Ergometrine: a pre-synaptic α-adrenoceptor agonist

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The ergot alkaloid ergometrine which has no post-junctional α-adrenoceptor antagonist activity (Brown & Dale, 1935) was found to inhibit the twitch response of the isolated mouse vas deferens to electrical stimulation (0.2 Hz, 2.0 ms, 64 V). This action was rapid in onset, dose related (10 nM–10 μM) and readily reversed by washing with Krebs solution. The mechanism of this inhibitory effect has been investigated.

The twitch response of the mouse vas deferens is inhibited by the indirectly acting amine tyramine (Marshall, Nasmyth & Shepperson, 1977a). This effect is prevented by cocaine. The ergometrine inhibition is not produced in the same manner as cocaine (10 μM) did not alter the dose-inhibition curve for the ergot alkaloid.

Drugs which inhibit the neuronal uptake of noradrenaline (NA) also reduce the twitch (Marshall, Nasmyth & Shepperson, 1977b). A number of ergot alkaloids may inhibit NA uptake (Pacha & Salzmann, 1970). However, ergometrine (3 μM) which inhibited the twitch by more than 60% did not alter the uptake of (7–^{3}H)–(–)–NA (10 ng/ml; 9.8 Ci/mmol).

Another mechanism by which ergometrine might have produced its inhibition was by stimulation of β-adrenoceptors (Jenkins, Marshall & Nasmyth, 1976). The dose-inhibition curve to isoprenaline (30–300 nM) was abolished by propraolol (200 nM) but it did not alter the ergometrine curve (100 nM–1 μM).

Clonidine inhibits the twitch response of the mouse vas deferens by stimulating pre-synaptic α-adrenoceptors (Marshall, Nasmyth, Nicholl & Shepperson, 1977). Three tests were used to evaluate this possibility for ergometrine. Firstly phenoxybenzamine (15 μM) a dose which blocks pre-synaptic α-adrenoceptors (Marshall *et al.*, 1977b) abolished the inhibition produced by ergometrine. Secondly, the selective pre-synaptic α-adrenoceptor antagonist yohimbine, (Starke, Borowski & Endo, 1975), 10 nM, shifted the ergometrine dose-response curve to the right. Thirdly, the effects of pre-synaptic α-agonists are inversely proportional to the rate of stimulation (Starke, Endo & Taube, 1975). Ergometrine (300 nM) inhibited the twitch by 75% at 0.2 Hz and this was reduced with increasing rates of stimulation to less than 5% at 16 Hz.

These results strongly suggest that ergometrine inhibits the twitch response of the mouse vas deferens by acting like clonidine as an agonist at pre-synaptic α-adrenoceptors supporting the observations of Ambache, Dunk, Verney & Zas (1973).

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References

AMBACHE, N., DUNK, L.P., VERNEY, J. & ZAS, M.A. (1973). An inhibition of post-ganglionic motor transmission in the mammalian vas deferens by D-lysergic acid diethylamide. *J. Physiol., Lond.*, **231**, 251–270.

BROWN, G.L. & DALE, H. (1935). The pharmacology of ergometrine. *Proc. R. Soc. B.*, **118**, 446–477.

JENKINS, D.A., MARSHALL, I. & NASMYTH, P.A. (1976). Is noradrenaline the motor transmitter in the mouse vas deferens? *J. Physiol., Lond.*, **254**, 49–50P.

MARSHALL, I., NASMYTH, P.A. & SHEPPERSON, N. (1977a). The effect of the depletion of the noradreenaline content on the response of the mouse vas deferens to electrical stimulation and tyramine. *J. Physiol.*, **265**, 45P.

MARSHALL, I., NASMYTH, P.A. & SHEPPERSON, N. (1977b). Pre-synaptic α-adrenoceptors and the inhibition by uptake blocking agents of the twitch response of the mouse vas deferens. *Br. J. Pharm.*, **59**, 511P.

MARSHALL, I., NASMYTH, P.A., NICHOLL, CLAIRE G. & SHEPPERSON, N. (1977). Pre-synaptic α-adrenoceptor regulation of the twitch response of the mouse vas deferens. *Br. J. Pharm.*, **59**, 510P.

PACHA, W. & SALZMANN, R. (1970). Inhibition of the re-uptake of neuronally liberated noradrenaline and α-receptor blocking action of some ergot alkaloids. *Br. J. Pharm.*, **38**, 439–440P.

STARKE, K., BOROWSKI, EVELYN & ENDO, T. (1975). Preferential blockade of pre-synaptic α-adrenoceptors by yohimbine. *Eur. J. Pharmac.*, **34**, 385–388.