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Effect of SB-243213, a selective 5-HT_{2C} receptor antagonist, on the rat sleep profile: A comparison to paroxetine

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Abstract

5-HT_2 receptor antagonists promote slow wave sleep (SWS) in humans and rats, conversely 5-HT_2 agonists inhibit SWS in rats. These alterations are thought to be predominantly mediated via the 5-HT_{2C} receptor subtype. It is evident that 5-HT_2 receptor function also plays an important role in depression. Here, we examine the acute effect of the selective 5-HT_{2C} receptor antagonist 5-methyl-1-[[-2-[(2-methyl-3-pyridyl)oxy]-5-pyridyl]carbamoyl]-6-triflouromethylindoline hydrochloride (SB-243213-A) on rat sleep in comparison to the selective serotonin reuptake inhibitor (SSRI) paroxetine. Both SB-243213-A (10 mg/kg po) and paroxetine (3 mg/kg po) significantly increased deep SWS (SWS2) quantity (27% and 24%, respectively) and reduced paradoxical sleep (PS) quantity (35%) during the sleep period. Following SB-243213-A, SWS2 occurrence frequency was reduced (24.1%); however, elevated quantity of SWS2 can be attributed to an increase in occurrence duration (81%). Reduced PS quantity results from a decrease in occurrence frequency (46%). In comparison, paroxetine increased SWS2 occurrence frequency (50%), with decreased frequency (27%) and duration (21%) of PS. The data for SB-243213-A in the present study is consistent with that following ritanserin supporting 5-HT_{2C} receptor subtype mediation of this response. The similar effect of SB-243213-A to paroxetine with regard to PS quantity provides further evidence that 5-HT_{2C} receptor antagonists maybe beneficial in the treatment of depression/anxiety.

Keywords: SB-243213-A; Paroxetine; 5-HT_{2C} receptors; Antagonist; Selective serotonin reuptake inhibitor; Sleep; Depression; 5-Hydroxytryptamine

1. Introduction

5-Hydroxytryptamine (5-HT) is one of the major neurotransmitters in the physiological regulation of the mammalian sleep–wake cycle, whereby 5-HT output from the dorsal raphe nucleus (DRN) is pivotal to the reciprocal interaction model of non-rapid eye movement (REM)/REM sleep stage cycling (Lydic et al., 1987a,b; Hobson et al., 1998). Indeed, the sleep–wake cycle of animals is sensitive to manipulation of brain 5-HT levels such that its elevation via administration of 5-HT itself, its precursors L-tryptophan and 5-hydroxytryptophan, monoamine oxidase inhibitors or stimulation of the raphe nuclei all increase slow wave sleep (SWS). Conversely reducing 5-HT levels by electrolytic lesions, lesions by 5,6- or 5,7-dihydroxytryptamine or *p*-chlororphenyl-alanine administration tends to decrease SWS and lead to insomnia (Koella, 1984).

SWS increases in response to selective 5-HT_2 receptor antagonists in both rodents (Dugovic and Wauquier, 1987) and humans (Declerck et al., 1987; Sharpley et al., 1990), and studies displaying decreases in SWS in response to 5-HT_2 receptor agonists (Dugovic and Van den Broeck, 1991) provide compelling evidence for a role of this receptor family in the regulation of mammalian sleep. Current characterisation of the 5-HT_2 receptor family identifies three distinct receptor subtypes, 5-$HT_{2A,\ B\ and\ C}$ (Humphrey et al., 1993), all of which are present in the CNS (Barnes and Sharp, 1999). In the absence of selective 5-HT_2 receptor subtype ligands Sharpley et al. (1994) have compared the effects of ritanserin to ketanserin on the human sleep profile. Ketanserin, an antagonist with greater potency at 5-HT_{2A} than 5-HT_{2C} receptors sites (Hoyer, 1988), produced smaller increases in SWS than ritanserin,

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an antagonist equipotent at these two receptor subtypes (Leysen et al., 1985; Hoyer, 1988). This data therefore argues in favour of a predominant role for 5-HT_{2C} receptors in mediation of mammalian SWS.

In addition to a role in sleep stage regulation, there is also accumulating evidence that the function of 5-HT_2 receptors contributes to various psychiatric disorders and to the mechanism of action for antidepressant drugs (Maes and Mekltzer, 1995). Increased densities of 5-HT_2 receptors have been observed in the frontal cortex of both suicide victims and depressed patients (McKeith et al., 1987; Mann et al., 1986; Yates et al., 1990). This elevation of 5-HT_2 receptor density appears to be disease state dependent with a return to control brain levels, observable postmortem, in depressed patients displaying clinical improvement of symptoms (Yates et al., 1990) or patients successfully treated with antidepressants (Biegon et al., 1990). Indeed, most classes of antidepressant drug including tricyclics (Peroutka and Snyder, 1980; Kellar et al., 1981), monoamine oxidase inhibitors (Kellar et al., 1981), selective serotonin reuptake inhibitors (SSRIs) (Nelson et al., 1989; Stolz et al., 1983) and 5-HT_2 receptor antagonists (Leysen et al., 1986) generally cause downregulation of 5-HT_2 receptors. Furthermore, differences in functional response to ritanserin have been observable in depressed patients compared to controls. For example, the dose-dependent increases in SWS observed with this drug are reduced in depressed patients (Stanner et al., 1992), suggesting an upregulation of 5-HT_2 receptor levels in patients displaying depressive symptoms, leading to a blunted functional response.

Depressed patients also display a variety of disturbances in their sleep profile. These include a lack of sleep initiation and continuance, reduced total sleep time, and fragmented sleep with reductions in SWS states and sleep efficiency (Hawkins and Mendels, 1966; Gillin et al., 1981). However, the most robust, and certainly the most studied, alteration concerns REM sleep. A decrease in latency and increase in amount of REM sleep early after sleep onset is observed in patients with major depressive disorder (Navarro and Davila, 1998; Thase, 1998, 1999). Despite REM sleep disturbances being well characterised in depressed patients it is still not established how, or indeed if, these abnormalities contribute to the progression and symptomatology of the disease (for review, see Lebon et al., 1997). However, total sleep deprivation leads to an immediate amelioration of depressed mood in 70% of patients who subside after the next night of sleep (Demet et al., 1999; Riemann et al., 1999). In addition, the SSRI class of antidepressant drugs have been shown to reduce this increased REM sleep amount and prolong REM sleep latencies in depressed patients (Stanner et al., 1995; Trivedi et al., 1999) and normal volunteers (Schlosser et al., 1998).

In the present study, we investigated the acute effects of the highly selective 5-HT_{2C} receptor antagonist 5-methyl-1-[[-2-[(2-methyl-3-pyridyl)oxy]-5-pyridyl]carbamoyl]-6-triflouromethylindoline hydrochloride (SB-243213-A; pK_i: 5-HT_{2A} 6.8, 5-HT_{2B} 7.0, 5-HT_{2C} 9.0) (Bromidge et al., 2000; Wood et al., 2001) on the sleep profile of rats and compared this to the actions of acutely administered paroxetine. SB-243213-A has previously been described as an inverse agonist at the 5-HT_{2C} receptor (Bromidge et al., 2000) when investigated in human recombinant HEK293 cells over expressing the 5-HT_{2C} receptor. However, in native tissue preparations, such as the pig choroid plexus, the compound manifests as a silent (neutral) antagonist (unpublished observation), therefore, in this manuscript, we will be using the term antagonist to describe SB-243213-A.

2. Materials and methods

2.1. Animals

All procedures in this study were in accordance with the UK Animals (Scientific Procedures) Act (1986) and conformed to GlaxoSmithKline ethical review. Male Hooded Lister rats (200–225 g on arrival, Charles River, UK) were housed in groups of four under 12/12-h dark/light conditions for at least 21 days prior to experimentation with ambient temperature maintained at 21 ± 1 °C. Access to food and water was allowed ad libitum. Subsequent to surgical preparation, rats were housed in pairs for 7 days prior to signal recording periods when animals were housed singly under the same environmental conditions.

2.2. Drugs

SB-243213-A and paroxetine, synthesised in the Department of Medicinal Chemistry, GlaxoSmithKline, UK, were suspended in 1% (w/v) methylcellulose in sterile water for oral (po) administration.

2.3. Surgical procedures

Rats were anaesthetised with Domitor (medetomidine HCl 0.4 mg/kg sc, Pfizer) and Sublimaze (fentanyl 0.45 mg/kg ip, Jansen-Cilag). Following a midline incision and retraction of connective tissue from the dorsal aspect of the skull, silver chloride ball electroencephalogram (EEG) electrodes were implanted through bore holes in the skull over the left/right frontal cortex (± 2 mm lateral to midline, 3 mm anterior to bregma) and left/right occipital cortex (± 3 mm lateral to midline, 4 mm anterior to lambda). Silver disc electromyogram (EMG) electrodes were placed between the nuchal muscle layers. All electrodes were soldered to a six-pin connecting block and encased in dental cement anchored by three screws. The wound was sutured around the anchoring cement and a further layer of cement applied to seal the wound. Anaesthesia was reversed with Antisedan (atipamexole HCl; 2.5 mg/kg sc, Pfizer) and postoperative

analgesia provided by Nubian (nalbuphine HCl; 2 mg/kg sc, Du Pont Pharmaceuticals). Appropriate postoperative care was applied for 7 days or until preoperative body weight had been restored.

2.4. Sleep recording procedure

Prior to recording of EEG and EMG signals, animals were first connected to recording leads and acclimatised to the singly housed recording environment for 24 h. EEG and EMG signals (amplified 1000–5000×, filtered to; EEG 0.1–30 Hz, EMG 0.1–300 Hz, PA400, Biodata, UK) were acquired continuously to PC (Compaq, UK) in 10-s epochs for 12 h post dose, at which time, the animals were returned to their home cages. This procedure has been previously described and shown to produce reliable sleep stage scores by Piper et al. (2000).

Two separate studies were performed to assess the effect of each compound. Firstly, each rat ($n=6$) received vehicle, 1, 3, and 10 mg/kg SB-243213-A (1 ml/kg po) on a randomised crossover basis with 72 hour intervals between each treatment. A second group of rats ($n=6$/group) received either vehicle or paroxetine (3 mg/kg po). In both studies, the treatments were administered at the interface of lights off to lights on. The doses of SB-243213-A used in this study (1, 3, and 10 mg/kg po) have been shown to dose-dependently inhibit mCCP-induced hypolocomotion with an oral ID_{50} of 1.1 mg/kg (Wood et al., 2001) in rats, a $5HT_{2C}$ receptor mediated response (Kennett et al., 1997; Fone et al., 1998), and also to produce anxiolytic activity, maximal at 10 mg/kg (Wood et al., 2001). The dose of 3 mg/kg (po) paroxetine has exhibited a consistent anxiolytic response in rats following chronic dosing (Lighthowler et al., 1994; Duxon et al., 2000), and similar dose levels (5 mg/kg) have been shown to increase extracellular 5-HT concentrations following acute administration (Hajos-Korcsok et al., 2000).

2.5. Signal analysis

Semi-automated signal analysis (Sleep Stage Analysis v3.11, GlaxoSmithKline) was employed to categorise each 10-s epoch of EEG and EMG recording into one of four sleep stages (arousal, light SWS (SWS1), deep SWS (SWS2), and paradoxical sleep (PS)—analogous to human REM sleep). EEG frequency bands used for sleep stage characterisation were 0.5–4.5 Hz (delta) and 5.5–8.5 Hz (theta). Reliability of automated sleep staged scoring was verified by the use of Kappa statistic as in Piper et al., (2000).

2.6. Data analysis

Data were presented as mean ± S.E.M. percentage distribution in hourly intervals and mean ± S.E.M. area under the curve (AUC) for regions of statistical significance. Statistical significance was assessed by one-way ANOVA. Significant ANOVA effects in the SB-243213-A protocol were followed by post hoc Duncan's multiple range test.

3. Results

3.1. Percentage sleep stage distribution

3.1.1. The effect of the selective 5-HT_{2C} receptor antagonist SB-243213-A

No significant alteration in the percentage distribution of any sleep stage was observed following 1 or 3 mg/kg of SB-243213-A (Fig. 1). In addition, SB-243213-A at 10 mg/kg

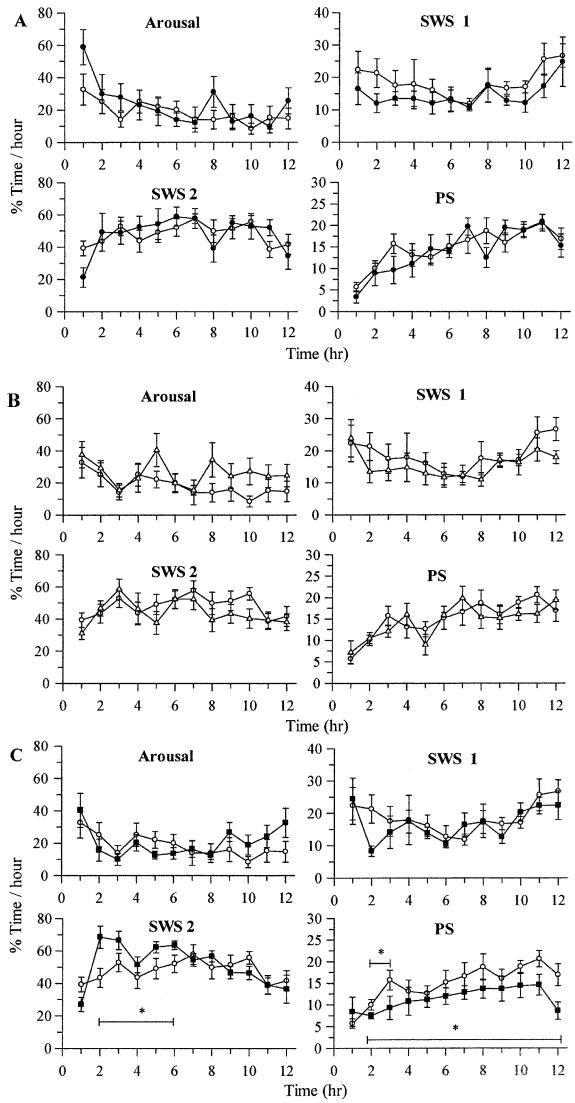

Fig. 1. Percentage distribution of arousal, SWS1, SWS2, and PS for each hour of the 12-h sleep period in the Hooded Lister rat. (A) Following vehicle (○), SB-243213-A 1mg/kg (●). (B) vehicle (○) and SB-243213-A 3 mg/kg (△). (C) Vehicle (○) and SB-243213-A 10 mg/kg (■) administered orally at Time 0. Statistical significance of AUC for periods indicated by ⊢⊣, as assessed by ANOVA are represented as $*P<0.05$, $P<0.05$ post hoc Duncan's.

did not significantly alter the distribution of either arousal or SWS1. However, the amount of SWS2 following the highest dose of SB-243213-A (10 mg/kg) was significantly [$F(3,19)=3.96$, $P=.02$ ANOVA, $P<0.05$ post hoc Duncan's] increased (veh = 193.5 ± 16.4, SB-243213-A = 246.4 ± 10.5 AUC) over the period 2–6 h post dose. Along with enhanced SWS2 was a reduction in PS quantity, which was significant [$F(3,19)=6.4$, $P=0.02$, ANOVA, $P<0.05$ post hoc Duncan's] 2–12 hour post dose (veh = 160.8 ± 11.1, SB-243213-A = 120.6 ± 12.6 AUC) and became most marked 2–3 hour post dose [veh = 12.9 ± 1.0, SB-243213-A = 8.4 ± 1.5 AUC; $F(3,19)=4.19$, $P=.045$, ANOVA, $P<0.05$ post hoc Duncan's] (Fig. 1).

3.1.2. The effect of the SSRI paroxetine

Similar to SB-243213-A, paroxetine (3 mg/kg) administration also promoted SWS2 [veh = 107.5 ± 5.2, paroxetine = 133.6 ± 2.7 AUC; $F(1,10)=19.95$, $P=0.001$, ANOVA] 2–4 h post-dose and suppressed PS [veh = 185.9 ± 6.7, paroxetine = 144.3 ± 6.1 AUC; $F(1,10)=20.95$, $P=0.001$, ANOVA] over the 12-h recording period with the most marked effect apparent 2–6 h post-dose [veh = 69.4 ± 3.7, paroxetine = 45.4 ± 5.2 AUC; $F(1,10)=14.4$, $P=0.004$, ANOVA]. No alteration of arousal or SWS1 states was observed (Fig. 2).

3.2. Number and duration of sleep stage bouts during peak change in sleep stage quantity (2–3 h post dose)

3.2.1. The effect of the selective 5-HT$_{2C}$ receptor antagonist SB-243213-A

Following SB-243213-A (10 mg/kg) administration, the number of SWS2 bouts was significantly [$F(3,19)=4.44$, $P=0.049$, ANOVA, $P<0.05$ post hoc Duncan's] reduced by 24.1%. The overall increase in quantity of SWS2 observed (Fig. 2) was therefore attributable to the 80.6% prolongation of bout duration [$F(3,19)=7.01$, $P=.016$, ANOVA, $P<0.05$ post hoc Duncan's]. The decrease in PS quantity following SB-243213-A (10 mg/kg, Fig. 1) was found to be attributable to a 46.0% reduction in the number of bouts [$F(1,10)=6.45$, $P=0.02$, ANOVA, $P<0.05$ post hoc Duncan's] (Fig. 3).

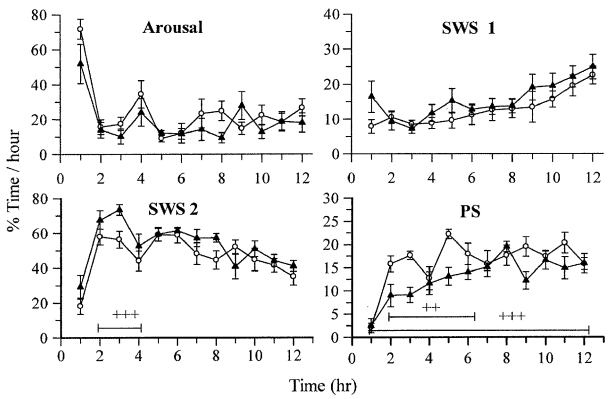

Fig. 2. Percentage distribution of arousal, SWS1, SWS2, and PS for each hour of the 12-h sleep period in the Hooded Lister rat. (A) Following vehicle (○) or paroxetine 3 mg/kg (▲) administered orally at Time 0. Statistical significance of AUC for periods indicated by as assessed by ANOVA are represented as $^{++}P<0.01$, $^{+++}P=0.001$.

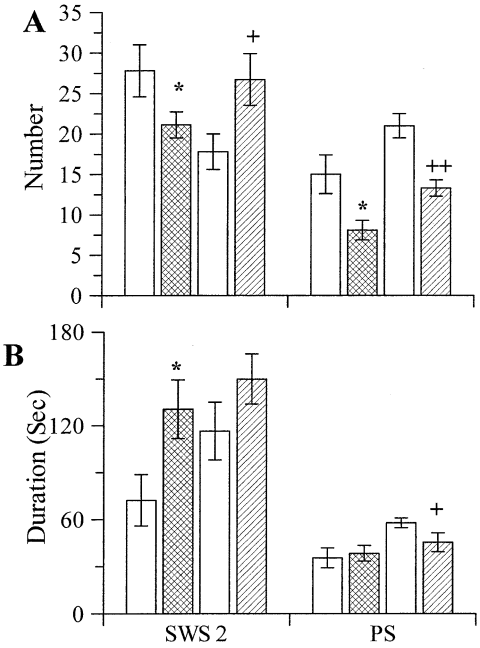

Fig. 3. The effect of SB-243213-A (10 mg/kg po ▨) and paroxetine (3 mg/kg po ▨) on A, the number, and B, the duration of SWS and PS bouts compared to vehicle (□) during the sleep period. Statistical significance, as assessed by ANOVA, is represented by $^{*}P<.05$, post hoc Duncan's; $^{+}P<.05$ and $^{++}P<.01$.

3.2.2. The effect of the SSRI paroxetine

In contrast to SB-243213-A, paroxetine produced a significant [$F(1,10)=5.31$, $P=0.043$, ANOVA] increase (50.0%) in the number of SWS2 bouts, with only a 28.6% [$F(1,10)=7.85$, $P=0.2$, ANOVA] prolongation of each bout. Paroxetine also significantly [$F(1,10)=10.45$, $P=0.009$, ANOVA, $F(1,10)=4.64$, $P=0.045$, ANOVA, respectively] inhibited both the number (27.1%) and duration (21.3%) of PS bouts (Fig. 3).

4. Discussion

The study described herein has attempted to asses the contribution of the 5-HT$_{2C}$ receptor subtype in the mediation of sleep–wake states using SB-243213-A, a potent 5-HT$_{2C}$ receptor antagonist with greater than 100-fold selectivity over 5-HT$_{2A}$ and 5-HT$_{2B}$ receptor subtypes. We have compared these effects to the clinically proven SSRI antidepressant drug paroxetine. Data in the present study confirms the findings that 5-HT$_2$ receptor antagonism leads to a promotion of SWS2 states and supports the conclusion of Sharpley et al. (1994) that these effects are predominantly

mediated via the 5-HT_{2C} receptor subtype. This study also reinforces the findings of Idozikowski et al. (1986) that 5-HT_2, via 5-HT_{2C} receptor antagonism, promotes SWS by prolongation of occurrence duration and suppresses PS (REM) sleep quantity by decreasing the number of bouts. Interestingly, SB-243213-A only induced changes in the sleep–wake profile at a dose level of approximately 10 × (10 mg/kg) the ID_{50} dose vs. mCPP-induced hypolocomotion. This could be attributable to a lower level of 5-HT_{2C} receptor activation following an acute challenge with mCPP, an agonist with little selectivity for the 5-HT_{2C} receptor, than the endogenous serotonergic tone regulating sleep stage cycling. Indeed, in another non-pharmacologically driven behavioural system, the high light social interaction model of anxiety (Wood et al., 2001), the same dose of 10 mg/kg is required to achieve maximal anxiolysis.

This overall profile of promoted SWS and suppressed PS for SB-243213-A is comparable to that produced by paroxetine. However, the mechanisms underlying these changes in sleep stage distribution appear to differ between the two compounds. With respect to SWS, paroxetine increased the number of bouts without affecting the duration of each bout, suggesting an enhanced sensitivity to SWS initiating processes and an increase in sleep stage cycling. In contrast, SB-243213-A reduced the number of occurrences but elicited a marked enhancement of the duration of each SWS2 bout indicative of a reduction in the cycling of sleep stages and an increase in SWS maintenance. PS occurrence number was decreased by both compounds, suggesting reduced PS-on drive with only paroxetine appearing to inhibit maintenance mechanisms as reflected by shortened bout duration.

The observation that SB-243213-A and paroxetine produce similar overall effects on sleep stage distribution forms something of a paradox. Paroxetine promotes 5-HT transmission via reuptake inhibition and SB-243213-A inhibits 5-HT transmission by acting as an antagonist at the 5-HT_{2C} receptor. Although it is impossible to deduce a site of action for the compounds from this study alone, it is interesting to speculate about the effects of these two compounds relative to the reciprocal interaction theory of sleep stage cycling (Hobson et al., 1998). According to this model (Fig. 4A),

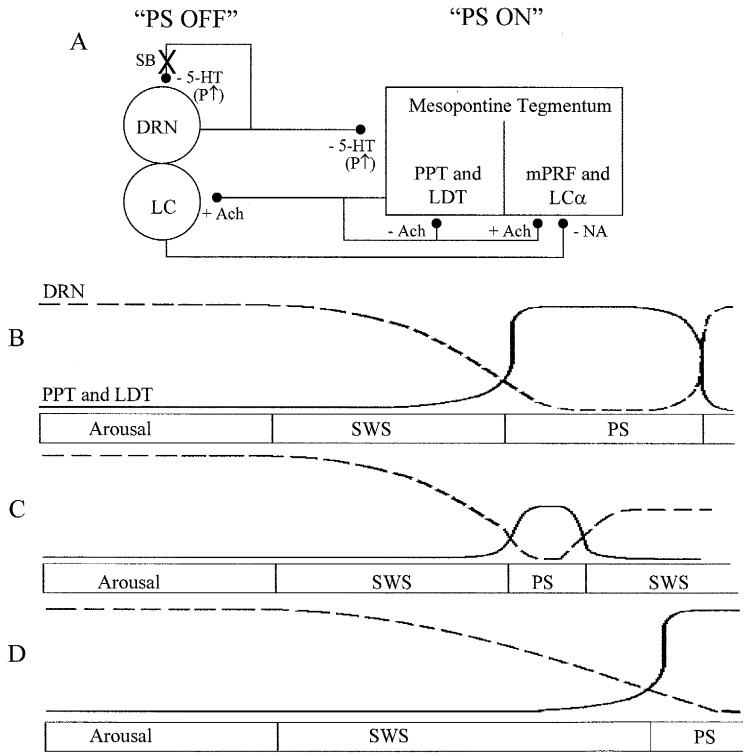

Fig. 4. Confirmed synaptic connections of the reciprocal interaction model and relative firing rates of "PS-off" and "PS-on" neurones. (A) Structural model of the reciprocal interaction model of SWS and PS sleep stage cycling showing confirmed synaptic connections (− inhibitory, + excitatory). Potential mode of action of SB-243213-A in inhibiting negative DRN feedback and for paroxetine induced 5-HT accumulation are indicated by SB × and P↑, respectively. (B–D) Hypothesised relative firing rates of PS-off neurones of the DRN and PS-on neurones of the PPT and LDT with associated sleep stage. (B) In the endogenous state. (C) Following paroxetine accumulation of 5-HT from DRN axon terminals at the LDT and PPT maintains inhibition for longer thereby suppressing the initiation of PS. However, increased 5-HT tone at the negative feedback mechanism within the DRN would lead to greater inhibition of DRN firing and increase the cycling of sleep stages. (D) Following SB-243213-A 10 mg/kg po. The firing of the DRN is prolonged by inhibiting negative feedback leading to increased suppression of PPT and LDT firing resulting in prolonged maintenance of SWS states. Abbreviations: 5-HT, 5-hydroxytriptamine; Ach, acetylcholine; NA, noradrenaline; PS, paradoxical sleep; SWS, slow wave sleep; DRN, dorsal raphé nucleus; LC, locus coeruleus; PPT, pedunculopontine tegmental nucleus; LDT, laterodorsal tegmental nucleus; mPRF, medical pontine reticular formation; LCα, peri-locus coeruleus alpha; SB, SB-243213-A; P, paroxetine.

serotonergic projections from the DRN and noradrenergic projections from the locus coeruleus (LC) inhibit firing of pedunculopontine tegmental nucleus (PPT), laterodorsal tegmental nucleus (LDT), medial pontine reticular formation, and peri-locus coeruleus alpha "REM-on" neurones of the mesopontine tegmentum. DRN firing through recurrent axonal collaterals of the DRN mediated via 5-HT (Portas et al., 1996) along with nonaxonal, somatodendritic 5-HT release (Adell et al., 1993) form a negative feedback loop also inhibiting DRN firing. Once enough inhibitory tone is exerted on the DRN, REM-on neurones disinhibit and begin firing, suppressing DRN firing (Fig. 4B) and also negatively feeding back on the PPT and LDT via acetylcholine (Hobson et al., 1998). Paroxetine induced increases in 5-HT accumulation from DRN axon terminals at the LDT/PPT would be expected to maintain inhibition of REM-on neurones for longer thereby suppressing the initiation of PS. However, increased 5-HT tone at the negative feedback mechanisms within the DRN would lead to greater inhibition of DRN firing and increase the cycling of sleep stages (Fig. 4C). Both these effects where observed in the present study following paroxetine. Clemett et al. (2000) report the presence of 5-HT_{2C} like immunoreactivity in the raphé nucleus. Therefore, it is interesting to speculate that the 5-HT_{2C} receptor mediates negative feedback to the DRN, either by regulating release or transmission of somatodendritic 5-HT release or transmission of recurrent collateral axonal 5-HT release. Blockade of this receptor would therefore be expected to produce maintenance of DRN firing leading to maintenance of SWS with suppression of REM-on episodes, as observed following SB-243213-A, without the increased sleep stage cycling observed following paroxetine (Fig. 4D). However, the localisation of 5-HT_{2C} receptors in the DRN (Clemett et al., 2000) is not a consistent finding (Abramowski et al., 1995). Absence of 5-HT_{2C} receptors within the DRN would clearly weaken the case for a role of this receptor in the modulation of somatodendritic release but may not preclude a role in axonal recurrent collateral negative feedback. Wright et al. (1990) provide further evidence to support a hypothesis for 5-HT_{2C} regulation of DRN negative feedback, showing that the selective 5-HT_2 receptor agonist DOI is a potent inhibitor of DRN firing.

As described earlier, depressed patients display a number of disruptions in the sleep profile. Reduced REM latency and increased REM quantity are characteristics of the depressed phenotype. A large majority of antidepressant drugs reverse these disruptions, as well as produce similar effects, i.e. reduced REM quantity and increased latency, in normal subjects. The ability of a compound to bring about these alterations on the endogenous sleep profile, in the absence of a well-accepted model of depression, may therefore provide a surrogate marker for drugs with potential antidepressant actions. There does, however, currently exist a paradox within the field of 5-HT_{2C} receptor research. 5-HT_{2C} receptor agonists have also been described as anxiolytic, as well as anxiogenic, depending on the behavioural paradigm. This may reflect the differing contributions of various 5-HT_{2C} expressing structures of the limbic system to the overall behaviour profile of the rat in a given anxiety paradigm (Graeff et al., 1996). Despite this paradox, the current dataset clearly shows that a rat administered with a 5-HT_{2C} antagonist in an undriven behavioural system demonstrates an antidepressant-like response. Therefore, alongside the wealth of evidence implicating 5-HT_2 receptor functionality in the depressed state, this study provides further evidence that a specific 5-HT_{2C} receptor antagonist maybe beneficial in the management of depressed mood. Indeed, SB-243213-A has already been shown to have an effective anxiolytic profile (Wood et al., 2001).

References

Abramowski D, Rigo M, Duc D, Hoyer D, Staufenbiel M. Localisation of the 5-hydroxytryptamine$_{2C}$ receptor protein in human and rat brain using specific antisera. Neuropharmacology 1995;34(12):1635–45.

Adell A, Carceller A, Artigas F. In vivo brain dialysis study of the somatodendritic release of serotonin in the raphé nuclei of the rat: effects of 8-hydroxy-2-(di-*n*-propylamino)tetralin. J Neurosci 1993;5:1673–81.

Barnes NM, Sharp T. A review of central 5-HT receptors and their function. Neuropharmacology 1999;38(8):1083–152.

Biegon A, Essar N, Israeli M, Elizur A, Bruch S, Bar-Nathan AA. Serotonin 5-HT_2 receptor binding on blood platelets as a state dependent marker in major affective disorder. Psychopharmacology 1990;102: 73–5.

Bromidge SM, Dabbs S, Davies DT, Davies S, Duckworth DM, Forbes IT, Gaster LM, Ham P, Jones GE, King FD, Mullholland KR, Saunders DV, Wyman PA, Blaney FE, Clarke SE, Blackburn TP, Holland V, Kennet GA, Lighthowler S, Middlemiss DN, Trail B, Riley GJ, Wood M. Biarylcarbamoylindolines are novel and selective 5-HT_{2C} receptor inverse agonists: identification of 5-Methyl-1-[[2-[(2-methyl-3-pyridyl)oxy]-5pyridyl]carbamoyl]-6-trifluoromethylindoline (SB-243213) as a potential antidepressant/anxiolytic agent. J Med Chem 2000;43:1123–34.

Clemett DA, Punhani T, Duxon MS, Blackburn TP, Fone KCF. Immunohistochemical localisation of the 5-HT_{2C} receptor protein in the rat CNS. Neuropharmacology 2000;39:123–32.

Declerck AC, Wauquier A, Van Der Ham-Veltman PHM, Gelders Y. Increase in slow wave sleep in humans with the serotonin-S2 antagonist ritanserin. Curr Ther Res 1987;41:427–32.

Demet EM, Chicz-Demet A, Fallon JH, Sokolski KN. Sleep deprivation therapy in depressive illness and Parkinsons disease. Prog Neuro-Psychopharmacol Biol Psychiatry 1999;23(5):753–84.

Dugovic C, Van den Broeck WAE. Sleep–wakefulness alterations produced by the putative serotonin 5-HT_{1C} agonist *m*-chlorophenylpiperazine in the rat. Sleep Res 1991;20A:129.

Dugovic C, Wauquier A. 5-HT_2 receptors could be primarily involved in the regulation of slow-wave sleep in the rat. Eur J Pharmacol 1987; 137:145–6.

Duxon MS, Starr KR, Upton N. Latency to paroxetine-induced anxiolysis in the rat is reduced by co-administration of the 5-HT_{1A} receptor antagonist WAY100635. Br J Pharmacol 2000;130:1713–9.

Fone KCF, Austin RH, Topham IA, Kennett GA, Punhani T. Effects of chronic M-CPP on locomotion, hypophagia, plasma corticosterone and 5-HT_{2C} receptor levels in the rat. Br J Pharmacol 1998;123(8): 1707–15.

Gillin JC, Duncan WB, Murphy DL, Post RM, Wehr TA, Goodwin FK, Wyatt RY, Bunney WE. Age-related changes in sleep in depressed and normal subjects. Psychiatry Res 1981;4:73–8.

Graeff FG, Guimaraes FS, De Andrade TGCS, Deakin JFW. Role of 5-HT in stress, anxiety, and depression. Pharmacol, Biochem Behav 1996; 54(1):129–41.

Hajos-Korcsok E, McTavish SFB, Sharp T. Effect of selective 5-hydroxytryptamine reuptake inhibitor on brain extracellular noradrenaline: microdialysis studies using paroxetine. Eur J Pharmacol 2000;407(1–2): 101–7.

Hawkins DR, Mendels J. Sleep disturbances in depressive syndromes. Am J Psychiatry 1966;123:682–90.

Hobson JA, Stickgold R, Pace-Schott EF. The neuropsychology of REM sleep dreaming. NeuroReport 1998;9:1–14.

Hoyer D. Molecular pharmacology and biology of 5-HT_{1C} receptors. TIPS 1988;9:89–94.

Humphrey PPA, Hartig P, Hoyer DA. Proposed new nomenclature for 5-HT receptors. TIPS 1993;14:233–6.

Idozikowski C, Mills FJ, Glennard R. 5-Hydroxytryptamine-2 antagonist increases human slow wave sleep. Brain Res 1986;278:164–8.

Kellar KJ, Cascio CS, Butler JA, Hurtzke RN. Different effect of electroconvulsive shock and antidepressant drugs on serotonin-2 receptors in the rat brain. Eur J Pharmacol 1981;69:515–8.

Kennett GA, Wood MD, Bright F, Trail B, Riley G, Holland V, Avenell KY, Stean T, Upton N, Bromage S, Forbes IT, Brown AM, Middlemiss DN, Blackburn TP. SB-242084, a selective and brain penetrant 5-HT_{2C}, receptor antagonist. Neuropharmacology 1997;36(4–5):609–20.

Koella WP. The organisation and regulation of sleep. Experientia 1984; 40:309–408.

Lebon O, Stanner L, Murphy JR, Hoffman G, Pull CH, Pelc I. Critical analysis of the theories advanced to explain short REM sleep latencies and other sleep anomalies in several psychiatric conditions. J Psychiatry Res 1997;31(14):433–50.

Leysen JE, Gommeren W, Van Gompel P, Wynants J, Janssen PFM, Laduron PM. Receptor-binding properties in vitro and in vivo of ritanserin. Mol Pharmacol 1985;27:600–11.

Leysen JE, Van Gompel P, Commeren W, Woestenborghs R, Janssen PA. Down regulation of serotonin-S2 receptor sites in rat brain by chronic treatment with serotoni-S2 receptor antagonists. Psychopharmacology 1986;88:434–44.

Lighthowler S, Kennet GA, Williamson IJ, Blackburn TP, Tulloch IF. Anxiolytic-like effect of paroxetine in a rat social interaction test. Pharmacol, Biochem Behav 1994;49:281–5.

Lydic R, McCarley RW, Hobson JA. Serotonin neurons and sleep: I. Long term recordings of dorsal raphé discharge frequency and PGO waves. Arch Ital Biol 1987a;125(5):317–43.

Lydic R, McCarley RW, Hobson JA. Serotonin neurons and sleep: II. Time course of dorsal raphé discharge, PGO waves, and behavioral states. Arch Ital Biol 1987b;126:1–28.

Maes M, Mekltzer HY. The serotin hypothesis of major depression. In: Bloom FE, Kupfer DJ, editors. Psychopharmacology: the fourth generation of progress. New York: Raven Press, 1995. pp. 933–44.

Mann JJ, Stanley M, McBride PA, McEwan BS. Increased serotonin2 and beta-adrenergic receptor binding in the frontal cortices of suicide victims. Arch Gen Psychiatry 1986;43:945–59.

McKeith IG, Marshale F, Ferrier IN, Armstrong MM, Kenedy WN, Perry RH, Perry EK. 5-HT receptor binding in post-mortem brain from patients with affective disorder. J Affect Disord 1987;13:67–74.

Navarro JF, Davila G. Psychopathology and sleep-III-depression. Sicologica Conductual 1998;6(2):231–7.

Nelson DR, Thomas DR, Johnson AM. Pharmacological effects of paroxetine after repeat administration to animals. Acta Psychiatr Scand 1989; 350(80):21–3.

Peroutka SJ, Snyder SH. Long-term antidepressant treatment decreases spiroperidol-labelled serotonin receptor binding. Science 1980;210: 88–90.

Piper DC, Upton N, Smith MI, Hunter AJ. The novel brain neuropeptide, orexin-a, modulates the sleep–wake cycle of rats. Eur J Neurosci 2000; 12:726–30.

Portas CM, Thakkar M, Rainnie D, McCarley RW. Microdialysis perfusion of 8-Hydroxy-2-(Di-*n*-Propylamino)Tetralin (8-OH-DPAT) in the dorsal raphé nucleus decreases serotonin release and increases rapid eye movement sleep in the freely moving cat. J Neurosci 1996;16(8):2820–8.

Riemann D, Koing A, Hohagen F, Kiemen A, Voderholzer U, Backhaus J, Bunz J, Wesiack B, Hermle L, Berger M. How to preserve the antidepressant effect of sleep deprivation: a comparison of sleep phase delay. Eur Arch Psych Clin Neurosci 1999;249(5):231–7.

Schlosser R, Roschke J, Rossbach W, Benkert O. Conventional and spectral power analysis of all night sleep EEG after subchronic treatment with paroxetine in healthy male volunteers. Eur Neuropsychopharmacol 1998; 8(4):273–8.

Sharpley AL, Solomon RA, Fenando JM, da Rosa Davis JM, Cowen PJ. Dose-related effects of selective 5-HT_2 receptor antagonists on slow wave sleep in humans. Psychopharmacology 1990;101:568–9.

Sharpley AL, Elliot JM, Attenburrow M-J, Cowen PJ. Slow wave sleep in humans: role of 5-HT_{2A} and 5-HT_{2C} receptors. Neuropharmacology 1994;33:467–71.

Stanner L, Kempenaeras C, Simonnet MP, Fransolet L, Mendlewicz J. 5-HT_2 receptor antagonism and slow wave sleep in major depression. Acta Psychiatr Scand 1992;86:133–7.

Stanner L, Kerhofs M, Detroux D, Leyman S, Linkowski P, Mendlewicz J. Acute, subchronic and withdrawal sleep EEG changes during treatment with paroxetine and amitriptyline: a double-blind randomized trial in major depression. Sleep 1995;18(6):470–7.

Stolz JF, Marsden CA, Middlemiss DN. Effects of chronic antidepressant treatment and subsequent withdrawal on [^{3}H]-5-hydroxytryptamine and [^{3}H]spiperone binding in rat frontal cortex and serotonin receptor mediated behaviour. Psychopharmacology 1983;80:150–5.

Thase ME. Depression, sleep and antidepressants. J Clin Psychiatry 1998; 59(4):55–65.

Thase ME. Antidepressant treatment of the depressed patient with insomnia. J Clin Psychiatry 1999;60(Suppl 17):28–31.

Trivedi MH, Rush AJ, Armitage R, Gullion CM, Grannemann BD, Orsulak PJ, Roffwarg HP. Effects of fluoxetine on the polysomnogram in outpatients with major depression. Neuropsychopharmacology 1999;20(5): 447–59.

Wood MD, Reavill C, Trail B, Wilson A, Stean T, Kennett GA, Lightowler S, Blackburn TP, Thomas D, Gager TL, Riley G, Holland V, Bromidge SM, Forbes IT, Middlemiss DN. SB-243213; a selective 5-HT_{2C} receptor inverse agonist with improved anxiolytic profile: lack of tolerance and withdrawal anxiety. Neuropharmacology 2001;41:186–99.

Wright IK, Garratt JC, Marsden CA. Effects of a selective 5-HT_2 agonist, DOI on 5-HT neuronal firing in the dorsal raphé nucleus and 5-HT realease and metabolism in the frontal cortex. Br J Pharmacol 1990;99: 221–2.

Yates M, Leake A, Candy JM, Fairbrain AF, McKeith IG, Ferrier IN. 5-HT_2 changes in major depression. Biol Psychiatry 1990;27:489–96.