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THE EFFECT OF CENTRAL AND PERIPHERAL ADMINISTRATION OF ACETYLCHOLINE AND EPINEPHRINE ON RESPIRATION

GÜLDEREN SAHİN, TÜLIN ORUC, GÖNÜL SİMSEK, İBRAHIM GÜNER

Department of Physiology,
Cerrahpasa Faculty of Medicine,
University of Istanbul,
Cerrahpasa, Istanbul, Turkey

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Abstract : The experiments were conducted in dogs anesthetized with Na-pentobarbital i.v. tidal volume (V_T) and respiratory frequency (f min^{-1}) were recorded. The central effects of acetylcholine (Ach) and epinephrine on respiration were investigated after injections of these substances directly into the cerebrospinal fluid by atlanto-occipital punction.

The peripheral effects of Ach and epinephrine on respiration were studied after i.v. injections. Both central and peripheral administration of epinephrine caused significant increase in f min^{-1} and V_T. After vagotomy the effects of centrally and peripherally administered epinephrine on f min^{-1} were abolished. The effect of central injection of epinephrine on V_T persisted after vagotomy. The increase in V_T in response to peripheral epinephrine administration was abolished by vagotomy. Both central and peripheral injection of Ach increased f min^{-1}. In V_T an initial decrease was followed by an increase. The initial decrease in V_T was abolished by atropine. After vagotomy the effects of central and peripheral administration of Ach on f min^{-1} were abolished. The effects of central injection of Ach on V_T persisted after vagotomy. Vagatomy abolished the effects of peripheral administration of Ach on V_T.

Key words : epinephrine, central respiratory pattern, central cholinergic tonus, acetylcholine

INTRODUCTION

Rhythmic respiratory activity is generated in a rather restricted area of the brain stem. This brain stem area contains different types of respiratory neurons connected in a network. The activity of respiratory neuronal network is regulated by impulses of peripheral and central origin (1–3). Brain stem respiratory neurons contain several chemical substances. Some of these chemical substances act as neurotransmitters causing rapid and short lasting effects. Others such as neuropeptides and neuroactive substances act with a slower time course and long duration (3).

The purpose of this study was to examine the effects of central and peripheral administration of acetylcholine (Ach) and

*Corresponding Author

epinephrine on respiratory frequency (f min^{-1}) and tidal volume (V_T).

METHODS

Dogs with mean body weight 18 ± 3.9 kg were used as experimental animals. The animals were anesthetized with pentothal-Na (30 mg kg^{-1} iv). Tracheotomy was done and cannula, connected to a inspiratory-expiratory valve, was inserted into the trachea. Tidal volume (V_T) and respiratory frequency (f) were recorded by means of a pneumotachograph and a Grass PT-5 transducer on a Grass model 7 polygraph. Ventilatory minute volume was calculated from the values of V_T and f. The femoral vein was catheterized. Central administration of epinephrine, acetylcholine and atropine was done by means of a trocar catheter placed in cisterna magna by atlanto-occipital punction. Peripheral administration of the same substances was done through the femoral vein. The doses of epinephrine and Ach injected centrally and peripherally were as follows:

	Central	*Peripheral*
Epinephrine	0,0025 mg	0,05 mg
Acetylcholine	0,075 mg	1,5 mg
Atropine	0,0075 mg	0,15 mg

The peripheral doses were determined by a dose response curve for each substance. The central doses were 1/20 of that of the peripheral. The central and peripheral effects of epinephrine, acetylcholine and atropine were tested before (control) after bilateral cervical vagotomy. For statistical analysis paired t-test was used.

RESULTS

Effects of epinephrine: Both central and peripheral administration of epinephrine increased f, V_T and $\dot{V}_E$ in control animals. Central administration of epinephrine caused an increased in V_T after vagotomy. Respiratory frequency, on the other hand, was not affected by central administration of epinephrine after vagotomy. Peripheral administration of epinephrine produced no significant change in V_T, f and $\dot{V}_E$ after vagotomy (Table I).

Effects of acetylcholine: Both central and peripheral administration of acetylcholine produced significant increases in f in control animals. V_T showed biphasic responses on central and peripheral administration. An initial decrease in V_T was followed by an increase. After vagotomy no changes were observed in f in response to central and

TABLE I : Mean and standard error (M ± SE) values of f, V_T and $\dot{V}_E$ with central and peripheral epinephrine administrations.

Administration	*Experimental group*		*f/min*	*V_T (ml)*	*$\dot{V}_E$ (ml)*
Central	Control n=15	A	19.4 ± 1.5	165.0 ± 8.1	3188.7 ± 325.7
		B	20.5 ± 1.7*	213.1 ± 10.0***	4467.1 ± 409.2***
	Vagotomy n=9	A	16.8 ± 1.7	248.1 ± 32.0	3969.0 ± 294.3
		B	16.8 ± 1.8	283.2 ± 34.8**	4532.3 ± 311.1**
Peripheral	Control n=9	A	19.8 ± 1.6	141.0 ± 7.4	2825.6 ± 330.9
		B	22.2 ± 1.8**	187.1 ± 12.5***	4185.9 ± 506.4**
	Vagotomy n=6	A	13.2 ± 1.5	277.6 ± 30.2	3434.1 ± 172.4
		B	13.0 ± 1.7	271.1 ± 29.5	3198.2 ± 326.1

*P<0.05, **P<0.01, ***P<0.001
A: Before administration B: After administration

TABLE II : Mean and standard error (M ± SE) values of f, V_T and $\dot{V}_E$ with central and peripheral acetylcholine administrations.

Administration	*Experimental group*		*f/min*	V_T *(ml)*	$\dot{V}_E$ *(ml)*
Central	Control n=9	A	18.0 ± 1.1	171.1 ± 12	3074.9 ± 277.4
		B	18.9 ± 1.3*	109.7 ± 15.9**	1898.1 ± 246.9**
				204.1 ± 16.8***	3860.4 ± 426.3**
	Vagotomy n=5	A	14.2 ± 1.8	243.7 ± 32.6	3263.1 ± 311.7
		B	14.2 ± 1.8	122.0 ± 21.6**	1596.0 ± 153.8**
				319.4 ± 43.7**	4229.2 ± 219.1**
Peripheral	Control n=11	A	20.3 ± 1.0	157.8 ± 13.3	3131.1 ± 208.7
		B	23.5 ± 1.2***	102.5 ± 13.3***	2017.2 ± 226.9***
				193.2 ± 13.0***	4444.6 ± 209.8***
	Vagotomy n=10	A	11.1 ± 1.4	342.5 ± 30.3	3374.5 ± 297.7
		B	11.2 ± 1.5	346.1 ± 27.8	3540.4 ± 268.9

*P<0.05, **P<0.01, ***P<0.001
A: Before administration B: After administration

TABLE III : Mean and standard error (M ± SE) values of f, V_T and $\dot{V}_E$ with central and peripheral atropine administrations.

Administration	*Experimental group*		*f/min*	V_T *(ml)*	$\dot{V}_E$ *(ml)*
Central	Control n=5	A	18.4 ± 1.6	159.7 ± 10.5	2869.8 ± 313.2
		B	18.8 ± 2.3	188.5 ± 15.9**	3513.0 ± 417.9**
	Vagotomy n=5	A	12.2 ± 1.6	292.4 ± 16.7	3541.6 ± 482.1
		B	12.4 ± 1.7	300.7 ± 14.4*	3717.6 ± 511.3*
Peripheral	Central n=5	A	18.0 ± 0.3	181.7 ± 18.5	3283.4 ± 374.8
		B	19.0 ± 0.4	213.1 ± 17.0***	4072.4 ± 390.1**
	Vagotomy n=5	A	12.8 ± 1.1	268.8 ± 60.3	4077.4 ± 252.6
		B	12.6 ± 1.0	311.1 ± 20.7	3849.4 ± 177.6

*P<0.05, **P<0.01, ***P<0.001
A: Before administration B: After administration

TABLE IV : Mean and standard error (M ± SE) values of f, V_T and $\dot{V}_E$ with central and peripheral atropine administrations after atropine.

Administration	*Experimental group*			*f/min*	V_T *(ml)*	$\dot{V}_E$ *(ml)*
Central	Control n=5	Atropin	A	17.4 ± 1.1	184.0 ± 5.1	2750.4 ± 651.8
			B	18.0 ± 1.0	198.0 ± 16.5	3516.0 ± 230.5
		Ach.	A	19.2 ± 2.1	194.0 ± 16.3	3712.0 ± 502.2
			B	21.0 ± 2.1	218.0 ± 23.6	4500.0 ± 463.3
Peripheral	Control n=5	Atropin	A	24.6 ± 1.7	167.1 ± 6.5	4103.1 ± 302.5
			B	24.6 ± 1.6	183.9 ± 7.8*	4558.7 ± 325.8
		Ach.	A	24.6 ± 1.6	183.0 ± 8.4	4498.1 ± 337.5
			B	26.2 ± 1.8	188.2 ± 9.1	4935.6 ± 412.3

*P<0.05, **P<0.01, ***P<0.001
A: Before administration B: After administration

peripheral administration of acetylcholine. Although, V_T response to central administration of acetylcholine was not affected by vagotomy, response to peripheral administration was abolished (Table II).

Effects of atropine: In order to determine whether the effects of Ach were due to muscarinic or nicotinic action atrophine was administered. No changes were observed in respiratory frequency of the control animals in response to central or peripheral administrations of atropine. V_T on the other hand was found to increase in response to both administrations. Increase in V_T in response to central administration persisted after vagotomy. The increase in V_T in response to peripheral administration was abolished after vagotomy (Table III).

Effects of acetylcholine administration after atropine: Both central and peripheral administrations of acetylcholine after atropine increased V_T significantly. The decrease in V_T which is observed on administration of acetylcholine disappeared when acetylcholine was administered after atropine. No change was observed in respiratory frequency (Table IV).

DISCUSSION

Both central and peripheral administrations of epinephrine led to increases in V_T and f in control animals. The increases in f in response to administration through both routes disappeared after vagotomy. This finding shows that the increase in f is mediated by vagal reflexes. Although, the increase in V_T in response to peripheral administration of epinephrine was abolished after vagotomy, the response to central administration was not affected. It is well known that release of catecholamines from sympathetic nerves or injection catecholamines inhibit vagal tone and induce the relaxation of the airway smooth muscle (4, 5). In addition catecholamines the effect of the peripheral chemoreceptors and lung receptors (6). The increase in V_T observed by us in response to peripheral administration of epinephrine appears to be due to stimulation of peripheral chemoreceptor, lung receptors and change of airway caliber.

Persistance of the V_T response to central administration of epinephrine after vagotomy indicates that the response is brought about by direct action of epinephrine on central inspiratory activity. It is well known that the locus ceruleus contains the cell bodies of norepinephrine secreting neurons, and increased activity of locus ceruleus stimulates respiration (7), supports our results.

It this study responses in V_T and f to peripheral administration of acetylcholine were abolished after vagotomy, indicates that these responses are mediated by vagal reflexes. As is well known acetylcholine released from postganglionic nerve fibers, activates muscarinic receptors of the airway smooth muscle (5). Acetylcholine induces contraction of the smooth muscle of all levels of tracheobronchial tree (8). Stimulation of the caudal end of the vagus nerve results in construction of airway smooth muscle (8). Thus the response we observed in V_T and f may be a result of vagal reflexes due to the stimulation of lung receptors induced by airway smooth muscle contraction.

On central administration of acetylcholine an increase in f and a biphasic

response in V_T was obtained. A significant decrease in V_T was followed by a significant increase. Vagotomy abolished the increase in f while it had no effect on V_T response. Central administration of atropine on the other hand caused a significant increase in V_T. The response in V_T was not affected by vagotomy. Central administration of acetylcholine after atropine produced no significant change in V_T. These results indicate that acetylcholine acting centrally inhibits central inspiratory activity by muscarinic involvement. In fact, inspiratory neuronal spike density has been shown to be affected by muscarinic receptor excitation (9). The subsequent increase in V_T in response to central acetylcholine application seems to be secondary to the initial decrease and the resultant decrease in PO_2 and increase PCO_2. In that condition stimulation of chemoreceptors causes an increase in V_T. The response in f to central application of acetylcholine disappeared after vagotomy. This finding clearly shows that the change in f is brought about vagal reflexes.

In conclusion, acetylcholine applied either centrally or peripherally diminishes V_T by muscarinic action. Epinephrine produced an excitatory effect on inspiratory neurons and hence increased V_T. Respiratory responses to peripheral administration of epinephrine, acetylcholine and atropine are brought about by vagal reflexes.

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