University of Iowa College of Medicine; and the Veterans Administration Hospital, Iowa City, Iowa 52242*

**ABSTRACT** Dopamine is present in the carotid body and has been postulated to be an inhibitory neurotransmitter. The purpose of this study was to determine the effects of dopamine on ventilation in man and to examine its mechanism of action. Dopamine (0.5–10  $\mu\text{g/kg}$  per min) was infused in eight normal men at different levels of arterial chemoreceptor activity, produced by varying the inspired  $\text{PO}_2$ . During normoxia dopamine produced a small decrease in minute ventilation ( $\dot{V}_E$ ) and an increase in arterial  $\text{PCO}_2$ . When arterial chemoreceptors were stimulated by hypoxia, infusion of dopamine produced a marked initial depression of  $\dot{V}_E$  followed by a sustained although less pronounced decrease in  $\dot{V}_E$ . An increase in  $\text{PA}_{\text{CO}_2}$  and a decrease in  $\text{PaO}_2$  were also observed. When arterial chemoreceptor activity was suppressed by hyperoxia, infusion of dopamine did not affect ventilation. Subjects also breathed a hypercarbic, hyperoxic gas mixture. The hypercarbia produces hyperventilation by stimulating central chemoreceptors, whereas the hyperoxia suppresses peripheral chemoreceptors. Dopamine did not alter ventilation while the subjects were breathing this gas mixture.

These studies suggest that dopamine suppresses ventilation in man through an action on the arterial chemoreceptor reflex. These findings support the hypothesis that dopamine is an inhibitory neurotransmitter in the carotid body, and that release of dopamine may modulate the sensitivity of peripheral arterial chemoreceptors.

### INTRODUCTION

The carotid body chemoreceptors are important regulators of ventilation in man (1). Dopamine and other catecholamines have been found in the carotid body of man and animals (2–7) and it has been proposed that the re-

lease of dopamine in the carotid body may suppress the sensitivity of the chemoreceptor nerve endings (8–11).

Physiologic studies of the function of dopamine in the carotid body have been performed in the cat and dog. In the cat dopamine produces a decrease in carotid body neural output and a depression of ventilation (12, 13). However, in the dog dopamine has been reported to stimulate ventilation (12, 14). In light of this species difference, it is important to determine the effect of dopamine on ventilation in man. There are no studies that have examined the role of dopamine in modulation of the arterial chemoreceptor reflex in man.

The present experiments were done to test the hypothesis that dopamine inhibits the chemoreceptor reflex and depresses ventilation in man. We postulated that the depression of ventilation by dopamine might be related to the level of chemoreceptor activity. Therefore, dopamine was infused intravenously while subjects breathed: room air; hypoxic gas mixtures, during which chemoreceptor activity is increased; and 100% oxygen, which suppresses arterial chemoreceptor activity (15).

In addition, responses were observed while subjects breathed hypercarbic hyperoxic gas mixtures. Hypercarbia produces hyperventilation by stimulation of central medullary chemoreceptors (16), and hyperoxia suppresses the activity of peripheral arterial chemoreceptors (15). We postulated that if the effect of dopamine were mediated through depression of the peripheral chemoreceptor reflex, the infusion of dopamine to subjects breathing this gas mixture would not alter ventilation. On the other hand, if the depressant effect of dopamine were a nonspecific effect related to hyperventilation, infusion of dopamine would depress ventilation.

We also attempted to determine whether alpha or beta adrenergic receptors contribute to the ventilatory effects of dopamine. Responses to infusion of dopamine

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during hypoxia were observed after administration of the beta adrenergic blocker, propranolol, and during the infusion of the alpha adrenergic blocking agent, phentolamine.

## METHODS

Eight healthy men, ages 19–25 yr, were studied. Approval of the Human Experimentation Committee (University of Iowa College of Medicine) and informed consent were obtained. A venous catheter was inserted in the basilic vein and connected to a syringe and Harvard pump (Harvard Apparatus Co., Inc., Millis, Mass.) for infusion of drugs. In three subjects another venous catheter was inserted for simultaneous infusion of phentolamine. A small polyethylene catheter was inserted percutaneously into the brachial artery. The catheter was connected to a pressure transducer for continuous recording of arterial pressure and to a syringe for obtaining blood samples. Heart rate was obtained from a cardi tachometer.  $PO_2$  and  $PCO_2$  of arterial blood were measured with an IL Ultra-micro gas analyzer (Instrumentation Laboratory, Inc., Lexington, Mass.). The  $O_2$  electrode was calibrated at 0 and 84 mm Hg, and the  $CO_2$  electrode was calibrated at 35 and 70 mm Hg.

The subjects were studied while supine. They breathed through a one-way low resistance Douglas valve. Expired gas was measured in a Tissot spirometer which was adapted to allow continuous recording of volume. Percent  $CO_2$  of expired air was monitored continuously with a Beckman LB-1  $CO_2$  analyzer (Beckman Instruments, Inc., Cedar Grove, N. J.). The gas removed by the  $CO_2$  analyzer was reintroduced into the expiratory line to avoid loss of volume.

Measurements were made before and during infusion of a "low dose" (0.5–2.5  $\mu\text{g}/\text{kg}$  per min) and a "high dose" (5  $\mu\text{g}/\text{kg}$  per min) of dopamine. Two subjects received an infusion of 10  $\mu\text{g}/\text{kg}$  per min of dopamine. The order of infusion was low dose first in one-half of the subjects and high dose first in the other half of the subjects.

The infusions of dopamine were given while subjects breathed: (a) room air; (b) 10% oxygen in nitrogen; (c) 100% oxygen; and (d) 5% carbon dioxide in 95% oxygen. The order of the four gas mixtures were randomized, and 10–20 min were allowed for recovery between each test period. The hypocapnia produced by breathing 10% oxygen was prevented by adding carbon dioxide to the inspired gas as described (17). After the flow rate of carbon dioxide was adjusted to maintain end-tidal  $CO_2$  at the control level, the rate was not altered during infusion of dopamine.

Before the measurements were made the subjects breathed the carbon dioxide in oxygen gas mixture for 10 min and the other gas mixtures for 4–5 min. The gas mixture was then continuously inhaled during the control measurements and during the infusion of the two doses of dopamine. Expired minute volume was then measured for 3 min and arterial blood gases were obtained in the middle of this period to provide control measurements. Dopamine was then infused for a total of 5 min while the subjects continued to breathe the same gas mixture. During the first 2 min the maximum decrease in ventilation was determined from the slope of the line inscribed by the recording Tissot. Minute volume was then measured with the Tissot spirometer from the 3rd to 5th min of the infusion and averaged to give the "sustained" response of minute volume to dopamine infusion. This period from the 3rd to 5th min appears to be a steady-state response because there was no significant difference between minute volume measured at the 3rd, 4th, or 5th min. Arterial blood samples were obtained  $\approx 4$  min after the start of the infusion. After stopping

the infusion of dopamine, 3 min were allowed for the drug effect to subside and then a second control measurement was made. The other dose of dopamine was then infused and the response was measured as described above.

In five subjects 8 mg of propranolol was injected intravenously in 5 min. This dose of propranolol blocks the ventilatory response to isoproterenol but does not change the ventilatory response to hypoxia (18). After 5 min, subjects began breathing 10% oxygen (isocapnic hypoxia was achieved as described above) and the response to dopamine was observed. In three other subjects the response to dopamine during isocapnic hypoxia was measured during an intravenous infusion of phentolamine tosylate at a dose of 0.5 mg/min. This dose of phentolamine blocks the decrease in ventilation produced by phenylephrine (18).

Measurements during infusion of dopamine were compared to measurements taken during the immediately preceding control period with a paired *t* test. Responses to the different doses of dopamine were compared with a two-factor analysis of variance (19).

## RESULTS

*Normoxia.* Dopamine depressed ventilation while subjects breathed room air (Table I). Minute ventilation decreased and arterial  $PCO_2$  increased during infusion of dopamine. During the control period, arterial  $PaO_2$  was  $92 \pm 3.5$  mm Hg (mean  $\pm$  SE) and it decreased  $10 \pm 2.9$  and  $7 \pm 3.8$  mm Hg during low and high dose dopamine, respectively ( $P < 0.05$  for each dose).

Mean arterial pressure was  $89 \pm 1.5$  mm Hg and did not change during either dose of dopamine. Heart rate was unchanged during low dose dopamine and increased from  $60 \pm 2.8$  beats/min during the control period to  $69 \pm 1.5$  beats/min with high dose dopamine ( $P < 0.05$ ).

*Normocapnic hypoxia.* In subjects breathing 10% oxygen,  $PaO_2$  decreased to  $40 \pm 2.4$  mm Hg and minute volume increased almost twofold as compared to normoxia. However,  $PaCO_2$  was maintained unchanged by addition of  $CO_2$  to the inspired gas mixture.

Dopamine consistently depressed ventilation during hypoxia (Fig. 1, Table I). During infusion of dopamine there was significant decrease in minute ventilation and increase in  $PaCO_2$ . The early response to infusion of dopamine always exceeded the sustained decrease in ventilation. The maximum decrease in minute ventilation observed with infusion of 5  $\mu\text{g}/\text{kg}$  per min of dopamine was significantly greater than that observed with doses of 0.5 and 1.0  $\mu\text{g}/\text{kg}$  per min ( $P < 0.05$ ).

Dopamine accentuated the degree of hypoxia, as a further reduction in  $PaO_2$  of  $6 \pm 1.8$  mm Hg and  $5 \pm 1.4$  mm Hg was observed with infusion of low and high dose dopamine, respectively ( $P < 0.05$ ). There was no change in arterial pressure with infusion of dopamine. Heart rate was  $86 \pm 7.7$  beats/min during hypoxia, and did not change during low dose dopamine, and increased  $4 \pm 1.4$  beats/min with infusion of high dose dopamine.

*Normocapnic hypoxia with alpha or beta adrenergic*

TABLE I  
Effects of Dopamine on Ventilation

	Minute ventilation									
	Dopamine-low dose						Dopamine-high dose			
	Control 1	Maximum response	Sustained response	Control 2	Maximum response	Sustained response	PCO <sub>2</sub>			
liter/min						mm Hg				
Normoxia (n = 8)	7.5 ±0.7	-1.5‡ ±0.4	-0.8‡ ±0.2	8.0 ±1.0	-1.5‡ ±0.3	-0.4 ±0.2	34.3 ±1.3	+1.8‡ ±0.5	37.4 ±1.9	+1.4‡ ±0.7
Normocapnic hypoxia (n = 8)	14.7 ±1.0	-3.6‡ ±0.9	-1.4‡ ±0.3	14.6 ±1.2	-6.1‡ ±0.8	-2.0‡ ±0.3	34.3 ±1.7	+1.5‡ ±0.7	35.1 ±1.5	+3.6‡ ±0.6
Hypercarbia and hyperoxia (n = 5)	24.1 ±3.3	+1.2 ±1.0	+0.9 ±0.5	25.3 ±2.9	+2.1 ±1.0	+1.7 ±0.8	40.4 ±2.2	+0.2 ±1.1	41.2 ±2.1	-1.6 ±1.2
Hyperoxia (n = 7)	8.4 ±0.7	-0.3 ±0.3	-0.2 ±0.4	8.4 ±0.7	-0.2 ±0.2	-0.2 ±0.2	32.9 ±1.4	+0.4 ±0.5	35.2 ±2.4	-0.3 ±0.4

\* The maximum response and sustained response refer to the change in minute ventilation during infusion of dopamine compared to the preceding control value. Dopamine-low dose refers to a dose of 0.5–2.5 μg/kg per min, and dopamine-high dose refers to an infusion of 5 μg/kg per min dopamine. Values are expressed as mean ± SE.

‡ Indicates that response represents a statistically significant change from the control value ( $P < 0.05$ ).

*blockade.* Administration of phentolamine did not alter the ventilatory response to dopamine during hypoxia in three subjects. Minute ventilation during the

control period was  $15.4 \pm 1.3$  liter/min and  $PA_{CO_2}$  was  $34 \pm 0.8$  mm Hg. The sustained decreases in minute ventilation with low and high dose dopamine were  $-1.0 \pm 0.2$  liter/min and  $-2.4 \pm 0.5$  liter/min respectively before phentolamine, and  $-1.0 \pm 0.5$  liter/min and  $-2.4 \pm 0.1$  liter/min after phentolamine. The corresponding changes in  $PaCO_2$  were  $+0.3 \pm 0.7$  mm Hg and  $+3.7 \pm 0.7$  mm Hg before phentolamine and  $+0.7 \pm 0.3$  mm Hg and  $+2.3 \pm 0.9$  mm Hg after phentolamine.

Similarly, beta adrenergic blockade in five subjects did not change the ventilatory response to dopamine during hypoxia. Minute ventilation during the control period was  $13.4 \pm 0.9$  liter/min and  $PaCO_2$  was  $35.8 \pm 1.3$  mm Hg. The sustained decreases in minute ventilation with low and high dose dopamine were  $-1.8 \pm 0.4$  liter/min and  $-1.9 \pm 0.3$  liter/min respectively before propranolol, and  $-1.9 \pm 0.3$  liter/min and  $-1.7 \pm 0.2$  liter/min after propranolol. The corresponding changes in  $PaCO_2$  were  $+2.7 \pm 0.9$  mm Hg and  $+3.6 \pm 0.9$  mm Hg before propranolol and  $+2.7 \pm 0.7$  mm Hg and  $+3.2 \pm 0.9$  mm Hg after propranolol.

There was no change in arterial pressure with administration of dopamine after either blocker. Heart rate did not change during infusion of dopamine after the adrenergic blockers, except an increase of  $14 \pm 2.0$  beats/min was observed with administration of high dose dopamine during phentolamine.

*Hypercarbia and hyperoxia.* Subjects breathing 5% carbon dioxide in 95% oxygen showed the expected increase in  $PaCO_2$ , increase in  $PaO_2$  to  $>400$  mm Hg in all subjects, and marked increase in minute ventilation (Table I). There were no significant changes in

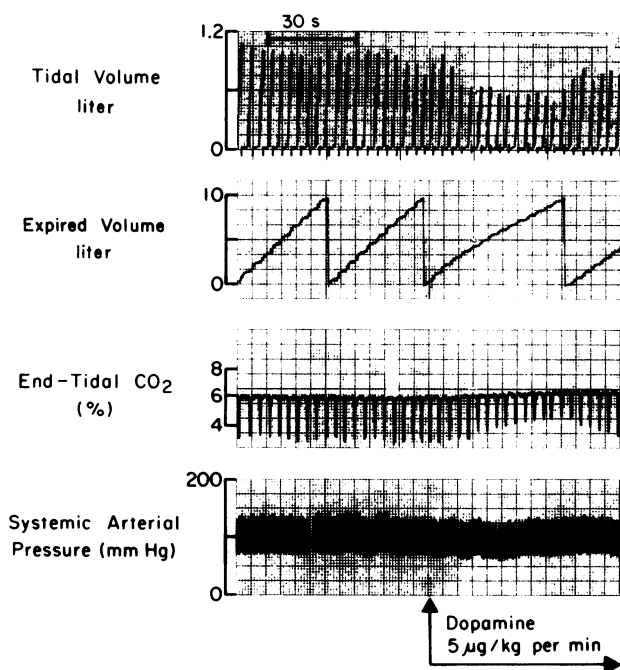


FIGURE 1 The ventilatory response to infusion of dopamine during normocapnic hypoxia. Inspiratory flow was measured with a Fleisch pneumotachograph and integrated to give tidal volume for purposes of illustration. Expired volume was recorded directly from a Tissot spirometer.

PaCO<sub>2</sub> or minute ventilation during the administration of dopamine. Heart rate and arterial pressure did not change with dopamine infusion.

**Hyperoxia.** While the subjects breathed 100% oxygen, there was no change in minute volume or PaCO<sub>2</sub> during infusion of dopamine (Table I). Arterial PO<sub>2</sub> was >400 mm Hg in all subjects. Mean arterial pressure was 96±3.0 mm Hg and increased 4.5±0.5 mm Hg ( $P < 0.05$ ) during infusion of the low dose of dopamine, but did not change during infusion of high dose dopamine. The heart rate was 64±5.5 beats/min and increased 6.6±2.4 beats/min during infusion of the high dose of dopamine.

**Response to dopamine 10 µg/kg per min.** Dopamine was infused at a rate of 10 µg/kg per min in two subjects during normoxia and hypoxia. During normoxia, infusion of dopamine tended to increase minute volume (0.1 and 2.0 liter/min) and PaCO<sub>2</sub> did not change. During hypoxia infusion of dopamine produced a sustained decrease in minute ventilation (-1.1 and -0.5 liter/min) and increase in PaCO<sub>2</sub> (6 and 2 mm Hg). After administration of propranolol, infusion of dopamine in hypoxic subjects decreased minute ventilation (2.1 liter/min in both subjects) and increased PaCO<sub>2</sub> (6 and 3 mm Hg).

## DISCUSSION

The present studies indicate that infusion of low doses of dopamine suppresses ventilation in man. When arterial chemoreceptor activity was increased by hypoxia, dopamine depressed ventilation. During normoxia, infusion of dopamine produced less suppression of ventilation. When arterial chemoreceptors were suppressed by breathing 100% oxygen, infusion of dopamine did not change ventilation. This relationship between the degree of suppression of ventilation and the level of chemoreceptor activity suggests that the depressant effect of dopamine on ventilation is mediated through an effect on the chemoreceptor reflex.

We considered the possibility that dopamine might depress ventilation in a nonspecific manner, whenever hyperventilation is present. To investigate this possibility, the ventilatory effect of infusion of dopamine was observed during hyperventilation produced by breathing an increased concentration of carbon dioxide in oxygen. Hypercarbia stimulates ventilation predominantly through an effect on the central medullary chemoreceptors (16) but also tends to stimulate the carotid bodies (20). When hyperoxia is combined with hypercarbia, the subjects hyperventilate while the peripheral chemoreceptors are suppressed. It has been shown that at a high level of PO<sub>2</sub>, neural output from peripheral chemoreceptors is minimal despite hypercapnia (20). Administration of

dopamine under these circumstances did not suppress ventilation. This observation indicates that the action of dopamine is not dependent primarily on a high level of ventilation nor due to suppression of central chemoreceptors. This finding supports the conclusion that suppression of ventilation by dopamine is mediated through an action on the peripheral chemoreceptor reflex.

Stimulation of central dopamine receptors, by intracisternal injection of apomorphine (21), depresses ventilation. The possibility that our findings are the result of a central action of dopamine, perhaps on central connections of the chemoreceptor reflex, should be considered. This possibility seems unlikely, because the blood-brain barrier minimizes the access of dopamine into the brain (22). Furthermore, dopamine did not alter the response of central chemoreceptors to hypercapnia, which suggests that intravenously administered dopamine may not have important effects centrally. Nevertheless it seems appropriate to emphasize that, although these studies indicate that dopamine inhibits the chemoreceptor reflex, it is not possible to determine the precise locus of action of dopamine.

During the infusion of dopamine, a two-phase ventilatory response was observed. During the maximum suppression of ventilation produced by infusion of 5 µg/kg per min of dopamine in hypoxic subjects, ventilation decreased from about 14 liter/min to ≈8 liter/min. When chemoreceptor activity was minimal, during hyperoxia, the minute volume was also about 8 liter/min. The depression of ventilation by dopamine to this level suggests that dopamine transiently abolished the increased peripheral chemoreceptor drive to ventilation during hypoxia. The second phase of the response was observed during the 3rd–5th min of dopamine infusion. During this time the minute volume was lower than during the control period but higher than the levels observed during the transient maximum depression of ventilation. The increase in ventilation from the level of maximal suppression to the sustained level may be accounted for in part by the increase in PaCO<sub>2</sub> with increased central chemoreceptor drive to ventilation.

Dopamine stimulates alpha, beta, and dopaminergic receptors (23). The depressant effect on ventilation of low doses of dopamine was unaltered after beta adrenergic receptor blockade. Infusion of phentolamine, at a dose that blocks the cardiovascular and ventilatory effects of phenylephrine (18), did not alter the ventilatory response to infusion of low doses of dopamine. However, high doses of alpha blockers may be required to block alpha adrenergic receptors in chemoreceptors (10), so that our studies do not exclude the possibility that the effect of dopamine is mediated through alpha receptors. We did not give agents

capable of producing dopaminergic receptor blockade because we were concerned about the safety of their experimental use in normal humans. Our findings during infusion of phentolamine, in addition to the observation that dopaminergic effects predominate at low doses of dopamine and alpha adrenergic effects predominate at high doses (23), suggest that the depressant effect on ventilation of low doses of dopamine may be mediated by dopaminergic receptors.

Dopamine has been observed to stimulate ventilation in man (24). Infusion of dopamine in two subjects at doses of 10 and 12  $\mu\text{g}/\text{kg}$  per min produced an increase in ventilation whereas four subjects who received doses ranging from 5 to 8  $\mu\text{g}/\text{kg}$  per min had no change in ventilation (24). Lower doses of dopamine were not used and responses were not observed during stimulation of chemoreceptors by hypoxia. In our two subjects given an infusion of 10  $\mu\text{g}/\text{kg}$  per min of dopamine, ventilation increased while they breathed room air and decreased only slightly during hypoxia. After beta receptor blockade, infusion of 10  $\mu\text{g}/\text{kg}$  per min of dopamine to hypoxic subjects produced a depression of ventilation similar to that observed at a dose of 5  $\mu\text{g}/\text{kg}$  per min of dopamine. The observation that ventilation is depressed by infusion of low doses and stimulated by high doses of dopamine suggests that the effects of dopamine on the chemoreceptor reflex may be mediated by more than one receptor. At low doses of dopamine, a depressant effect on the chemoreceptor reflex may be produced by stimulation of dopaminergic or alpha adrenergic receptors. At high doses of dopamine, stimulation of beta adrenergic receptors may increase ventilation (18) and mask the depressant effects observed at lower doses.

Arterial  $\text{PO}_2$  decreased in response to infusion of dopamine during normoxia and hypoxia. The decrease in  $\text{PO}_2$  was larger than that which would be expected from the degree of hypoventilation. From the alveolar gas equation (25) if the respiratory exchange ratio is assumed to be 0.8, the increase in  $\text{PCO}_2$  which was observed would be expected to reduce  $\text{PO}_2$  by 2–4.5 mm Hg; the observed decrease in  $\text{PO}_2$  was 5–10 mm Hg. It is possible that the decrease in  $\text{PO}_2$  during infusion of dopamine is due in part to pulmonary vasodilation and shunting. Based on studies in patients with heart failure, it has been suggested that dopamine may open arteriovenous anastomoses, resulting in an increase in ventilation-perfusion inequality (26). Other studies suggest that the increase in pulmonary shunting is secondary to the increase in cardiac output, with a passive increase in blood flow to poorly ventilated regions of the lung (27). Although pulmonary shunting has not been reported during infusion of dopamine in normal subjects, it may contribute to the decrease in  $\text{PO}_2$  which we observed in

response to dopamine. We should point out that dopamine-induced shunting and hypoxia would increase ventilation and tend to mask the depressant effect of low doses of dopamine on the chemoreceptor reflex. Therefore the magnitude of the effect of dopamine in inhibition of the chemoreceptor reflex may be underestimated in the present studies.

Dopamine has been observed to produce different effects on chemoreceptors in different species (12). In cats dopamine depresses ventilation and decreases carotid chemoreceptor neural output (12, 13). In dogs dopamine stimulates ventilation (12, 14), but the response to dopamine has not been observed during stimulation of chemoreceptors with hypoxia. Our findings indicate that in man, as in cats, dopamine depresses the chemoreceptor reflex.

Several investigators have suggested that dopamine may be released in the carotid body during hypoxia and decrease the sensitivity of chemoreceptors (8–11). An alternate theory is that chemoreceptor fibers discharge tonically, that the discharge rate is reduced by a continuous high rate of secretion of dopamine in the carotid body, and that reduction in the secretion of dopamine during hypoxia results in increased neural discharge (28). Our study does not offer insight into the validity of either theory, but the findings are compatible with the hypothesis that dopamine is an inhibitory neurotransmitter in the carotid body of man.

In a previous study we reported that norepinephrine and isoproterenol increase ventilation in humans through a beta adrenergic effect on the chemoreceptor reflex (18). In contrast, results of this study suggest that low doses of dopamine decrease ventilation through an effect on the chemoreceptor reflex. It is possible that both neurotransmitters may be physiologically important modulators of chemoreceptor function and that they mediate a reciprocal function. A similar relationship between norepinephrine and dopamine has been proposed to exist in the central nervous system (29).

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