Cholinergic Mechanisms on Cardiovascular Regulation in the Ventrolateral Medulla of the Rat

Seong Yun Kim*, Taek Lip Koh and Sang Bok Lee

Department of Pharmacology, Catholic University Medical College, Seoul Korea

ABSTRACT

This study was carried out to determine the role of cholinoceptors in the ventrolateral medulla on central control of blood pressure (BP) and heart rate (HR). In rats anesthetized with urethane and paralyzed, microinjections of the neuroexcitatory amino acid L-glutamate (300 ng/site) were performed to functionally identify the vasopressor area (VLPA) and the vasodepressor area (VLDA) in the ventrolateral medulla oblongata.

1. The bilateral microinjection of carbachol (300 ng/site) into the VLPA produced significantly an increase in BP and HR which was not blocked by bilateral pretreatment of hexamethoium (4 μg/site).

2. The bilateral microinjection of physostigmine (200 ng/site) and oxotremorine (300 ng/site) into the VLPA produced signficantly an increase in BP respectively.

3. The bilateral microinjection of atropine (4 μg/site) into the VLPA produced significantly a decrease in BP and HR.

4. The bilateral microinjection of acetylcholine (500 ng/site) and dimethylphenylpiperazinium (500 ng/site) into the VLDA produced significantly a decrease in BP and HR respectively.

5. The depressor and bradycardiac responses elicited by the bilateral microinjection of acetylcholine (500 ng/site) into the VLDA were blocked by bilateral pretreatment of hexamethonium (4 μg/site).

The results suggest that the activation of cholinoceptors in VLPA produce hypertensive and tachycardiac responses which may be mediated by muscarinic receptors, and the activation of cholinoceptors in VLDA produce hypotensive and bradycardiac responses which may be mediated by nicotinic receptors.

Key Words: Cholinergic mechanism, Blood pressure, Ventrolateral medulla, Vasopressor area, Vasodepressor area

INTRODUCTION

In rescent years, it has become apparent that neurons in the vasopressor area of the ventrolateral medulla (VLPA) play an integral role as a tonic vasomotor center (Guertzenstein et al., 1978; Dampney and Moon, 1980; Ross et al., 1983; Granata et al., 1985b) Electrical or chemical stimulation of the VLPA causes an increase in BP, while lesions of the VLPA result in reductions of BP comparable to those produced by sectioning the spinal cord (Dampney et al., 1982; Granata et al., 1983; Punnen and Sapru, 1985; McAllen, 1986). Anatomical and electrophysiological studies indicate that the VLPA contains neurons which project to the intermediolateral column of the thoracolumbar spinal cord (Ross et al., 1984; Brown and Guyenet, 1985; Levedev et al., 1986; Dampney et al., 1987).

In contrast with the VLPA, neurons in the vasodepressor area of the ventrolateral medulla (VLDA) exert opposing action on BP. Electrical

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*To whom reprint requests should be addressed.

stimulation or L-glutamate microinjection to the VLDA lowers BP, and bilateral destruction by electrolytic lesions or tetrodotoxin microinjection to this area raises BP (Blessing and Reis, 1982a; Blessing and Reis, 1982b; Minson and Chalmers, 1984; Willette et al., 1987).

There is much evidence that the acetylcholine in brain is implicated in the central control of cardiovascular functions, for exemple: first, intracerebroventricular (i.c.v.) injection of cholinomimetics evokes hypertension (Hoffman and Phillips, 1976; Lee and Kim, 1984); second, only acetylcholinesterase inhibitors that can enter the central nervous system evoke a pressor response after systemic administration (Varagić, 1955), and reductions in brain acetylcholine levels after i.c.v. injection of hemicholinium-3 result in a reduction of the pressor response to physostigmine (Brezenoff and Rusin, 1974); third, a central cholinergic antagonist lowers BP in spontaneously hypertensive rats (Coram and Brezenoff, 1982).

However, variable cardiovascular effects were reported following central administration of cholinomimetics (Armitage and Hall, 1967; Brezenoff and Jenden, 1970; Guertzenstein, 1973; Kubo and Misu, 1981). The differing results obstained by these investigators may arise from either differences in receptor function at various neuronal sites in the central nerovous system or the species of animals used.

The present sutdy was, therefore, carried out to clarity the role of cholinoceptors in the ventrolateral medulla on central control of BP and HR. Thus, after bilateral microinjections of cholinergic agonists, cholinesterase inhibitors, or cholinergic antagonists into the VLPA or the VLDA, the cardiovascular effects were observed.

MATERIALS AND METHODS

General procedures

Male Wistar rats weighing 300-350 g were anesthetized with urethane (1.25-1.4 g/kg, i.p.). A short trachea cannula was inserted to allow a clear surgical field. A common carotid artery was cannulated for measurement of blood pressure. The sternohyoideus muscles and omohyoideus muscles were cut at their insertions and reflected caudally. The upper part of the trachea, together with esophagus, were ligated, cut, and retracted rostrally. The longus capitis muscles were retract-ed caudally, exposing the occipital foramen and the basal aspect of the occipital bone. The basal occipital bone was removed with a drill, creating a window 5 mm long and 6 mm wide. The ventral surface of the medulla was then exposed by incising the dura and arachnoid under the stereomicroscope (Reichert). To avoid secondary cardiovascular effects, the animals were paralyzed with d-tubocurarine (0.7 mg/kg, i.m.) and artificially ventilated with room air using respirator (Harvard) as described by Kleinman and Radford (1964). The pulsatile arterial blood pressure recordings were made using a Toyo pressure transducer connected to a Biophysiograph (San Ei). The mean blood pressure

was calculated as diastolic pressure $+ 1/3$ (Systolic pressure minus diastolic pressure). Heart rate was computed by a heart rate meter (San Ei-2140). Rectal temperature was monitored and maintained at $37 \pm 0.5°C$ by a heat plate.

Microinjection technique

The rats were fixed supine in a stereotaxic instrument (David Kopf Instruments). Glass micropipettes were pulled to an outside tip diameter of 50-70 μm and were connected to a 10 μl Hemilton syringe by polyethylene tube (PE 20). Drug solutions were microinjected in a volume of 100 nl in 5 s with a micrometer. The rostrocaudal, mediolateral and ventrodorsal stereotaxic standard coordinates were determined to the most caudal aspect of the occipital foramen, basilar artery and ventral surface of the medulla, respectively. L-Glutamate excitatory aminoacid (300 ng /site) was microinjected in 250 μm steps from the stereotaxic standard coordinates into the ventrolateral medulla and then the VLPA and VLDA were identified observing a transient hypertensive and hypotensive responses, respectively. In present study, the VLPA and VLDA were located 2.6 to 3.5 mm and 1.8 to 2.3 mm rostral from the most caudal aspect of the occipital foramen, 1.6-2.0 mm and 1.6-1.8 mm lateral to the basilar artery and 0.5-1.0 mm and 0.5-1.1 mm dorsal from the ventral surface of medulla, respectively. Following the identification of the VLPA or the VLDA each drug solution was microinjected into the VLPA or the VLDA and the pulsatile arterial pressure and heart rate responses were recorded. Microinjections of 0.9% NaCl solution were used as controls. After observing each drug responses, 1%

fast green solution was microinjected into the same injection site of each drug. At the end of the experiments, rats were perfused through the heart with 10% formalin in 0.9% NaCl. The brains were removed and postfixed into the same fixative. Microinjection sites were then confirmed on 50 μm sections.

Drugs

All drugs microinjected were dissolved in 0.9 % NaCl and pH was adjusted to 7.2 to 7.4 with NaOH or HCl. The following drugs were purchased from Sigma: L-glutamate monosodium, carbamylcholine chloride, physostigmine sulfate, oxotremorine, atropine sulfate, acetylcholine bromide, dimethylphenylpiperazinium iodide (DMPP) and hexamethonium bromide.

Statistical analysis

All values were expressed as the mean ± S.E.M. Paired two-tailed t-tests were used to determine significance of differences between means.

RESULTS

Cardiovascular effects of carbachol, physostigmine, oxotremorine and atropine in the VLPA.

The VLPAs were functionally identified by

microinjection of the neuroexcitatory amino acid L-glutamate monosodium (300 ng/site) into the rostral ventrolateral medulla which caused a transient increase in BP and HR (Fig. 1A). These microinjection sites were identified histologically (Fig. 1B). Each drug responses were observed in the VLPA identified functionally with L-glutamate.

Carbachol: Bilateral microinjections of carbachol chloride (300 ng/site) into the VLPA produced an increase in BP and HR. Control BP and HR in these animals (n=7) were 93±6 mmHg and 368±22 beats per min (bpm), respectively. The magnitude of the increase in BP and HR was 46±8 mmHg (P<.01) and 23±7 bpm (P<.05), respectively (Fig. 2). In four experiments, pretreatment by the bilateral microinjections of hexamethonium bromide (4 μg/site) into the VLPA did not affect the cardiovascular responses to carbachol chloride (300 ng/site) injected into the same area.

Physostigmine: Bilateral microinjections of physostigmine sulfate (200 ng/site) into the VLPA produced an increase in BP with little or no change in HR. Control BP and HR in these animals (n=7) were 89±5 mmHg and 353±13 bpm, respectively. The magnitude of the increase in BP was 28±4 mmHg (P<.001) (Fig. 3).

Oxotremorine: Bilateral microinjections of oxotremorine (300 ng/site) into the VLPA produced an increase in BP with little or no change in
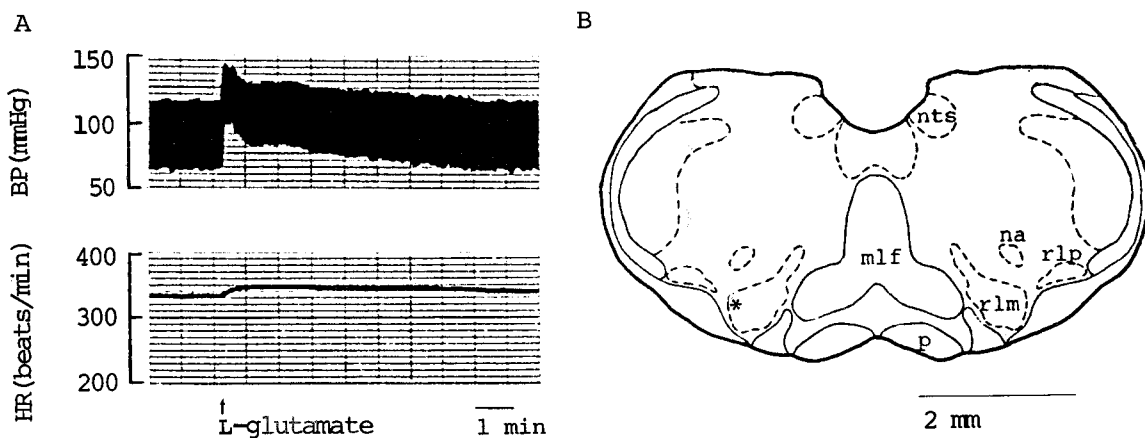

A

B

Fig. 1. The VLPA was functionally identified by observing hypertensive response after microinjection of L-glutamate (300 ng/site) into the rostral ventrolateral medulla (A). The location of the site (*) was determined histologically (B, Adapted from Pellegrino et al., 1979).
Abbreviation : BP, blood pressure ; HR, heart rate ; mlf, medial longitudinal fasciculus ; na, nucleus ambiguus ; nts, nucleus tractus solitarius ; p, pyramidal tract ; rlm, nucleus reticularis lateralis magnocellularis ; rlp, nucleus reticularis lateralis parvocellularis.
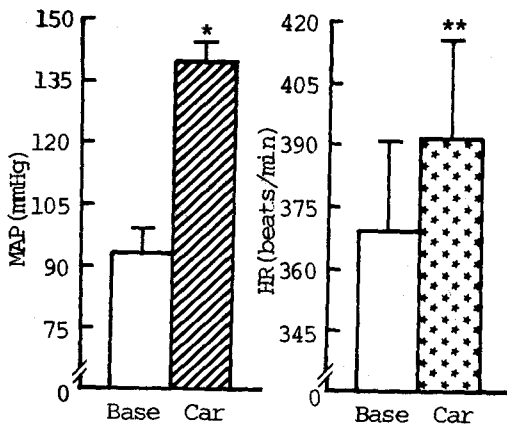
Fig. 2. Effects of bilateral microinjection of carbachol (300 ng/site) into the VLPA on mean arterial pressure (MAP) and heart rate (HR). Number of rats = 7, * P < .01, ** P < .05
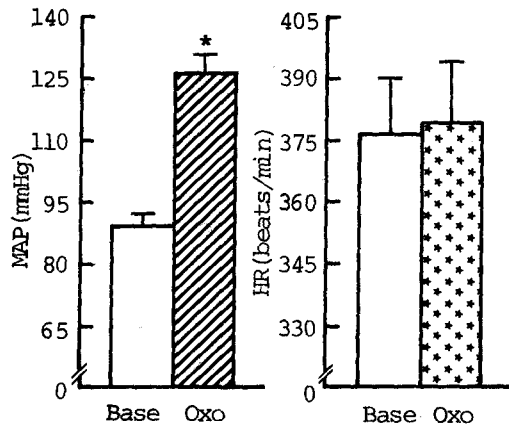Base, baseline ; Car, carbachol

Fig. 4. Effects of bilateral microinjection of oxotremorine (300 ng/site) into the VLPA on mean arterial pressure (MAP) and heart rate (HR). Number of rats = 7, * P < .001
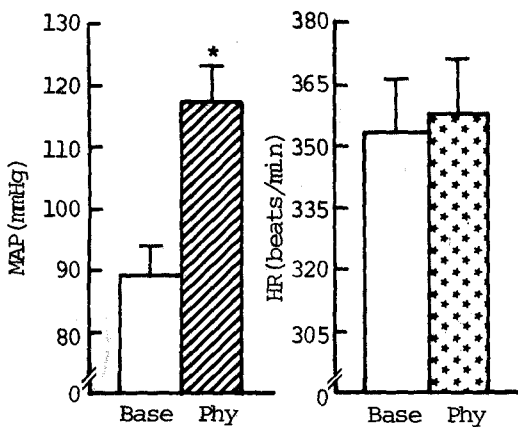Base, baseline; Oxo, oxotremorine

Fig. 3. Effects of bilateral microinjection of physostigmine (200 ng/site) into the VLPA on mean arterial pressure (MAP) and heart rate (HR). Number of rats = 7, * P < .001
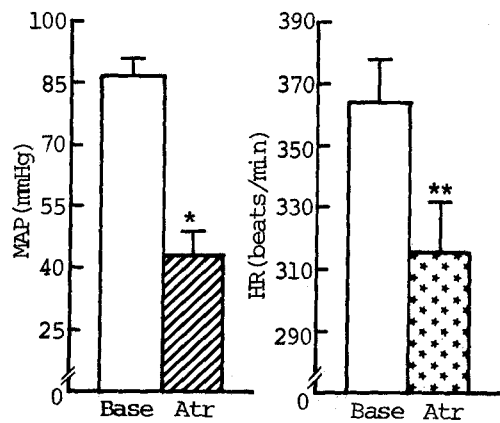Base, baseline ; Phy, physostigmine

Fig. 5. Effects of bilateral microinjection of atropine (4 μg/site) into the VLPA on mean arterial pressure (MAP) and heart rate (HR). Number of rats = 7, * P < .001, ** P < .01
Base, baseline; Atr, atropine

HR. Control BP and HR in these animals (n = 7) were 89 ± 3 mmHg and 376 ± 14 bpm, respectively. The magnitude of the increase in BP was 37 ± 3 mmHg (P < .001) (Fig. 4).

Atropine: Bilateral microinjections of atropine sulfate (4 μg/site) into the VLPA produced a decrease in BP and HR. Control BP and HR in these animals (n = 7) were 87 ± 4 mmHg and $364 \pm$

14 bpm, respectively. The magnitude of the decrease in BP and HR was 44 ± 4 mmHg (P < .001) and 49 ± 8 bpm (P < .01), respectively. (Fig. 5).

Cardiovascular effects of acetylcholine, DMPP and hexamethonium in the VLDA

The VLDAs were functionally identified by

A   B
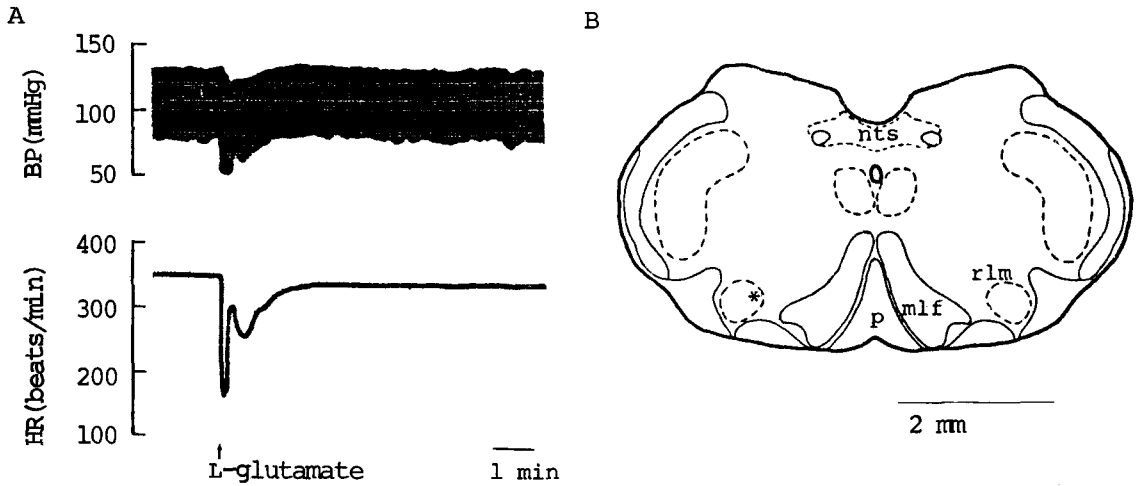
Fig. 6. The VLDA was functionally identified by observing hypotensive response after microinjection of L-glutamate
(300 ng/site) into the caudal ventrolateral medulla (A). The location of the site (*) was determined histologi-
cally (B, Adapted from Pellegrino et ai., 1979).
Abbreviation : BP, blood pressure ; HR, heart rate ; mlf, medial longitudinal fasciculus ; nts, nucleus tractus
solitarius ; p, pyramidal tract ; rlm, nucleus reticularis lateralis magnocellularis

microinjection of L-glutamate (300 ng/site) into
the caudal ventrolateral medulla which caused a
transient decrease in BP and HR (fig. 6A). These
microinjection sites were identified histologically
(Fig. 6B). Each drug responses were observed in
the VLDA identified functionally with L-gluta-
mate.

Acetylcholine: Bilateral microinjections of
acetylcholine bromide (500 ng/site) into the
VLDA produced a decrease in BP and HR.
Control BP and HR in these animals (n=7) were
83 ± 3 mmHg and 351 ± 12 bpm, respectively. The
magnitude of the decrease in BP and HR was $28\pm$
2 mmHg (P< .001) and 52 ± 9 bpm (P< .01) res-
pectively (Fig. 7).

DMPP: Bilateral microinjections of dimethyl-
phenylpiperazinium iodide (500 ng/site) into the
VLDA produced a decrease in BP and HR.
Control BP and HR in these animals (n=7) were
82 ± 4 mmHg and 369 ± 9 bpm, respectively. The
magnitude of the decrease in BP and HR was $27\pm$
3 mmHg (P< .001) and 66 ± 21 bpm (P< .05)
respectively (Fig. 8).

**Blockade of acetylcholine responses by hexa-
methonium pretreatment:** In five experiments,
bilateral microinjections of hexamethonium bro-
mide (4 μg/site) into the VLDA produced little or
no change in BP and HR. Ten minutes after
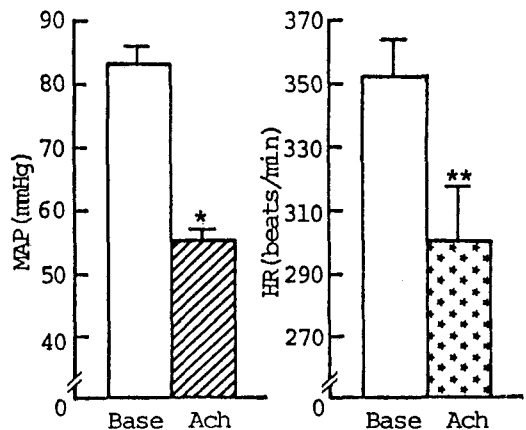
Fig. 7. Effects of bilateral microinjection of acetylcholine
(500 ng/site) into the VLDA on mean arterial
pressure (MAP) and heart rate (HR). Number of
rats = 7, * P < .001, ** P < .01
Base, baseline ; Ach, acetylcholine

administration of hexamethonium, acetylcholine
bromide (500 ng/site) was microinjected bilateral-
ly into the same VLDA site. Cardiovascular ef-
fects of acetylcholine were blocked by pretreat-
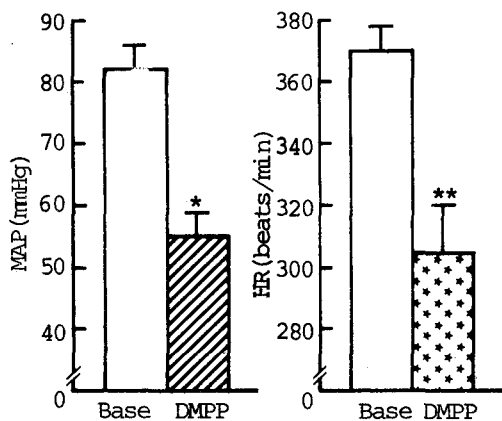ment of hexamethonium.

Fig. 8. Effects of bilateral microinjection of DMPP (500 ng/site) into the VLDA on mean arterial pressure (MAP) and heart rate (HR). Number of rats = 7, * $P < .001$, ** $P < .05$
Base, baseline; DMPP, dimethylphenylpiperazinium.

DISCUSSION

The VLPA and the VLDA located in the ventrolateral medulla oblongata seem to be important sites for the neural regulation of BP. The VLPA is involved in the maintenance of vasomotor tone (Ross et al., 1983), in baroreceptor and chemoreceptor reflex mechanisms (Granata et al., 1983; Caverson et al., 1984) and in mediating the cerebral ischemic response and the somatosympathetic reflexes (Rohlicek and Polosa, 1983; McAllen, 1985). The VLPA is known to contain adrenergic neurons (C_1 cells) which project directly to the preganglionic sympathetic cells in the intermediolateral cell column of the thoracolumbar spinal cord (Hökfelt et al., 1974; Goodchild et al., 1984). On the other hand, neurons in the VLDA provide a tonic inhibition of vasomotor activity (Blessing and Reis, 1982a; Willette et al., 1984a) and are also involved in the control of the secretion of vasopressin (Blessing and Willoughby, 1985), but are not directly involved in the baroreflex (Granata et al., 1985b). The VLDA includes the noradrenergic neurons (A_1 cells) (Dahlström and Fuxe, 1964; Blessing et al., 1978) and there exists no direct pathway which descend from the VLDA to spinal cord (Blessing et al., 1981). Changes in the activity of

neurons in the VLDA mediate the activity of preganglionic sympathetic neurons via neurons in the VLPA (Granata et al., 1985a; Punnen and Sapru, 1985). Neurochemical studies have shown that in addition to epinephrine-, norepinephrine-, serotonin- and peptide- containing perikarya, the ventrolateral medulla also contains a cholinergic system which has been identified by the presence of acetylcholine esterase (Palkovits and Jacobowitz, 1974), choline acetyltransferase (Kimura et al., 1981), acetylcholine (Helke et al., 1980), muscarinic receptors (Hershkowitz et al., 1983) and nicotinic receptors (Yamada et al., 1987).

In this study, the VLPA and VLDA were functionally identified bilaterally by microinjection of the neuroexcitatory amino acid L-glutamate (300 ng/site) which caused a transient increase and a decrease in BP, respectively. L-Glutamate is known to depolarize cell bodies but not to excite axons of passage (krinjevic and Phillips, 1963; Fries and Zieglgansberger, 1974), and therefore it could be thought that the VLPA and the VLDA identified with L-glutamate contain vasopressor- and vasodepressor-neuron pools, respectively.

In the present study, stimulation of cholinergic receptors in the VLPA with carbachol caused an increase in BP and HR. Willette et al. (1984b) and Benarrhoch et al. (1986) also demonstrated the presence of excitatory cholinergic receptors in the VLPA. In addition, vasopressor and tachycardiac responses to carbachol in the VLPA were not blocked by local pretreatment with the nicotinic blocking agent hexamethonium. Thus, to ascertain the role of muscarinic cholinergic receptors in the VLPA which may be involved in cardiovascular regulation, the selective muscarinic cholinergic receptor agonist, oxotremorine (Cho et al., 1962) and the same receptor antagonist, atropine, were microinjected into the VLPA. In the VLPA, oxotremorine caused an increase in BP and atropine did a decrease in BP and HR. Furthermore, the bilateral microinjection of physostigmine into the VLPA caused an increase in BP. Since the action of physostigmine results from the inhibition of cholinesterase, it could be thought that the cardiovascular response to physostigmine was mediated via the accumulation of acetylcholine released from terminals of cholinergic neurons innervated in the VLPA. These results indicate the presence of excitatory muscarinic cholinoceptors in the VLPA which may be tonically involved in cardiovascular regulation.

On the other hand, bilateral microinjection of acetylcholine into the VLDA caused a decrease in BP and HR. Dev and Loeschcke (1979) also demonstrated the presence of inhibitory cholinergic receptors in caudal ventrolateral medulla by observing facts that the topical administration of acetylcholine in the ventral surface of the medulla caused a decrease in BP and HR. Bisset and Chowdrey (1984) reported that nicotinic receptors are located on neurons in the caudal ventrolateral medulla of the rabbit. Thus, to clarify the role of nicotinic cholinergic receptors in the VLDA on cardiovascular regulation, the hypotensive and bradycardiac responses were observed when the selective nicotinic cholinergic receptor agoinst, DMPP, was microinjected into the VLDA. In addition, the responses to acetylcholine in the VLDA were blocked by hexamethonium-pretreatment in this area which itself did not alter the BP and HR. These results indicate the presence of inhibitory nicotinic cholinoceptors in the VLDA which may be involved in cardiovascular regulation.

In summary, the results suggest that the activation of cholinoceptors in the VLPA produce the hypertensive and tachycardiac responses which may be mediated by muscarinic receptors, and the activation of cholinoceptors in the VLDA produce the hypotensive and bradycardiac responses which may be mediated by nicotinic receptors.

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== 국문초록 ==

흰쥐 복외측 연수에서 심혈관 조절에 대한 Choline성 기전

가톨릭대학 의학부 약리학교실

김 성 윤 · 고 택 립 · 이 상 복

혈압과 심박수의 중추조절에 대한 복외측 연수의 choline성 수용체의 역할을 규명하기 위하여 본 연구를 실시하였다. urethane으로 마취한 흰쥐에서 신경흥분성 아미노산인 L-glutamate(300 ng/site)를 복외측 연수에 미세주사하여 승압부위(VLPA)와 감압부위(VLDA)를 각각 기능적으로 확인하였다. VLPA와 VLDA에 각각 여러가지 choline성 약물들과 choline성 수용체의 길항제들을 양측으로 미세주사하여 다음과 같은 결과를 관찰하였다.

1. VLPA에 carbachol(300 ng/site)를 미세주사한 후 현저한 혈압상승 및 빈맥이 일어났으며, 이 반응은 hexamethonium(4 μg/site)의 전처치에 의하여 차단되지 않았다.

2. VLPA에 physostigmine(200 ng/site)과 oxotremorine(300 ng/site)을 미세주사한 후 각각 현저한 혈압상승이 일어났다.

3. VLPA에 atropine(4 μg/site)을 미세주사한 후 현저한 혈압하강 및 서맥이 일어났다.

4. VLDA에 acetylcholine(500 ng/site)과 dimethylphenylpiperazinium(500 ng/site)을 미세주사한 후 각각 현저한 혈압하강 및 서맥이 일어났다.

5. VLDA에 acetylcholine(500 ng/site)을 미세주사한 후 유발된 혈압하강 및 서맥반응은 hexamethonium(4 μg/site) 전처치에 의하여 차단되었다.

이상의 결과로 보아 흰쥐의 복외측 연수의 승압부위에서는 muscarine성 수용체를 통하여 혈압상승 및 빈맥반응이 일어나고 감압부위에서는 nicotine성 수용체를 통하여 혈압하강 및 서맥반응이 일어나는 것으로 사료된다.