Activation of intramural inhibitory neurones of the rabbit caecum by nicotine

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Circular smooth muscle of the rabbit caecum had a non-adrenergic inhibitory innervation (Small, 1972) and is sparsely innervated by noradrenergic fibres. The inhibitory action of nicotine (1×10^{-6} to 1×10^{-4} M) upon this tissue has been analysed using tissue bath and sucrose gap recording techniques.

Muscle strips (which lack spontaneous activity or tone) were exposed to either atropine (1.7×10^{-7} M) or methacholine (2×10^{-6} M). In both cases the nicotine induced inhibition was assessed by the hyperpolarization produced. In the latter case a simultaneous reduction in mechanical activity could also be observed (Figure 1). The hyperpolarization induced by nicotine analysed similarly in both situations.

The action of nicotine was abolished by hexamethonium (5×10^{-4} M), strongly antagonized by tetrodotoxin (3.1×10^{-7} M) but unaffected by guanethidine (1×10^{-5} M). Pretreatment of animals with reserpine (2 mg/kg i.p. day 1, 2 mg/kg i.p. day 2, sacrifice day 3) or with 6-hydroxydopamine (30 mg/kg i.v. day 1, 2 x 20 mg/kg i.v. day 2, sacrifice day 3) each reduced the noradrenaline content of caecal tissue by more than 65% yet neither modified the response of the tissue to nicotine. Phentolamine (1×10^{-5} M) slightly reduced responses to nicotine. The hyperpolarizing action of nicotine was not shared by equimolar doses of tyramine but could be mimicked by large doses (10^{-5} moles) of ATP.

These results suggest that the action of nicotine in this tissue is mediated largely by excitation of non-adrenergic inhibitory neurones. A similar proposal was made for the action of nicotine on the guinea-pig taenia caeci by Burnstock, Campbell & Rand (1966). Such findings are consistent with the suggestion of Burnstock (1972) that the preganglionic input to the intrinsic inhibitory neurone in some regions of the gut is cholinergic and plays onto nicotinic postsynaptic receptors.

The significance of the tetrodotoxin resistant component of the action of nicotine observed in the present study will be discussed.

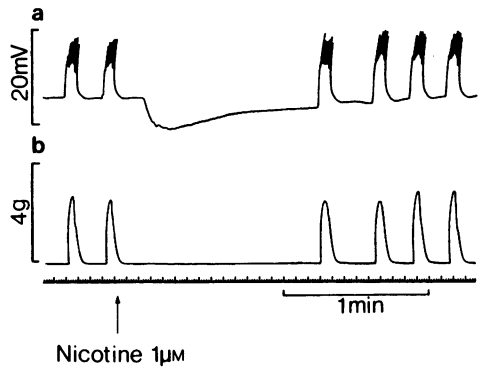

Fig. 1 Sucrose gap recording of the electrical (a) and mechanical (b) activity of circular smooth muscle from the rabbit caecum. The tissue was superfused with Kreb's solution containing methacholine (2×10^{-6} M) and at the arrow an E.D. 100 (10^{-6} moles) of nicotine was injected into the flow of solution. Note the hyperpolarization and abolition of mechanical activity induced by nicotine.

References

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A quantitative assessment of the effects of clonidine on pre-ganglionic sympathetic nerve activity in the cat

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A method has been developed for the quantitative measurement of the effects of drugs on sympathetic nerve activity. It has been used to study the effects of clonidine, a drug known to inhibit spontaneous sympathetic activity (Schmitt, Schmitt, Boissier & Giudicelli, 1967).

Cats were anaesthetized with ether followed by chloraloseurethane and using gallamine and artificial respiration. Spontaneous preganglionic sympathetic nerve activity was recorded from a left splanchnic nerve, cut before its entry into the coeliac ganglion. The amplified neurogram was fed into a Nicolet 1072 laboratory computer which recorded the number of impulses above a pre-

Table 1 Effect of clonidine on preganglionic splanchnic nerve activity, blood pressure and heart rate in the cat

	Cumulative dose of clonidine (μg/kg)	*Sympathetic nerve activity (counts/min)*	*Blood pressure (mmHg)*	*Heart rate (beats/min)*
Before drug	–	2470 ± 98	123 ± 7	196 ± 8
After drug	2.5	1600 ± 120	112 ± 7	174 ± 9
	5	722 ± 89	113 ± 4	158 ± 6
	10	234 ± 71	121 ± 7	155 ± 6

Each value is the mean ±s.e. of 10 consecutive readings.

determined threshold. Throughout each experiment, nerve activity was counted for a period of 1 min every 3 min and heart rate and blood pressure noted during each measuring period.

Experiments commenced with a control period during which nerve activity was recorded until 10 similar readings had been obtained. Control experiments in five cats showed that there was no decline in sympathetic activity for at least 2 h after stable control readings had been obtained.

The effects of clonidine on sympathetic nerve activity, heart rate and blood pressure were tested in five cats at doses of 2.5, 2.5 and 5 μg/kg i.v., given at 30 min intervals. Each dose was infused at 0.5 (μg/kg)/min to avoid marked pressor effects. Since the effects of clonidine at 2.5 μg/kg were known to persist for more than 90 min, the results were expressed as the responses to the cumulative dose administered.

Clonidine induced dose-dependent bradycardia but had little effect on blood pressure. Sympathetic nerve activity was reduced by 35.4, 70.8 and 90.5% in response to cumulative doses of 2.5, 5 and 10 μg/kg of clonidine respectively. The cumulative dose of clonidine necessary to produce 50% inhibition of spontaneous sympathetic activity was calculated to be 3.4 μg/kg i.v.

Reference

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Antagonism by ICI 66082 of the effects of electrical stimulation on the right ansa subclavia of the dog

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It has been reported previously that the effects on the heart of sympathetic nerve stimulation cannot be antagonized completely by β-adrenoreceptor blocking drugs in doses which do not produce any direct depressant effect on the heart (e.g. for propranolol see Donald, Ferguson & Milburn, 1968). ICI 66082 (4-(2-hydroxy-3-isopropylaminopropoxy)phenylacetamide) is a new β-adrenoreceptor blocking drug with no other action on the heart in doses up to 20 mg/kg (Harry, Knapp & Linden, 1973). In this investigation an attempt was made completely to block the effects of sympathetic nerve stimulation by using high doses of ICI 66082.

Dogs were anaesthetized with chloralose, artificially respired and the chest opened in the mid-line. Both ansae subclaviae were clamped for 5 min and then stimulating electrodes were placed on the cardiac end of the right ansa subclavia. The vagus nerves were sectioned in the neck. The right ansa subclavia was stimulated with supramaximal pulses (15 volts; 5 ms) at two frequencies, one (0.5-3 Hz) which produced increases in heart rate ranging from 36-66 beats/min, and the other (7-15 Hz) which produced maximal increases in heart rate ranging from 110-160 beats/minute. In each experiment the effects of the two rates of stimulation were recorded before ICI 66082 was given and in the presence of increasing doses of ICI 66082, given intravenously. The results of these experiments are summarized in Table 1.

The results demonstrate that the effects of stimulation of the right ansa subclavia at the lower frequency (0.5-3 Hz) could be completely antagonized by ICI 66082 but that it was not always possible completely to block the effects of stimulation at the frequency of 7-15 Hz, at which the maximal response had been obtained. Maximum