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Metiamide – absence of presynaptic α-adrenoceptor antagonist properties in the pithed rat

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The antagonism by metiamide of the hypotensive effects of clonidine has prompted the suggestion that the hypotensive effect is mediated in part by stimulating histamine H_2 receptors in the central nervous system of the rat, (Karppanen, Paakkari & Paakkari, 1977). The hypotensive effect of clonidine is also antagonized by α-adrenoceptor antagonists (Schmitt, Schmitt & Fénard, 1971). It has been reported recently that metiamide is an antagonist at presynaptic α-adrenoceptors in the mouse vas deferens (Griffith, Marshall & Nasmyth, 1978). The interaction of metiamide with presynaptic α-adrenoceptors has been studied in the rat using both *in vitro* and *in vivo* models.

Vasa deferentia from CFY rats were suspended in Krebs and stimulated at a frequency of 0.1 Hz as described previously (Doxey, Smith & Walker, 1977). The twitch response was inhibited by clonidine (3 ng/ml). Metiamide (1–10 μg/ml) and phentolamine (10–300 ng/ml) produced a dose related antagonism of the clonidine inhibition. These studies confirmed previous experiments carried out in the mouse vas deferens by Griffith, Marshall & Nasmyth (1978).

In the pithed rat presynaptic activity was assessed by determining the ability of metiamide to reverse the inhibitory effects of clonidine (30 μg/kg i.v.) on sympathetic outflow from cardiac nerves (Drew, 1976; Doxey & Everitt, 1977) and hypogastric nerves (Doxey & Everitt, 1977). Post synaptic antagonism was assessed by determining the inhibition of the pressor response associated with clonidine.

Cardiac acceleration was induced by stimulation of the sympathetic outflow at either 1 Hz, 10 v, 0.5 ms continuously (Drew, 1976) or 1 Hz, 10 v, 0.5 ms for 10 s every 2 min (Doxey & Everitt, 1977). Hypogastric outflow was induced using stimulus parameters of 20 v, 50 μs, 6 Hz for 3 s every 30 seconds. Metiamide in doses up to 3 mg/kg i.v. had no effect on the inhibitory action of clonidine on either cardiac or hypogastric nerves. The clonidine pressor response was also unaffected by metiamide. The reversibility of the effects of clonidine on cardiac nerves, hypogastric nerves and blood pressure was verified by injecting phentolamine (1 mg/kg i.v.) at the end of each experiment. This dose of phentolamine produced complete reversal in all experiments. It has been shown previously that the threshold dose of phentolamine required to antagonise clonidine on hypogastric nerves and cardiac nerves was 10–30 μg/kg i.v. (Drew, 1976; Doxey & Easingwood, 1978).

In conclusion metiamide, in doses up to 3 mg/kg i.v., had no antagonistic effect at peripheral pre- and postsynaptic α-adrenoceptors in the pithed rat.

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Effects of α-adrenoceptor agonists on peripherally evoked parasympathetic submaxillary salivation in the cat

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Clonidine, a centrally acting antihypertensive drug, has been shown to diminish submaxillary salivation produced by either brainstem or peripheral parasympathetic nerve stimulation in anaesthetized cats

(Green, O'Brien, Wilson & Yates, 1978). On peripheral stimulation the reduction in salivation is greatest at low frequencies compatible with the presence of presynaptic α-adrenoceptors inhibiting cholinergic transmission (Paton & Vizi, 1969). In the present study this concept has been further investigated by examining the effect of α-adrenoceptor agonists with different pre/post synaptic potency ratios (Starke, Endo & Taube, 1975) on salivation evoked by chorda tympani nerve stimulation. The magnitude of the clonidine-induced salivary depression was also determined 30 min after the intravenous administration of the α-adrenoceptor antagonists phentolamine and yohimbine.

Cats were anaesthetized with pentobarbitone (40 mg/kg i.p.) and the chorda tympani stimulated with supramaximal square wave impulses of pulse width 0.5 msec at frequencies of 5 and 15 Hz for 30 s every 3 min. Submaxillary saliva was collected every 3 min during a 45 min control period and then for up to 90 min after the intravenous administration of the α-adrenoceptor agonists. The doses of the agonists were chosen to give similar increases in blood pressure. The maximum percentage changes in salivation and mean arterial blood pressure are shown in the Table.

Methoxamine, the most potent postsynaptic α-agonist, produced the greatest increase in parasympathetically induced salivation and this augmented secretion was most evident at the lower stimulation frequency. Noradrenaline and naphazoline which have similar potencies for pre- and postsynaptic α-receptors both increased salivation but to a lesser degree than methoxamine at 5 Hz. Tramazoline and clonidine (preferential presynaptic α-agonists) both decreased salivation, the reduction being greatest at the lower frequency. Yohimbine, a preferential presynaptic α-antagonist, (Starke, Borowski & Endo, 1975) reduced the clonidine-induced salivary depression to a greater extent than phentolamine (Table 1).

These results provide further evidence to suggest that clonidine diminishes peripheral parasympathetic submaxillary salivation in the cat by activation of presynaptic α-adrenoceptors inhibiting cholinergic transmission.

Table The maximum percentage change produced by different α-adrenoceptor agonists on peripherally evoked submaxillary salivation and mean arterial pressure

	Methoxamine 200 µg/kg	*Noradrenaline 1 µg/kg*	*Naphazoline 10 µg/kg*	*Tramazoline 10 µg/kg*	*Clonidine 10 µg/kg*	*Clonidine 10 µg/kg +Phentolamine 0.5 mg/kg*	*Clonidine 10 µg/kg +Yohimbine 0.5 mg/kg*
	(*n*=4)	(*n*=6)	(*n*=5)	(*n*=5)	(*n*=6)	(*n*=4)	(*n*=4)
Agonist equimolar potency* ratio, pre/post	32.5	1.6	0.41	0.07	0.15	0.15	0.15
Salivation							
5 Hz	↑ 44.1 ± 6.5	↑ 10.1 ± 2.0	↑ 1.6 ± 1.0	↓ 13.8 ± 2.0	↓ 34.8 ± 6.2	↓ 21.0 ± 1.0	↓ 2.7 ± 1.6
15 Hz	↑ 8.5 ± 1.4	↑ 10.5 ± 2.2	↑ 10.0 ± 1.8	0	↓ 15.0 ± 2.6	↓ 4.7 ± 0.5	↓ 1.0 ± 0.7
Mean arterial pressure							
initial increase	41.5 ± 5.2	75.8 ± 5.5	123.8 ± 7.2	90.6 ± 8.3	56.8 ± 6.7	22.3 ± 2.2	42.2 ± 3.8
subsequent decrease	0	0	9.6 ± 1.2	18.2 ± 4.5	22.4 ± 2.0	20.4 ± 2.5	0

*results obtained in rabbit pulmonary artery (Starke, Endo & Taube, 1975) all values are given as mean ± s.e. mean *n* = number of cats. arrows indicate increase or decrease in salivation from control values.

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