prazosin and phentolamine on cardiac presynaptic α-adrenoceptors in the cat, dog and rat. *Clin. Exper. Hypertension*, **1**, 87–101.

ROBSON, R.D., ANTONACCIO, M.J., SAELENS, J.K. & LIEBMAN, J. (1978). Antagonism by mianserin and classical α-adrenoceptor blocking drugs of some cardiovascular and behavioural effects of clonidine. *Eur. J. Pharmac.*, **47**, 431–442.

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.

References

DOXEY, J.C. & EASINGWOOD, R.E. (1978). Profiles of α-adrenoceptor antagonists in the pithed rat. *Br. J. Pharmac.*, **63**, 401–402P.

DOXEY, J.C. & EVERITT, J. (1977). Inhibitory effects of clonidine on responses to sympathetic nerve stimulation in the pithed rat. *Br. J. Pharmac.*, **61**, 559–566.

DOXEY, J.C., SMITH, C.F.C. & WALKER, J.M. (1977). Selectivity of blocking agents for pre- and postsynaptic α-adrenoceptors. *Br. J. Pharmac.*, **60**, 91–96.

DREW, G.M. (1976). Effects of α-adrenoceptor agonists and antagonists on pre- and postsynaptically located α-adrenoceptors. *Eur. J. Pharmac.*, **36**, 313–320.

GRIFFITH, O.R., MARSHALL, J. & NASMYTH, P.A. (1978). Blockade of pre-synaptic α-adrenoceptors by metiamide. *Br. J. Pharmac.* In Press.

KARPPANEN, H., PAAKKARI, I. & PAAKKARI, P. (1977). Further evidence for central histamine H_2 receptor involvement in the hypotensive effect of clonidine in the rat. *Eur. J. Pharmac.*, **42**, 299–302.

SCHMITT, H., SCHMITT, H. & FENARD, S. (1971). Evidence for an α-sympathomimetic component in the effects of catapresan on vasomotor centres: Antagonism by piperozane. *Eur. J. Pharmac.*, **14**, 98–100.

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