Changes in brain monoamine concentrations during the oestrous cycle in the mouse: possible pharmacological implications

Concentrations of noradrenaline in the hypothalamus change during periods in which hormone levels are fluctuating (Stefano & Donoso, 1967; Green & Miller, 1966) but information on changes in the concentrations of the biogenic amines in other areas of the brain, or on changes occurring at specified times during the oestrous cycle is scant. Because of the need of such information for the interpretation of the nervous control of ovulation and sexual behaviour we have investigated changes in tyrosine, dopamine, noradrenaline, tryptophan and 5-hydroxytryptamine concentrations during the oestrous cycle in the mouse.

The stage of the oestrous cycle in virgin albino mice (20–25 g) was established by vaginal smear immediately before the animals were killed by stunning and decapitation. The brains were removed and dissected on an ice-cold tile into the fore-brain (cortex), the mid-brain (thalamus, hypothalamus and striatum) and the hind-brain (corpora quadrigemina, pons, medulla and cerebellum). The dissection procedure gave highly reproducible results, with very low standard deviation when the weights of samples from 54 animals were compared. Noradrenaline and dopamine were determined by the method of Welch & Welch (1969), 5-hydroxytryptamine by the method of Snyder, Axelrod & Zweig (1965); tyrosine by the method of Waalkes & Udenfriend (1957) and tryptophan by the method of Hess & Udenfriend (1959).

Brain portions from three mice were pooled for the determinations. In the Tables, figures represent the mean ± s.e. nmol/g brain for six groups of mice. Statistical significance was calculated using the Student's *t*-test. The results show that changes in the concentrations of noradrenaline, dopamine and 5-HT, and their precursor amino-acids occur in both the fore- and mid-brain portions of the mouse brain during the oestrous cycle. These changes appear to be related to changes in sex hormone concentrations in the blood.

At dioestrus, the concentrations of 5-HT, noradrenaline and dopamine in the fore- and mid-brain are at their maxima. There is little hormonal activity at this time,

Table 1. *Tyrosine, dopamine and noradrenaline concentrations in the brains of mice at different stages of the oestrous cycle.*

	Tyrosine			Dopamine			Noradrenaline		
Brain portion	Fore	Mid	Hind	Fore	Mid	Hind	Fore	Mid	Hind
Dioestrus	72 ± 3	193 ± 10	104 ± 10	2·5 ± 0·2	8·2 ± 0·5	2·7 ± 0·5	2·3 ± 0·2	5·9 ± 0·2	2·5 ± 0·5
Proestrus	62 ± 5	*154 ± 9	1·5 ± 10	2·9 ± 0·4	*5·5 ± 0·6	2·2 ± 0·4	2·0 ± 0·3	4·9 ± 0·6	2·3 ± 0·3
Oestrus	58 ± 6	*141 ± 5	104 ± 11	*1·7 ± 0·2	**3·3 ± 0·4	2·6 ± 0·3	*1·0 ± 0·1	**2·7 ± 0·4	2·0 ± 0·3
Metoestrus	60 ± 7	166 ± 16	104 ± 10	2·3 ± 0·4	7·5 ± 0·4	2·4 ± 0·2	1·7 ± 0·3	*4·0 ± 0·6	2·1 ± 0·3

All figures are the mean ± s.e. of determinations on six groups in which the brains from three mice were pooled, expressed in nmol/g brain tissue. Statistical significance is shown as $*P = 0{\cdot}05$, $**P = 0{\cdot}01$.

Table 2. *Tryptophan and 5-hydroxytryptamine concentrations in the brains of mice at different stages of the oestrous cycle.*

	Tryptophan			5-hydroxytryptamine		
Brain portion	Fore	Mid	Hind	Fore	Mid	Hind
Dioestrus	31 ± 2·5	26 ± 1·5	21 ± 2·3	2·2 ± 0·4	8·7 ± 1·0	4·1 ± 0·6
Proestrus	26 ± 1·6	*16 ± 0·8	18 ± 1·3	2·0 ± 0·4	7·5 ± 0·8	3·7 ± 0·6
Oestrus	*19 ± 1·3	*14 ± 0·7	*15 ± 1·0	1·6 ± 0·2	*5·6 ± 0·8	3·9 ± 0·7
Metoestrus	*24 ± 1·6	*18 ± 1·2	20 ± 1·2	2·3 ± 0·3	7·2 ± 0·9	3·9 ± 0·6

All figures are the mean ± s.e. of determinations on six groups in which the brains from three mice were pooled, expressed in nmol/g brain tissue. Statistical significance is shown as $*P = 0{\cdot}05$, $**P = 0{\cdot}01$.

oestrogen and progesterone concentrations being low (Schwartz, 1969). During proestrus, the ovarian follicles mature under the influence of follicle-stimulating hormone and blood oestrogen concentrations rise steeply (Schwartz, 1969); mid-brain tyrosine, tryptophan and dopamine concentrations decrease significantly at this time. At oestrus, when ovulation is stimulated by luteinizing hormone, the concentrations of all three amines and their precursors are at their minima. During metoestrus, the corpora lutea in the ovary produce progesterone; amine and amino-acid concentrations begin to return to their dioestrus concentrations.

It has been shown that drugs which affect monoamine concentrations in the brain can produce ovulation in animals (Labhsetwar, 1971). The fact that changes in monoamine concentrations during oestrus are not specifically localized in the mid-brain (containing the hypothalamus), but also occur in the fore-brain, suggests that changes in monoamine concentrations may be important not only in the direct regulation of ovarian function but also in the initiation of oestrous behaviour. This suggestion is supported by the observations of Meyerson (1964, 1966, 1970) that oestrous behaviour can be elicited in ovariectomized animals by combinations of oestrogen with drugs affecting monoamine metabolism, and by the fact that cortical and limbic lesions abolish heat behaviour without affecting the pituitary-ovarian cycle (Beach, 1944). There is also some evidence that oestrogen and progesterone have direct effects on brain monoamine concentrations (Tonge & Greengrass, 1971).

It may be suggested that the well-established concept of a feed-back link between the hypothalamus and the ovary, controlling ovulation, should be extended to include a more wide-spread effect of ovarian hormones in the central nervous system, affecting behaviour. The growing acceptance of the monoamine theory of affective disorders (Coppen, 1967) invites speculation on the role of the sex hormone induced changes in brain monoamine concentrations in the aetiology of pre-menstrual, post-partum and menopausal depressions in women, since in all these conditions oestrogen and progesterone levels fluctuate widely.

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