J. Pharm. Pharmacol. 1983, 35: 182–183
Communicated June 28, 1982

0022–3573/83/030182–02 $02.50/0

Yohimbine antagonism of the inhibitory effects of pethidine and profadol in the mouse isolated vas deferens

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The inhibitory effect of pethidine on the isolated vas deferens preparation of the mouse has previously been described by Hughes et al (1975). The opiate antagonist naloxone was observed by these authors to reverse this effect. Profadol, *m*-(1-methyl-3-propyl-3-pyrrolidinyl) phenol, has been shown to have mixed opiate agonist and antagonist actions in the guinea-pig isolated ileum (Kosterlitz & Watt 1968) and man (Jasinski et al 1971).

In this study the inhibitory effects of the analgesics were compared on the two vas deferens from the same mouse, one tissue being pretreated with either naloxone or yohimbine or a mixture of both antagonists the other tissue was free of antagonists.

Method

The method used was as follows: mice, T.O. strain, 25–35 g, were killed by cervical dislocation. Both vasa deferentia were removed complete and suspended in a 6 ml organ bath and continuously perifused at 12 ml min^{-1} with Mg^{2+}-free Krebs solution consisting of (mM): NaCl 118·4, KCl 4·8, $K_2H_2PO_4$ 1·2, $CaCl_2$ 2·5, Na HCO_3 25·0, and glucose 11·1 at 35 °C. The Krebs was gassed with a 95% O_2/5% CO_2 mixture. Contractions of the tissue were recorded with SR1 isotonic transducers under a 0·2 g load. After a 30 min equilibration period the tissues were continuously stimulated at a frequency of 0·1 Hz, 1 ms pulse width and 100 mA supramaximal current using an SRI stimulator coupled to a constant current device, with ring electrodes placed above and below the tissue.

One vas deferens from each animal was perifused in Krebs solution which contained antagonist (either naloxone 10^{-6} M, yohimbine 5×10^{-7} M or a mixture of naloxone 10^{-6} and yohimbine 10^{-7}). The antagonists were introduced into the Krebs 15 min before the first exposure to the analgesic agent. The other vas deferens was maintained in antagonist-free Krebs solution. Analgesic agents were added to the perifusates in increasing concentration of 10^{-7}, 3×10^{-7}, 10^{-6}, 3×10^{-6}, 10^{-5} and 3×10^{-5} M. Each concentration was in contact with the tissue for 6 min followed by a 10–30 min washout period.

The effects of analgesic agents in antagonist-free and antagonist-treated tissues were observed simultaneously. The size of the stimulation-induced twitch response in the presence of the analgesic was expressed as a percentage of the response immediately before that concentration of the analgesic entered the organ bath. Groups of tissues treated with antagonists were compared with the untreated preparations from the same animals using a two-tailed paired *t*-test. The drugs used were pethidine HCl (MacFarlan-Smith), profadol HCl (Parke, Davis & Co.) naloxone HCl (Endo) and morphine sulphate (MacFarlan-Smith).

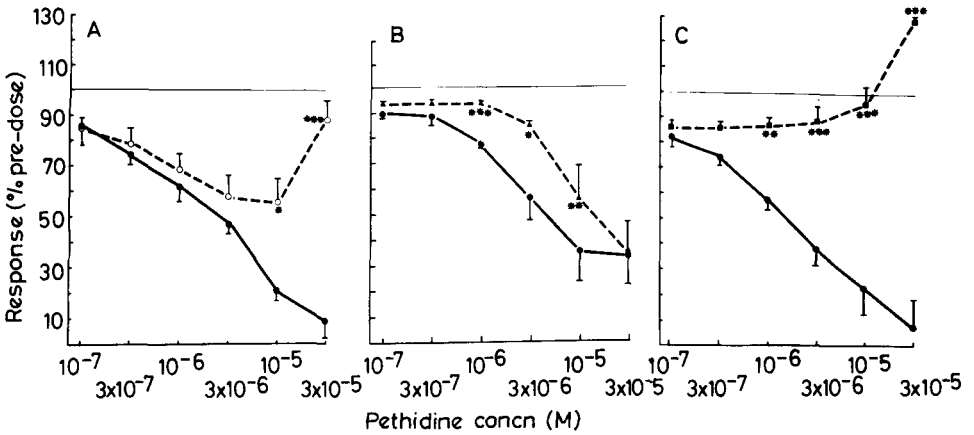

FIG. 1. The effects of pethidine on the mouse vas deferens preparation and the interactions with naloxone, yohimbine and a mixture of yohimbine and naloxone. The points are the means with s.e.m. of groups of paired tissues, one tissue from each animal in the presence the other in the absence of antagonist. A: pethidine with (broken line) and without (solid line) naloxone, 10^{-6} M (n = 4). B: pethidine with (broken line) and without (solid line) yohimbine, 5×10^{-7} M (n = 4). C: pethidine with (broken line) and without (solid line) a mixture of naloxone, 10^{-6} M and yohimbine, 10^{-7} M (n = 4). * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

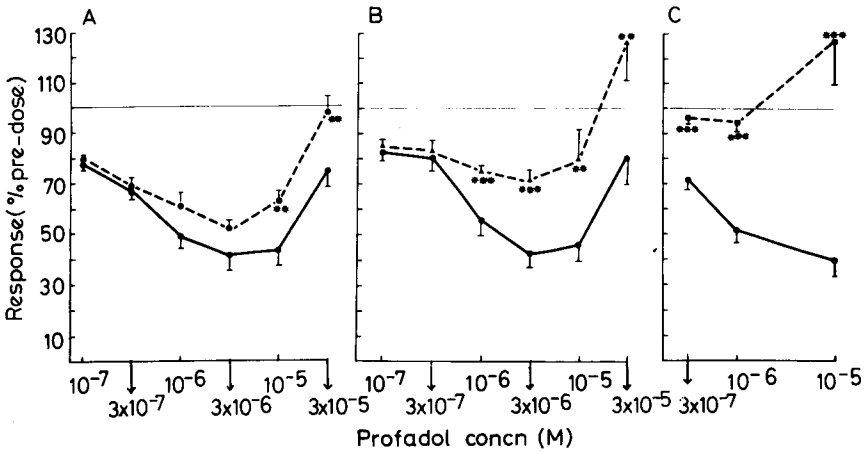

FIG. 2. The effects of profadol on the mouse vas deferens preparation and the interactions with naloxone, yohimbine and a mixture of yohimbine and naloxone. The points are the means with s.e.m. of groups of paired tissues, one tissue from each animal in the presence the other in the absence of antagonist. A: profadol with (broken line) and without (solid line) naloxone, 10^{-6} M (n = 4). B: profadol with (broken line) and without (solid line) yohimbine, 5×10^{-7} M (n = 4). C: profadol with (broken line) and without (solid line) a mixture of naloxone, 10^{-6} M and yohimbine, 10^{-7} M (n = 4). * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Results

The dose-response curve to morphine was shifted to the right by naloxone 10^{-6} M with a dose-ratio of 214 (n = 4). However, this concentration of naloxone had little effect on the inhibition produced by concentrations up to 10^{-5} M pethidine. The inhibition induced by higher concentrations of pethidine was blocked by naloxone (Fig. 1a). Naloxone also had little effect on the responses to the lower concentrations of profadol though there was some antagonism of the effect of 10^{-5} and 3×10^{-5} M profadol (Fig. 2a).

Yohimbine (5×10^{-7} M) produced a parallel shift to the right in the pethidine dose-response curve (dose-ratio of 4·0) and a marked reduction in the inhibitory effects of profadol (Figs 1B, 2B). In the presence of both naloxone 10^{-6} M and yohimbine 10^{-7} M neither analgesic produced an inhibition of the response (Figs 1C, 2C) and at the highest concentrations tested both profadol and pethidine potentiated the response to stimulation.

Naloxone alone had no obvious effect on the response to stimulation and yohimbine 5×10^{-7} M produced a potentiation of 18·5 ± 3·32 (n = 12) per cent of the predose value. This effect of yohimbine was of less than 5 min duration.

Discussion

The inhibition of the stimulation-induced responses of the vas deferens by pethidine and profadol appears to have two components, one sensitive to naloxone blockade the other to yohimbine, a combination of both antagonists being necessary to give complete block. It is possible that a direct or indirect α-adrenoceptor agonist action may be involved in the yohimbine-sensitive component as this compound is an α_2-adrenoceptor antagonist (Starke et al 1975) and α-agonists do have inhibitory actions in this preparation (Jenkins et al 1976). Other mechanisms of action cannot be excluded.

In the presence of both yohimbine and naloxone the effect of both profadol and pethidine in concentrations in excess of 10^{-5} M is to potentiate the response of the vas deferens. Huidobro et al (1980) have reported a potentiation of the responses of the rat vas deferens to electrical stimulation in the presence of a variety of opiate analgesics, including pethidine, in this concentration range.

The mouse vas deferens in the presence of naloxone and yohimbine thus appears to resemble the rat vas deferens in its response to pethidine.

In conclusion, both pethidine and profadol exert an inhibitory effect on the mouse vas deferens response to stimulation which is in part resistant to blockade by naloxone. Yohimbine partially antagonized the inhibitory effects of the analgesics but a combination of naloxone and yohimbine was required for a complete block. Thus, part of the inhibitory effect of the analgesics may not be mediated by opiate receptors.

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