Available online at www.sciencedirect.com
ScienceDirect
Pharmacology, Biochemistry and Behavior 87 (2007) 386–392
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

The $5HT_7$ receptor subtype is involved in the regulation of female sexual behaviour in the rat

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Received 3 April 2007; received in revised form 4 May 2007; accepted 17 May 2007
Available online 24 May 2007

Abstract

5-Hydroxytryptamine (5-HT) regulates sexual behaviour in the female rat via a number of its receptors. The role of the $5HT_7$ receptor was investigated in ovariectomised rats primed with 10 μg oestradiol benzoate (OB) followed at 48 h by 0.5 mg progesterone, which induced receptivity in approximately half of the animals. These animals were treated with three agonists all effective at $5HT_{1A}$ and $5HT_7$ receptors; 5-hydroxytryptophan, 8-hydroxy-2-(di-*n*-propylamino)tetralin 1-Br (8-OH DPAT) and 5-carboxy-aminotryptamine (5-CT) in the presence or absence of selective $5HT_{1A}$ and $5HT_7$ antagonists: WAY 100135 and SB 269970-A. The three agonists inhibited lordosis in the receptive group, and this was prevented by both the selective $5HT_{1A}$ and $5HT_7$ antagonists. When given alone, both WAY 100135 and SB 269970-A increased the lordosis in the non-receptive rats indicating that endogenous 5-HT acting on $5HT_{1A}$ and $5HT_7$ receptors may have a tonic inhibitory effect on receptivity. A comparison of OB priming doses on the effect of serotoninergic agents showed that the higher OB doses attenuated the inhibitory effect of 8-OH DPAT and enhanced the stimulatory effect of WAY 100135, but did not affect the actions of 5-CT or SB 269970-A. The interaction between oestradiol and 5-HT activity on sexual behaviour may therefore be selective to the $5HT_{1A}$ pathway.

Keywords: 5-HT; $5HT_{1A}$; $5HT_7$; 5-CT; 8-OH DPAT; WAY 100135; SB 269970-A; Lordotic activity

1. Introduction

Female sexual behaviour in the rat is entirely dependent on the gonadal steroids acting at the hypothalamic level (Pfaff and Schwartz-Giblin, 1988). The steroid effect is mediated by neurotransmitter activity in specific hypothalamic nuclei (in particular the ventromedial nucleus and the medial preoptic area) (Pfaff and Schwartz-Giblin, 1988; James et al., 1989; Wilson, 1993; Gonzalez et al., 1997). 5-Hydroxytryptamine (5-HT) has been implicated as one of these transmitters (Wilson 1993; Uphouse, 2000). It is now known that 5-HT has up to 14 receptor subtypes (Barnes and Sharp, 1999) and with the relatively recent availability of selective pharmacological agents for these subtypes the involvement of some specific 5-HT receptors in the regulation of female sexual behaviour has been elucidated. Thus, although the early reports using non-selective serotoninergic agents indicated that 5-HT had a solely inhibitory effect on lordotic activity (Frankfurt et al., 1985; Wilson, 1993), it is now known that the 5-HT exerts an inhibitory effect via $5HT_{1A}$ post-synaptic receptors (Mendelson and Gorzalka, 1986; Uphouse et al., 1991; Aiello-Zaldivar et al., 1992; Kishitake and Yamanouchi, 2003) while activation of $5HT_2$ receptors stimulates female sexual behaviour (Mendelson and Gorzalka, 1985; Wilson and Hunter, 1985; Gonzalez et al., 1997; Wolf et al., 1998) and pharmacological evidence indicates that $5HT_3$ receptors are also stimulatory (Maswood et al., 1997, 1998). Studies employing putative $5HT_{1B}$ agents provide conflicting data due to their lack of selectivity (Gorzalka et al., 1990; Mendelson and Gorzalka, 1990; Aiello-Zaldivar et al., 1992).

In this study, we have investigated the possible involvement of the $5HT_7$ receptor subtype in the regulation of female sexual behaviour. The likelihood that this receptor is involved is based on the fact that $5HT_7$ receptors are involved in the inhibitory effect of 5-HT on LH release (Siddiqui et al., 2004) which like sexual behaviour is a steroid-dependent function and the two are often controlled in a related manner (McEwen and Parsons, 1982). In addition, although the intracellular pathways mediating

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0091-3057/$ - see front matter © 2007 Published by Elsevier Inc.
doi:10.1016/j.pbb.2007.05.012

the effects of $5HT_{1A}$ and $5HT_7$ receptor activation are different and can be in opposition (see Barnes and Sharp, 1999), the two subtypes appear to have similar effects on a number of physiological functions including hypothermia (Hedlund et al., 2004), phase re-setting of the circadian rhythm in the suprachiasmatic nucleus (Sprouse et al., 2005), anxiety (Delgado et al., 2005; Takeda et al., 2005), inhibition of LH release in vivo (Siddiqui et al., 2000, 2004) and stimulation of GnRH activity in vitro (Hery et al., 1995, 1997). They have opposing effects on other functions such as pro-nociceptive response (Rocha-Gonzalez et al., 2005), mood (Lucki et al., 1994; Hedlund et al., 2005) and regulation of REM sleep (Thomas et al., 2003; Harvey et al., 2004). Since $5HT_{1A}$ agonists have a marked inhibitory effect on female sexual behaviour (Gorzalka et al., 1990; Uphouse et al., 1991; Kishitake and Yamanouchi, 2003) it is possible that activation of the $5HT_7$ receptor may also affect sexual behaviour either in a similar or in an opposite manner to $5HT_{1A}$ activation.

The effect of three serotoninergic agonists, 5-hydroxytryptophan (5-HTP; this is converted to 5-HT once within the central nervous system;CNS), 8-hydroxy-2-(di-*n*-propylamino)tetralin 1-Br (8-OH DPAT) and 5-carboxy-aminotryptamine (5-CT), on female sexual behaviour has been observed in the absence and presence of a selective $5HT_{1A}$ antagonist, WAY 100135 (Fletcher et al., 1993) or a selective $5HT_7$ antagonist, SB 269970-A (Hagan et al., 2000;Thomas et al., 2000). In order to reveal putative stimulatory or inhibitory effects, the treatments were tested on rats that were subdivided into two groups according to their level of receptivity after steroid priming and before treatment with the serotonergic agents. It is assumed that rats exhibiting a low level of receptivity (Lordosis Quotient <50%) would reveal possible stimulatory effects of the 5HT agonists, while rats with a higher Lordosis Quotient (>50%) would reveal any inhibitory effects. The three agonists are non-selective (Hoyer et al., 1994; Bonaventure et al., 2002) with different order of potencies on $5HT_{1A}$ and $5HT_7$ receptors. This has been assessed on transfected Hela cells expressing $5HT_{1A}$ receptors or guinea-pig brain hippocampal neuronal membranes expressing both $5HT_{1A}$ and $5HT_7$ receptors. The order of potency on $5HT_{1A}$ receptors is 5-CT > 8-OH DPAT > 5-HT (Boddeke et al., 1992) and on $5HT_7$ receptors, 5-CT > 5HT > 8-OH DPAT (Thomas et al., 1999).

There are a number of reports showing that in ovariectomised rats, increasing the dose of the priming oestradiol benzoate treatment and repetition of steroid priming before repeated tests for sexual behaviour can induce desensitization of the response to the $5HT_{1A/7}$ agonist, 8-OH DPAT (Jackson and Uphouse, 1996, 1998; Jackson and Etgen, 2001). We have extended these findings by observing the desensitizing effects of oestrogen priming on the more potent $5HT_{1A/7}$ agonist, 5-CT.

2. Methods

2.1. Animals

Female pups born of Wistar dams raised in the Animal Housing Facilities at Aga Khan University were weaned at 25 days post-partum. These weanlings were then housed in groups of 4 to 5, maintained at 24 °C in a 12 h light–dark cycle (lights on at 6 pm). Food and water were supplied ad lib. At 10 to 11 weeks of age, the females were ovariectomised under diethyl ether anaesthesia and the animals from this time were kept in a reversed 12 h light–dark cycle (lights off at 6 am). All studies were conducted in accordance with the guidelines of Animal Ethics Committee at the Aga Khan University, Karachi, Pakistan.

2.2. Treatment

Two weeks after ovariectomy, the rats were primed with either 10 or 25 μg oestradiol benzoate (OB)/rat subcutaneously (s.c.) followed at 48 h by 0.5 mg progesterone/rat all in 0.1 ml corn oil/rat. It should be noted that rats bred at the Aga Khan University appear to be relatively insensitive to steroid priming. Ten and 25 μg OB followed by progesterone according to many reports in the literature normally induce full receptivity. Our rats treated with this regime tended to fall into two sub-groups exhibiting either 15–20% Lordosis Quotient (LQ) or 50–60% LQ, which were designated as non-receptive and receptive, respectively.

Groups of animals received one of the following by intraperitoneal injection (i.p.), saline (1 ml/kg), 5-hydroxytryptophan (5-HTP; 10 mg/kg; Sigma Co Ltd. Poole, UK), 8-hydroxy-2-(di-*n*-propylamino)tetralin 1-Br (8-OH DPAT; 0.15 mg/kg; RBI, Natick, MA, USA) or 5-carboxyamidotryptamine (5-CT; 1 mg/kg; Tocris Bioscience, MO, USA). These were given alone or in animals pre-treated i.p. with either saline (1 ml/kg) or the $5HT_{1A}$ antagonist WAY 100135 (5 mg/kg; Wyeth Research Centre, Taplow, Bucks, UK) or the $5HT_7$ antagonist SB 269970-A (1 mg/kg; Tocris Bioscience, MO, USA). All drugs were dissolved in 0.9% w/v saline.

2.3. Test for female sexual behaviour

Behavioural tests were carried out under red light at 4–5 h into the dark period and consisted of placing each female with a series of vigorous males in observation arenas (a perspex cylinder 30 cm diameter, 50 cm high) and noting the number of lordotic responses to male mounts in a 15 min period or until they reached 10 mounts. The results were expressed as LQ% (number of lordoses/number of mounts × 100).

2.4. Experimental design

All rats received a 15 min test for sexual behaviour, 50 h and 2 h after the OB and progesterone priming, respectively (pre-injection test). They then received either saline or one of the serotoninergic antagonists, (WAY 100135 or SB 269970-A). Twenty minutes after SB 269970-A and 60 min after WAY 100135, the animals received either saline or one of the serotoninergic agonists, 5-HTP, 8-OH DPAT or 5-CT and 15 min later they were tested for a second time (post-injection test).

Based on the LQ% of the pre-injection test, rats in each treatment group were subdivided into non-receptive (NR; LQ% <50%) or receptive (R; LQ% >50%) and the effect of the treatments on these two sub-groups was assessed separately. It was assumed that any putative inhibitory effect would be revealed in the R subgroup and any stimulatory effect in the NR subgroup.

2.4.1. Experiment 1

All rats receiving 10 μg/rat OB plus 0.5 mg/rat progesterone (s.c.) as the priming regime were tested (pre-injection) and then received either saline followed by the agonists or were pre-treated with the antagonists before administering the agonists. The treated animals were then tested again (post-injection).

2.4.2. Experiment 2

Groups of rats received either 10 μg or 25 μg OB followed by 0.5 mg progesterone. They were then tested for sexual receptivity followed by administration of 8-OH DPAT or 5-CT and tested again 15 min later. This procedure was repeated twice at 14 day intervals, the same rats receiving the same agonist each time. Thus the effect of three consecutive administrations of the priming regime and the agonists was observed.

2.5. Statistical analysis

Comparison of pre-injection and post-injection LQ%s was made by Students' paired *t*-test. Comparison of groups receiving different OB priming doses three times at fortnightly intervals was assessed by 1-way Analyses of Variance (ANOVA) with Repeated Measures. In all cases $P<0.05$ was considered statistically significant.

3. Results

3.1. Experiment 1: The effect of 5-HTP, 8-OH DPAT and 5-CT and selective $5HT_{1A}$ and $5HT_7$ antagonists on female sexual behaviour

Ovariectomised rats primed with 10 μg OB and 0.5 mg progesterone were subdivided into receptive (LQ>50%) and non-receptive (LQ<50%) based on their pre-injection behavioural test. The effect of the three agonists, 5HTP, 8-OH DPAT, (predominantly a $5HT_{1A}$ agonist with some $5HT_7$ activity) and 5-CT (with a higher affinity than the other agonists for the $5HT_7$ receptor, but also exerting potent effects on the $5HT_{1A}$ receptor) was assessed by comparison of the results of the post-injection test for behaviour with the pre-injection test.

Table 1 shows that in the receptive animals, which should reveal putative inhibitory effects, all 3 agonists inhibited sexual behaviour and significantly ($P<0.001$ for the three agonists) reduced the LQ, compared to pre-injection values noted in the same animals. In the non-receptive animals, which should reveal any stimulatory effects, none of the agonists significantly affected behaviour. The two selective $5HT_{1A}$ and $5HT_7$ antagonists had no effect when given alone in the receptive animals,

Table 2
The effect of the selective $5HT_7$ (SB 269970-A) and $5HT_{1A}$ (WAY 100135) antagonists on lordosis in non-receptive and receptive female rats

Treatment	Lordosis Quotient%+/−SEM			
	Non-receptive		Receptive	
	Pre-injection	Post-injection	Pre-injection	Post-injection
Saline alone	16.3+/−1.5	18.3+/−1.9 (13)	61.0+/−1.6	58.1+/−0.3 (15)
SB alone	17.2+/−0.9	22.1+/−2.0 (14)*	60.9+/−1.5	65.1+/−1.7 (13)
Saline alone	17.5+/−1.0	17.6+/−1.8 (12)	56.6+/−1.5	55.2+/−1.9 (12)
WAY alone	17.5+/−1.0	24.9+/−1.8 (11)*	58.7+/−1.5	59.6+/−2.5 (12)

Rats were primed with 10 μg OB followed by 0.5 mg progesterone s.c. Tests for sexual receptivity were carried out before i.p. administration of SB 269970-A (SB; 1 mg/kg) or WAY 100135 (WAY; 5 mg/kg) and then tested 15 min after SB or 60 min after WAY. Before assessing the results, the rats were subdivided into non-receptive (LQ<50%) and receptive (LQ>50%)according to their LQ observed in the pre-injection test. Comparison of pre- and post-injection results were assessed by the Student's paired *t*-test. *$P<0.05$.

Table 1
Inhibitory effect of 5-HT agonists on lordosis in the absence and presence of the selective $5HT_7$ (SB 269970-A) and $5HT_{1A}$ (WAY 100135) antagonists in non-receptive and receptive female rats

	Lordosis Quotient%+/−SEM			
	Non-receptive		Receptive	
	Pre-injection	Post-injection	Pre-injection	Post-injection
5-HTP				
+Saline	12.3+/−2.8	11.7+/−2.1 (12)	55.7+/−1.24	26.5+/−4.4 (11)***
+SB 269970-A	19.7+/−2.8	30.1+/−3.5 (12)*	53.2+/−1.1	61.1+/−2.2 (11)
+WAY 100135	21.6+/−2.6	18.2+/−3.2 (13)	55.9+/−1.5	51.1+/−2.4 (12)
8-OH DPAT				
+Saline	24.2+/−3.5	16.9+/−2.8 (14)	59.7+/−1.4	40.9+/−3.2 (14)***
+SB 269970-A	11.1+/−1.3	16.0+/−2.3 (13)	52.6+/−1.1	46.3+/−2.9 (11)
+WAY 100135	20.9+/−3.0	29.5+/−4.1 (21)	52.5+/−0.9	55.8+/−2.2 (12)
5-CT				
+Saline	11.1+/−2.3	15.2+/−1.9 (13)	58.6+/−1.8	40.4+/−2.6 (12)***
+SB 269970-A	18.0+/−2.2	22.7+/−2.6 (13)	52.7+/−1.2	58.2+/−2.1 (12)
+WAY 100135	18.7+/−2.1	20.4+/−2.7 (13)	52.7+/−1.3	58.1+/−2.8 (11)

Rats were primed with 10 μg OB followed by 0.5 mg progesterone s.c. Tests for sexual receptivity were carried out before i.p. administration of SB 269970-A (1 mg/kg) or WAY 100135 (5 mg/kg). 20 min after SB 269970-A or 60 min after WAY 100135. Groups were treated i.p. with either saline (1 ml/kg), 5HTP (10 mg/kg), 8-OH DPAT (0.5 mg/kg), or 5-CT (1 mg/kg). Tests were then repeated 15 min after administration of the agonists. Before assessing the results, the rats were subdivided into non-receptive (LQ<50%) and receptive (LQ>50%) according to their LQ observed in the pre-injection test. Figures in brackets indicate the number of rats in the group. Comparison of pre- and post-injection results was assessed by the Student's paired *t*-test: *$P<0.05$;***$P<0.0001$.

but in the non-receptive group both exerted a small but significant ($P<0.05$) stimulatory effect (Table 2). Both antagonists were also successful in preventing the inhibitory effects of 5-HTP, 8-OH DPAT and 5-CT (Table 1).

3.2. Experiment 2: The effect of OB priming doses and repeated OB priming on the behavioural response to 8-OH DPAT and 5-CT

Groups of rats were given either 10 μg or 25 μg OB followed by 0.5 mg progesterone. The two agonists, 8-OH DPAT and 5-CT, were tested 3 times at 14 day intervals, the animals being freshly steroid-primed for each test and the same group always receiving the same agonist.

The concentration of the OB priming dose significantly influenced the response of the rats towards the inhibitory effect of 8-OH DPAT, with the higher dose of 25 μg OB attenuating the inhibitory effect of 8-OH DPAT compared to that observed after 10 μg OB (1-way ANOVA with repeated measures $F(1,25)=9.625$, $P=0.005$; Table 3). This difference was maintained at a similar level over the three fortnightly tests, thus while the concentration of OB had a significant effect on response to 8-OH DPAT the effect of repeating the OB treatment was not significant ($F(1,25)=0.07$, $P=0.79$, NS; Table 3). The experiment was repeated employing 5-CT as the agonist. This compound inhibited the LQ in receptive rats treated with either10 μg or 25 μg OB plus 0.5 mg progesterone. The concentration of the priming dose did not significantly affect the response of the rats to 5-CT ($F(1,25)=0.112$, $P=0.741$, NS), nor did the response change over the three fortnightly primings and tests ($F(1,25)=1.46$, $P=0.27$, NS; Table 3).

Interestingly, the OB priming dose affected the response to the selective $5HT_{1A}$ antagonist, WAY 100135. Two groups of rats were injected with either 10 μg OB or 25 μg OB and 0.5 mg progesterone and given a pre- and post-WAY 100135 injection test only once. The stimulatory effect of WAY 100135 was significantly greater after priming with 25 μg OB than 10 μg OB ($P<0.05$). There was no significant effect of the priming doses on the effect of the $5HT_7$ antagonist, SB 269970-A.

Table 3
The effect of oestradiol benzoate priming dose and repeated priming on the effect of 8-OH DPAT and 5-CT treatment on lordotic activity expressed as a percentage of the pre-treatment response

Compound	Priming dose of OB	No. in group	Day 1	Day 14	Day 28
8-OH DPAT	10 μg	13	69.6+/−4.3	69.5+/−4.1	68.2+/−3.8
	25 μg	14	78.9+/−2.8	78.8+/−2.7	79.3+/−2.0
5-CT	10 μg	13	73.8+/−4.2	87.1+/−3.2	86.9+/−4.7
	25 μg	14	81.6+/−8.3	84.5+/−4.3	85.4+/−2.8

Rats were primed with 10 μg or 25 μg followed by 0.5 mg progesterone s.c. before each test which was carried out 3 times at fortnightly intervals. 8-OH DPAT (0.5 mg/kg i.p.) or 5-CT (1 mg/kg i.p.) was injected 15 min before each test. Results shown are the post-injection results expressed as a percentage of the pre-injection results.
1-way ANOVA with Repeated Measures, was used to assess the significance of difference between the effects of the OB priming doses ($P=0.005$) over the 3 test periods and the repetition of the priming (NS) for the 8-OH DPAT groups. The effect of the priming doses and their repetition was NS for the 5-CT treated groups.

4. Discussion

The $5HT_7$ receptor is the most recently discovered subtype. It acts via the G-protein Gαs to stimulate adenyl cyclase (AC) and thence cAMP (Barnes and Sharp 1999). It is involved in a variety of functions listed in the Introduction; on some exerting a similar effect to the activation of the $5HT_{1A}$ receptor while on others having the opposite effect (see Introduction). The $5HT_{1A}$ receptor couples negatively with G-proteins, $G\alpha_1$ and the family of $G\alpha_0$ ($G\alpha_0$, $G\alpha i_1$, $G\alpha i_3$ and $G\alpha i_2$) (Mannoury la Cour et al; 2006) to inhibit AC and thence cAMP production (Fargin et al., 1991). There are, however, circumstances and sites, when $5HT_{1A}$ activation can participate in stimulation of AC (in the guinea-pig hippocampus) (Thomas et al., 1999; see Hoyer et al., 1994). $5HT_{1A}$ receptor activation also stimulates phospholipase C via $G\alpha i_3$ (Fargin et al., 1991) and finally it can induce hyperpolarization by G-protein-induced opening of K+ channels, this being independent of cAMP (Barnes and Sharp 1999).

In spite of the differences in their intracellular signalling pathways, $5HT_{1A}$ and $5HT_7$ receptors are considered to be pharmacologically similar and as mentioned above they do affect a number of functions in a similar manner. They also have mutual ligands, examples being 8-OH DPAT which predominantly binds to $5HT_{1A}$ receptors and has a lesser affinity to the $5HT_7$ subtype and 5-CT which binds with a high affinity to both receptors and is currently the most potent agonist for the $5HT_7$ receptor (Thomas et al., 1999). Thus selective $5HT_{1A}$ and $5HT_7$ agonists are not available, but in contrast, selective $5HT_{1A}$ and $5HT_7$ antagonists exist e.g. WAY 100135 ($5HT_{1A}$) (Fletcher et al., 1993) and SB 269970-A ($5HT_7$) (Hagan et al., 2000; Thomas et al., 2000).

In a previous report we have shown that activation of both $5HT_{1A}$ and $5HT_7$ receptors mediates the inhibitory effect of 5-HT on LH release (Siddiqui et al., 2000, 2004). In present study we now compare the effects of stimulation of these two receptor subtypes on female sexual behaviour. It is well established that 8-OH DPAT exerts an inhibitory effect on lordotic activity acting on post-synaptic receptors (Uphouse, 2000). As far as we know, the effect of 5-CT on lordosis has not been investigated. In this report we have shown that the two 5-HT agonists (8-OH DPAT and 5-CT) with an affinity for both $5HT_{1A}$ and $5HT_7$ receptors as well as 5-HTP with an affinity for all the 5-HT receptors significantly reduced lordotic activity in receptive (LQ>50%) animals and had no significant effect on the non-receptive subgroup (LQ<50%). The inhibitory effects of all three agonists in receptive animals were prevented by both the $5HT_{1A}$ antagonist, WAY 100135, and the $5HT_7$ antagonist, SB 269970-A. This indicates that both receptors are involved in regulating female sexual behaviour. In the non-receptive animals treated with 5-HTP, SB 269970-A induced a rise in lordotic activity suggesting that the 5-HT_7 antagonist revealed a stimulatory effect of 5-HTP.

SB 269970-A is a selective $5HT_7$ antagonist (Thomas et al., 2000) and when administered alone, systemically, to non-

receptive rats significantly increased lordotic activity. This suggests that endogenous $5HT_7$ activity might exert a tonic inhibitory control on female sexual behaviour. Interestingly, SB 269970-A given alone does not affect LH release (Siddiqui et al., 2004) so the putative endogenous inhibitory action of $5HT_7$ activity appears to be selective for female sexual behaviour, at least, compared to gonadotrophin release. WAY 100135 is a selective $5HT_{1A}$ antagonist but it can also exhibit a partial agonist effect on $5HT_{1A}$ autoreceptors (Assie and Koek, 1996; Fornal et al., 1996) which might affect (i.e., probably enhance) its antagonistic action. Systemic administration of WAY 100135 alone, like SB 269970A, stimulated lordotic activity in non-receptive animals and this indicates that endogenous $5HT_{1A}$ activity may also exert a tonic inhibitory effect on sexual behaviour. This effect has also been shown after central administration of WAY 100135 and WAY 100635 (Uphouse et al., 1996; Uphouse and Wolf, 2004). The selective $5HT_{1A}$ antagonist, WAY 100635 also stimulated lordotic activity after systemic administration (Kishitake and Yamanouchi, 2004).

It is assumed that after 5-HTP is administered peripherally, it passes the blood–brain barrier to be converted within the CNS to 5-HT. In receptive rats an injection of 5-HTP inhibited lordotic activity and this effect was prevented by both WAY 100135 and SB 269970-A. This inhibitory effect of 5-HTP has been shown before in receptive animals (Hunter et al., 1985) and in that same report 5-HTP had a stimulatory effect on non-receptive rats, probably acting via $5HT_2$ receptors (Hunter et al., 1985). It is not clear why this latter effect was not seen in the current experiments, except to note that the animals used in these experiments are relatively insensitive to steroid priming (seeMethods section), so perhaps they are also less sensitive to other stimulatory influences. It can also be noted that prior administration of SB 269970-A revealed the stimulatory effect of 5-HTP.

A number of reports have shown that increasing the OB priming dose attenuates or desensitizes the response of animals to the inhibitory effect of 8-OH DPAT on female sexual behaviour (Jackson and Uphouse, 1996, 1998; Trevino et al., 1999). Binding studies indicate that this is not due to any changes in $5HT_{1A}$ receptor affinity or density (Jackson and Etgen, 2001). It may, however, be due to an oestrogen-induced reduction in the coupling of the $5HT_{1A}$ receptor to Gi/o proteins as shown that can occur in the cortex, hippocampus and amygdala (Mize and Alper, 2000).The oestrogen effect may be due to an alteration downstream to the receptor as oestrogen reduces the hypothalamic concentration of certain Gαi/o proteins including $G\alpha_Z$, $G\alpha i_1$ and $G\alpha i_3$ which couple with the $5HT_{1A}$ receptor (Raap et al., 2000). This reduction correlates with a desensitization of the effect of 8-OH DPAT, on hormone release, and it is suggested by the authors may be the cause of the reduced effect on sexual behaviour as well (Raap et al., 2000). In addition, OB in a dose-dependent manner up-regulates the RGS ZI protein (regulator of G-protein signalling-ZI). This is a $G\alpha_2$-selective RGS protein which accelerates $G\alpha_2$ GTP hydrolysis and regulates the duration of interaction between $G\alpha_2$ proteins and effector systems (Carrasco et al., 2004). The $5HT_{1A}$ receptor reduces AC activity via a number of Gi/o proteins including $G\alpha_2$ (Mannoury la Cour et al., 2006) and there is some evidence that the inhibitory effect of 8-OH DPAT on lordosis, is associated with a reduction in AC activity and thence cAMP production (Uphouse, 2000). If the action of $G\alpha_2$ protein on effector systems is altered by OB, this may be manifested as a reduction in the inhibitory effect of $5HT_{1A}$ activation on AC activity and thence lordosis (Carrasco et al., 2004). Our experiments employing 10 and 25 μg OB priming doses support this hypothesis (Jackson and Uphouse, 1996, 1998; Trevino et al., 1999), as the action of 8-OH DPAT was significantly less after 25 μg OB compared to 10 μg OB. We have also shown that the stimulatory effect of WAY 100135, the $5HT_{1A}$ antagonist, is significantly more effective after 25 μg OB compared to 10 μg OB. Thus it seems that while the inhibitory effect of $5HT_{1A}$ activity is attenuated by OB, the stimulatory effect due to blocking $5HT_{1A}$ activity is enhanced by OB. In contrast to their effect on $5HT_{1A}$, OB priming doses had no effect on the action of the predominantly $5HT_7$ agonist (5-CT) or its selective antagonist, SB 269970-A. This is presumably because the intracellular signalling pathways involved in regulating lordotic activity are different for $5HT_{1A}$ and $5HT_7$ receptors.

Uphouse (2000) have also shown that repeated hormonal priming before repeated tests for female sexual activity can desensitize the response to 8-OH DPAT. The interval between hormone treatments has to be at least 3 days and can last up to 7 days; longer periods were not tried (Jackson and Uphouse, 1996; Trevino et al., 1999). In our experiments we subjected the animals to 3 OB plus progesterone treatments at 14 day intervals and found no effect of the repeated priming. Probably this longer period allowed the system to recover from any changes induced by previous treatments.

In summary, we have shown that $5HT_7$ receptor activation mediates an inhibitory effect on female sexual behaviour and this may be a physiological effect as the selective $5HT_7$ antagonist, SB 269970-A exerts an effect on the endogenous system and stimulates behaviour. We have also indicated that while there is an interaction between oestrogen and the response to activation of $5HT_{1A}$ receptors by 8-OH DPAT, this relationship does not exist between oestrogen and the $5HT_7$ receptor.

Acknowledgement

This research was supported by Pakistan Science Foundation Grant S-AKU/BIO (281).

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