Korean J. of Pharmacology
Vol.28, No.2, pp.171-179, 1992

Studies on the Interactions of M_1-,M_2-receptors with Nicotinic Receptors in Rabbit Sympathetic Ganglia

Jong Keun Kim[1], Choon Sik Rhu* and Sam Suk Kang*

Department of Pharmacology and Neurosurgery, Chonnam University Medical School, Kwangju 501-190, Korea*

ABSTRACT

Effects of a M_1 receptor antagonist, pirenzepine, a M_2 receptor antagonist, AF-DX116, and a nicotinic receptor antagonist, mecamylamine on the pressor responses to preganglionic sympathetic nerve stimulation (PNS) and McN-A-343 and DMPP in spinal (pithed) rabbits were investigated, in order to elucidate a functional role of M_1, M_2 and nicotinic receptors in ganglionic transmission. Pirenzepine and AF-DX116 selectively inhibited the McN-A-343-induced pressor response in chlorisondamine-treated rabbit and the BCh-induced bradycardia, respectively. Electrical stimulations of preganglionic sympathetic outflow at T8 level produced increases in blood pressure. Pirenzepine (3 μg/kg) significantly inhibited the PNS-induced pressor response and the degree of inhibition was not changed by increasing the doses to 100 μg/kg. AF-DX116 (100 μg/kg) had no effect on the PNS-induced pressor response. Mecamylamine inhibited the PNS-induced pressor response in a dose-dependent manner. The inhibitory action of mecamylamine was significantly augmented by combined-treatment with pirenzepine (30 μg/kg) but AF-DX116 (100 μg/kg) did not affect the inhibitory action of mecamylamine. McN-A-343 and DMPP elicited pressor response in the spinal rabbit. Pirenzepine and AF-DX116 dose-dependently inhibited the McN-A-343-induced pressor response but they did not affect DMPP-induced pressor response. Mecamylamine inhibited both pressor responses induced by McN-A-343 and DMPP. These results suggest that not only nicotinic receptors but also M_1 receptors play a facilitatory role in ganglionic transmission but M_2 receptors do not contribute the transmission in spinal (pithed) rabbits.

Key Words: Ganglionic transmission, M_1, M_2 receptors, Nicotinic receptors, Pirenzepine, AF-DX116, Mecamylamine

INTRODUCTION

It has been shown that preganglionic sympathetic stimulation elicits hypertension and tachycardia not only through nicotinic receptors but also through muscarinic receptors in sympathetic ganglia of dog, cat, rat, guinea pig and rabbit (Flacke and Gillis, 1968; Brown, 1969; Willfert *et al.*, 1982; Alsip and DiMicco, 1986; Yoo, 1989). Acetylcholine released from the preganglionic nerve terminals acts on nicotinic receptors to generate s-EPSP and s-IPSP as well as on muscarinic receptors to generate f-EPSP (Libet, 1986).

Recently muscarinic receptors are classified into M_1 and M_2 receptors characterized by high (M_1) or low (M_2) affinity for the muscarinic antagonist pirenzepine (Birdsall *et al.*, 1984; Hammer and Giachetti, 1992) and it was demonstrated that the two types of muscarinic receptor were present

[1]To whom requests for reprints should be addressed.

[2]This paper was supported in part by NON DIRECTED RESEARCH FUND, Korea Research Foundation to JKK, 1991.

in sympathetic ganglia (Hammer and Giachetti, 1982; Libet, 1986). Pirenzepine was shown to block selectively the generation of the s-EPSP and to suppress selectively agonist-induced depolarization in the rabbit and rat isolated sympathetic ganglia (Ashe and Yarosh, 1984; Newberry and Gilbert, 1989; Newberr and Gilbert, 1989; Newberry and Priestley, 1987; Yarosh and Ashe, 1987). It has been reported that AF-DX116 was a selective M_2-receptor antagonist (Giachetti *et al.*, 1986; Hammer *et al.*, 1986), and AF-DX116 blocked selectively s-IPSP in the rabbit sympathetic ganglia (Mochida and Kobayashi, 1988; Yarosh *et al.*, 1988).

In the present study, it was attempted to functionally elucidate interactions of M_1 and M_2 receptors with nicotinic receptors, by examining the effects of pirenzepine, AF-DX116 and mecamylamine on the pressor responses to preganglionic sympathetic nerve stimulation and dimethylphenylpiperazium (DMPP)- and McN-A-343-induced pressor responses in spinal rabbits.

METHODS

Rabbits of either sex (1.9~2.4 kg) were anesthetized with 1 g/kg urethane s.c. The trachea was cannulated and the animal was fastened prone with its head extended.

Blood pressure was taken from left femoral artery and recorded on a recorder (Gould model 3400) through pressure transducer (Statham P23ID). Blood pressure was expressed as mean arterial pressure (mean±SE). Heart rate was simultaneousely recorded with blood pressure by means of biotachometer and expressed as beats per minute (mean±SE). Drugs were administered into the left ear vein.

Preganglionic nerve stimulation (PNS) in pithed rabbits: Under artificial respiration a small hole was made in the parietal bone, at the midline of the skull, close to its junction with frontal bone and a copper rod inserted 17 cm down the spine as measured from the hole. The rod was 2 mm in diameter and covered with plastic tubing, giving it a final diameter of 4.0 mm, and 1 cm of the end of the rod was left exposed. The tip reached approximately the spinal vertebra T8. The reference electrode was made of silver wire (3 cm of length) and was inserted into the muscle at the back of neck. To block skeletal muscle contraction during stimulation, d-tubocurarine chloride (0.25 mg/kg, iv) was given into the animal. To increase blood pressure, electrical stimulation was performed by rectangular pulses of 1 msec duration and 20V (supramaximal voltage) at 5 Hz delivered with electrical stimulator (Grass S9). The stimulation was maximal for increasing blood pressure without affecting heart rate.

Spinal rabbits were prepared by transecting the cervical cord at the level of C1 under artificial respiration.

In preliminary experiments, it was confirmed that the responses to repetitive trials of PNS and administration of McN-A-343 or DMPP were reproducible during experiment (for 2~3 hr). The time intervals from the administration of an antagonist to PNS and those of McN-A-343 or DMPP were 5 min in case of pirenzepine and mecamylamine and 3 min in case of AF-DX116. Pirenzepine or AF-DX116 was injected simultaneously with mecamylamine in experiments observing the effects of the combination of two drugs.

<Drugs>

McN-A-343 (RBI), dimethylphenylpiperazium iodide (DMPP, Sigma), pirenzepine 2HCl (Sigma), AF-DX116 (Dr. Karl Thomae GmBH), mecamylamine HCl (RBI), chlorisondamine HCl (Ciba), d-tubocurarine HCl (Sigma) and bethanechol HCl (Sigma) were used. Drugs except AF-DX116 were dissolved in saline. AF-DX116 was dissolved in 0.1 N HCl. These solutions were diluted with saline before use.

The 50% inhibitory doses (ID_{50}s) and 95% confidence limits of antagonists were calculated using least square linear regression analysis. The Student's t-test was employed in analyzing the data statistically.

RESULTS

Effect of pirenzepine and AF-DX116 on bethanechol-induced bradycardia and the McN-A-343-induced pressor response

In order to determine the doses producing selective blocking activity on M_1 or M_2 receptors, the effects of pirenzepine and AF-DX116 on pressor response to the M_1 receptor agonist, McN-A-343 (200 μg/kg) in chlorisondamine-treated rabbits and bradycardiac response to bethanechol (50 μg/kg) were examined.

In hypotensive state (40~70 mmHg, n=12) by administration of chlorisondamine (0.4 mg/kg), McN-A-343 (200 μg/kg) increased mean blood pressure from 51±2.9 mmHg to 94±3.7 mmHg. The mean magnitude of the pressor response was 43±2.9 mmHg. Pirenzepine selectively inhibited the pressor response to McN-A-343 (Fig. 1). The ID_{50} of pirenzepine against the pressor response obtained from Fig. 1. was 30 (19~47) μg/kg (Table 1). The pressor response was hardly affected by

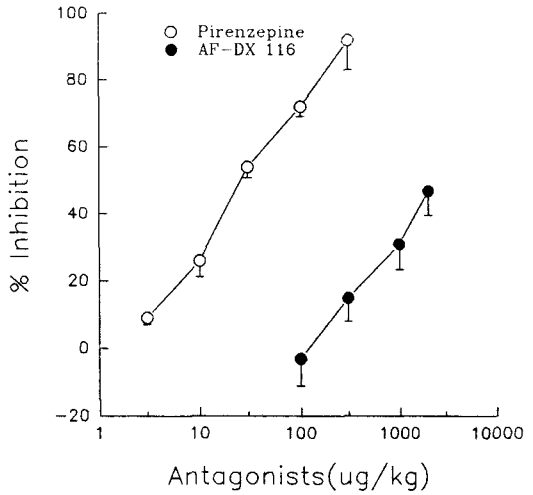

Fig. 1. % Inhibitory effects of pirenzepine and AF-DX116 on the McN-A-343 (200 μg/kg)-induced pressor response in chlorisondamine-pretreated rabbits. Each point represents the mean of % inhibition obtained from 8~12 rabbits. Vertical bars are SEM.

Table 1. The 50% inhibitory doses (ID_{50s}; μg/kg) of pirenzepine, AF-DX116 and mecamylamine against BCh-induced bradycardia and PNS-, McN-A-343- and DMPP-induced pressor response in rabbits

	Piressor(CS-treated) McN-A-343	Bradycardia BCh	Pressor PNS	Pressor(Spinal) NcN-A-343	Pressor(Spinal) DMPP
Prenzepine	30 (19~47)	150 (98~234)	–	1.8 (0.6~5.2)	–
AF-DX116	–	27 (8.7~42)	–	121 (78~186)	–
Mecamylamine			485 (263~912)	673 (444~1000)	294 (200~436)
+ PZ(30 μg/kg)			181 (134~244)		
+ AF-DX(100 μg/kg)			473 (252~889)		

CS-treated: Chlorisondamine(0.4 mg/kg) treated rabbits.

Numerals in parenthesis are 95% confidence limits of ID_{50s}.

–: Indicate that the experiments were under taken but data could not calculate ID_{50} because of low inhibitory effect of the antagonist.

100 μg/kg of AF-DX116, but 2 mg/kg of AF-DX116 inhibited the pressor response by 47±7.4% (Fig. 1). Bethanechol (BCh, 50 μg/kg) reduced heart rate from 223±11 to 179±9 beats/min. (n=8) during control experiment and the magnitude of the bradycardiac response was 44±4.8 beats/min. The bradycardia was more potently inhibited by AF-DX116 than by pirenzepine (Fig. 2). The ID_{50}s of AF-DX116 and pirenzepine against the bradycardia were 27 (8.7~42) μg/kg and 150 (98~234) μg/kg, respectively (Table 1). AF-DX116 inhibited the BCh-induced bradycardia more potently than the pressor response to McN-A-343. The degrees of inhibition by 100 μg/kg of AF-DX116 to the bradycardia and the pressor response were 81±4.3 and −3±8.1%, respectively.

Effects of pirenzepine and AF-DX116 on the pressor response to preganglionic sympathetic nerve stimulation (PNS)

The electrical stimulations (5Hz, 1msec duration, 20V for 30 sec.) of preganglionic sympathetic outflow at T8 were performed in pithed rabbits.

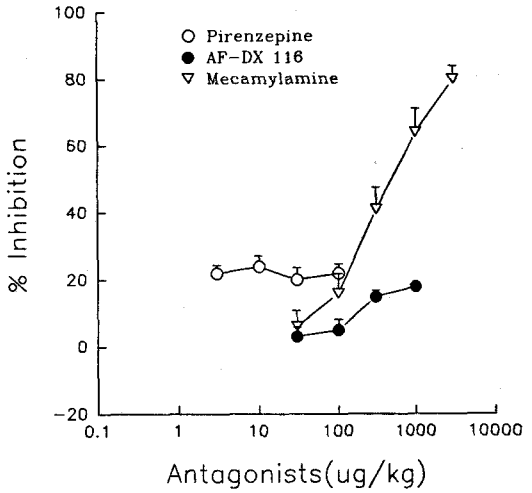

Fig. 3. % Inhibitory effects of pirenzepine, AF-DX116 and mecamylamine on the pressor response to PNS in pithed rabbits. Each point represents the mean of % inhibition obtained from 4~8 rabbits. Vertical bars are SEM.

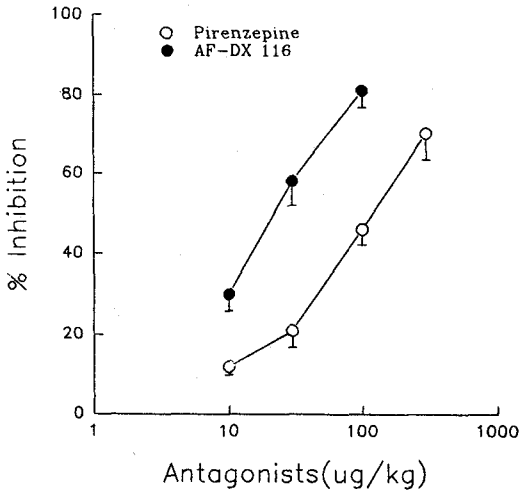

Fig. 2. % Inhibitory effects of pirenzepine and AF-DX116 on the BCh (50 μg/kg)-induced bradycardia in rabbits. Each point represents the mean of % inhibition obtained from 8 rabbits. Vertical bars are SEM.

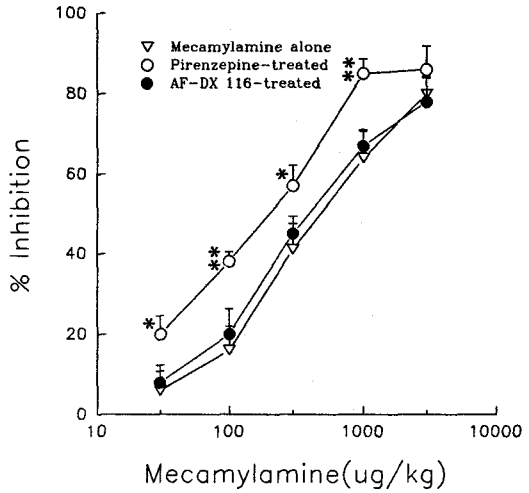

Fig. 4. % Inhibitory effects of mecamylamine and the combination of mecamylamine pirenzepine or AF-DX116 on the pressor response to PNS in pithed rabbits. Asterisks indicate significant difference from the % inhibitory effect of mecamylamine (*P<0.05, **P<0.01). Other legends are the same as in Fig. 3.

The pre-stimulation mean arteral pressure was 33 ±2.9 mmHg and heart rate was 209±8 beats/min (n=29). The PNS increased the blood pressure but had little effect on the heart rate. The magnitude of the increase in blood pressure was 24± 1.8 mmHg (n=29).

The original blood pressure was hardly changed by administration of pirenzepine (dose range: 3~ 100 μg/kg) and AF-DX116 (dose range: 30 μg/kg~ 1 mg/kg). The pressor responses to PNS before and after 3 μg/kg of pirenzepine were 25±1.8 and 19.5±1.5 mmHg, respectively (n=5, $p<0.01$, 22± 1.9% inhibition). The degree of inhibition (20~25 %) was almost same in all doses using in this experiment (3~100 μg/kg) (Fig. 3). AF-DX116 did not inhibit the pressor response in low doses (30 and 100 μg/kg) but caused slight but significant inhibition in doses of 300 and 1000 μg/kg ($p<0.05$) (Fig. 3).

Effects of mecamylamine, combination of mecamylamine and pirenzepine or AF-DX116 on the pressor response to PNS

The blood pressure showed slight fall (3~5 mmHg) by the administration of mecamylamine in doses over 300 μg/kg. Mecamylamine in doses of 0.1~3 mg/kg inhibited the pressor response to PNS in a dose-dependent manner (Fig. 3, 4). ID_{50} of mecamylamine against the pressor response was 485 (263~912) μg/kg (Table 1).

The dose-dependent inhibitory action of mecamylamine to the pressor response was significantly augmented by combined-treatment with 30 μg/kg of pirenzepine (Fig. 4). Under the combined-treatment with 30 μg/kg of pirenzepine, the ID_{50} of mecamylamine against the pressor response was 181 (134~244) μg/kg. AF-DX116 (100 μg/kg) did not affect the inhibitory action of mecamylamine (Fig. 4).

Effect of pirenzepine, AF-DX116 and mecamylamine on DMPP-and McN-A-343-induced pressor responses in spinal rabbits

To further evaluate the functional role of cholinergic receptors in ganglionic transmission, the effects of pirenzepine, AF-DX116 and mecamylamine on the pressor responses to McN-A-343 and DMPP were investigated in spinal rabbits.

Blood pressure of spinal rabbits ranged from 26 to 40 mmHg (mean±SE: 33±2.2 mmHg, n=58).

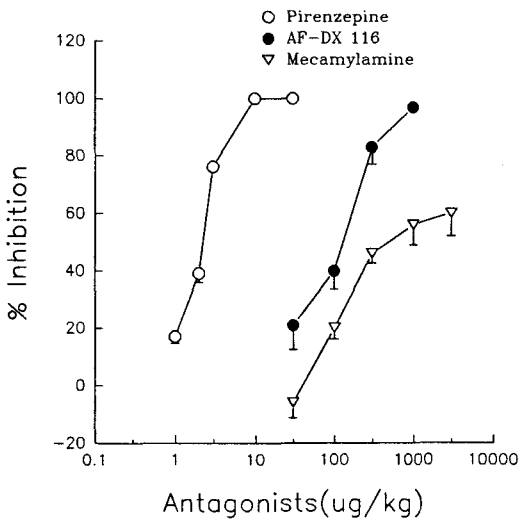

Fig. 5. % Inhibitory effects of pirenzepine, AF-DX116 and mecamylamine on the pressor response to McN-A-343 (100 μg/kg) in spinal rabbits. Other legends are the same as in Fig. 3.

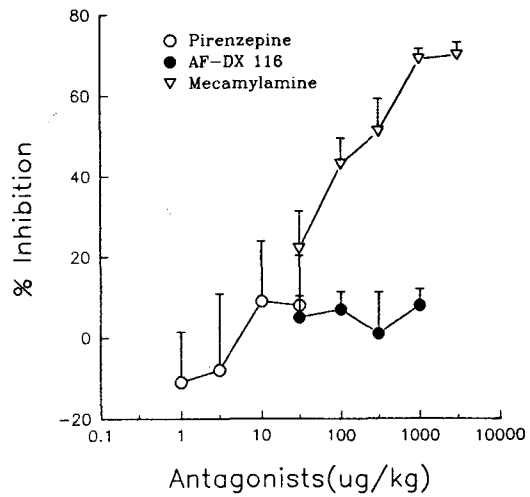

Fig. 6. % Inhibitory effects of pirenzepine, AF-DX116 and mecamylamine on the pressor response to DMPP (100 μg/kg) in spinal rabbits. Other legends are the same as in Fig. 3.

McN-A-343 produced an increase of blood pressure in the animals. The magnitudes of the pressor response to 30 μg/kg and 100 μg/kg McN-A-343 were 12±2.9 mmHg (n=6) and 28±2.6 mmHg (n=28), respectively. DMPP (100 μg/kg) also increased the blood pressure. The magnitude of the response was 20±1.6 mmHg (n=24). The pressor response to 100 μg/kg of McN-A-343 was inhibited by pirenzepine, AF-DX116 or mecamylamine in a dose-dependent manner (Fig. 5). 10 μg/kg of pirenzepine and 1 mg/kg of AF-DX116 almost abolished the pressor response. 3 mg/kg of mecamylamine inhibited the pressor response by 60%. The ID_{50}s of pirenzepine, AF-DX116 and mecamylamine agaist McN-A-343 induced pressor response were 1.8 (0.6～5.2), 121 (78～186) and 673 (444～1,000) μg/kg, respectively (Table 1). The pressor response to DMPP was inhibited by mecamylamine in a dose-dependent manner, but was not affected by pirenzepine or AF-DX116 (Fig. 6). The ID_{50} of mecamylamine against DMPP-induced pressor response was 294 (200～436) μg/kg (Table 1).

DISCUSSION

McN-A-343 is a selective agonist on M_1 receptor (Roszkowski, 1961; Rattan and Goyal, 1984). It has been shown that McN-A-343 caused a pressor response which was prevented by atropine or pirenzepine in cat, dog and rat (Roszkowski, 1961; Hammer and Giachett, 1982; Wess *et al.*, 1987). Yoo (1989) in our laboratory reported that McN-A-343, in contrast to the pressor response in cat, dog and rat, produced the depressor response in rabbit which reversed to a pressor one after the treatment of rabbit with ganglionic nicotinic receptor blockers (chlorisondamine or hexamethonium). And the pressor response in rabbit was also prevented by pirenzepine. Thus the McN-A-343-induced pressor response in this study is thought to be due to stimulation of M_1 receptor in sympathetic ganglia. BCh is a muscarinic agonist (Gilman *et al.*, 1990a). And the BCh-induced bradycardia in this study is considered to be due to M_2 receptor mediated slowing of pacemaker activity, because cardiac muscarinic receptors are classified as M_2 receptors (Hammer and Giachetti, 1982; Birdsall and Hulme, 1983; Giachetti, *et al.*, 1986). In the present study ID_{50} of pirenzepine against the McN-A-343-induced pressor response was 30 (19～47) μg/kg but 2 mg/kg of AF-DX116 inhibited the pressor response 47±7.4% in chlorisondamine-treated rabbits. In contrast, BCh-induced bradycardia was antagonized with a greater potency by AF-DX116, the ID_{50} being 27 (8.7～42) μg/kg, i.e. about 5 times lower than that of pirenzepine: 150 (98～234) μg/kg. These indicate that pirenzepine and AF-DX116 selectively act on M_1 and M_2 receptor respectively in the rabbit as in other experimental animals.

Pirenzepine in doses of 3, 10, 30 and 100 μg/kg significantly attenuated the PNS-induced pressor response and the degree of attenuation was similar at all doses. On the other hand, AF-DX116 in a dose of 100 μg/kg, which effectively inhibited the BCh-induced bradycardia, did not affect the PNS-induced pressor response. In support of these observation, Mukaiyama *et al.* (1991) reported that pirenzepine (30 μg/kg and 100 μg/kg) significantly attenuated tachycardia induced by preganglionic cardiac sympathetic nerve stimulation but AF-DX116 (10, 30 and 100 μg/kg) did not affect the tachycardia. Mecamylamine inhibited the PNS-induced pressor response in a dose-dependent manner. The inhibitory effect of mecamylamine was significantly augmented by the 30 μg/kg of pirenzepine but not affected by the 100 μg/kg of AF-DX116. There results are demonstrating that the pressor response to PNS is induced not only by the stimulation of ganglionic nicotinic receptors but also by the stimulation of ganglionic M_1 receptors and also suggested that M_1 receptors play a facilitatory role to some extent in ganglionic transmission and M_2 receptors do not contribute to the transmission.

In spinal rabbit, McN-A-343 and DMPP increased blood pressure. Pirenzepine and AF-DX116 inhibited the McN-A-343-induced pressor response in a dose-dependent manner but did not affect the DMPP-induced pressor one. The ID_{50} of pirenzepine against the McN-A-343-induced pressor response was 1.8 (0.6～5.2) μg/kg, i.e. about 67 times lower than that of AF-DX116: 121 (78～186) μg/kg. These results indicated that the pressor response to McN-A-343 be elicited by the stimula-

tion of M_1 receptor in spinal rabbits. The ID_{50} of pirenzepine (1.8 μg/kg) against McN-A-343-induced pressor reponse in spinal rabbits was about 16 times lower than the that (30 μg/kg) in chlorisondamine-treated rabbits. AF-DX116 in a dose of 1 mg/kg almost abolished the McN-A-343-induced pressor response and the ID_{50} of AF-DX116 against the pressor response was 121 μg/kg but AF-DX116 in a dose of 2 mg/kg inhibited the pressor response by 47±7.4% in chlorisondamine-treated rabbits. These differences between spinal and chlorisondamine-treated rabbits implied that preganglionic sympathetic nerve activity may modify the sensitivity of muscarinic antagonist for M_1 receptors. Kim (1990) reported that the sensitivity of the ganglionic muscarinic receptor is altered by ganglionic nicotinic blockade, by the decrease of central sympathetic outflow on the sympathetic ganglia or by spinalization in rabbits. Tonic influence of the brain on sympathetic outflow to sympathetic ganglia was removed in spinal or pithed rabbits. In the present study, the pressor response to PNS in pithed rabbits was slightly but significantly inhibited by 3 μg/kg of pirenzepine and 300 and 1000 μg/kg of AF-DX116. The doses of both antagonists are larger than ID_{50s} of both antagonists against McN-A-343-induced pressor response in spinal rabbit (pirenzepine: 1.8 μg/kg, AF-DX116: 121 μg/kg, Table 1). Thus the inhibitory effects of the doses of both antagonists on the PNS-induced pressor response resulted from antagonizing ganglionic M_1 receptors.

In present study, mecamylamine dose-dependently inhibited both DMPP-induced and the McN-A-343-induced pressor responses. Since mecamylamine is a well known ganglionic nicotinic antagonist (Gilman *et al.*, 1990b), the inhibitory effect of mecamylamine on the McN-A-343-induced pressor response is difficult to be figured out. Some reports suggested that hexamethonium, a ganglionic nicotinic antagonist, may modify the responses to muscarinic agonists in ileum (Geddes *et al.*, 1974), ganglia (Brown *et al.*, 1980) and cardiac tissue (Leung and Michelson, 1982), and that chlorisondamine, another ganglionic nicotinic antagonist, inhibited the McN-A-343-induced catecholamine release in rat adrenal medulla (Lim and Hwang, 1991).

In conclusion, the present results suggest that M_1 receptors play a functional role but M_2 receptors have no functional role in ganglionic transmission. Activation of M_1 receptors would facilitate nicotinic transmission in spinal rabbit.

REFERENCES

Alsip NL and DiMicco JA: *Evidence for transmission through sympathetic ganglia mediated by muscarinic receptors in anesthetized guinea pigs. Neuropharmacol 25: 515-518, 1986*

Ashe JH and Yarosh CA: *Differential and selective antagonism of the slow-inhibitory postsynaptic potential and slow-excitatory postsynaptic potential by gallamine and pirenzepine in the superior cervical ganglion of the rabbit. Neuropharmacology 23: 1321-1329, 1984*

Birdsall HJ and Hulme EC: *Muscarinic receptor subclasses. Trends Pharmacol Sci 4: 459-463, 1983*

Birdsall NJM, Hulme EC and Stockton JM: *Muscarinic receptors heterogeneity. Trends Pharmacol Sic 5 (Suppl): 4-8, 1984*

Brown AM: *Sympathetic ganglionic transmission and the cardiovascular changes of the defense reaction in the cat. Circulation Res 24: 843-849, 1969*

Brown DA, Fatherazi S, Garthwaite J and White RD: *Muscarinic receptors in rat sympathetic ganglia. Br J Pharmacol 70: 577-592, 1980*

Flacke W and Gillis RA: *Impulse transmission via nicotinic and muscarinic pathways in the stellate ganglion of the dog. J Pharmacol Exp Ther 163: 266-276, 1968*

Geddes BA, Bogart LF and Hamilton JT: *Conditions affecting the interaction of cholinergic agents on the longitudinal muscle of the guinea-pig ileum-unexpected effects with hexamethonium. J Pharm Pharmacol 26: 699, 1974*

Giachetti A, Micheletti R and Montagna E: *Cardioselective profile of AF-DX116, a muscarine M_2 receptor antagonist. Life Sci 38: 1663-1672, 1986*

Gilman AG, Rall TW, Nies AS and Taylor P: *The Pharmacological Basis of Therapeutics, 8th ed, New York, Macmillan, pp 122-127, 1990a*

Gilman AG, Rall TW, Nies AS and Taylor P: *The Pharmacological Basis of Therapeutics, 8th ed, New York, Macmillan, pp181-184, 1990b*

Hammer R and Giachetti A: *Muscarinic receptor subtypes: M_1 and M_2 biochemical and functional characterization. Life Sci 31: 2991-2998, 1982*

Hammer R, Giraldo E, Schiavi GB, Monterini E and Ladinsky H: *Binding profile of a novel cardioselective muscarinic receptor antagonist, AF-DX116, to membranes of peripheral tissues and brain in the rat. Life*

Sci 38: 1653-1662, 1986

Kim JB: *Pressor action of physostigmine in the rabbit. Korean J Pharmacol 26: 101-111, 1990*

Leung E and Mitchelson F: *Modification by hexamethonium of the muscarinic receptor blocking activity of pancuronium and homatropine in isolated tissues of the guinea-pig. European J Pharmacol 80: 11-17, 1982*

Libet B: *Nonclassical synaptic functions of transmitters. Fed Proc 45: 2678-2686, 1986*

Lim DY and Hwang DH: *Studies on secretion of catecholamines evoked by DMPP and McN-A-343 in the rat adrenal gland. Korean J Pharmacol 27: 53-67, 1991*

Mochida S and Kobayashi H: *A novel muscarinic receptor antagonist AF-DX116 differentially blocks slow inhibitory and slow excitatory postsynaptic potentials in the rabbit sympathetic ganglia. Life Sci 42: 2195-2201, 1988*

Mukaiyama O, Takeuchi A, Kimura T and Satoh S: *Effects of pirenzepine and AF-DX116 on ganglionic transmission in the cardiac sympathetic nerves of the dog: interaction of M_1 and M_2 receptors with nicotinic receptors. J Pharmacol Exp Ther 256: 525-529, 1990*

Newberry HR and Gilbert MJ: *Biphasic dose-response curve to muscarine on the rat superior cervical ganglion. Eur J Pharmacol 163: 237-244, 1989*

Newberry HR and Priestley T: *Pharmacological differences between two muscarinic responses of the rat superior cervical ganglion in vitro. Br J Pharmacol 92: 817-826, 1987*

Rattan S and Goyal RK: *Identification of M_1 and M_2 muscarinic receptor subtypes in the control of the lower esophageal sphincters in the opossum. Trends Pharmacol Sci 5 (Suppl): 78-81, 1984*

Roszkowski AP: *An unusual type of sympathetic ganglionic stimulant. J Pharmacol Exp Ther 132: 156-170, 1961*

Wess J, Lambrecht G, Moser U and Mutshler E: *Stimulation of ganglionic muscarinic M_1 receptors by a series of tertiary arecaidine and isoarecaidine esters in the pithed rat. Eur J Pharmac 134: 61-67, 1987*

Willfert B, Gouw MAM, De Jonge A, Timmermans PBMWM and van Zwieten PA: *Indications for vascular α-and β_2-adrenoceptors in synapses of the muscarinic pathway in the pithed normotensive rat. J Pharmac Exp Ther 223: 219-223, 1982*

Yarosh CA and Ashe JH: *Antagonist discrimination of two muscarinic responses elicited by applied agonists and orthodromic stimuli in superior cervical ganglion of rabbit. Neuropharmacology 26: 1549-1560, 1987*

Yarosh CA, Olito AC and Ashe JH: *AF-DX116: A selective antagonist of the slow inhibitory postsynaptic potential and methacholine-induced hyperpolarization in superior cervical ganglion of the rabbit. J Pharmacol Exp Ther 245: 419-425, 1988*

Yoo H: *Depressor action of atropine and pirenzepine in the rabbit. Chonnam J Med Sci 2: 79-89, 1989*

= 국문초록 =

가토 교감신경절에서 무스카린성 수용체 아형과 니코틴성 수용체의 상호작용에 대한 연구

전남대학교 의과대학 약리학교실 및 신경외과학교실*

김 종 근 · 류 춘 식* · 강 삼 석*

교감신경절 전달에 무스카린성 수용체 아형과 니코틴성 수용체가 기능적으로 어떻게 작용하는지를 알아 보기 위하여 척수가토에서 척수를 통한 교감신경절전섬유의 자극에 의한 승압반응과 신경절 M_1수용체 및 니코틴성 수용체 흥분제인 McN-A-343과 DMPP의 승압반응에 대한 M_1수용체 길항제인 pirenzepine, M_2수용체 길항제인 AF-DX116 및 니코틴성 수용체 길항제인 mecamylamine의 영향을 조사하였다.

먼저 M_1 및 M_2수용체의 작용을 선택적으로 차단하는 pirenzepine과 AF-DX116의 용량을 구하기 위해 chlorisondamine-처리가토에서의 M_1수용체를 통한 작용인 McN-A-343의 혈압상승작용과 M_2수용체를 통한 작용인 bethanechol (BCh)에 의한 심박수감소작용을 50% 억제하는 양(LD_{50})을 각각 구한 결과 pirenzepine의 혈압상승작용에 대한 ID_{50}가 30 μg/kg였으며 AF-DX116의 심박수감소작용에 대한 ID_{50}가 27 μg/kg였다. 제 8 흉추부위에 삽입한 전극을 통한 교감신경절전섬유 전기자극에 의해 혈압상승작용 (24±1.8 mmHg)을 나타냈으며 이 혈압상승작용은 pirenzepine 3, 10, 30 및 100 μg/kg에 의해 20~25%정도 용량에 관계없이 비슷한 정도로 억제되었으나 AF-DX116 100 μg/kg에 의해서는 영향받지 않았다. Mecamylamine은 용량의존적으로 이 승압작용을 억제하였으며 mecamylamine의 이 억제작용은 pirenzepine 30 μg/kg에 의해서는 유의하게 강화되었으나 AF-DX116 100 μg/kg에 의해서는 영향받지 않았다. 척수이단가토에서 McN-A-343 (100 μg/kg) 및 DMPP (100 μg/kg)는 혈압상승작용을 나타냈으며 pirenzepine과 AF-DX116은 McN-A-343의 승압작용은 용량의존적으로 억제하였으나 DMPP의 승압작용에는 영향을 미치지 못하였고 mecamylamine은 양약물의 승압작용을 모두 용량 의존적으로 억제하였다.

이상의 실험성적은 척수가토에서 절전교감신경절 자극에 의한 혈압상승에는 M_1수용체의 흥분이 일부 관여하나 M_2수용체의 흥분은 관여하지 않으며 교감신경절전달에서 M_1수용체의 흥분이 니코틴성 전달을 부분적으로 용이하게 하나 M_2수용체는 작용하지 않음을 시사하고 있다.