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Serotonine
Dopamine
Noradrenaline
Adrenaline
Hormones
Comportement sexuel

SEROTONIN, CATECHOLAMINES AND SEXUAL RECEPTIVITY OF FEMALE RATS. PHARMACOLOGICAL FINDINGS

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Sérotonine, catécholamines et réceptivité sexuelle chez des rates. Résultats pharmacologiques,

par BARRY J. EVERITT, KJELL FUXE and TOMAS HÖKFELT, *J. Pharmacol.* (Paris), 1975, *6*, 3, 269-276.

RÉSUMÉ. 1. Les rôles de la 5-hydroxytryptamine (5 HT) de la dopamine (DA) de la noradrénaline (NA) et de l'adrénaline (A) dans le contrôle de la réceptivité sexuelle, ont été recherchés chez des rates ovariectomisées et traitées par un œstrogène ou par une association œstrogène-progestérone.

2. Une diminution des taux de 5 HT, DA ou A (ou bien une diminution de l'activité de leurs récepteurs) est associée à un accroissement de la réceptivité, accroissement qui pourrait aussi être en relation avec une augmentation d'activité NA.

3. Inversement, une augmentation des taux de 5 HT et de DA, une stimulation de leurs récepteurs et une diminution des taux de NA sont associées à une diminution de la réceptivité activée par œstrogène-progestérone.

4. Ces résultats suggèrent que plusieurs amines interviennent dans le contrôle hormonal du comportement sexuel chez les rats femelles.

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INTRODUCTION

Some disagreement has arisen as to the extent of involvement of 5 hydroxytryptamine (5 HT) and catecholamines (CA) in explaining the effects of drugs on sexual behaviour (AHLENIUS, ENGEL, ERIKSSON, MODIGH and SÖDERSTEN, 1972). Early experiments using e.g. reserpine and MAO inhibitors (MEYERSON, 1964) implied that 5 HT was inhibitory in the control of oestrous behaviour. Similar results were gained more recently from experiments with the 5 HT synthesis inhibitor, parachlorophenylalanine (PCPA, MEYERSON and LEWANDER, 1970). But these treatments all considerably affect CA levels and the latter may, therefore, be involved in their behavioural effects. Furthermore, specific depletion of CA (with α-méthyl-*p*-tyrosine, AMPT) will increase sexual receptivity to a level similar to that induced by PCPA (AHLENIUS et al., 1972). Unfortunately this data implicating CA allows no distinction to be made between possibly separate roles of dopamine (DA), noradrenaline (NA) or, indeed, adrenaline (A) in the control of oestrous behaviour. We have attempted, therefore, to clarify this situation by using drugs which more precisely alter 5 HT, DA, NA and A neurotransmission.

Materials and Methods.

Animals used were ovariectomized Sprague-Dawley rats (250-300 g). They were tested for sexual receptivity (expressed here as lordosis : mount ratio or lordosis quotient, L.Q.) by pairing them with males for 5 minutes periods and recording sexual interaction by methods described in detail elsewhere (EVERITT, FUXE, HÖKFELT and JONSSON, 1974 *a*).

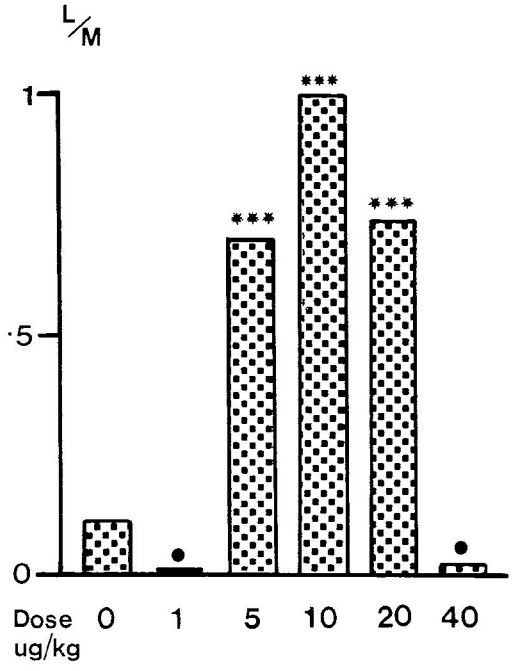
Females were treated with œstrogen alone (2.0 µg/kg/day œstradiol benzoate) or in combination with progesterone (500 µg/Rat, 4-6 h before observation) and various drugs (see below) superimposed upon this hormone regime. All drugs (unless stated otherwise) were given I.P. in a volume of 1 cc. per Rat. Animals in control groups (which have been combined to ease presentation of the Results) have, throughout, been treated in a way identical to experimental animals except that they received saline injections instead of drugs.

RESULTS

a. DRUGS ACTING ON 5 HYDROXYTRYPTAMINE NEURONS.

It may be seen in Table I that PCPA (a tryptophan hydroxylase inhibitor — KOE and WEISSMAN, 1966, 150 mg/kg base of the methylester) given to oestrogen-treated females caused an increase in L.Q. 2-4, 26-28 and 50-52 hours after injection.

d-lysergic acid diethylamide (LSD) has been reported to both inhibit firing of 5 HT neurons (AGHAJANIAN and HAIGLER, 1974) and the release of 5 HT (CHASE, BREESE and KOPIN, 1967) if given in low dosage. In figure 1, it may be seen that 5, 20 and optimally 10 μg/kg LSD (given 12 minutes before



The effects of *d*-LSD 1, 5, 10, 20 and 40 μg/kg on lordosis behaviour of oestrogen-treated female rats. All LSD injections were made 12 minutes before observation
Abbreviations and statistical comparisons as in Table I.

observation) markedly stimulated receptivity in oestrogen-treated females — 10 μg/kg activating the full oestrous behaviour pattern, including the characteristic hopping and darting movements. 40 μg/kg, alternatively, caused some inhibition of the already low receptivity of these females (fig. 1), whilst the 10 μg dose itself had a much less marked effect if observations were made 25 minutes after injection (EVERITT, unpublished).

Using a converse approach, it has proved possible to partially inhibit oestrogen/progesterone induced receptivity by treatment with 5 mg/kg fenfluramine (a 5 HT releasing agent, CLINESCHMIDT, 1973) given 45 minutes before observation (Table I).

b. DRUGS ACTING ON CATECHOLAMINE NEURONS.

The tyrosine hydroxylase inhibitor (CORRODI and HANSEN, 1966) α-methyl-p-tyrosine (AMPT 100 mg/kg, 2-4 h before testing) caused a marked increase in lordotic responding of œstrogen treated females (Table I). The treatments below may allow a distinction to be made *between* the catecholamines in explaining the effets of AMPT.

TABLE I. — *The effects of drugs on lordosis quotient of oestrogen (2.0 μg/kg a day) or oestrogen/progesterone (500 μg/Rat, 4-6 h before observation) — treated female rats. Values shown are medians. n.s. = not significant ; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < .001$; a) $p < 0.001$ cf. ET 495 ; b) $p < .001$ cf. pimozide ; c) p = n.s. cf. ET 495. Comparisons made using the Mann-Whitney 'U' test between treatments and oestrogen or oestrogen/progesterone-treated controls, except a), b) and c).*

Drug	Oestrogen only pre-treatment	Oestrogen/Progestrone pre-treatment
Combined control :		
(saline) groups	0.15	1.00
PCPA (2- 4 h)	0.86***	
(6- 8 h)	0.85***	
(50-52 h)	0.84***	
Fenfluramine		0.76**
AMPT	0.68***	
Pimozide	0.66***	
Phenoxybenzamine	0.10n.s.	
ET 495		0.50***
ET 495 + Fenfluramine		0.13*a*
Pimozide + Amphetamine	0.84*b*	
FLA 63		0.90*
FLA 63 + ET 495		0.55*c*
Piperoxane	0.74***	
Yohimbine	0.52**	

1. *Dopamine*: Pimozide, a DA receptor blocker (ANDÉN et al., 1970) 1 mg/kg 2-3 h before observation caused a significant increase in L.Q. of œstrogen-treated females (Table I). The duration of lordosis responses in these females was also considerably increased (EVERITT et al., 1974). Conversely, ET 495, a DA receptor stimulating agent (CORRODI et al., 1972) 25 mg/kg, 30 minutes before observation, caused a 50 % inhibition of oestrogen/progesterone-induced receptivity (Table I). In addition, a combined ET 495, fenfluramine treatment *completely* inhibited hormone-activated receptivity (Table I).

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2. *Noradrenaline:* Phenoxybenzamine, a NA receptor blocker (ANDÉN et al., 1967) did not increase the L.Q. of oestrogen-treated females. However, (+)-amphetamine, a CA releasing agent (CARLSSON et al., 1966) 3 mg/kg base, 30 minutes before observation imposed on pimozide pre-treatment (as above) caused a consistent, additional increase in L.Q. when compared with pimozide alone (Table I). We suggest that, in this regime, amphetamine selectively enhances NA receptor activity since the released DA would be ineffective on receptors blocked by pimozide. Conversely, the DA-β-hydroxylase inhibitor FLA 63 (SVENSSON and WALDECK, 1960) 25 mg/kg, 4-6 h before observation, caused a small (10 %) though significant decrease in oestrogen/progesterone-induced receptivity (Table I) which, it may be suggested, depends on the concurrent depletion of brain NA (CORRODI et al., 1970). The addition of FLA 63 to ET 495 did not, however, potentiate the effect of the latter in inhibiting hormone-induced receptivity (Table I).

3. *Adrenaline:* The so-called α-adrenergic receptor blockers piperoxane and yohimbine have recently been suggested to preferentially block A-receptors if given in the correct (low) dosage (BOLME et al., 1974; FUXE et al., 1974). Both drugs (piperoxane 5 mg/kg, yohimbine 1 mg/kg) given 30 minutes before observation caused significant increases in the L.Q.'s of oestrogen-treated females (Table I) which disappeared by 1 h.

DISCUSSION

The results of these experiments not only support the previously suggested hypothesis of an inhibitory role of 5 HT in the control of sexual behaviour (MEYERSON, 1964 *a*), but also suggest separate roles for NA, DA and A.

Contrary to a report (AHLENIUS et al., 1972) that PCPA affects sexual receptivity only during a short period after injection when CA levels are depressed, it was shown herein that this drug caused increases in L.Q. up to 52 h after injection when CA levels have long since returned to normal (AHLENIUS et al., 1972), so confirming other work (ZEMLAN et al., 1973). It is most probable, therefore, that the effects of PCPA at the longer time intervals depend on 5 HT and not CA depletion, though this is not to imply that the latter is of no importance (see below). We suggest that the mechanism by which LSD caused the dramatic increase in receptivity depends on a decrease in serotonin transmission (see AGHAJANIAN et al., 1974; CHASE et al, 1967), but the actions of this drug are complicated since in high dosage it will stimulate 5 HT receptors (ANDÉN et al., 1968) and *inhibit* hormone-activated receptivity (ELIASSON et al., 1972). It is generally accepted that LSD acts rather specifically on 5 HT neurons and a clearer understanding of its dose-dependent actions could make this an important drug in elucidating the function of 5 HT-containing neural systems.

The effects of PCPA and LSD, taken together with the receptivity-inhibiting actions of fenfluramine (see also MICHANEK and MEYERSON, 1964), clearly implicate 5 HT in the control of oestrous behaviour. But data obtained in earlier (AHLENIUS et al., 1972) and the present experiments using AMPT suggest that CAs are also involved.

However, as a result of the rather specific treatments used herein, it is possible to explain, partly, the effects of AMPT on CA and sexual behaviour in terms of DA, NA and A. Since blockade of DA receptors is associated with increased lordotic responding whilst stimulation of DA receptors is associated with inhibition of oestrous behaviour, it seems likely that DA serves an inhibitory role in the control of sexual behaviour somewhat similar to 5 HT, a suggestion supported by the complete inhibition of receptivity after combined 5 HT release and DA receptor stimulation. Adrenaline may also be suggested to play a similar part since blockade of A-receptors is associated with increased sexual receptivity (this hypothesis has received recent support using more specific β-receptor blocking drugs — EVERITT and FUXE (to be published).

Noradrenaline, on the other hand, may have a facilitatory function in the control by hormones of sexual behaviour, although the evidence for such a role is indirect. Thus, amphetamine-induced release of NA and DA in combination with DA receptor blockade caused an increase in L.Q. which was significantly greater than that induced by DA receptor blockade alone and which may, therefore, be correlated with the increased NA receptor activity during the combined treatment. Conversely, decreasing NA levels in the brain slightly decreased oestrogen/progesterone-activated receptivity. It will prove difficult to assess the role of NA since all treatments which affect NA neurons will most probably also affect A neurons (e.g. uptake blockers such as protryptiline) so confounding any distinction between their separate and possibly opposite roles.

These pharmacological data, taken together, suggest that progesterone may activate sexual receptivity in oestrogen-treated female rats by in some way depressing 5 HT, DA and A activity in the CNS whilst, at the same time, enhancing NA activity. The ways in which such changes occur and their interrelationships are important problems to be solved in order to understand more clearly the ways in which hormones control sexual behaviour.

SUMMARY

1. The roles of 5 hydroxytryptamine (5 HT), dopamine (DA), noradrenaline (NA) and adrenaline (A) in the control of sexual receptivity have been investigated in ovariectomized, oestrogen or oestrogen/progesterone-treated female rats.

2. Decreased 5 HT, DA or A levels and/or receptor activity is associated with an increase in the receptivity of oestrogen-treated females. Increased NA activity may also be associated with increased receptivity.

3. Conversely, increased 5 HT and DA levels and/or receptor activity and decreased NA levels are associated with a decrease in oestrogen/progesteroné activated receptivity.

These results suggest roles for a number amines in the control by hormones of sexual behaviour in female rats.

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