(b) Plasma concentrations of 100-200 μg/ml may be tolerated for a few minutes, but if maintained an abrupt rise may occur with death at concentrations >200 μg/ml;
(c) Sustained plasma concentrations <100 μg/ml are not lethal.

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Effect of the (−)- and (+)-isomers of fenfluramine and norfenfluramine on glucose uptake by the isolated rat hemidiaphragm

MARILYN J. KIRBY* & P. TURNER

Clinical Pharmacology Department, St Bartholomew's Hospital, London, EC1A 7BE

We have previously shown that fenfluramine and its main metabolite norfenfluramine cause an increase in glucose uptake by the rat hemidiaphragm preparation (Kirby & Turner, 1974). We have now studied the effects of the (−)- and (+)-isomers of fenfluramine and norfenfluramine on this preparation. The method used was as described by Frayn & Adnitt (1972). In all experiments 100 μU/ml of insulin were included in the incubation medium, as it had been shown previously by us that no significant increase in glucose uptake occurred with either fenfluramine or norfenfluramine in the absence of insulin.

From the results shown in Table 1 it can be seen that the (−)-isomer of fenfluramine has significantly greater activity than the (+)-isomer over the therapeutic range of 50-100 ng/ml (Campbell, 1971). However, no significant difference is seen between the activity of the two isomers of norfenfluramine, both causing a similar increase in glucose uptake in therapeutic concentrations. No change in glycogen content could be detected following treatment with the isomers of either compound. We also studied the effect of 10,

Table 1 Effect of fenfluramine and norfenfluramine isomers on glucose uptake by the isolated rat hemidiaphragm (with 100 μU/ml insulin)

Fenfluramine (+) ng/ml	10	50	100	1000
Mean % change ± s.e.*	+1.4 ± 3.8	+4.2 ± 8.3	+9.6 ± 8.9	+8.2 ± 6.7
t	0.36	0.51	1.08	1.22
Significance (*P*)	NS	NS	NS	NS
Fenfluramine (−) ng/ml	10	50	100	1000
Mean % change ± s.e.*	+15.8 ± 3.2	+25.0 ± 5.1	+33.9 ± 8.7	+19.3 ± 6.1
t	4.02	4.90	3.90	3.16
Significance (*P*)	$0.001 > p$	$0.001 > p$	$0.01 > p > 0.001$	$0.02 > P > 0.01$
Norfenfluramine (+) ng/ml	10	50	100	1000
Mean % change ± s.e.*	−0.3 ± 4.6	+12.9 ± 7.7	+12.1 ± 6.4	+13.9 ± 5.9
t	0.07	1.68	1.89	2.36
Significance (*P*)	NS	NS	NS	$0.05 > P > 0.02$
Norfenfluramine (−) ng/ml	10	50	100	1000
Mean % change ± s.e.*	+12.1 ± 8.4	+12.1 ± 6.2	+16.9 ± 5.6	+13.1 ± 5.0
t	1.44	1.90	3.02	2.62
Significance (*P*)	NS	NS	$0.02 > P > 0.01$	$0.05 > P > 0.02$

* All comparisons are made on a 'within rat' basis $n = 10$.
NS = not significant.

100, 1000 ng/ml of (±), (−) and (+) amphetamine in the presence of insulin, but obtained no significant increase in glucose uptake, except with 100 ng/ml of the (−) isomer, which gave an increase of 12.5%, significant at the 10% level.

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Influence of prostaglandins and oestrus cycle on the spasmodic action of angiotensin II and oxytocin on rat uterus

M.Y. BAUDOUIN-LEGROS*, PH. MEYER & M. WORCEL

Physiologie & Pharmacologie, Inserm U7, Hôpital Necker, Paris

The uterine contractility is increased by oestrogen-treatment (Marshall, 1959) and depressed by progesterone (Kuriyama, 1961). On the other hand, the contribution of endogenous prostaglandins (PGs) to the oxytocin-induced contraction has been demonstrated (Vane & Williams, 1972).

The purpose of this work was:

1. To investigate the variations of the responses to angiotensin II, oxytocin and prostaglandin $F_{2\alpha}$, during the oestrus cycle.
2. To examine the possible role of prostaglandins as mediators of the spasmogenic action.
3. To look for some relation between the potentiating effect of sex hormones and the relative importance of the contribution made by endogenous PGs, angiotensin II- and oxytocin-induced contractions.

Uterine horns from Wistar rats were excised and equilibrated at 37°C in normal Ringer solution. Spontaneous and provoked contractions were measured isotonically.

The uterine contractility is *minimum in metaoestrus.* In this stage, the maximal responses are obtained with the respective concentrations of 5×10^{-7} M, 5×10^{-8} M and 10^{-5} M of angiotensin II, oxytocin and $PGF_{2\alpha}$, and the corresponding ED_{50} values are 10^{-8} M, 2.5×10^{-9} M and 10^{-6} M. Both the spontaneous activity and the sensitivity to agonists are *maximal in proestrus.* The maximal response and ED_{50} are observed at 10^{-7} M and 3×10^{-9} M for angiotensin, 5×10^{-9} M and 5×10^{-11} M for oxytocin, 5×10^{-6} M and less than 10^{-8} M for $PGF_{2\alpha}$ respectively.

For angiotensin II, the oestrus response does not differ from the proestrus and dioestrus responses. On the contrary, for oxytocin and $PGF_{2\alpha}$, the response in oestrus is intermediate between the metaoestrus and proestrus.

Indomethacin 5×10^{-6} M, which inhibits prostaglandin synthesis (Vane, 1971) shifts to the right the curves obtained with angiotensin and oxytocin in dioestrus and proestrus (respective ED_{50} 5×10^{-9} M and 2.5×10^{-10} M). It is inactive on these agonists in metaoestrus and on $PGF_{2\alpha}$ throughout the cycle.

Polyphloretin phosphate (PPP), a prostaglandin inhibitor administered at the concentration of 10 $\mu g\ ml^{-1}$ decreases the sensitivity of proestrus and dioestrus uteri to angiotensin (ED_{50} 10^{-8} M), oxytocin (ED_{50} 2.5×10^{-10} M) and $PGF_{2\alpha}$ (ED_{50} 10^{-7} M). A shift to the right of the metaoestrus curves is obtained at the concentration of 50 $\mu g\ ml^{-1}$.

On the contrary, a previous exposition to $PGF_{2\alpha}$ shifts the metaoestrus angiotensin dose-response curve towards the proestrus one.

These data demonstrate:

1. The physiological rôle of steroid-hormone impregnation as modulator of the uterine motility, for the oestrogen progesterone ratio is maximal in proestrus and minimal in metaoestrus (Hori, Ide & Miyake, 1968; Uchida, Kadowaki & Miyake, 1969).
2. A participation of endogenous PG in the contractile response to angiotensin II and oxytocin.
3. A good correlation between the importance of the contribution of endogenous PG to the contraction and the uterine hypersensitivity observed under oestrogen impregnation.