DEPRESSED RESPIRATION INDUCED BY INTRAVENOUSLY ADMINISTERED DOPAMINE IN ANESTHETIZED DOGS

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Dopamine has increasingly become the drug of choice for treating patients with cardiogenic shock (1, 2). Numerous studies on the cardiovascular actions of dopamine revealed that dopamine itself has a specific action, which is distinct from its stimulating actions on α- and β-adrenergic receptors (3). This action is associated with specific dopamine receptors, except for those in the central nervous system, which exist mainly in the renal and mesenteric vascular beds. The specific action of dopamine is partly antagonized by haloperidol or chlorpromazine (3). In contrast, there are relatively few reports concerning the respiratory actions of dopamine. In our studies we found that exogenous dopamine was a transient but potent depressant of respiration in anesthetized dogs. Dopamine therapy in the treatment of shock is a comparatively new maneuver, and the therapeutic value and adverse effects are still open to assessment. Using anesthetized dogs, the respiratory and cardiovascular effects of dopamine, especially as a depressant of respiration, were examined. The current concepts of dopamine as an inhibitory modulator in respiratory control were then studied.

Mongrel dogs (approximately 10 kg body weight) of both sexes were anesthetized with sodium pentobarbital (30 mg/kg, i.v.). Femoral arterial pressure and respiration were simultaneously recorded on a polygraph using a pressure transducer and a respiratory resistance meter connected with an endotracheal cannula, respectively. All drugs were injected into the cannulated femoral vein and doses were expressed as salts. Four experiments were performed with each of the doses of 1, 5, 10, 20, 30 and 40 μg/kg of dopamine.

Figures 1A and B show typical recordings of the effects of dopamine hydrochloride (1–40 μg/kg) on respiration and blood pressure in anesthetized dogs. An intravenous administration of dopamine (1 μg/kg) slightly depressed respiration either in tidal volume or in respiratory rate. In the range of doses investigated, the respiratory depression induced by dopamine was transient, dose-dependent and was accompanied by a biphasic blood pressure change, i.e., an initial rise and the subsequent fall in blood pressure. In doses over 30 μg/kg, the depressed respiration induced by dopamine lasted for several minutes, while the rise in blood pressure remained transient and the subsequent fall became inconspicuous. The depressant effects of dopamine (10 μg/kg, corresponding to the therapeutic dose com-
monly used) on respiration are summarized in Table 1, in terms of four physiological parameters.

Figure 1C shows the effects of dopamine (10 μg/kg) on respiration and blood pressure in the anesthetized dogs pretreated with phenoxybenzamine (5 mg/kg) and next with propranolol (200 μg/kg). For the reference standard, adrenaline (1 μg/kg) was used in parallel experiments. The depressed respiration induced by dopamine was not antagonized but rather was enhanced by pretreatment with phenoxybenzamine, while the initial rise in blood pressure by dopamine was completely antagonized. On the other hand, adrenaline slightly

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**Fig. 1.** A and B: Effects of increasing doses of dopamine (1–40 μg/kg) on respiration and systemic arterial blood pressure in an anesthetized dog. C: Effects of adrenaline and dopamine on respiration and systemic arterial blood pressure in the anesthetized dogs pretreated with phenoxybenzamine and then with propranolol. Top recordings show controls. D: Antagonistic effect of chlorpromazine against the respiratory depression induced by dopamine in an anesthetized dog. Top recording shows control.
decreased tidal volume but markedly increased the respiratory rate accompanied by a concomitant and profound fall in blood pressure. In the anesthetized dogs pretreated with both phenoxybenzamine and propranolol, the depressed respiration by dopamine was unaffected, and adrenaline, in this small dose, caused a typical "adrenaline apnea" accompanied by a rise in blood pressure.

The four parameters were measured during 30 sec after injection of dopamine. Minimum tidal volume represents the minimum value during the period. Breathing volume was obtained from the average tidal volume multiplied by respiratory rate during the period.

Our results show that the depressed respiration with dopamine dosing can be related to its specific action on dopamine receptors, since the action of dopamine was not antagonized by α- and β-adrenergic blockers but was partly antagonized by chlorpromazine. The depressed respiration by dopamine cannot be due to either a direct inhibition of the respiratory center or to a reflex inhibition of the center via the baroreceptor mechanism, since the injected dopamine does not cross the blood-brain barrier and the depressed respiration was still observed during the absence of the rise in blood pressure after phenoxybenzamine. The mechanism of respiratory depression by dopamine thus seems to be due mainly to a reflex inhibition of the respiratory center via the carotid chemoreceptor mechanism in which dopamine is involved.

The precise mechanism whereby the carotid chemoreceptor functions is more complex than formerly believed, and still controversial. However, a new theory for receptor mechanism of carotid chemoreceptors was proposed (4) in consideration of the following evidence: 1) the glomus cell of the carotid body contains dopamine in large amounts (5), 2) the glomus cells are interconnected with sensory nerve endings by reciprocal synapses (6), and 3) the glomus cells may be dopaminergic interneurons that regulate the sensitivity of chemoreceptor nerve endings (7). The theory suggests that a hyperpolarizing transmitter, dopamine secreted from the glomus cells modulates the frequency of spontaneous discharge of the sensory nerve fibers, assuming that a high rate of dopamine secretion corresponds to
normoxia. It also suggests that another depolarizing transmitter, possibly acetylcholine from the efferent synapses of the nerve endings suppressively regulates the high rate of dopamine secretion from the glomus cell when the blood gas tensions result in a state of hypoxia. Thus the glomus cells and sensory nerve endings are forming a positive feedback loop to respond to changes in blood gas tensions. Consequently, the intravenously administered dopamine will probably hyperpolarize the sensory nerve endings at afferent synapses (8) and might reduce the spontaneous discharge frequency, thereby eventually resulting in a depressed respiration.

The depressed respiration with this dose range of dopamine disagrees with findings in a previous report (9) in which dogs were given intracarotid injections of dopamine, whereas our observations agree with the results obtained in the cat (10). Intracarotid injection of dopamine may exert effects on the carotid body vessels as well as on the chemoreceptors, since the carotid body is a highly vascularized organ. Vasoactive effects of dopamine on the carotid body appear more potent by intracarotid than by intravenous administration because of the higher blood content of dopamine in the domain of the carotid body. If the intracarotid injected dopamine causes vasoconstrictions and results in hypoxia in the carotid body, a respiratory reflex excitation could occur. Zapata (11) reported that dopamine exerts both inhibitory and excitatory effects on the chemosensory fibers of the cat carotid body superfused in vitro where vasoactive effects of dopamine can be eliminated and also that the excitatory effects of dopamine on chemoreceptors were unaffected with dopaminergic or α-adrenergic blockers. Dual actions of dopamine have been observed also in other synapses, autonomic ganglia and neuromuscular junction. Dopamine released from the interneurons in autonomic ganglia causes inhibitory post-synaptic potential, but also facilitates the slow excitatory post-synaptic potential (12). Possibly, the glomus cells would act similarly as interneurons in the autonomic ganglia, however, a detailed discussion awaits further study. Dopamine induced depressed respiration in anesthetized dogs; in humans’ depressed respiration (13) and hypoxemia (14) in patients with left heart failure. In conclusion, our intention is to point out that when dopamine is given i.v. to treat patients in shock, care should be taken that the O₂ supply is adequate, particularly since the noncardiac adverse effects of dopamine have been only nausea and vomiting.

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CORRELATION BETWEEN VASODILATOR POTENCIES
OF β-ADRENOCEPTOR BLOCKING DRUGS AND
THEIR CHEMICAL STRUCTURES

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Nakano and Kusakari (1) and Shanks (2) reported that an i.a. injection of propranolol
produced relatively short-lived vasodilation and Shanks suggested that the local anes-
thetic action of propranolol was probably involved in the vasodilation. Recently, our
group found that alprenolol directly dilates several vascular beds in anesthetized dogs and
we suggested that the hypotensive effect of i.v. alprenolol would be largely due to a direct
vasodilator action (3). The present study was designed to determine possible relationships
between chemical structures and vasodilator potencies of β-adrenoceptor blocking drugs.

Experiments were carried out on 28 mongrel dogs of either sex, weighing between 9.5-
17 kg and anesthetized with sodium pentobarbital (30 mg/kg i.v.). The femoral arterial
bed was perfused through the cannulated femoral artery with blood from the carotid artery,
using a cam pump (Tokyo Rikakikai Co., Model 16). Perfusion pressure was kept constant
at approx. 120 mm Hg by shunting a fraction of blood through a Starling pneumatic re-
sistance to the external jugular vein (3). Sodium heparin was given at a dose of 500 units/
kg i.v. Blood flow through the femoral artery was measured with an electromagnetic