BLOOD PRESSURE RESPONSE IN RATS TO INTRACISTERNAL ADMINISTRATION OF CHOLINE

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Central administration of acetylcholine or nicotine to rats induces changes in blood pressure and heart rate via central cholinergic mechanisms (1, 2). Physostigmine, a cholinesterase inhibitor also modifies blood pressure and heart rate (3, 4). Thus, central cholinergic mechanisms may be physiologically involved in the central control of cardiovascular function. In the present experiments, we studied the cardiovascular effects of choline injected into the cisterna magna.

Male Wistar rats, weighing 250–300 g, were anaesthetized with urethane (1.2 g/kg, i.p.). The left femoral artery and femoral vein were cannulated and then the head was fixed downward at an angle of 45° in a stereotaxic apparatus. A polyethylene cannula was introduced into the cisterna magna for intracisternal injections. Throughout each experiment, the rectal temperature was maintained at about 36°C. Blood pressure recordings were made via the femoral cannula using a pressure transducer (Sanei Model MPU-0.5–290) connected to a Sanei recorder. Mean blood pressure was calculated as diastolic pressure+1/3 (systolic pressure minus diastolic pressure). Heart rate was continuously computed from the blood pressure pulse wave by a cardiotachometer (Sanei-2140). Drugs were dissolved in 0.9% NaCl solution and were administered intracisternally in a volume of 5 μl. The following drugs were used: choline chloride (Sigma), atropine sulphate (E. Merck), hexamethonium bromide (Yamanouchi Pharmaceutical), physostigmine salicylate (E. Merck), hemicholinium-3 (Aldrich Chemical). All doses of drugs refer to the free base.

Control mean blood pressure was 96±3 mmHg (means±S.E. from 35 experiments) and heart rate was 376±9 beats/min (n=35). Choline (12.5, 25 and 50 μg), injected into the cisterna magna, produced a decrease in blood pressure by 11±2 mmHg (n=5), 18±2 mmHg (n=5) and 35±4 mmHg (n=5), respectively, and such decreases were accompanied by a decrease in heart rate by 10±3 beats/min, 31±4 beats/min and 52±6 beats/min, respectively. The hypotensive response began 20–40 sec after injection of choline and reached a maximum within 2 min. With the highest dose, the depressor response was followed by a slight pressor response (5–8 mmHg) which was too small for analysis (Fig. 1). Intravenous administration of choline (50 μg) produced no observable cardiovascular effect.

When choline (50 μg) was injected into the cisterna magna at intervals of 30 min, the depressor response was not appreciably altered. In 5 experiments, hexamethonium (20 μg), given intracisternally 5 min before the second administration of choline (50 μg), abolished the blood pressure responses to choline (Fig. 1). Atropine (20 μg), given intracisternally 5 min before the second administration of choline (50 μg), had no effect on the maximal fall in blood pressure induced by choline, but did retard the
recovery from the fall (Fig. 1). The depressor response to choline after atropine reverted toward initial levels 11.2±1.0 min after injection, as compared with 4.7±0.4 min of that before atropine (n=5, P<0.001). Hexamethonium itself caused a slight pressor effect (5–8 mmHg) while atropine itself produced a slight depressor effect (8–10 mmHg). Physostigmine (0.5 μg), injected into the cisterna magna 3 min before the second administration of choline (12.5 μg), potentiated the fall in blood pressure caused by choline injected into the cisterna magna (Fig. 2). The depressor response to choline was 32±4 mmHg after physostigmine as compared with 9±2 mmHg of that before physostigmine (n=5, P<0.001). Physostigmine alone produced no observable effects on blood pressure. Hemicholinium-3 (20 μg), injected into the cisterna magna 20 min before the second administration of choline (50 μg), abolished the blood pressure response to choline similarly injected (n=5). Hemicholinium-3 alone produced no noticeable changes in blood pressure.

The present experiments demonstrate that choline injected into the cisterna magna produces a decrease in blood pressure and heart rate in anesthetized rats. Since the intravenous administration of choline (50 μg) had no effect on these parameters, the cardiovascular effects are centrally mediated. The depressor effect of choline appears to be mediated via central nicotinic mechanisms, since the response was abolished by hexamethonium injected into the cisterna magna, but not by atropine injected via the same route.

Choline might act presynaptically by increasing synthesis or release of acetylcholine, or postsynaptically by direct stimulation of the nicotinic receptors. In the present experiments, the depressor effect of choline was enhanced by physostigmine.
injected into the cisterna magna. Furthermore, the effect of choline was abolished after intracisternal administration of hemicholinium-3. Hemicholinium-3 is thought to block the high affinity uptake of choline into cholinergic neurons (5, 6). Thus, the depressor effect of choline appears to be mainly mediated by increase in synthesis or release of acetylcholine.

In addition to the central depressor effect, choline has a central pressor effect which appears to be mediated via central muscarinic mechanisms, since intracisternally injected atropine retarded the recovery from the depressor response to choline. This result may be compatible with our previous findings (4) which showed that intravenous administration of physostigmine produced a pressor response via central muscarinic mechanisms. From the results of the present study, it would appear that in rats, cholinergic mechanisms are involved in the central cardiovascular control.

REFERENCES