Moderate to high doses of non-analgesic drugs such as physostigmine (0·01–0·05 mg kg^{-1}, i.v.) chlorpromazine (3–10 mg kg^{-1}, i.v.) and mephenesin (30–70 mg kg^{-1}, i.v.) did not produce any inhibitory effect, although they are effective in the mouse writhing test (Charnov et al 1967). This indicates that the present method is probably the more specific of the two for the evaluation of analgesics.

Our present findings suggest that the method described overcomes the drawbacks in the anti-bradykinin test previously reported by Blane (1967) and Abe et al (1971) and is useful for testing various analgesics, particularly narcotic agonist-antagonists and anti-inflammatory analgesics.

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The inhibitory effects of sex steroid hormones on electrically-induced contractions of the guinea-pig isolated ileum

JEANINE FONTAINE, ISABELLE SEAMAN, JEAN-PIERRE FAMAEY*, JEAN REUSE, *Laboratory of Pharmacology, School of Medicine and Institute of Pharmacy, University of Brussels, 115 boulevard de Waterloo, 1000 Brussels, Belgium*

Progesterone, pregnenolone, testosterone, ethinyloestradiol, oestrone and oestriol reversibly inhibit guinea-pig isolated ileum contractions to PGE_1 and $F_{2\alpha}$ (Seaman et al 1978), acetylcholine, histamine (Seaman et al 1977a) nicotine and 5-hydroxytryptamine (5-HT) (Seaman et al 1977b) and these four last inhibitions can be reversed by PGE_1 or $F_{2\alpha}$. It was concluded that sex steroids exert a spasmolytic effect on ileal smooth muscle which was also the conclusion of Ishida et al (1972) who noted a papaverine-like action of some sex hormones on the guinea-pig ileum. These inhibitory actions are similar to those induced by non-steroidal and steroidal anti-inflammatory drugs (NSAID and SAID) (Famaey et al 1975, 1977a,b). These anti-inflammatory compounds are also able to inhibit guinea-pig isolated ileum contractions induced by transmural electrical stimulations and these inhibitions are reversed by PGE_1, E_2 and $F_{2\alpha}$ (Famaey et al 1975, 1977a), caerulein (Fontaine 1976) and metoclopramide (Fontaine et al 1979).

* Correspondence.

We have now investigated whether similar inhibitions and similar reversals occur with steroid sex hormones.

Four cm lengths of guinea-pig ileum were suspended under an initial load of 1 g in Krebs-Henseleit solution

Table 1. Inhibitory effects of two sex steroid hormones on the responses of the guinea-pig isolated ileum to coaxial stimulation (12 min contact time). The results (mean ± s.e.m., n = 6) have been analysed with the Student's *t*-test for paired data.

Sex steroids	μg ml^{-1}	% inhibition
Testosterone	0·5	47* ±9
	1	62*** ±10
	5	96*** ±2
Ethinyloestradiol	0·5	21* ±5
	1	53** ±11
	5	96*** ±2

* $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$

maintained at 37° C and gassed with a mixture of 5% CO_2 in oxygen. Isometric contractions (registered by a transducer) were elicited by coaxial electrical stimulation (pulse width 0·5 ms, pulse strength 5–25 V, frequency 0·1 Hz; Paton 1955). The hormones were added to the bath after a 5 min period of constant contractions.

At concentrations similar to those used previously by Seaman et al (1977a,b; 1978) for inhibiting contractions to acetylcholine, histamine, nicotine, 5-HT, PGE_1 or $F_{2\alpha}$ (progesterone 0·5, pregnenolone 1, oestrone 1, ethinyloestradiol 1, and oestriol 20 $\mu g\ ml^{-1}$) these sex steroid hormones inhibit the electrically-induced contractions by approximately 50%. The effects of various concentrations of two of these hormones (ethinyloestradiol and testosterone) were quantified and analysed by Student's *t*-test for paired data (Table 1).

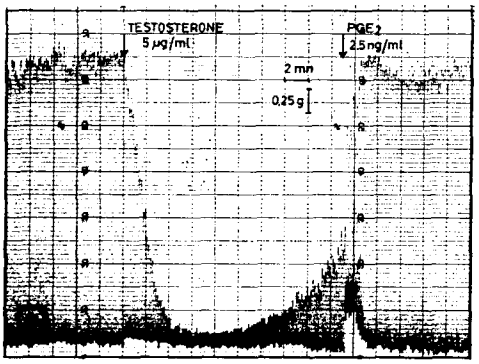
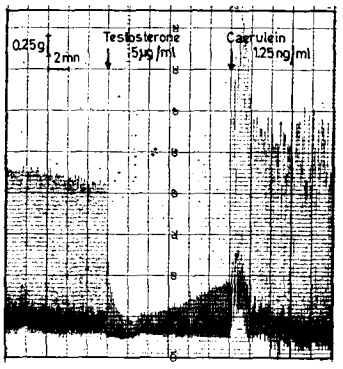
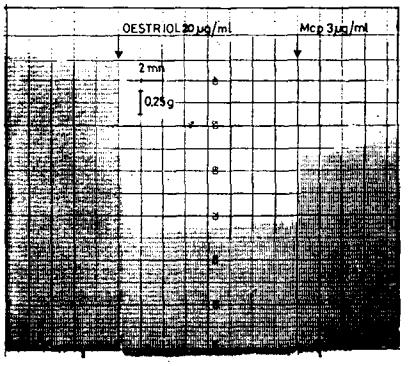


FIG. 1A. Inhibition by testosterone 5 $\mu g\ ml^{-1}$ reversed by PGE_2 2·5 ng ml^{-1}.



B. Inhibition by testosterone 5 $\mu g\ ml^{-1}$ reversed by caerulein 1·25 ng ml^{-1}.



C. Inhibition by oestriol 20 $\mu g\ ml^{-1}$ reversed by metoclopramide (Mcp) 3 $\mu g\ ml^{-1}$.

All these inhibitions were reversible after washing out the hormones from the bath and appear to be in the same order of magnitude than those found previously by us on acetylcholine or histamine-induced contractions (Seaman et al 1977a) but less important than those exerted by most of these compounds on nicotine, 5-HT, PGE_1 or $F_{2\alpha}$ (Seaman et al 1977b, 1978).

Small concentrations of PGE_1 or E_2 (2·5 ng ml^{-1}) and to a lesser degree, $PGF_{2\alpha}$ (25 ng ml^{-1}) reverse inhibitions when added to the bath after about 12 to 15 min (when the inhibitions are well stabilized) (Fig. 1A). Small concentrations of caerulein (0·63 ng ml^{-1} to 1·25 ng ml^{-1}) are also able to reverse these inhibitions when similarly added to the bath (Fig. 1B) as well as 3 $\mu g\ ml^{-1}$ of metoclopramide (Fig. 1C).

In conclusion it appears that sex steroid hormones exert non-specific inhibitions of guinea-pig isolated ileum contractions to electrical coaxial stimulations as do NSAID and SAID, and that these inhibitions were similarly non-specifically reversed by either PG (E_1, E_2 or $F_{2\alpha}$), caerulein or metoclopramide.

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