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Studies Into the Dual Effects of Serotonergic Pharmacological Agents on Female Sexual Behaviour in the Rat: Preliminary Evidence That Endogenous 5HT is Stimulatory

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HUNTER, A J , D R HOLE AND C A WILSON *Studies into the dual effects of serotonergic pharmacological agents on female sexual behaviour in the rat Preliminary evidence that endogenous 5HT is stimulatory* PHARMACOL BIOCHEM BEHAV **22**(1) 5–13, 1985 —The potential stimulatory and inhibitory effects on female sexual behaviour of five 5HT antagonists and five agents that increase 5HT activity, were noted in ovariectomised rats primed with various steroid regimes such that they were either "receptive" (LQ>50%) or "non-receptive" (LQ<50%) The 5HT antagonists cinanserin, mianserin, ketanserin and metergoline all inhibited behaviour in receptive rats. Methysergide and cinanserin stimulated behaviour in non-receptive rats All the drugs which increased 5HTP activity, i e , 5HTP, zimelidine, alaproclate, WY 26002 and quipazine stimulated sex behaviour in non-receptive rats In rats that had been ovariectomised only, part of this effect was probably due to stimulation of adrenal progesterone, but a significant stimulatory effect could still be observed in ovariectomised-adrenalectomised rats 5HT also had a significant inhibitory effect on receptive rats, and the other agonists showed a similar but non-significant tendency In view of the fact that 4 out of 5 of the 5HT antagonists inhibited sexual behaviour, we hypothesise that 5HT has a stimulatory role in the control of female sexual behaviour The possible mechanisms mediating the dual action of 5HTP on female sexual behaviour are discussed

5HT Serotonin Female receptivity Lordosis

IT is well established that the serotonergic system within the CNS inhibits male sexual behaviour [11] and many reports indicate that it is also inhibitory to female sexual behaviour The evidence for this inhibitory action is mainly based on the effects of pharmacological agents that alter serotonin activity on sexual receptivity in ovariectomised steroid-primed rats. Thus agents that inhibit 5HT synthesis [15, 51, 79] 5HT receptor blockers [12, 15, 73, 78] or depletors of 5HT [14, 48, 51] facilitate female sexual behaviour while agents that enhance serotonergic activity [15, 17, 47, 51, 59] inhibit lordotic activity. However, not all these reports have been confirmed and others have shown that 5HT depletors either have no effect [65, 67, 68] or, in the case of PCPA, can be inhibitory [2, 25, 29, 61] In addition, in experiments where PCPA did stimulate sexual behaviour, the action did not correlate with depletion of 5HT within the CNS [74], in fact the stimulatory effect of PCPA correlated better with the production of the PCPA metabolite-p-chlorophenylethylamine (PCPEA) which induces a release of endogenous 5HT [66,74]. Selective 5HT uptake inhibitors which increase 5HT activity can also stimulate female sexual behaviour [29]. These latter findings indicate that rather than being inhibitory, 5HT may exert a stimulatory control on female sexual behaviour.

In this report we have investigated the possible inhibitory and stimulatory effects of a number of 5HT agonists and antagonists in animals primed with different steroid regimes. It has been suggested that the steroids, particularly progesterone, may exert their effect on sex behaviour via the serotonergic system [37,51] and conversely that the effects of manipulating 5HT activity may be different in different steroid milieux [63,64]

METHOD

Female Wistar rats (220–250 g: Bantin and Kingman, Hull, Yorkshire) were ovariectomised under halothane (May and Baker, Ltd., Dagenham, Essex) anaesthesia. In one ex-

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TABLE 1

THE EFFECT OF 5HT RECEPTOR BLOCKERS ON SEXUAL RECEPTIVITY IN OVARIECTOMISED RATS PRIMED WITH STEROIDS

Treatment and Dose	State of Rat	Mean Lordosis Quotient % (±SEM) in rats primed with 200 μg EB Vehicle	200 μg EB Drug	10 μg EB Vehicle	10 μg EB Drug	2 μg EB + 0 2 mg P Vehicle	2 μg EB + 0 2 mg P Drug
Methysergide 10 mg/kg	R	(10) 78 ±3 74	56 5 ±10 7	(3) 67	72	(5) 89 ±7 2	75 ±12 7
	NR	(2) 42	85	(9) 17 ±5 7	50 5‡ ±11 9	(7) 9 ±6 0	34* ±12 0
Cinanserin 10 mg/kg	R	(26) 94 ±2 2	83* ± 4 2	(6) 78 ±7 9	29* ±15 2	(6) 87 ±5 4	28* ±11 4
	NR	— —	— —	(9) 8 ±3 8	33* ±10 7	(6) 12 ±7 5	30 ±15 5
Mianserin 10 mg/kg	R	(9) 84 ±5 5	53* ± 7 0	(17) 76 ±4 2	36 5§ ± 6 3	(14) 81 5 ±4 6	45‡ ± 9 1
	NR	(2) 30	10	(9) 21 ±5 2	29 ±10 1	(10) 22 ±3 0	24 ± 9 1
Metergoline 5 mg/kg	R	(12) 92 ±3 3	69† ± 8 2	(16) 79 ±4 6	48‡ ± 7 3	(11) 76 ±5 0	55‡ ± 7 4
	NR			(10) 12 5 ±4 0	22 ± 9 4	(6) 17 ±3 7	21 ±12 4
Ketanserin 10 mg/kg	R	(14) 84 ±4 5	39‡ ± 8 7	(6) 75 ±7 3	35 5* ± 4 1		
	NR	(7) 30 ±7 4	27 ±10 8	(8) 13 ±6 0	10 5 ± 5 8		

Significance of difference from vehicle treated controls *$p<0.05$, †$p<0.02$, ‡$p<0.01$, §$p<0.001$ (Wilcoxan Matched-Pair Test)
Figures in parentheses to the left of the results indicate the number of animals in the group
R, receptive, NR, non-receptive

periment rats were adrenalectomised as well as ovariectomised and these rats were maintained on 0.9% w/v saline. All the other rats received water and all rats were fed on 41B diet (Dixon Ltd.) ad lib. The animals were kept in cages of 3 in 12 hour dark:12 hour light reversed illumination cycle (lights off 11.00–23.00 hr). Behavioural testing was carried out under red light at least 3 hours into the dark period and consisted of placing each female with a vigorous male in an observation arena and then noting the number of lordotic responses to 20 mounts. The strength of lordosis was noted using a scoring system modified from Hardy and de Bold [32], i e , 0=no lordosis, 1=slight arch of the back, 2=full lordosis. This enabled a lordosis quotient (LQ) corrected for strength of response to be obtained [i e , corrected LQ% = (score/40) × 100]. The percentage of animals showing hopping/darting and ear-wiggling behaviour was also recorded A rat was considered to be receptive if it exhibited a LQ% of more than 50%

Treatments

Animals were primed with one of the following steroid hormone regimes. oestradiol benzoate (EB) alone (200 μg or 10 μg per rat) 48 hours before testing, or 2 μg/rat EB 48 hours before testing followed by 0.2 mg/rat progesterone (P) 4 hours before testing. The steroids were all administered subcutaneously dissolved in corn oil 0.1 ml/rat. All drugs were given by intraperitoneal (IP) injection in a volume of 0.1 ml/100 g body weight and were injected 1, 2 or 4 hours prior to the test. The doses chosen were either taken from reports in the literature or a graded series of doses was tried. The time between administration and testing was chosen as the time of maximum activity and was assessed in pilot experiments when groups of rats were tested 1, 2 and 4 hours after administration of the drugs. Rats were tested with either drug or vehicle (usually saline) and then two weeks later the treatments were reversed, the rats receiving the same hormonal treatment as before. Treatments were balanced so that in any one group half the rats received saline first and half the drug first. When each rat had received both treatments, the value of their LQ% after saline treatment indicated whether they should be put in the "receptive" group (LQ%>50%) or non-receptive group (LQ%<50%)

Drugs

Unless otherwise stated the drugs were dissolved in 0.9% saline. Methysergide bimaleate 10 mg/kg (Sandoz Products Ltd., Feltham, Middlesex), Metergoline 5 mg/kg dissolved in 1% ascorbic acid (Farmitalia Carlo Erba Ltd., Milan, Italy), Mianserin hydrochloride 10 mg/kg (Organon Labs. Ltd., Oss, Holland); Cinanserin hydrochloride 10 mg/kg (E.R Squibb & Son Ltd., Twickenham, Middlesex); Ketanserin tartrate 10 mg/kg as a suspension in saline (Janssen Pharmaceutica Research Lab , Breese, Belgium), Zimelidine dihydrochloride 20–30 mg/kg (Astra Pharmaceuticals Ltd., Sodertalje, Sweden); Alaproclate hydrochloride 20–30 mg/kg as a suspension in saline (Astra Pharmaceutical Ltd., Soder-

tolje, Sweden); Wy 26002 (1-Benzoyl-3, 1- (2-napthylmethyl) piperid-4-yl) urea, hydrochloride 10–40 mg/kg as a suspension in saline (Wyeth Res. Centre, Taplow, Bucks); Quipazine maleate 2.5–10 mg/kg (Miles Lab. Res. Products, USA); 5-hydroxytryptophan (5HTP) 5–20 mg/kg (Sigma London Ltd., Poole, Dorset).

Measurement of Plasma Progesterone

Some animals were killed by decapitation after behaviour testing and trunk blood taken. This was centrifuged at 400 g at 5°C for 10 minutes and the plasma stored at −20°C until assayed for progesterone using a kit obtained from NETRIA London E.C.1., U.K.

Statistical Analysis

Lordosis quotient data was analysed by means of a Wilcoxan Matched-Pair test. Progesterone plasma concentrations were compared by Sheffé's test after one way analysis of variance.

RESULTS

The Effect of 5HT Antagonists on Female Sexual Behaviour

Table 1 shows that nearly all the rats primed with 200 μg EB showed a LQ above 50% and the mean LQ's for the group were between 78 and 94%. Of the five antagonists screened, four of them, i.e., mianserin, cinanserin, ketanserin and metergoline significantly reduced receptivity. Methysergide also reduced the LQ in the rats primed with 200 μg EB but this did not reach statistical significance

Approximately half the rats primed with 10 μg EB exhibited an LQ of less than 50% when given vehicle before the test. In these animals, defined as non-receptive, methysergide and cinanserin significantly increased sexual activity and mianserin, ketanserin and metergoline had no effect. As in the receptive animals primed with 200 μg EB, mianserin, metergoline, ketanserin and cinanserin reduced the LQ in the receptive animals primed with 10 μg EB. A third set of tests were carried out on rats primed with 2 μg EB followed by a low dose of P, and the results were very similar qualitatively and quantitatively to those observed in the group primed with 10 μg EB. Changes in soliciting behaviour have not been shown in Table 1 but in fact, parallelled the changes in lordotic activity.

The Effect of Agents That Increase 5TH Activity on Female Sexual Behaviour

Table 2 shows the effect of a selection of agents that increase 5HT activity within the CNS All the rats were primed with 10 μg EB and then given the compounds in graded dose levels, 48 hours later. Taking the results on animals that had been ovariectomised only, all the compounds increased receptivity in the non-receptive rats and in some cases (5 mg/kg quipazine, and 10 and 20 mg/kg Wyeth 26002) a stimulatory effect was seen even in animals already exhibiting a high level of receptivity (see Tables 2 and 4). These stimulatory effects, however, were probably due to stimulation of adrenal progesterone secretion, since quipazine and Wyeth 26002 raised plasma progesterone levels 2 hours after their administration (Table 3). For this reason the 5HT agonists were all tested again on rats that had been ovariectomised and adrenalectomised, although this time only one dose level was used.

In contrast to the findings in the ovariectomised-only group, in the ovariectomised-adrenalised rats, the agonists had a dual effect in that while they still significantly stimulated sexual activity in the non-receptive rats, they also tended to inhibit activity in the receptive animals, although this effect was only significant after 5HTP (Table 2). This inhibitory effect was also seen in the highly receptive ovariectomised-only animals primed with 200 μg OB after zimelidine treatment (Table 4). This drug does not stimulate adrenal progesterone (Table 3) and so its inhibitory effect would not be masked as it may well have been with the other compounds.

DISCUSSION

The effects of five 5HT antagonists and five agents that increase 5HT activity have been observed on sexual receptivity in suitably primed ovariectomised female rats. The experiments were designed such that any inhibitory effect could be noted in fully receptive rats and any stimulatory effect on non-receptive rats. In order to achieve these two states of sexual activity a variety of priming regimes were employed. In our rats 200 μg OB induces a high level of receptivity in nearly all the animals, while 10 μg OB and 2 μg OB plus 0.2 mg P have a submaximal effect and induce receptivity (LQ>50%) in approximately half the animals.

In this report we have shown that the antagonists, mianserin, cinanserin, ketanserin and metergoline [13, 21, 43, 49] can all exert an inhibitory effect on female sexual activity in rats made receptive by any of the priming regimes. Methysergide [45] did not have an inhibitory effect, but instead stimulated receptivity in the non-receptive rats as did cinanserin, which therefore seems to have dual actions. The stimulatory effects of methysergide and cinanserin have been noted several times before whether they were given systemically [12, 59, 78] or centrally [17, 19, 73, 78]; their potential inhibitory effects do not appear to have been investigated and so the dual action of cinanserin has not been observed before None of the agents are completely selective for 5HT receptors (see Table 5) and so the differences between their actions may be due to activity on other systems or, more probably, some partial agonist activity [8].

However, of the five antagonists investigated, four of them can exert an inhibitory effect and so it is possible that the role of endogenous serotonin on female sexual behaviour is stimulatory. Further evidence for this is provided by the facts that: PCPA inhibits sex behaviour at a time when 5HT depletion is maximal [25,61] and this effect can be reversed by 5HTP (unpublished results); quipazine and selective 5HT uptake inhibitors stimulate the lordotic reflex [29,38], and lesions of the midbrain raphe (the site of origin of ascending and descending serotonergic tracts) can disrupt female behaviour [33]

The effects of agents which increase 5HT activity were also investigated. Zimelidine, alaproclate and Wy 26002 are all reported to be selective 5HT uptake inhibitors [44, 54, 57]. Quipazine is a 5HT post-synaptic receptor agonist [27] and 5HTP is the precursor of 5HT. Although all these agents have individual side effects (see Table 5), all the compounds acted similarly in these experiments. In females that had only been ovariectomised, they all stimulated sexual behaviour in non-receptive rats and sometimes even in rats that were already receptive. There was no evidence for a decrease in stimulatory activity with increase in dose as noted by Everitt and Fuxe [16] using a different range of 5HT

TABLE 2

EFFECT OF SOME AGENTS THAT INCREASE 5HT ACTIVITY ON FEMALE SEXUAL BEHAVIOUR IN OVARIECTOMISED OR OVARIECTOMISED-ADRENALECTOMISED FEMALE RATS PRIMED WITH 10 μg OESTRADIOL BENZOATE

			Mean Lordosis Quotient % (±SEM)			
			Ovariectomised		Ovariectomised-adrenalectomised	
Treatment	Dose mg/kg	State of Rat	Vehicle	Drug	Vehicle	Drug
5HTP at 1 hour	5 0	R	(4) 72 5 ±13 1	42 5 ±14 4		
		NR	(8) 3 ± 2 1	36 ±13 8		
	10 0	R	(7) 69 ± 5 0	64 ± 7 5		
		NR	(8) 15 ± 6 2	59† ± 7 7		
	20 0	R	(1) 55	90	(11) 85 ±4 8	50† ± 9 8
		NR	(10) 3 ± 1 5	35 5† ±10 8	(18) 9 ±2 9	43† ± 9 2
Quipazine at 2 hour	2 5	R	(5) 66 ± 5 8	69 ±18 1	(6) 81 ±8 3	57 ±18 3
		NR	(6) 26 8 ± 7 6	94† ± 4 2	(6) 19 ±9 0	44* ±13 4
	5 0	R	(8) 80 ± 4 7	95* ± 3 7	Toxic (rats appeared ill and flaccid)	
		NR	(15) 22 ± 4 6	78‡ ± 7 8		
	10 0	R	(4) 80 ±11 4	97 5 ± 1 4		
		NR	(7) 25 ± 6 2	73† ±12 3		
Wyeth 26002 at 2 hour	10 0	R	(6) 65 ± 6 8	90* ± 4 5		
		NR	(6) 13 ± 2 3	35* ± 6 7		
	20 0	R	(8) 79 5 ± 5 4	95 5 ± 3 5	(9) 91 ±3 6	62 ±14 2
		NR	(13) 22 ± 4 15	96‡ ± 3 1	(8) 14 ±5 3	39* 13 8
	40 0	R	(6) 63 ±12 6	62 5 ± 4 6		
		NR	(7) 22 ± 4 6	73 5† ± 6 7		
Zimelidine at 4 hour	20 0	R	(11) 82 ± 4 8	61 ±12 3		
		NR	(10) 7 ± 4 7	27 5 ±11 1		
	30 0	R	(8) 86 ± 5 6	97 5 ± 2 5	(2) 90	0
		NR	(14) 9 ± 5 3	51† ±12 4	(9) 3 ±2	39† ±12 3

(Continued)

TABLE 2

EFFECT OF SOME AGENTS THAT INCREASE 5HT ACTIVITY ON FEMALE SEXUAL BEHAVIOUR IN OVARIECTOMISED OR OVARIECTOMISED-ADRENALECTOMISED FEMALE RATS PRIMED WITH 10 μg OESTRADIOL BENZOATE (*Continued*)

			Meal Lordosis Quotient % (±SEM)			
			Ovariectomised		Ovariectomised-adrenalectomised	
Treatment	Dose mg/kg	State of Rat	Vehicle	Drug	Vehicle	Drug
Alaproclate at 2 hour	20 0	R	(7) 81 ± 6 0	85 ± 6 3	(7) 77 ±6.8	62 ±12.3
		NR.	(6) 28 ± 7 4	94* ± 2 4	(9) 12 ±5 6	27* ±11 3
	30 0	R	(4) 77 5 ± 4.8	79 ±12 6		
		NR	(12) 19 ± 5.7	63† ±11 5		

Significance of difference from vehicle treated controls· *$p<0.05$, †$p<0$ 02, ‡$p<0$ 01 (Wilcoxan Matched-Pair Test).

Figures in parentheses to left of the results indicate the number of animals in the group

R, receptive, NR, non-receptive

agonists, although we may not have reached sufficiently high concentrations to show this As administration of quipazine and Wyeth 26002 raised plasma progesterone, all the compounds were tested again in ovariectomised-adrenalectomised rats to control for the effects of adrenal progesterone. In this experiment all the compounds again stimulated behaviour, although their effect was not as marked as in the ovariectomised rats. Other examples of inhibitors of 5HT uptake (Org. 6582, femoxetine and chlorimipramine) have also been shown to stimulate receptivity in ovariectomised and ovariectomised-adrenalectomised animals [29].

5HTP exerted a significant inhibitory effect on receptive ovariectomised-adrenalectomised animals and so did zimelidine in ovariectomised rats. The other agonist drugs showed a similar, although non-significant tendency. The fact that of all the agonists, zimelidine alone inhibited behaviour in receptive rats that had been ovariectomised only, may be due to its being the only drug which did not stimulate adrenal progesterone.

The dual effect of 5HTP and another 5HT agonist (LSD) has been seen before in animals exhibiting differences in receptivity due to different steroid priming regimes [63,64] and an inverted-U shaped dose-response can be observed after giving graded doses of various hallucinogenic 5HT agonists [16]. The authors of both these reports assume that 5HT is inhibitory to female sexual receptivity; they suggest that the stimulatory effect of the agonists is due to stimulation of presynaptic receptors inhibiting endogenous serotonergic transmission and occurs only when 5HT activity is increased slightly. The inhibitory effect is seen when high concentrations of 5HT are present in the synapse and is due to post-synaptic stimulation.

A similar hypothesis has been put forward on the mechanism of action of steroids. Both oestrogen and progesterone effect serotonergic transmission; oestrogen increases $5HT_1$ receptors [4,5] and alters the response of the $5HT_2$ system [36] and progesterone increases 5HT levels and turnover [9, 10, 40]. Sietniks and Meyerson [64] have suggested that progesterone stimulates activity by increasing 5HT turnover which then acts presynaptically inhibiting further serotonergic transmission. This suggestion is reasonable in view of the results published up to date, i.e., that 5HT receptor antagonists stimulate sexual behaviour [12, 17, 73, 78] and indeed, may be the explanation for the dual effects of the agonists and cinanserin that we have obtained.

However, by using a wider range of 5HT antagonists we have shown that they can exert an inhibitory effect on behaviour and so various alternative hypotheses can be presented for the dual effect of 5HT agonists. For instance, instead of acting presynaptically to stimulate behaviour we suggest that progesterone and the 5HT agonists act post-synaptically on a stimulatory serotonergic system and that their effect would be additive when release of endogenous 5HT is low, as for instance after low doses of steroid priming. After high steroid priming, 5HT activity and receptivity are both highly stimulated and the additional effect of exoge-

TABLE 3

THE EFFECT OF 5HT AGONISTS ON PLASMA PROGESTERONE CONCENTRATIONS IN OVARIECTOMISED RATS TREATED WITH 10 μg OB

Treatment and Dose	Progesterone Concentration ng/ml ± SEM
Saline 0.2 ml	(16) 4.38 ± 0.67
Quipazine 2 5 mg/kg	(10) 7 18 ± 0 53†
Quipazine 5 mg/kg	(11) 8 79 ± 1 2†
Wyeth 26002 20 mg/kg	(7) 8 5 ± 1.45*
Zimelidine 20 mg/kg	(5) 4.41 ± 0.75

Significance of difference from saline treated controls: *$p<0.05$, †$p<0$ 01 (Scheffès test after one way analysis of variance).

Figures in parenthesis indicate number of animals in the group

TABLE 4

THE EFFECT OF SOME AGENTS THAT INCREASE 5HT ACTIVITY ON SEXUAL RECEPTIVITY IN OVARIECTOMISED RATS PRIMED WITH 200 μg OB

Treatment and dose	State of rat	Lordosis Quotient % (±SEM) Vehicle	Drug
Quipazine	R	(11) 94	99
5 mg/kg at 2 hr		±4 6	± 0 45
	NR	—	—
Alaproclate	R	(16) 90	72 5
20 mg/kg at 2 hr		±4 1	± 9 2
	NR	(3) 35	66
Wyeth 26002	R	(11) 83	97†
20 mg/kg at 2 hr		±4 3	± 0 9
	NR	(1) 5	100
Zimelidine	R	(10) 89	50*
20 mg/kg at 4 hr		±5 6	±16 0
	NR	—	—

Significance of difference from vehicle treated controls *$p<0$ 05, †$p<0$ 01 (Wilcoxan Matched-Pair Test)

Figures in parenthesis to left of the results indicate the number of animals in the group

R, receptive, NR, non-receptive

TABLE 5

ACTIONS OF PHARMACOLOGICAL AGENTS THOUGHT TO ACT PRIMARILY ON THE SEROTONERGIC SYSTEM

A *Antagonists*

1 Metergoline
Binds to 5HT receptors strongly and has 20 times more affinity for $5HT_2$ receptors than $5HT_1$ [43] It also binds to dopamine (DA) receptors [69] and is said to have DA agonist and antagonist activity in vivo [39,69]

2 Methysergide
Binds to 5HT receptors strongly and has 8 times more affinity for $5HT_2$ receptors compared to $5HT_1$ [43] It has a partial 5HT agonist activity in vivo [8] as well as a DA antagonist action and via one of its metabolites a DA agonist effect too [39,42]

3 Mianserin
Binds with a hundred times more affinity for $5HT_2$ receptors compared to $5HT_1$ [43] It has partial 5HT agonist activity in vivo [8], although this effect is 20 times less than that of methysergide Mianserin has a high affinity for histamine receptors [43,55], inhibits noradrenaline (NA) uptake and blocks presynaptic α-adrenergic receptors [55]

4 Cinanserin
Binds weakly to 5HT receptors [22,28], but has little affinity for other receptor types [43] It has 90 times greater affinity for $5HT_2$ than $5HT_1$ receptors [43] Possible agonist activity has not been investigated

5 Ketanserin
This compound is a selective $5HT_2$ antagonist, having a high binding affinity for $5HT_2$ receptors, none for $5HT_1$ receptors and no 5HT-agonist activity in vivo [43] In vivo, its distribution in the brain correlates with sites of $5HT_2$ receptors [41] It has, however, moderate binding affinity for histamine and α-adrenergic receptors [43] and the action on the latter receptors may account for its hypotensive activity [35]

B *Agonists*

1 Quipazine
This compound not only stimulates 5HT post-synaptic receptors, but also blocks 5HT uptake, stimulates 5HT release and inhibits monoamine oxidase [20, 27, 30] It has some activity in both the dopaminergic and noradrenergic systems [18, 26, 53]

2 Zimelidine
It is a selective 5HT uptake inhibitor, when assessed in vitro [60], but in vivo also inhibits uptake of NA via its metabolite [54]

3 Alaproclate
It is a selective 5HT uptake inhibitor as assessed in vitro [44]

4 Wyeth 26002 It is a selective 5HT uptake inhibitor as assessed in vitro and in vivo [54]

5 5HTP Is the precursor of 5HT and is converted within neurones to the transmitter It can however enter catecholaminergic neurones and induce release of NA and DA [3, 56, 62], it can also inhibit the synthesis of the catecholamines [76]

nous agonists may cause post-synaptic desensitization. It is well established that tolerance occurs after chronic administration of agents that stimulate 5HT activity [50,75]. In catecholaminergic systems desensitization can occur as quickly as one hour after an acute administration [7,24] so perhaps the serotonergic system is equally sensitive.

Another view of our results, still based on the hypothesis that 5HT is stimulatory to female behaviour is similar to the one provided by Walker [70] for the dual effect of 5HT on gonadotrophin release. He suggests that it is the circadian rhythm in 5HT activity which is important for the rhythmic secretion of gonadotrophin release and that enhancement of the rhythm will stimulate LH release, while maintaining constant raised or constant reduced levels of 5HT will be inhibitory [71,72]. The serotonergic tract involved in this rhythmic control probably originates in the midbrain raphe and interacts with the suprachiasmatic nucleus [6,34]. As far as the control of sexual receptivity is concerned, therefore, in non-receptive rats enhancement of the circadian 5HT activity [58] will increase receptive behaviour by increasing the rhythmic pattern of sexual activity [31]. One can imagine in the case of an attenuated rhythm, administration of an exogenous agonist will suddenly enhance the serotonergic oscillation, but when the surge in 5HT activity is already maximal, prolongation of it will inhibit behaviour.

The solely inhibitory role of 5HT indicated by the work of Luine [46, 47, 48] in which localised intra-hypothalamic manipulation of 5HT activity was carried out, may be due to a separate intra-hypothalamic serotonergic tract. Such a tract has been postulated [23] and appears to be independent of extra-hypothalamic forebrain influence [77].

In conclusion we have shown that the serotonergic influence on female sexual behaviour is more complicated and different to that in the male. Further research on the effect of central administration of serotonergic drugs and changes in endogenous 5HT activity with receptivity is being carried out.

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