The Effect of Intracerebroventricular Dopamine Administration on the Respiratory Response to Hypoxia

İBRAHİM GÜNER, NERMIN YELMEN, GÜLDEREN ŞAHİN and TÜLİN ORUÇ

Department of Physiology, Cerrahpaşa Medical Faculty, University of Istanbul, Istanbul, Turkey

GÜNER, İ., YELMEN, N., ŞAHİN, G. and ORUÇ, T. *The Effect of Intracerebroventricular Dopamine Administration on the Respiratory Response to Hypoxia.* Tohoku J. Exp. Med., 2002, **196**(4), 219–230 — Acute hypoxia produces an increase in ventilation. When the hypoxia is sustained, the initial increase in ventilation is followed a decrease in ventilation. The precise mechanism of this decline in ventilation during sustained hypoxia is unknown. Recent studies hypothesized that the accumulation of dopamine in the central nervous system might have a major role in production of hypoxic respiratory depression. The purpose of this study was to examine whether dopamine has an effect on occurrence of central ventilatory depression which is seen in acute hypoxia in peripheral chemoreceptors denervated animals. The experiment were conducted in rabbits anesthetized with Na-pentobarbital ($25 \text{ mg} \cdot \text{kg}^{-1}$ i.v.). For intracerebroventricular (ICV) injections of dopamine ($1 \mu\text{g}$) in each animal, canula was placed in left lateral cerebral ventricle by stereotaxic method. Respiratory frequency ($f \cdot \text{min}^{-1}$), tidal volume (V_T) ventilation minute volume (V_E) and systemic arterial blood pressure (BP) were recorded during air and 3 minutes hypoxic gas mixture ($8\% \text{O}_2$ - $92\% \text{N}_2$) breathing. ICV administration of dopamine during normoxia decreased V_T , f , V_E and BP, significantly. When rabbits were injected with an ICV dopamine on hypoxic gas mixture breathing in control animals, there was depression of hypoxic ventilatory responses. After ICV administration of dopamine antagonists haloperidol (0.1 mg) and domperidone (0.07 mg) in chemodenervated rabbits, the significant increases in V_T , V_E and BP were observed. On the breathing of hypoxic gas mixture of chemodenervated and ICV dopamine antagonists administrated rabbits, hypoxic depression was completely abolished. These results of this study show that accumulation of dopamine in the brain seems to reduce the response of the central control mechanisms to chemoreceptor impulses during normoxia and hypoxia. In conclusion present study suggests important role played by central dopaminergic pathways in the occurrence of acute hypoxic ventilatory depression. ——— dopamine; hypoxia; central respiratory pattern; haloperidol; domperidone
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Address for reprints: Prof. Dr. Gülderen Şahin, Department of Physiology, Cerrahpaşa Medical Faculty, University of Istanbul, Cerrahpaşa Istanbul, Turkey.

e-mail : ggullde@Istanbul.edu.tr

Dopamine is an amine which affects the respiratory responses to hypoxia. It is present in large amounts in the type I cells of the carotid body and acts as a neuromodulator of carotid body function (Nishino and Lahiri 1972; Steele and Hintberger 1972). Exogenously administered dopamine depresses ventilation by inhibiting the neural activity of the carotid body. Peripheral dopamine receptor blockage, on the contrary, stimulates carotid body neural activities and ventilation (Ward and Bellville 1982; Van Lunteren et al. 1984; Pedersen et al. 1997, 1999). Dopaminergic nerve endings were demonstrated to exist in brainstem regions responsible for the regulation of respiration (Lundberg et al. 1985).

A biphasic response following hypoxic ventilatory depression (HVD), which is also called roll-off, is seen after the initial hyperventilation phase in acute sustained hypoxia (Vizek et al. 1987; Long et al. 1993). The mechanism of this decrease in ventilation is not clear. Acute sustained hypoxia is believed to increase inhibitory neurotransmitters (dopamine, adenosine, γ -amino butyric acid [GABA]) in the central nervous system (CNS), thereby disrupting the balance between inhibitory and excitatory neurotransmitters and causing a depression of respiratory-related neurons (Melton et al. 1990; Karaturan et al. 1996; O'Halloran et al. 1998).

Recent studies have suggested that dopamine may play an important role in the accumulation of neurotransmitters in the central nervous system in acute sustained hypoxia, and the occurrence of HVD (Bonora and Gautier 1988; O'Halloran et al. 1988). Tatsumi et al. (1992) have shown that haloperidol abolishes HVD in awake and anesthetized cats. Dahan et al. (1996) suggested that in awake humans an appreciable ventilatory response during sustained hypoxia is necessary for hypoxic ventilatory depression to develop and dopamine reduces the magnitude of HVD. Pederson et al. (1997) on the contrary, were not

able to show haloperidol to decrease HVD in humans, as it does in cats. Also, domperidon was shown to increase acute hypoxic ventilatory response in humans, while having no effect on HVD magnitude (Walsh et al. 1998).

It was attempted to demonstrate dopamine's effects on the occurrence of HVD, mostly by using i.v. dopamine antagonists.

In the present study, we aimed to investigate whether dopamine has an effect on the occurrence of central ventilatory depression which is seen in acute hypoxia in animals whose peripheral chemoreceptors were denervated. We administered dopamine directly using the intracerebroventricular route to investigate:

- a) whether dopamine induces respiratory depression in rabbits with intact peripheral chemoreceptors;
- b) whether dopamine affects respiratory responses to acute hypoxia, and
- c) when dopamine antagonists are used in peripheral chemoreceptor-denervated rabbits, whether inhibitory dopaminergic mechanisms are functional in acute hypoxic depression.

MATERIAL AND METHODS

We used 10 albino rabbits (mean body weight 2.4 ± 0.75 kg) anaesthetized with sodium pentobarbital ($25 \text{ mg} \cdot \text{kg}^{-1}$ i.v.). Tracheotomy was performed and the tracheal cannula, connected to an inspiratory-expiratory valve, was inserted into the trachea. The right femoral artery, in order to record the systemic blood pressure and to obtain arterial blood samples, and the right femoral vein, in order to administer anesthesia medicines as required, were cannulated. All rabbits were given $500 \text{ U} \cdot \text{kg}^{-1}$ liquemine i.v. before the experiment.

Carotid nerves were isolated and severed, and the surrounding tissues were damaged, at the bifurcation level of *a. carotis communis* bilaterally, for denervation of peripheral chemoreceptors. These regions were also

flushed with alcohol and then phenol, after which the sites were rinsed thoroughly with physiologic serum. Denervation was completed with first isolating Cyt nerves and cutting them bilaterally. Denervation procedure was tested with an injection of NaCN ($40 \mu\text{g}\cdot\text{kg}^{-1}$ i.v.).

A cannula was placed intracerebroventricularly (ICV) to the left lateral ventricle with stereotaxy. Skulls of the animals were fixed to the stereotaxy device (No. 51400; Stoelting Co., Wood Dale IL, USA), after which the scalp was incised at eye-level and the periosteum covering the bone was peeled. Skull was penetrated at a point anterior to Lambda and 2.5 mm to the left of the midline with a dentist's drill without damaging the dura mater. A screw was placed (to approximately 2 mm distance from the hole) in order to fixate the cannula after placement. The tip of the cannula, fixed to the stereotaxy device was positioned opposite the hole in the skull. The cannula was placed in the left lateral ventricle, at 9 mm depth. Acrylic cement (Croform acrylic powder + cold liquid) was used to fixate the cannula.

Central dopamine (Sigmachemical, Co, St. Louis, MO, USA) injection was made with a Hamilton injector, at a dose of $1 \mu\text{g}$ from the ICV cannula. This dose of dopamine was determined, as choosing $10 \mu\text{g}\cdot\text{kg}^{-1}$ i.v. of peripheral dose. The peripheral doses were firstly determined by a dose response curve, for central doses, constant quantities on an average of 1/20 of the peripheral doses were used.

The experimental procedure

In both experimental groups (intact peripheral chemoreceptors group [Control] and peripheral chemoreceptors denervated group [Chemodenervated]) the tidal volume (V_T), respiratory frequency (f) and systemic arterial pressure (BP) of the animals were recorded with a polygraph (Grass Model 7 Sigma) while they breathed an air and a hypoxic gas mixture (8%

O_2 -92% N_2). Respiratory minute volume (V_E) and mean BP were calculated from the parameters recorded. Also, PaO_2 , PaCO_2 and pHa were measured from arterial blood samples obtained at each phase, using AVL gas check type 937, at a temperature of 37°C .

Dopamine was injected from the ICV catheter in one minute while the animal breathed room air and changes in the parameters were recorded. After the air-breathing phase of 15 minutes duration, ICV dopamine was administered at the beginning of hypoxic gas mixture breathing. The same sequence of hypoxia, ICV dopamine administration, ICV dopamine + hypoxia phases were applied to the test animals whose peripheral chemoreceptors were denervated.

Dopamine antagonists haloperidol (0.1 mg) (central and peripheral dopamine receptor antagonist which can pass through the brain-blood barrier) and domperidone (0.07 mg) (peripheral dopamine antagonist and D_2 -specific antagonist, which cannot pass through the brain-blood barrier) were administered from the ICV route to this group of test animals, after which the effects of haloperidol and domperidone administration during hypoxic gas mixture breathing were determined.

After the experiment, 1/10 N HCl were administered from the ICV catheter to control the increase in respiratory parameters, after which methylene blue was injected from the ICV catheter and craniotomy was done. Cerebrum was divided at the midline and methylene blue was detected in the lateral ventricle, thereby confirming the placement of the catheter in the lateral ventricle (Fig. 1).

The statistical significance of the changes in respiratory parameters between before and after ICV injection of dopamine and dopamine antagonists during normoxia and hypoxia were tested with Wilcoxon-Matched Pairs test, and the statistical significance of the differences between the groups were tested with Mann-Whitney U-test.

Fig. 1. Methylene blue injection into the left ventricle.

RESULTS

Control group

On the breathing of hypoxic gas mixture by the animals with intact peripheral chemoreceptors (control) V_T , f , V_E and BP were significantly increased ($p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.01$, respectively) (Fig. 2) (Table 1).

ICV dopamine. ICV dopamine were administered after the animal breathed air for 15 minutes, in order to determine whether

dopamine inhibits respiration at the eupneic level by affecting central respiratory neurons. V_T , f , V_E and BP decreased significantly ($p < 0.05$, $p < 0.05$, $p < 0.05$, $p < 0.05$, respectively) in comparison to the values obtained before dopamine administration. In this way, centrally administered dopamine was detected to depress ventilation in test animals with intact peripheral chemoreceptors (Table 1).

ICV dopamine + hypoxia. Centrally administered dopamine was observed to depress

Fig. 2. Responses to systemic hypoxia (8% O_2 -92% N_2) (A) and ICV dopamine (1 mg) + hypoxia (B) in peripheral chemoreceptors intact rabbits (Control Group). Traces from top to bottom are systemic arterial blood pressure (BP), tidal airflow, tidal volume (V_T), respectively.

Fig. 3. Responses to systemic hypoxia (8% O₂-92% N₂) (A) and ICV haloperidol (0.07 mg) + hypoxia (B) in peripheral chemoreceptors denervated rabbits (Chemodenervated Group). Traces from top to bottom are systemic arterial blood pressure (BP), tidal airflow, tidal volume (V_T), respectively.

hypoxic ventilatory responses in control animals during hypoxic gas mixture breathing after ICV dopamine (Table 1). The expected significant increase in V_T in hypoxia was not observed, on the contrary, a significant decrease was detected ($p < 0.01$). Significant decreases in f , V_E and BP were also observed ($p < 0.05$, $p < 0.01$, $p < 0.01$, respectively) (Fig. 2).

Chemodenervated group

Significant decreases in f , V_T , V_E and BP of rabbits with denervated peripheral chemoreceptors were observed during hypoxic gas mixture breathing in comparison with the former air-breathing phase ($p < 0.05$, $p < 0.01$, $p < 0.01$, $p < 0.01$, respectively) (Table 1). Acute hypoxia elicited the expected respiratory depression in chemodenervated rabbits (Fig. 2).

ICV dopamine. We attempted to test whether the hypoventilation which occurs when no impulse comes from the peripheral chemoreceptors increases, by administering ICV dopamine to rabbits with denervated peripheral chemoreceptors. While inducing significant

decreases in V_T , V_E and BP in normoxia ($p < 0.05$, $p < 0.05$, $p < 0.05$, respectively), ICV dopamine did not elicit a significant change in f (Table 1).

ICV dopamine + hypoxia. We attempted to test whether ICV dopamine would further increase the depression elicited by hypoxia in chemodenervated rabbits. When hypoxic gas mixture was breathed to rabbits during ICV dopamine administration, significant decreases in f , V_T , V_E and BP were observed ($p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.01$) (Table 1).

Although there were no significant difference in V_T and V_E in control condition among the groups of hypoxia, ICV dopamine and ICV dopamine + hypoxia, f was found to be significantly lower ($p < 0.05$) in chemodenervated group in control condition of hypoxia (Table 1).

The effect of dopamine antagonists in chemodenervated rabbits

ICV Haloperidol. Haloperidol, a peripheral and central antagonist of dopamine, which

TABLE 1. The mean and standard error (Mean $\pm$ S.E.) values of f , V_T , V_E and BP of the Control (peripheral chemoreceptor-intact) and chemodenervated (peripheral chemoreceptor-denervated) groups of rabbits in the indicated experimental phases

Experimental Phase	f /min.		V_T (mL)		V_E (mL/min.)		BP (mmHg)	
	Control	Change	Control	Change	Control	Change	Control	Change
Control								
Hypoxia ($n=10$)	55.1 $\pm$ 3.5	60.9 $\pm$ 3.7**	22.9 $\pm$ 3.5	28.9 $\pm$ 3.5**	1273.2 $\pm$ 198.2	1763.2 $\pm$ 234.9**	77.3 $\pm$ 4.1	84.8 $\pm$ 4.8**
ICV dopamine ($n=5$)	71.0 $\pm$ 3.7	67.6 $\pm$ 4.0*	17.0 $\pm$ 2.7	15.0 $\pm$ 2.2*	1178.3 $\pm$ 148.0	988.9 $\pm$ 112.8*	86.2 $\pm$ 3.1	79.2 $\pm$ 4.1*
ICV dopamine + hypoxia ($n=10$)	57.2 $\pm$ 5.3	54.6 $\pm$ 5.6*	25.6 $\pm$ 3.7	23.3 $\pm$ 3.7**	1433.0 $\pm$ 217.1	1249.4 $\pm$ 210.1**	82.3 $\pm$ 5.0	75.9 $\pm$ 7.0**
Chemodenervated								
Hypoxia ($n=10$)	38.0 $\pm$ 4.6 ^a	35.4 $\pm$ 4.2*	26.8 $\pm$ 3.2	21.6 $\pm$ 2.6**	908.2 $\pm$ 58.3	698.6 $\pm$ 44.4**	99.8 $\pm$ 8.0	85.0 $\pm$ 9.4**
ICV dopamine ($n=5$)	54.0 $\pm$ 0.8	54.6 $\pm$ 1.0	23.3 $\pm$ 1.5	21.3 $\pm$ 1.6*	1256.1 $\pm$ 71.0	1161.8 $\pm$ 79.7*	100.5 $\pm$ 8.8	93.0 $\pm$ 8.3*
ICV dopamine + hypoxia ($n=10$)	54.7 $\pm$ 1.3	52.5 $\pm$ 2.1**	20.2 $\pm$ 1.3	18.3 $\pm$ 1.2**	1107.5 $\pm$ 73.6	962.7 $\pm$ 78.0**	103.1 $\pm$ 10.9	87.1 $\pm$ 10.3**

* $p < 0.05$, ** $p < 0.01$ for change compared with control (beginning value).

f , respiratory frequency; V_T , Tidal volume; V_E , Respiratory minute volume; BP, Mean arterial blood pressure.

^a $p < 0.05$ indicates significance when control conditions were compared among the groups.

also can pass the brain-blood barrier, was administered directly from the ICV route in our experiments. When chemodenervated rabbits were given ICV haloperidol in normoxia, significant increases in V_T , V_E and BP occurred ($p < 0.05$, $p < 0.05$, $p < 0.05$, respectively). There was no significant change in the frequency of respiration (Table 2).

ICV haloperidol + hypoxia. As the main aim of our investigation, hypoxic gas mixture was breathed to peripherally chemodenervated rabbits after ICV haloperidol administration in order to determine the role of dopamine in acute hypoxic depression in chemodenervated rabbits. V_T and V_E increased significantly and hypoxic depression was completely abolished in this condition ($p < 0.01$, $p < 0.01$, respectively) (Table 2). On the other hand there were significant decreases in f and BP ($p < 0.01$, $p < 0.01$) (Table 2) (Fig. 2).

ICV domperidone. Significant increases in V_T , V_E and BP were observed, with no changes in the frequency of respiration, in peripherally chemodenervated rabbits given domperidone, which is a peripheral dopamine D_2 receptor antagonist, during normoxia ($p < 0.05$, $p < 0.05$, $p < 0.05$, respectively) (Table 2).

ICV domperidone + hypoxia. After administration of ICV domperidone, the hypoxic depression was observed to disappear in chemodenervated rabbits during hypoxic gas mixture breathing. A significant increase in V_T and V_E was observed ($p < 0.01$, $p < 0.01$), with a significant fall in BP ($p < 0.01$). There was no significant change in the frequency of respiration (Table 2).

When the respiratory responses to ICV haloperidol and to ICV domperidone were compared, a significant difference in V_T was observed between the increases elicited by these agents (Table 2). The increase in V_T of ICV haloperidol administrated rabbits was

found to be higher than that of other group. On the other hand there was significant difference between the increases they induced in V_E , when they blocked the hypoxic depression. The significant increase in V_E of haloperidol injected chemodenervated rabbit was due to the non significant increase in f (Table 2).

As is shown in Table 3 variations in PaO_2 , $PaCO_2$ and pHa values reflected the changes of the respiratory parameters during each experimental phase.

DISCUSSION

The increases in tidal volume (V_T), respiratory frequency (f), respiratory minute volume (V_E) and systemic arterial pressure (BP) of the control animals with intact peripheral chemoreceptors during hypoxic gas mixture breathing were due to stimulation of peripheral chemoreceptors. In the control group, ICV administration of dopamine in normoxia produced significant decrease in (V_E) as a result of a significant decreases in (V_T) and (f). The decrease in BP in response to ICV dopamine administration was found to be significant. As is well known, peripheral chemoreceptors are active during normoxia and the facilitatory input from peripheral chemoreceptors bursts central inspiratory activity (CIA) and VT in normoxia (Oruç et al. 1982; Şahin and Terzioğlu 1985). In the present study, ICV dopamine was observed to decrease ventilation by its inhibitory effect on central respiratory neurons in spite of the impulses originating from the peripheral chemoreceptors during air breathing.

Low dose ($3-10 \mu\text{g}\cdot\text{kg}^{-1}$) i.v. dopamine depresses respiration by decreasing carotid body neural activity, thereby decreasing systemic arterial blood pressure (BP) and the respiratory response to hypoxia (Welsh et al. 1978; Van Lunteren et al. 1984; Ide et al. 1995; O'Halloran et al. 1998). When dopamine is administered intravenously in high doses (50

TABLE 2. The mean and standard error (Mean $\pm$ s.e.) values of f , V_T , V_E and BP of the peripheral chemoreceptor-denervated rabbits in the indicated experimental phases

Experimental Phase	f/min.		V_T (mL)		V_E (mL/min.)		BP(mmHg)	
	Control	Change	Control	Change	Control	Change	Control	Change
Chemodenervated								
ICV haloperidol (n=5)	46.6 $\pm$ 0.2	46.4 $\pm$ 0.3	18.2 $\pm$ 0.4	19.2 $\pm$ 0.4 ^{a,c}	851.2 $\pm$ 24.7	893.7 $\pm$ 23.1 ^a	93.0 $\pm$ 2.7	96.0 $\pm$ 2.7 ^a
ICV haloperidol+hypoxia (n=10)	46.0 $\pm$ 0.4	44.2 $\pm$ 0.3 ^a	18.5 $\pm$ 0.4	21.6 $\pm$ 0.5 ^b	855.0 $\pm$ 22.9	958.0 $\pm$ 28.0 ^{b,d}	86.0 $\pm$ 2.0	50.4 $\pm$ 3.2 ^{b,e}
ICV domperidone (n=5)	44.8 $\pm$ 1.6	44.8 $\pm$ 1.9	52.2 $\pm$ 0.7	55.2 $\pm$ 0.7 ^a	2336.4 $\pm$ 76.2	2471.4 $\pm$ 105.6 ^a	105.8 $\pm$ 6.9	115.6 $\pm$ 3.1 ^a
ICV domperidone + hypoxia (n=10)	45.3 $\pm$ 1.1	44.1 $\pm$ 1.4	44.6 $\pm$ 1.8	51.2 $\pm$ 2.2 ^b	2015.7 $\pm$ 82.1	2246.0 $\pm$ 90.9 ^b	121.1 $\pm$ 4.4	115.7 $\pm$ 3.3 ^b

^a $p < 0.05$, ^b $p < 0.01$ for change compared with control (beginning value).
^c $p < 0.01$ for the response to ICV haloperidol compared with that of ICV domperidone.
^d $p < 0.05$, ^e $p < 0.001$ for the response to ICV haloperidol + hypoxia compared with that of ICV domperidone + hypoxia.
 f , Respiratory frequency; V_T , Tidal volume; V_E , Respiratory minute volume; BP, Mean arterial blood pressure.

TABLE 3. The mean and standard error (Mean $\pm$ S.E.) values of PaO₂, PaCO₂, pH_a of the control and peripheral chemoreceptor-denervated groups of rabbits in the indicated experimental phases

Experimental Phase	PaO ₂ (Torr)		PaCO ₂ (Torr)		pH _a	
	Control	Change	Control	Change	Control	Change
Control						
Hypoxia (n=10)	84.7 $\pm$ 4.2	39.5 $\pm$ 3.8***	39.0 $\pm$ 3.7	33.5 $\pm$ 3.2***	7.36 $\pm$ 0.05	7.38 $\pm$ 0.06*
ICV dopamine+hypoxia (n=10)	75.2 $\pm$ 5.6	38.7 $\pm$ 4.1***	42.3 $\pm$ 7.2	45.6 $\pm$ 6.7***	7.24 $\pm$ 0.15	7.22 $\pm$ 0.01***
Hypoxia (n=10)	76.3 $\pm$ 2.8	37.9 $\pm$ 4.6***	39.9 $\pm$ 2.1	46.2 $\pm$ 3.7***	7.35 $\pm$ 0.02	7.22 $\pm$ 0.05***
Chemodenervated						
ICV dopamine+hypoxia (n=10)	79.2 $\pm$ 3.2	36.3 $\pm$ 2.6***	41.2 $\pm$ 6.1	41.9 $\pm$ 2.1	7.34 $\pm$ 0.01	7.33 $\pm$ 0.03
ICV haloperidol+hypoxia (n=10)	75.1 $\pm$ 2.7	38.2 $\pm$ 4.6***	38.9 $\pm$ 3.2	35.4 $\pm$ 2.6**	7.37 $\pm$ 0.02	7.40 $\pm$ 0.01**
ICV domperidone+hypoxia (n=10)	77.6 $\pm$ 3.2	39.4 $\pm$ 4.1***	37.8 $\pm$ 4.6	36.4 $\pm$ 3.1**	7.38 $\pm$ 0.01	7.39 $\pm$ 0.02**

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for change compared with control (beginning value).

$\mu\text{g}\cdot\text{kg}^{-1}$), blood pressure increases and respiration is inhibited for some time as a result of vasoconstriction induced by its adrenergic effect (Loos et al. 1998; O'Halloran et al. 1998). In our study, the significant decrease in BP clearly indicate the effect of low dose ICV dopamine.

When the control group of rabbits were given ICV dopamine while breathing the hypoxic gas mixture, no hypoxic ventilatory increase were observed; on the contrary, significant decreases in f , V_T and V_E were detected. Central dopamine depresses the excitatory effects of increased impulses from peripheral chemoreceptors on CIA (Oruç et al. 1982; Şahin and Terzioğlu 1985). It is known that hypoxic ventilatory response can be modulated by dopamine D₂ receptors in both the carotid body arterial chemoreceptors and the nucleus tractus solitarius (NTS), the primary synapse site of carotid body afferents (Huey et al. 2000). When ICV dopamine was administered in normoxia, after peripheral chemodenervation, a significant decrease in V_E were detected due to a decrease in V_T . As dopamine is administered

from the ICV route in the present study, D₂ receptors in regions where peripheral circulation is effective cannot be responsible from the effect.

The ventilation depressing effect of ICV dopamine in the intact experimentation group is not caused by impulses originating from peripheral chemoreceptors. O'Halloran et al. (1998) have shown the presence of a ventilatory inhibitor effect of exogenous IV dopamine in goats, modulated by both CB and non-CB mediation, by a dose-dependent decrease in phrenic nerve activity. These investigators have suggested that domperidone decreases this ventilatory inhibition in peripheral chemoreceptor-denervated goats, therefore the response is mediated by dopamine-D₂ peripheral receptors.

Huey and Powel (2000) have investigated the changes that take place in D₂ receptors in hypoxia at D2R mRNA levels. An increase in rostral NTS and a biphasic response in the form of an increase and decrease in caudal NTS were observed. Thus, dopamine was shown to increase in respiratory neurons during an

extended period of hypoxia. Also, in another *in vitro* study, in cell cultures of mesencephalic and diencephalic mature cells, an increase in dopamine during hypoxia was shown in both the cells and the medium, 30 minutes after which dopamine normalizes and 255 minutes later dopamine decreases (Gao et al. 1999). Hence, dopamine was shown to increase in central neurons with protracted acute hypoxia in *in vitro* conditions (Gao et al. 1999; Huey and Powel 2000).

Thus, dopamine depresses the ventilation by not only decreasing carotid body neural discharges, but by also its direct effect on central respiratory neurons in normoxia and hypoxia, causing a decrease in f and V_T . When the peripheral chemoreceptor denervated rabbits was allowed to breathe the hypoxic gas mixture, there were decreases in V_T , f , V_E and BP. In the absence of peripheral chemoreceptor input, hypoxia depresses the central mechanisms (Oruç et al. 1982; Şahin and Terzioğlu 1985). In the present study, the expected depressor effect of hypoxia was observed. When the same group of rabbits were administered ICV dopamine as they breathed the hypoxic gas mixture, no change in the occurrence rate or amplitude of ventilatory depression were observed. This shows that, if dopamine which accumulates in the central nervous system has a role in the occurrence of hypoxic depression, then because of receptor saturation, ICV dopamine administration is not thought to strengthen the effect.

Although there were no significant difference in V_T and V_E in control condition among the groups of hypoxia, ICV dopamine and ICV dopamine + hypoxia, f was found to be significantly lower ($p < 0.05$) in chemodenervated group in control condition of hypoxia. This may be due to the absence of chemoreceptors impulses in chemodenervated group.

The effects of dopamine antagonists; when ICV haloperidol, a D_1 and D_2 dopamine receptors antagonist, was administered to chemodenervated rabbits in normoxia, ventila-

tion increased as a result of the increase in V_T . When chemodenervated rabbits which were administered ICV haloperidol breathed a hypoxic gas mixture, the hypoxic depression completely abolished and ventilation increased as a result of the increase in V_T . This finding shows that, in the absence of peripheral chemoreceptors, in acute hypoxia, dopamine in the brain causes ventilatory depression.

Tatsumi et al. (1992) has shown that IV haloperidol, which can pass the brain-blood barrier, abolishes HVD in anesthetized or awake cats. Long and Anthonisen (1995) has investigated the effect of haloperidol ($0.1 \text{ mg} \cdot \text{kg}^{-1}$) on the ventilatory response to hypoxia in awake cats. These investigators have shown that, haloperidol is not effective in moderate hypoxia ($\text{PETO}_2 = 61 \text{ Torr}$), while it decreases the hypoxic ventilatory depression in severe hypoxia ($\text{PETO}_2 = 42 \text{ Torr}$). We used $8\% \text{O}_2$ - $92\% \text{N}_2$ of hypoxic gas mixture in the present study. PaO_2 value is near 40 mmHg .

We also investigated the effects of domperidone, which is a specific antagonist of D_2 receptors. ICV domperidone was also observed to increase ventilation by increasing V_T , without affecting f . When hypoxic gas mixture was respired after domperidone administration, as a result of the increase in V_T with blocked hypoxic depression, ventilation was detected to increase. In contrast, Walsh et al. (1998) showed an increase in hypoxic hyperventilation in only 50% of the subjects, when they investigated the effects of domperidone on acute ventilatory response to isocapnic hypoxia in humans. In our study with rabbits, the effects of dopamine antagonists show that dopamine is responsible for the acute hypoxic depression.

In the present study BP of the control rabbits was found to be increase significantly on the breathing of hypoxic gas mixture. This increase is due to periferal chemoreceptors impulses impinging on vasomotor area (Şahin and Terzioğlu 1985). Therefore BP decreased significantly in chemodenervated group in

hypoxia. Low dose (1 μ g) ICV dopamine produced significant decreases in BP of control and chemodenervated group on the breathing of normoxic and hypoxic gas mixture. As is well known dopamine produces an increase in blood pressure by its systemic effect via the peripheral chemoreceptors. On the other hand central (ICV) administration of low dose of dopamine produces no systemic effect, but only central effect and therefore in our both control and chemodenervated groups no increase in BP was observed after dopamine administration.

The inhibitor effects of dopamine on respiratory motor impulse output were shown to be independent of the hemodynamic effects resulting from dopamine administration. Our BP findings also support this result (O'Halloran et al. 1998).

Our results show that:

- a) ICV dopamine creates respiratory depression by decreasing both the volume and frequency of respiration in normoxia,
- b) ICV dopamine inhibits the increase in ventilation during acute hypoxia,
- c) ICV dopamine can still induce respiratory depression, after peripheral chemodenervation.
- d) ICV dopamine antagonists completely abolish the ventilatory depression observed in chemodenervated rabbits during acute hypoxia.

In conclusion; the results of our study suggest an important role played by central dopaminergic pathways in the occurrence of acute hypoxic ventilatory depression.

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