SNYDER, S. H., PASTERNAK, G. W., CREESE, I. & PERT, C. B. (1975). *Neurosci. Res. Progm. Bull.*, in the press.
STERN, P., ĆATOVIĆ, S. & STERN, M. (1974). *Arch. exp. Pharmac.*, **281**, 233–239.
TERENIUS, L. (1973). *Acta pharmac. tox.*, **33**, 377–388.
TERENIUS, L. (1974). *Ibid.*, **34**, 88–91.
TERENIUS, L. & WAHLSTRÖM, A. (1974). *Ibid.*, **35**, *Suppl. I.*
WONG, D. T. & HORNG, J. S. (1973). *Life Sci.*, **13**, 1543–1556.
ZIMMERMANN, E. & KRIVOY, W. (1974). *Proc. Soc. exp. Biol. Med.*, **146**, 575–579.

Are spinal excitatory muscarinic receptors important for cardiovascular control?

It is well known that transection of the spinal cord cranial to the spinal sympathetic outflow decreases sympathetic tone and leads to a fall in arterial blood pressure. Conceivably, this is due to an interruption of excitatory pathways descending from supraspinal nervous structures. The transmitters of the spinal descending neurons responsible for the maintenance of sympathetic tone are not known. Noradrenaline is an unlikely candidate since its amino acid precursor L-3,4-dihydroxyphenylalanine (L-dopa), does not produce a pressor response in the spinal rat (Henning, Rubenson & Trolin, 1972) pretreated with a peripheral decarboxylase inhibitor (hydrazinomethyldopa, MK 486). Neither does the 5-hydroxytryptamine (5-HT) precursor, DL-5-hydroxytryptophan under the same conditions (Henning & Trolin, unpublished) so 5-HT is excluded also. In a search for a spinal excitatory transmission mechanism acting on the sympathetic nervous system we have investigated the role of muscarinic receptors on blood pressure regulation at spinal levels.

In all experiments, male Sprague-Dawley rats (200–220 g) were spinalized at the level of the seventh cervical vertebra under pentobarbitone anaesthesia (40 mg kg^{-1}, i.p.) and venous and arterial catheters were implanted as previously described (Henning, 1969). A few experiments were made on rats with both vagi cut or which had been adrenodemedullated (Farris & Griffith, 1949) under pentobarbitone anaesthesia 7 days previously.

On the day after the spinal transection, mean arterial blood pressure was recorded in conscious animals using Statham P23 Dc pressure transducers writing on a Grass Model 7 Polygraph; heart rate was triggered by the pressure signal. Oxotremorine (2 mg kg^{-1}, i.p.) (97%, Aldrich-Europe, Beerse, Belgium), was injected 20–40 min after methylscopolamine nitrate (10 mg kg^{-1}, i.p.) or atropine sulphate (10 mg kg^{-1}, i.p.). The doses refer to the salts. A solution of 0·9% NaCl was always injected after the drugs to a final volume of 0·5 ml. Significant differences were determined with Student's *t*-test. The results are shown in Fig. 1.

The methylscopolamine-pretreated group did not differ significantly from the atropine-pretreated group in blood pressure ($P > 0{\cdot}1$) or heart rate ($P > 0{\cdot}1$) at the time for the oxotremorine injection. The blood pressure increase after oxotremorine in the methylscopolamine group (22·0 ± 3·5, 22·8 ± 2·2, 20·8 ± 2·0, 16·0 ± 2·7 and 8·5 ± 2·5 mm Hg) was significantly higher than the pressure changes after oxotremorine in the atropine group (8·6 ± 4·0, 2·6 ± 2·0, 2·0 ± 0·9, 0·2 ± 0·8 and −1·4 ± 0·6 mm Hg) at 5, 10, 15, 30 and 60 min ($P < 0{\cdot}05$, $P < 0{\cdot}001$, $P < 0{\cdot}001$, $P < 0{\cdot}001$ and $P < 0{\cdot}01$, resp.). The heart rate increase after oxotremorine in the methylscopolamine group (26·7 ± 9·5, 35·0 ± 8·9, 35·8 ± 9·0) was significantly different from the decrease in heart rate in the atropine group (−18·0 ± 7·3; −16·0 ± 4·0, −40 ± 4·0) at 5, 10 and 15 min ($P < 0{\cdot}01$, $P < 0{\cdot}005$ and $P < 0{\cdot}05$, resp.). At 30 and 60 min the difference was not significant ($P > 0{\cdot}05$ and $P > 0{\cdot}25$, resp.).

Section of the vagi or adrenal demedullation did not change the effect of oxotre-

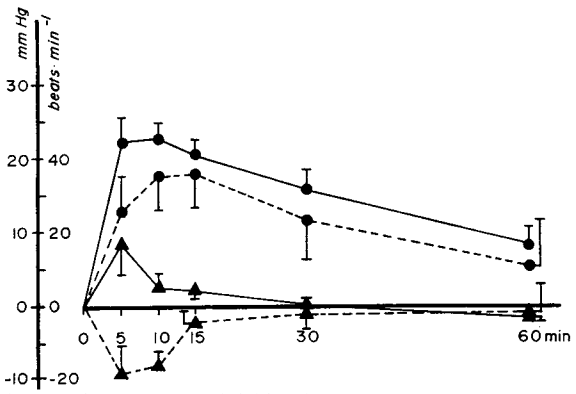

FIG. 1. Absolute changes in mean arterial blood pressure (solid lines) and heart rate (broken lines) after the injection of oxotremorine (2 mg kg^{-1}, i.v.) in the rat. 6 rats were pretreated with methylscopolamine (10 mg kg^{-1}, i.v.) (●) and 5 rats with atropine (10 mg kg^{-1}, i.v.) (▲) 20–40 min before the injection of oxotremorine. The values are means with their s.e.m. indicated.

morine. In some rats a test dose of carbachol (10 μg kg^{-1}, i.v.) was given to check muscarinic receptor blockade after methylscopolamine or atropine. The test dose caused pronounced hypotension and bradycardia before the administration of the antimuscarinic drugs but was afterwards without effect on blood pressure or heart rate.

Methylscopolamine blocks peripheral muscarinic receptors but does not pass the blood brain barrier. Atropine on the other hand passes this barrier and thus blocks muscarinic receptors both in the peripheral and in the central nervous system. When the muscarinic receptor agonist oxotremorine (George, Haslett & Jenden, 1962) was given to methylscopolamine-pretreated spinal rats a longlasting increase in blood pressure and heart rate was seen. This was not changed by adrenal demedullation or section of the vagi. When both peripheral and central muscarinic receptors were blocked with atropine, the effects of oxotremorine were almost totally abolished, indicating that the effects after methylscopolamine pretreatment were of spinal muscarinic origin, and that the adrenal medulla does not play a major part in this sympathetic activation.

The fact that muscarinic receptor stimulation at the spinal level seems to activate the peripheral sympathetic system might indicate that some descending neurons from the medulla oblongata and higher centres with an excitatory effect on the sympathetic nervous system are cholinergic. It seems probable that some of the descending excitatory nerves in some way affect muscarinic receptors in the spinal cord.

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REFERENCES

FARRIS, E. J. & GRIFFITH, J. Q. (1949). *The Rat in Laboratory Investigation*, 2nd edn., p 542. New York: Hafner Publishing Co.

GEORGE, R., HASLETT, W. L. & JENDEN, D. J. (1962). *Life Sci.*, **1**, 361–363.

HENNING, M. (1969). *Acta physiol. scand.*, Suppl. 322.

HENNING, M., RUBENSON A. & TROLIN, G. (1972). *J. Pharm. Pharmac.*, **24**, 447–451.