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SPURIOUS EFFECTS OF COMMERCIAL PREPARATIONS OF OXYTOCIN ON THE ISOLATED VAS DEFERENS OF THE RAT

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1 The inhibitory effect of a commercial preparation of oxytocin (Syntocinon) was studied on the isolated vas deferens of the rat.

2 The inhibition of contractions to agonists and to field stimulation obtained were mimicked by appropriate dilutions of chlorbutol, a preservative present in Syntocinon.

3 Preservative-free synthetic oxytocin had no inhibitory effect on the tissue and slightly potentiated contractions evoked by field stimulation.

4 It is concluded that inhibitory effects of Syntocinon on the vas deferens are due to chlorbutol, not oxytocin.

Introduction

The lack of an apparent role for oxytocin in male animals has led to an intensive examination of its diverse effects on smooth muscle in the hope of finding additional functions for the hormone. Often, commercial preparations of oxytocin (e.g. Syntocinon) are used for such studies. Whereas *in vivo* studies with commercial preparations are probably valid, the investigation of the effects of Syntocinon on isolated preparations containing smooth muscle is complicated by the presence of chlorbutol 0.5% which is added to the hormone solution as a preservative.

Such a study has recently been published by Beneit, Hidalgo & Tamargo (1980), where dilutions of Syntocinon to 25–400 mu/ml were shown to inhibit responses of vas deferens of the rat to field stimulation and agonist drugs. Since such dilutions of Syntocinon contain 0.14 to 1.13 mM chlorbutol, a smooth muscle relaxant, the experiments described below were designed to compare the effects of dilutions of chlorbutol within this range with those of Syntocinon and preservative-free synthetic oxytocin.

Methods

Male Wistar rats were killed by stunning and exsanguination. The vasa were removed and suspended in an organ bath containing modified Krebs fluid at 37°C (Botting & Salzmann, 1974) gassed with 95% O_2 and 5% CO_2.

Contractions were measured with a Harvard smooth muscle isotonic transducer and recorded on a Devices pen recorder. After a 1 h period at a load of 1 g, constant, submaximal responses to agonist drugs were obtained and the effects of oxytocin preparations and chlorbutol, added 30 s before a dose of agonist, were determined. Field stimulation was applied (supramaximal voltage, 0.5 ms, 10 Hz) for 5 s every minute and chlorbutol and hormone preparations were added to the bath fluid for 6 min periods. Drugs used were: chlorbutol (BDH), noradrenaline acid tartrate (Winthrop), dopamine hydrochloride (Sigma), Syntocinon (Sandoz) and preservative-free synthetic oxytocin (Sandoz). Preservative-free oxytocin was checked for potency on rat isolated uterus against a recent batch of Syntocinon ampoules.

Results and Discussion

Experiments were performed on vasa deferentia from six rats. Typical results are illustrated in Figure 1.

Syntocinon from ampoules supplied for therapeutic use inhibited the contractions induced by field stimulation, noradrenaline and dopamine. (The difficulty of obtaining a satisfactory dose-effect relationship for acetylcholine on the vas precluded the use of this agonist.) Similar inhibitions were obtained with equivalent dilutions of chlorbutol.

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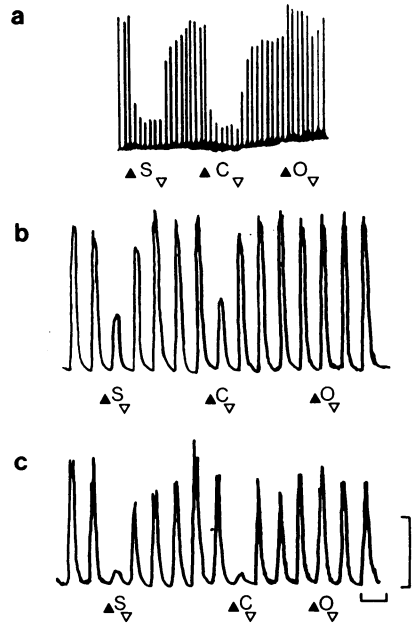

Figure 1 The effect of Syntocinon (S) 250 mu/ml, equivalent dilutions of chlorbutol (C) 1.5 mM and preservative-free synthetic oxytocin (O) 250 mu/ml on rat isolated vas deferens: (a) field stimulated every minute, 10 Hz, 5 s, 0.5 ms supramaximal voltage; (b) stimulated every 3 min by noradrenaline 3 μM for 30 s; (c) stimulated every 3 min by dopamine 8 μM for 30 s. ▽ = wash. Vertical bar 2 cm. Horizontal bar 5 min.

Preservative-free synthetic oxytocin caused no inhibition of responses to agonists or field stimulation. In fact pure oxytocin caused a potentiation of contractions due to field stimulation, but had no such effect on contractions produced by noradrenaline and dopamine.

It would thus appear that the inhibitory action of Syntocinon on the vas deferens is due to the preservative chlorbutol and not to the oxytocin itself. Chlorbutol is a potent vasodilator (Katz, 1964) and relaxes smooth muscle in various isolated organs (Somlyo, Woo & Somlyo, 1966; Botting & Manley, 1967). As was emphasised by Rudinger & Krejci (1968) the fact that the presence of chlorbutol in commercial preparations of oxytocin (1 mg chlorbutol with 2 iu oxytocin) can lead to spurious results is perhaps obvious but nevertheless requires continued emphasis.

The selective potentiation of responses to field stimulation might indicate that oxytocin can facilitate the release of transmitter from intramural nerves in the vas, although one would hesitate to propose that this was of physiological significance in view of the concentration of oxytocin used, which was well in excess of probable plasma concentrations.

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References

BENEIT, J.V., HILDAGO, A. & TAMARGO. J.L. (1980). Effects of oxytocin on the isolated vas deferens of the rat. *Br. J. Pharmac.*, **69**, 379–382.

BOTTING, J.H. & MANLEY, D.G. (1967). The action of commercial preparations of oxytocin and vasopressin on the smooth muscle of the gut. *J. Pharm. Pharmac.*, **19**, 66.

BOTTING, J.H. & SALZMANN, R. (1974). The effect of indomethacin on the release of prostaglandin E_2 and acetylcholine from guinea-pig ileum at rest and during field stimulation. *Br. J. Pharmac.*, **50**, 119–124.

KATZ, R.L. (1964). Antiarrhythmic and cardiovascular effects of synthetic oxytocin. *Anaesthesiology*, **25**, 653–661.

RUDINGER, J. & KREJCI, I. (1968). Antagonists of neurohypophysial hormones. In *Neurohypophysial Hormones and Similar Peptides*, ed. Berde, B. pp. 748–801. Berlin: Springer.

SOMLYO, A.V., WOO, C.Y. & SOMLYO, A.P. (1966). Effect of magnesium on posterior pituitary hormone action on vascular smooth muscle. *Am. J. Physiol.*, **210**, 705–714.

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