J. Pharm. Pharmacol. 1987, 39: 491–492
Communicated November 25, 1986

Stimulant action of pethidine on the pregnant rat uterus in-vitro

J. FAZACKERLEY, B. J. PLEUVRY*, *Departments of Anaesthesia and Pharmacology, Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT*

Pethidine's stimulant action on the 22-day pregnant rat isolated uterus does not involve receptors sensitive to methysergide and is unlikely to involve the synthesis and release of endogenous prostaglandins. The sensitivity of pethidine-induced contractions to verapamil suggests that mobilization of extracellular calcium is necessary for pethidine's action.

Pethidine is widely used for the provision of analgesia in labour. Campbell et al (1961) noticed that women who received pethidine had shorter labours than those who received morphine. Sivalingham & Pleuvry (1985) showed that pethidine, but not other opioids, increased the frequency and amplitude of contraction, of the 22-day pregnant rat uterus in-vitro. This stimulation was not antagonized by naloxone, and the concentrations of pethidine used did not correlate with its known potencies at opioid receptors. The purpose of this study was to investigate possible mechanisms by which pethidine might achieve its stimulatory action.

Three lines of approach have been tried, the involvement of endogenous prostaglandin release, mobilization of extracellular calcium ions and specific interactions with tryptaminergic receptors. The last investigation was prompted by the observation that pethidine, but not morphine, had significant interactions with tryptaminergic systems in other circumstances (Carlsson & Lindqvist 1969; Ahtee & Saarnivaara 1973).

Methods

Sprague-Dawley rats on day 22 of pregnancy were killed by a blow to the head and cervical dislocation. The uterus was freed of foetal and placental tissue and four longitudinal strips (10 × 5 mm) were suspended in Krebs-Henseleit solution at 37 °C under a tension of 1 g and bubbled with 5% carbon dioxide in oxygen. Contractions were measured by an isometric transducer connected to a Rikadenki pen recorder. Measurements were taken over 15 min for pethidine stimulation, and 2 min for other agonists such as acetylcholine and 5-hydroxytryptamine (5-HT). Verapamil 10^{-7} to 10^{-5} M, indomethacin 10^{-7} to 10^{-4} M and methysergide 500 ng mL^{-1} were left in contact with the preparation for 30 min before other drugs were added. An equal number of time-matched control preparations received pethidine and either acetylcholine or 5-HT alone. Drugs were diluted with distilled water from either pure substance or commercially available solution. Results are expressed as means ± s.e.m. of not less than six preparations, each from a different rat. Statistical comparison between test and control groups was carried out using Student's *t*-test.

* Correspondence.

Results

Maximal stimulant response occurred with 40 μg mL^{-1} pethidine, 100 ng mL^{-1} acetylcholine and 5 μg mL^{-1} 5-HT. Although the frequency of the contractions induced by pethidine exhibited a clear concentration-response relationship throughout the day (Table 1), the amplitude of the contractions became independent of concentration of pethidine as the day progressed. In view of this, time-matched control preparations from the same rat were used for all analyses of results.

Indomethacin suppressed spontaneous uterine contractions at all the concentrations used but had no effect on pethidine-induced contractions at 10^{-7} to 10^{-5} M. At 10^{-4} M there was a decrease in amplitude of contractions due to pethidine (2·5 g ± 0·7 g) compared with time-matched controls (4·4 g ± 0·5 g).

Verapamil, like indomethacin, reduced the spontaneous contraction of the uterus and also antagonized the stimulation due to pethidine at 10^{-7} and 10^{-6} M, compared with time-matched controls (Fig. 1). The effect of 10^{-7} M verapamil was greater on the amplitude than on the frequency of contractions (Table 1). Higher concentrations of verapamil reduced both amplitude and frequency responses to pethidine and prevented the increase in basal tone induced by 80 μg mL^{-1} pethidine.

Table 1. Effect of verapamil on the increase in frequency of contraction induced by pethidine on the 22-day pregnant rat isolated uterus. Results are expressed as mean ± s.e.m. increase in contractions min^{-1}, compared with the 15 min immediately before drug administration.

Pethidine (μg mL^{-1})	Alone	Verapamil 10^{-7} M	Time-matched control
10	1·60 ± 0·35	0·08 ± 0·06*	0·77 ± 0·18
20	2·00 ± 0·31	0·98 ± 0·32	1·35 ± 0·21
40	2·59 ± 0·34	1·54 ± 0·41	1·87 ± 0·24
80	3·80 ± 0·67†	2·37 ± 0·90†	2·28 ± 0·25†

* Significantly different from time-matched control ($P < 0·05$).

† Includes several preparations with an increase in basal tone.

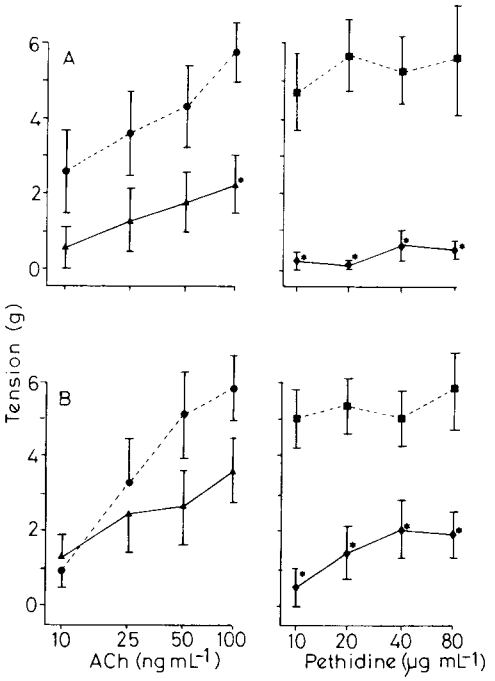

FIG. 1. Effects of verapamil A 10^{-6} M and B 10^{-7} M on the amplitude of the response of the pregnant rat isolated uterus to pethidine and acetylcholine (ACh). Results are expressed as means ± s.e.m. (n = 6) in verapamil-treated preparations (solid line) and time-matched control preparations (dashed line). * $P > 0.05$.

Verapamil was less effective in reducing the amplitude of the contraction induced by acetylcholine (Fig. 1). Acetylcholine did not induce rhythmic contractions.

Methysergide had no effect on the action of pethidine, but it did decrease the contractile response to 5-HT. The % increase in tension after 5 μg mL^{-1} 5-HT alone was 298 ± 56 but this was reduced to 89% ± 13 in the presence of methysergide.

Discussion

The concentration-related effects of pethidine on the uterus was an increase in the frequency of contraction, rather than an increase in amplitude of contraction, although some concentration-dependent effects could be seen in this measure of response in the first hour of experimentation. Thus, the response to pethidine with respect to amplitude of contraction was all or none. This contrasts with the actions of acetylcholine and 5-HT which produce concentration-dependent increases in contraction amplitude throughout the day. Although the relevance of both concentrations of drug on rat tissue to blood concentrations in man is debatable, pethidine concentrations as high as 27 μg mL^{-1} have been reported in maternal blood (Reddin 1966). Pethidine, 10 μg mL^{-1} produced uterine stimulation in the present study. But it is unlikely that that level would be found in modern UK obstetric practice.

The stimulatory effect of pethidine on the uterus was depressed by 10^{-5} M indomethacin. However, it is unlikely that this indicates that release of endogenous prostaglandins are involved in pethidine's action.

Indomethacin inhibits the biosynthesis of prostaglandins in this tissue at concentrations well below 10^{-4} M (Dubin et al 1979) and prevents the spontaneous activity of the preparation which is believed to be due to release of endogenous prostaglandins (Phillips & Poyser 1981). In the present study, spontaneous activity of the uterus was abolished by 10^{-7} M indomethacin, a concentration which had no effect on pethidine-induced stimulation. There is evidence that higher concentrations of indomethacin may have calcium antagonist properties (Anderson & Kohn 1978) and this may have contributed to the inhibition of pethidine's stimulant activity. This is supported by the diminution of pethidine's effects by the calcium antagonist verapamil. Since uterine contraction is generally held to be largely dependent on extracellular rather than intracellular calcium (Bolton 1979), it might be expected that a calcium antagonist would inhibit most spasmogens on this tissue. Despite this, it was possible to differentiate acetylcholine-induced activation of the tissue from pethidine activation. Acetylcholine has been shown to produce contractions of the uterus in calcium-free media (Sakai et al 1985) and to displace calcium ions from intracellular stores by electro-mechanical coupling (Mironneau et al 1984). Thus pethidine's stimulant action is more dependent on extracellular calcium than is acetylcholine's activity. The use of calcium-free medium is not suitable for differentiating extracellular from intracellular calcium in the rat uterus (Edwards et al 1986).

Tryptaminergic activity is clearly irrelevant to the uterine stimulant activity of pethidine.

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