Short communications

Blocking effect of McN-A-343 on cardiac slowing produced by vagal stimulation

S. CHIBA, K. HASHIMOTO, K. KUBOTA AND S. SATOH

Department of Pharmacology and Experimental Therapeutics, Tohoku University School of Medicine, Sendai, Japan 980

The effect of McN-A-343 was studied by direct administration into the sinus node artery of dogs vagotomized at the mid-cervical level. McN-A-343 blocked sinus bradycardia caused by electrical stimulation of the right vagus, while bradycardia induced by administration of acetylcholine or nicotine into the sinus node artery was not modified.

4-(*m*-Chlorophenylcarbamoyloxy)-2-butynyltrimethyl ammonium chloride (McN-A-343) was introduced as a selective stimulant of muscarinic sites in sympathetic ganglia (Roszkowski, 1961). Smith (1966) observed that McN-A-343 usually produced an initial bradycardia followed by marked tachycardia. Since the tachycardia occurred even in adrenalectomized and sympathectomized cats, he presumed that McN-A-343 was stimulating the cardiac sympathetic ganglia remaining close to the heart which were found by Cooper, Gilbert, Bloodwell & Grout (1961). The mechanism of bradycardia was left for further study. Recently Taira, Matsumura & Hashimoto (1971) clarified that the muscarinic sites of parasympathetic ganglion cells were also stimulated by McN-A-343.

In these experiments, we attempted to study the effects of McN-A-343 on sinoatrial activity in the dog heart *in situ* by direct administration into the sinus node artery.

Methods.—Eleven mongrel dogs of either sex, 8–13 kg b.wt., were anaesthetized with sodium pentobarbital (30 mg/kg i.v). The direct perfusion of the sinus node artery with blood led from the femoral artery was arranged. The details of the preparation were described in a previous paper (Hashimoto, Tanaka, Hirata & Chiba, 1967). Heart rate was continuously recorded by a cardiotachograph (Nihon Kohden RT-2), triggered by the R wave of lead II. Both vagi were cut at the mid-cervical level. Electrical stimulation, 1 ms pulses, supramaximal voltage (5–10 V), 3 Hz for 5 s, through bipolar silver electrodes was applied to the distal portion of the cut right vagus nerve. Drug solution was injected, in a volume of 0·01 ml over 4 s by use of a microinjector, into the perfusion system to the sinus node artery.

Drugs used were McN-A-343 chloride (McNeil Labs), acetylcholine chloride (Daiichi Seiyaku), nicotine sulphate (Tokyo Kasei), tetrodotoxin (Sankyo Cent. Inst.) and atropine sulphate (Merck), which were dissolved in physiological saline.

Results.—McN-A-343 (1 to 10 μg) caused a dose-related decrease of the sinus rate of between 3 and 15%. No tachycardia was observed. The sinus bradycardia reached a maximum at about 30 s after injection and disappeared within 5 minutes. No tachyphylaxis was seen when 10 μg doses of McN-A-343 were given at 10 min intervals. The slowing of the sinus rate

TABLE 1. *Blocking effect of McN-A-343 on the sinus bradycardia induced by electrical stimulation of the vagus nerve (1 ms, supramaximal voltage 5–10 V, 3 Hz, for 5 s)*

Dose of McN-A-343 (μg)	No. of experiments	% Decrease in sinus rate by vagal stimulation (mean ± S.E.M.)			
		Before	After McN-A-343		
			1 min	3 min	5 min
1	4	40·2±4·2	24·2±6·9*	—	37·4±3·6
3	4	39·2±4·8	14·5±5·2*	—	32·5±6·3
10	6	37·8±7·1	4·1±2·3*	15·4±2·1*	28·8±3·1*

* $P<0.05$ for comparison with control values.

induced by 10 μg McN-A-343 was completely blocked by prior administration of 1 μg of atropine, but not by 0·3–1 μg of tetrodotoxin.

It was tested whether the effect of McN-A-343 would modify bradycardia induced by electrical stimulation of the vagus nerve. The results showed that McN-A-343 blocked the bradycardia due to vagal stimulation (Table 1) but not the bradycardia induced by acetylcholine or nicotine. The percentage decrease in heart rate induced by 0·1 or 0·3 μg of acetylcholine was $38{\cdot}9 \pm 7{\cdot}7$ (mean $\pm$ S.E., $n=5$) and 1 min after 10 μg of McN-A-343 it was $37{\cdot}3 \pm 8{\cdot}6$ ($n=5$). The percentage decrease induced by 3 or 10 μg of nicotine was $22{\cdot}1 \pm 3{\cdot}9$ (mean $\pm$ S.E., $n=5$) and was $20{\cdot}8 \pm 3{\cdot}1$ ($n=5$) 1 min after 10 μg of McN-A-343. These changes were not significant.

Discussion.—In these experiments we did not observe an increase of sinus rate; only sinus bradycardia was induced by direct administration of McN-A-343 into the sinus node artery. This bradycardia, like the bradycardia caused by acetylcholine, was easily blocked by atropine but resistant to tetrodotoxin. Thus, the bradycardia caused by McN-A-343 can be explained by stimulation of muscarinic receptors at the sinoatrial node because tetrodotoxin acts only like acute denervation (Hashimoto & Chiba, 1969).

It is surprising that McN-A-343 reduced or abolished vagally-induced sinus bradycardia without affecting the negative chronotropic effect of nicotine. Nicotine-induced bradycardia was explained by activation of nicotinic receptors at the parasympathetic ganglia around the sinoatrial node (Chiba, Satoh & Hashimoto, 1969). The ganglion blocking effect of McN-A-343 which has been demonstrated by Ginsborg (1965) is hardly considered as common ganglion blockade because the effect of nicotine is not modified by McN-A-343 at all. We cannot provide any valid explanation at present, but there may be some difference in sensitivity between nerve stimulation and stimulation by exogenous nicotine in the cardiac parasympathetic ganglia.

REFERENCES

CHIBA, S., SATOH, S. & HASHIMOTO, K. (1969). Effects of nicotine and dimethylphenylpiperazinium on the S-A node activity of dogs *in situ*. *Tohoku J. exp. Med.*, **99**, 407–409.

COOPER, T., GILBERT, J. W., BLOODWELL, R. D. & GROUT, J. R. (1961). Chronic extrinsic cardiac denervation by regional neural ablation. *Circulation Res.*, **9**, 275–281.

GINSBORG, B. L. (1965). The action of McN-A-343, pilocarpine and acetyl-β-methylcholine on sympathetic ganglion cells of the frog. *J. Pharmac. exp. Ther.*, **150**, 216–219.

HASHIMOTO, K., TANAKA, S., HIRATA, M. & CHIBA, S. (1967). Responses of the sinoatrial node to change in pressure in the sinus node artery. *Circulation Res.*, **21**, 297–304.

HASHIMOTO, K. & CHIBA, S. (1969). Pharmacologic isolation of sinoatrial activity from effects of neural excitation by use of tetrodotoxin. *J. Pharmac. exp. Ther.*, **170**, 91–96.

ROSZKOWSKI, A. P. (1961). An unusual type of sympathetic ganglionic stimulant. *J. Pharmac. exp. Ther.*, **132**, 156–170.

SMITH, J. C. (1966). Observations on the selectivity of stimulant action of 4-(*m*-chlorophenylcarbamoyloxy) - 2 - butynyltrimethylammonium chloride on sympathetic ganglia. *J. Pharmac. exp. Ther.*, **153**, 266–275.

TAIRA, N., MATSUMURA, S. & HASHIMOTO, K. (1971). Excitation of the parasympathetic ganglia of the canine urinary bladder through a muscarinic mechanism. *J. Pharmac. exp. Ther.*, **176**, 93–100.

(*Received June* 28, 1971)