Modification by oestrogen of the effects of (D)-amphetamine sulphate on noradrenaline metabolism in discrete areas of rat brain

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The changes in brain monoamine concentrations which accompany hormonal changes in female animals may be partially explained as direct effects of ovarian steroids on central monoamine metabolism (Greengrass & Tonge, 1974). Fludder & Tonge (1975) have shown changes in monoamine concentrations in eight areas of rat brain during the oestrous cycle which were expected to affect both behaviour and the effects of psychotropic drugs. The effects of endogenous oestrogen, of ethinyloestradiol, and of (+)-amphetamine sulphate in the eight areas previously described have now been examined in female rats at the four stages of the oestrous cycle and in litter-mates ovariectomized six weeks prior to use. To some extent, the effects seen were dependent upon

Table 1 Effects of oestrogens and amphetamine on catecholamine concentrations in rat brain

	Dopamine (nmol/g ± s.e. mean)	*cf.*	*Noradrenaline (nmol/g ± s.e. mean)*	*cf.*	*Normetanephrine (nmol/g ± s.e. mean)*	*cf.*
Dioestrus (Di., minimal oestrogen secretion)						
amygdala	0.60 ± 0.10		2.64 ± 0.02		0.64 ± 0.09	
midbrain	2.52 ± 0.10		2.86 ± 0.02		3.52 ± 0.09	
Di. + Amphetamine (A, 10 mg/kg, i.p., cf. Di.)						
amygdala	1.12 ± 0.09	(+)	1.48 ± 0.01	(–)	2.04 ± 0.09	(+)
midbrain	3.10 ± 0.14	(+)	1.36 ± 0.02	(–)	5.28 ± 0.02	(+)
Di. + ethinyloestradiol (EO, 100 µg/kg, s.c., cf. Di.)						
amygdala	0.64 ± 0.05	(0)	2.67 ± 0.07	(0)	0.65 ± 0.08	(0)
midbrain	3.23 ± 0.03	(+)	4.58 ± 0.15	(+)	3.80 ± 0.11	(0)
Oestrus (Oe., maximal oestrogen secretion, cf. Di.)						
amygdala	2.80 ± 0.01	(+)	1.47 ± 0.05	(–)	2.23 ± 0.16	(+)
midbrain	1.75 ± 0.07	(–)	2.33 ± 0.10	(–)	4.35 ± 0.20	(+)
Oe. + A (cf. Oe.)						
amygdala	0.38 ± 0.01	(–)	1.57 ± 0.04	(0)	2.06 ± 0.09	(0)
midbrain	1.53 ± 0.03	(0)	2.05 ± 0.01	(0)	3.25 ± 0.23	(–)
Ovariectomized (Ov., 6 weeks prior to use, cf. Di. litter-mates)						
amygdala	1.61 ± 0.16	(+)	3.30 ± 0.26	(+)	7.31 ± 0.50	(+)
midbrain	2.94 ± 0.36	(0)	0.53 ± 0.08	(+)	2.77 ± 0.01	(–)
Ov. + EO (cf. Ov.)						
amygdala	1.03 ± 0.24	(–)	1.78 ± 0.18	(–)	0.61 ± 0.06	(–)
midbrain	3.45 ± 0.48	(0)	0.86 ± 0.12	(+)	2.51 ± 0.01	(0)
Ov. + A (cf. Ov.)						
amygdala	2.47 ± 0.47	(+)	3.38 ± 0.15	(0)	8.10 ± 0.33	(0)
midbrain	2.92 ± 0.05	(0)	0.45 ± 0.01	(0)	2.52 ± 0.10	(0)
Ov. + EO + A (cf. Ov.)						
amygdala	2.39 ± 0.47	(+)	3.09 ± 0.19	(+)	0.81 ± 0.01	(–)
midbrain	4.36 ± 0.51	(+)	7.00 ± 0.35	(+)	2.01 ± 0.05	(–)
Ov. + EO + A (cf. Ov + EO)						
amygdala		(+)		(+)		(+)
midbrain		(+)		(+)		(–)
Ov. + EO + A (cf. Ov. + A)						
amygdala		(0)		(0)		(–)
midbrain		(+)		(+)		(–)

Only statistically significant changes ($P < 0.05$, Student's t test) are shown as increases (+) or decreases (–) in the *'cf.'* columns. There were at least 5 rats per group.

the relative preponderance of noradrenaline (NA) terminals or of NA axons/bodies in each brain area, suggesting that NA metabolism cannot be treated as a single, homogenous system in the CNS; the amygdala region is an example of an area in which terminals predominate, and the midbrain region of an area in which axons/bodies predominate. The effects of oestrogens and amphetamine are shown in Table 1.

NA depletion after synthesis blockade with α-methyl-*p*-tyrosine (500 mg/kg, i.p.) was slower in ovariectomized than in dioestrous litter-mates, including a reduced NA turnover rate; depletion was accelerated by ethinyloestradiol. NA depletion after 4,α-dimethyl-*m*-tyramine (2 × 12.5 mg/kg, i.p.), which reflects changes in NA neuronal uptake mechanisms, was antagonized in the amygdala, but not in the midbrain, regions by ethinyloestradiol.

It is suggested that both amphetamine and oestrogens release newly-synthesized NA, amphetamine by its well-established action of stimulating release from catecholamine terminals, whilst inhibiting impulse flow (Graham & Aghajanian, 1971) and oestrogens by stimulating total turnover of NA. Endogenous ovarian steroids appear to be necessary for the maintenance of 'normal' NA turnover rates; in their absence, or when oestrogen levels are high (at oestrus) so that maximal NA release is already occurring, amphetamine cannot show its expected effects.

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L-Dopa and (–)-deprenil in the treatment of Parkinson's disease: a long-term study

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L-Dopa plus a peripheral decarboxylase inhibitor has been used with some success in the treatment of Parkinson's Disease (Birkmayer, Linauer, Mentasti & Riederer, 1974). However, therapeutic success decreases as the illness progresses and various side effects, e.g. on-off effect, occur with this form of treatment.

In a recent study on Parkinsonian patients we demonstrated that deprenil (a selective inhibitor of monoamine oxidase (MAO) 'type B') can significantly potentiate the anti-akinetic effect of L-dopa in akinetic patients (Brikmayer, Riederer, Youdim & Linauer, 1975). Furthermore, the addition of deprenil results in a daily reduction of daily dose requirements of Madopar (L-dopa and the peripheral decarboxylase inhibitor of Benseracide (N-^{1}, DL-seryl-N-^{2}, (2, 3, 4-trihydroxybenzyl) hydrazine)). The aim of this study has been to examine the long-term effects of Madopar plus deprenil treatment in Parkinsonian patients.

Two hundred and twenty-three patients have been treated with Madopar plus deprenil since October 1974. The average oral dose of Madopar was 250 mg three times daily, and of deprenil 5–10 mg once daily. In a few patients 50 mg of L-dopa and 10 mg of deprenil were administered intravenously; in these patients intravenous therapy was more effective than oral therapy but side effects occurred more often and to a greater extent and this mode of treatment was therefore discontinued. As shown in Table 1 the addition of deprenil to Madopar therapy resulted in a statistically significant reduction in patients' functional disability (Birkmayer & Neumayer, 1972). Of the 223 patients, abnormal involuntary movements occurred in 16, psychosis in 14, orthostatic hypotension in 5 and nausea in eight. In patients with side-effects deprenil treatment was either terminated or reduced to 5 mg resulting in the disappearance of some of the side-effects. Madopar-deprenil therapy produced no response in 13.9% of patients.

The improvement in disability following deprenil therapy occurred within 20–120 min after a single dose and lasted for one to three days. Thus, deprenil may act not only by inhibiting MAO but also as a psycho-stimulant by releasing dopamine in a fashion similar to amphetamine (Knoll, Ecseri, Kelemen, Nievel & Knoll, 1965; Fuxe & Ungerstedt, 1970; Christmas, Coulson, Maxwell & Riddell, 1972).

This study has shown that the addition of deprenil