Blockade of pre-synaptic α-adrenoceptors by metiamide

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The inhibition of the electrically induced twitch response of the mouse vas deferens produced by clonidine is antagonized by yohimbine and is mediated by pre-synaptic α-adrenoceptors (Marshall, Nasmyth, Nicholl & Shepperson, 1978). Histamine also inhibits the twitch response but via a histamine H_2-receptor (Marshall, 1978) and this effect is antagonized by metiamide (10 μM) and cimetidine (10 μM) but not by yohimbine. There are reports that some effects of clonidine can be antagonized by histamine H_2-receptor antagonists (e.g. Karppanen, Paakkari, Paakkari, Huotari & Orma, 1976). This interaction has been investigated.

Vasa deferentia from 6–8 week old mice were suspended in a magnesium-free Krebs solution and stimulated at 0.2 Hz, 2 ms, 256 mA. The twitch responses produced were inhibited by clonidine (0.7–44.8 nM) in a dose-related manner and the curve was shifted to the right by more than one log unit by metiamide (10 μM). The antagonism was unrelated to histamine H_2-receptors because cimetidine (10 μM), did not affect the clonidine inhibition curve. This evidence suggests that to produce its inhibitory effect clonidine is not acting on histamine H_2-receptors in addition to pre-synaptic α-adrenoceptors.

Noradrenaline (0.1–3.0 μM) and ergometrine (0.03–1.0 μM) are agonists at pre-synaptic α-adrenoceptors in the mouse vas deferens (Marshall *et al.*, 1978; Marshall, Nasmyth, Russell & Shepperson, 1977). Their inhibition of the twitch response, like that of clonidine, was also reduced by metiamide (10 μM), but not by cimetidine (10 μM). Metiamide, therefore, antagonizes the effects of a number of structurally different agonists at pre-synaptic α-adrenoceptors.

Clonidine decreases the stimulated overflow of [^{3}H]-noradrenaline from vasa deferentia preloaded with [^{3}H]-noradrenaline as described previously (Marshall, Nasmyth & Shepperson, 1978). The effect of metiamide on this effect mediated by pre-synaptic α-adrenoceptors was studied.

Metiamide (10 μM), did not alter the fractional release of [^{3}H]-noradrenaline elicited using 1.0 Hz, 2.0 ms in vasa from 10–13 week old mice. Clonidine (11.2 nM), inhibited the twitch response by $47.0 \pm 1.6\%$ (mean ± s.e. mean) and this was reduced by metiamide (10 μM), to $38.8 \pm 2.5\%$. In the same tissues the fractional release of [^{3}H]-noradrenaline was significantly reduced by clonidine (*t* test, $P < 0.025$) and this was abolished by metiamide (10 μM) ($P > 0.05$). This finding supports the hypothesis that metiamide is an antagonist at pre-junctional α-adrenoceptors.

The specificity of action of metiamide was investigated further. Firstly, contractions of the mouse vas deferens elicited by noradrenaline (0.3–30 μM) by stimulating post-synaptic α-adrenoceptors were unaltered by metiamide (10 μM). Secondly, inhibition of the twitch responses by morphine (0.03–10 μM) acting on pre-synaptic opiate receptors (Henderson, Hughes & Kosterlitz, 1972) was also unaffected by metiamide, 10 μM.

In conclusion metiamide, in addition to its antagonism at histamine H_2-receptors, is also an antagonist at pre-synaptic α-adrenoceptors.

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