Modification by ethinyloestradiol and progesterone of the effects of imipramine on 5-hydroxytryptamine metabolism in discrete areas of rat brain

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Fludder & Tonge (1975) have shown changes in monoamine metabolism in eight areas of rat brain during the oestrous cycle which may be expected to modify both behaviour and the actions of psychotropic drugs. The fluctuations in the relative levels of endogenous oestrogen and progesterone which occur during female reproductive cycles may be directly responsible for the changes in brain monoamine concentrations at these times (Greengrass & Tonge, 1974).

The effects of imipramine, alone and in combination with ethinyloestradiol or progesterone, have been examined in female rats ovariectomized six weeks prior to use and in litter-mate intact females. Ethinyloestradiol and progesterone administration have been found to modify the effects of imipramine on 5-hydroxytryptamine (5-HT) metabolism in the eight areas of brain described by Fludder & Tonge (1975); the effects in two of these areas, the amygdala (representing brain areas containing a high proportion of neurone terminals) and the midbrain (representing areas containing principally axons/cell bodies), are shown in Table 1.

5-HT depletion after synthesis blockade with *p*-chlorophenylaline (PCPA; 400 mg/kg) was slower in the midbrain and faster in the amygdala in ovariectomized than in dioestrous rats, suggesting reduced and accelerated turnover rates respectively in the two areas. Depletion was accelerated by ethinyloestradiol and reduced by progesterone (unpublished results).

Imipramine failed to cause a statistically significant change in indoleamine concentrations in ovariectomized rats. However, when administered together with either ethinyloestradiol or progesterone, the same dose of imipramine produced effects similar to those seen in intact dioestrous rats. It therefore appears that the detectable effects of imipramine upon central 5-HT metabolism are dependent on the existent levels of oestrogen and/or progesterone and it is conceivable that the actions of the drug may be similarly susceptible in the human female.

It is suggested that both progesterone and imipramine reduce the uptake of 5-HT into nerve terminals, thereby increasing the concentrations of the amine at the receptor sites Ethinyloestradiol has been shown to affect both the turnover and the synthesis (unpublished results) of 5-HT and these effects may explain the influence of the hormone upon the actions of imipramine.

Table 1 Effects of ethinyloestradiol and progesterone on the changes in 5-HT and 5-HIAA concentrations produced by imipramine in two areas of rat brain

	5-HT/5-HIAA (n moles/g ± s.e. mean)	*Amygdala*	*Midbrain*
Intact rats at dioestrus (D)	5-HT	4.35 ± 0.14	2.98 ± 0.14
	5-HIAA	0.97 ± 0.02	3.35 ± 0.01
D + imipramine (cf. D)	5-HT	7.34 ± 0.05‡	4.40 ± 0.09‡
	5-HIAA	0.71 ± 0.05‡	1.46 ± 0.06‡
Ovariectomized litter-mates (O)	5-HT	4.18 ± 0.07	1.45 ± 0.04
	5-HIAA	0.95 ± 0.09	5.24 ± 0.45
O + imipramine (cf. O)	5-HT	4.73 ± 0.17	1.11 ± 0.08*
	5-HIAA	1.10 ± 0.06	4.14 ± 0.09
O + EO	5-HT	3.35 ± 0.19	1.05 ± 0.20
	5-HIAA	0.76 ± 0.04	4.14 ± 0.32
O + EO + imipramine (cf. O + EO)	5-HT	4.73 ± 0.25†	2.70 ± 0.23‡
	5-HIAA	0.70 ± 0.03	3.89 ± 0.11
O + progesterone	5-HT	2.88 ± 0.26	1.80 ± 0.07
	5-HIAA	0.66 ± 0.04	2.79 ± 0.10
O + progesterone + imipramine (cf. O + progesterone)	5-HT	3.30 ± 0.08	2.47 ± 0.08‡
	5-HIAA	0.63 ± 0.01	2.85 ± 0.11

Statistically significant differences –Student's *t* test) are shown as * $P<0.05$, † $P<0.01$, ‡ $P<0.001$. Each value is the mean of determinations on 5 brains.

References

FLUDDER, J.M. & TONGE, S.R. (1975). Variations in the concentrations of monoamines and their metabolites in eight regions of rat brain during the oestrous cycle: a basis for interactions between hormones and psychotropic drugs. *J. Pharm. Pharmac.*, **27 Suppl.** 39.

GREENGRASS, P.M. & TONGE, S.R. (1974). Suggestions on the pharmacological actions of ethinyloestradiol and progesterone on the control of monoamine metabolism in three areas from the brains of gonadectomized male and female mice and the possible clinical significance. *Arch. Int. pharmacodyn.*, **211**, 291–303.

Effects of testosterone and ethinyloestradiol on the synthesis and uptake of noradrenaline and 5-hydroxytryptamine in rat hindbrain: evidence for a presynaptic regulation of monoamine synthesis?

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The participation of brain monoamines in the regulation of pituitary secretory activity is well established (Ganong, 1975) and the feedback control of plasma levels of gonadal steroids is dependent upon the ability of oestrogens, progestogens and androgens to affect central catecholamine and 5-hydroxytryptamine (5-HT) metabolism. Some of the actions of injected hormones on monoamine metabolism are presumably identical to those of endogenous hormones, with the caveat that there may be additional dose-dependent effects. Studies of the effects of hormones on defined neuronal processes may, therefore, provide some information on the physiological regulation of monoaminergic function as opposed to the pharmacological changes produced by foreign drugs.

The effects of testosterone (10 mg/kg s.c.) and

Table 1 Effects of testosterone (T) and ethinyloestradiol (EO) on the uptake and synthesis of noradrenaline (NA) and 5-HT in two hind-brain regions of male rats

	5-HT (n moles/g ± s.e. mean)		*NA (n moles/g ± s.e. mean)*	
Treatment	*Midbrain*	*Pons/medulla*	*Midbrain*	*Pons/medulla*
None	4.48 ± 0.17	3.68 ± 0.07	7.30 ± 0.48	4.94 ± 0.44
Testosterone (T)	3.59 ± 0.19	3.24 ± 0.23	6.49 ± 0.33	4.54 ± 0.31
Phenelzine (P)	4.79 ± 0.18	4.24 ± 0.27	8.90 ± 0.52	6.23 ± 0.25
P + T	8.16 ± 0.09	6.85 ± 0.29	11.07 ± 0.95	6.66 ± 0.60
% age change due to T	+120%	+96%	+49%	+20%
None	5.64 ± 0.41	5.23 ± 0.19	6.11 ± 0.44	4.07 ± 0.13
Ethinyloestradiol (EO)	5.49 ± 0.23	5.91 ± 0.26	5.67 ± 0.22	4.72 ± 0.30
Phenelzine (P)	6.87 ± 0.38	5.83 ± 0.14	6.80 ± 0.18	5.12 ± 0.22
P + EO	8.12 ± 0.47	7.48 ± 0.46	7.04 ± 0.34	5.28 ± 0.25
% age change due to EO	+26%	+15%	+13%	+14%
None	8.94 ± 0.80	6.22 ± 0.33	2.82 ± 0.13	2.54 ± 0.20
Testosterone (T)	6.18 ± 0.38	4.59 ± 0.27	2.41 ± 0.27	3.19 ± 0.42
H75/12	6.18 ± 0.42	4.24 ± 0.16		
H77/77			2.06 ± 0.40	2.35 ± 0.14
T + H75/12 or H77/77	6.18 ± 0.42	3.88 ± 0.07	3.90 ± 0.39	2.45 ± 0.28
% age change	−31%	−16%	−14%	0
None	6.76 ± 0.60	4.74 ± 0.40	5.03 ± 0.24	3.83 ± 0.36
Ethinyloestradiol (EO)	5.53 ± 0.20	3.60 ± 0.20	5.75 ± 0.33	4.12 ± 0.16
H75/12	6.07 ± 0.17	3.95 ± 0.17		
H77/77			4.88 ± 0.33	3.77 ± 0.21
EO + H75/12 or H77/77	5.79 ± 0.29	4.03 ± 0.11	5.39 ± 0.20	3.83 ± 0.29
% age change	−15%	−24%	0	0

Each value is the mean of determinations from 5 rats. The % age changes shown are statistically significant (Student's *t* test) at least the $P < 0.05$ level.