Pre-synaptic α-adrenoceptors and the inhibition by uptake blocking agents of the twitch response of the mouse vas deferens

I. MARSHALL, P.A. NASMYTH & N.B. SHEPPERSON

Department of Biochemical and Experimental Pharmacology, St. Mary's Hospital Medical School, London W2 1PG

Field stimulation of the mouse vas deferens releases noradrenaline (Henderson, Hughes & Kosterlitz, 1972; Jenkins, Marshall & Nasmyth, 1975) and elicits a twitch response. Inhibition of neuronal uptake by cocaine potentiates the response of sympathetically innervated organs to electrical stimulation, especially at low rates of stimulation (< 1 Hz) (Iversen, 1973). The effect of uptake inhibitors in the mouse vas deferens has now been investigated.

The inhibition of noradrenaline uptake by cocaine, cocaine plus oestradiol, or phenoxybenzamine was measured in intact vasa deferentia. A single vas deferens was incubated with [7-^{3}H]-(−)-noradrenaline (10 ng/ml; specific activity 9.8 Ci/mmol) for 10 min, washed, homogenized and the catechols then adsorbed onto alumina. The tritium counts were taken to represent [^{3}H]-noradrenaline uptake and this was 28.53×10^5 d min^{-1} g^{-1} tissue controls. The addition of cocaine (10 μM) decreased this by 93%; cocaine (10 μM) plus oestradiol (3.7 μM) by 87%, and phenoxybenzamine (15 μM) by 89% ($P < 0.001$ for all 3 cases).

The effect of these drugs on the twitch response was examined. An isolated vas deferens was stimulated at 0.2 Hz, 256 mA and pulse widths of 0.25–2.0 ms. The addition of cocaine (10 μM) or cocaine (10 μM) plus oestradiol (3.7 μM) significantly inhibited the twitch at all pulse widths ($P < 0.05$). Conversely, phenoxybenzamine (15 μM) significantly potentiated the twitch at all pulse widths ($P < 0.001$).

The differing effect of these uptake inhibitors on the twitch may be related to the pre-synaptic α-adrenoceptor blocking activity of phenoxybenzamine, a property not shared by the other uptake inhibitors. Stimulation of these receptors by noradrenaline can inhibit the twitch response in the mouse vas deferens (Marshall, Nasmyth, Nicholl & Shepperson, this Meeting). To test this possibility yohimbine, a selective pre-synaptic α-receptor blocking agent (Starke, Borowski & Endo, 1975) was used. Yohimbine (3.2–128 nM) reversed the inhibition produced by cocaine plus oestradiol and the twitch was now potentiated.

These results suggest that, in the presence of cocaine and oestradiol, noradrenaline released by electrical stimulation of the mouse vas deferens inhibits the twitch response via a pre-synaptic α-adrenoceptor.

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Further evidence for dopaminoceptors in the vas deferens

F.M. TAYO (introduced by G. OSUIDE)

Department of Pharmacy and Pharmacology, Ahmadu Bello University, Zaria, Nigeria

There are conflicting reports about the neurotransmitter role of noradrenaline (NA) in the vas deferens of most species because large doses of NA are required to elicit a contraction (Graham, Al Katib & Spriggs, 1968; Birmingham, 1970). In most studies contractions of the vas deferens are resistant to alpha-adrenoceptor antagonists except at very high concentrations (Ambache & Zar, 1971). These led Ambache & Zar (1971) to challenge the concept that NA acts as the motor neurotransmitter substance in the vas deferens.

However there is little or no study on the effect of dopamine (DA) on the vas deferens. Tayo (1977) reported that in the isolated vas deferens of the rat, DA

was more potent than NA whereas the reverse was true in the guinea-pig. Furthermore, pimozide reduced or abolished DA-induced effect without modifying NA-induced contraction. Guanethidine or 6-hydroxydopamine induced supersensitivity towards NA whereas there was none towards DA (Tayo, unpublished observations).

The aim of the present studies is to investigate the presence of prejunctional inhibitory DA receptors in the rat vas deferens. The vas deferens was isolated with the hypogastric nerve intact and mounted in a 20-ml organ bath containing Tyrode solution bubbled with 5% CO_2 in oxygen at 35°C.

Stimulation of the nerve produced contractions which were readily abolished by guanethidine. DA (5 pg/ml–50 ng/ml) produced graded decreases in the contractions. NA in the same range produced quantitatively less effect. Higher concentrations of DA and NA (500 ng/ml–5 μg/ml) directly stimulated the vas smooth muscle to contract but reduced or totally abolished the effect of nerve stimulation. This effect was more marked at lower than at higher frequencies of stimulation.

DA receptor antagonists, pimozide (5 ng/ml–50 ng/ml) and haloperidol (500 ng/ml–5 μg/ml), increased the effect of nerve stimulation. These agents abolished the inhibitory action of DA on nerve stimulation. The effect of NA was also abolished by haloperidol but not by pimozide.

The regulation of transmitter release by prejunctional receptors have been reported in various tissues (Hotta, 1969; Langer, 1973; Rand, McCullough & Story, 1975; Stjarne, 1975; Hedqvist, 1976). The present results indicate that low concentrations of DA probably act on prejunctional inhibitory dopaminoceptors to modify neurotransmission by reducing the rate of transmitter release. The increase in response produced by DA antagonists is compatible with this concept since blockade of inhibitory receptors would uncover more of the excitatory receptors. The inhibition of nerve stimulation produced at higher DA concentration (prejunctional) and the excitation at the same concentrations (postjunctional) suggest a possible dual effect of DA.

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