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SB-258741: A 5-HT$_7$ Receptor Antagonist of Potential Clinical Interest

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ABSTRACT

Recently, series of 5-HT$_7$ receptor antagonists have been developed (24,29,36,68). Among them SB-258741, *R*-(+)-1-(toluene-3-sulfonyl)-2-[2-(4-methylpiperidin-1-yl)ethyl]-pyrrolidine, (compound "13" in 36,37) was one of the most potent and specific compounds. Due to a lack of specific ligands the pharmacology of 5-HT$_7$ receptor antagonists is still relatively unexplored. It has been suggested, however, that 5-HT$_7$ receptor ligands could be useful in the therapy of various disorders such as sleep disorders, schizophrenia, depression, migraine, epilepsy, pain, or memory impairment. Many of these conceivable indications are not supported by pharmacological data. It is, therefore, of particular interest to review the data generated from studies of one of these most potent and specific 5-HT$_7$ receptor antagonists, SB-258741, with a goal of testing the validity of the proposed clinical indications. In this review, the author describes pharmacology of this compound in order to define its potential clinical use. The available safety pharmacology data are discussed in an attempt to predict potential side effects of specific 5-HT$_7$ receptor antagonists.

INTRODUCTION

SB-258741 is a potent and specific 5-HT$_7$ ligand. Recently, several series of 5-HT$_7$ receptor antagonists have been developed (24,29,36). SB-258741 (*R*-(+)-1-(toluene-3-sulfonyl)-2-[2-(4-methylpiperidin-1-yl)ethyl]-pyrrolidine) (See compound "13" in 36,37), SB-269970 ((*R*)-3-(2-(2-(4-Methylpiperidin-1-yl)-ethyl)pyrrolidine-1-sulfonyl)-

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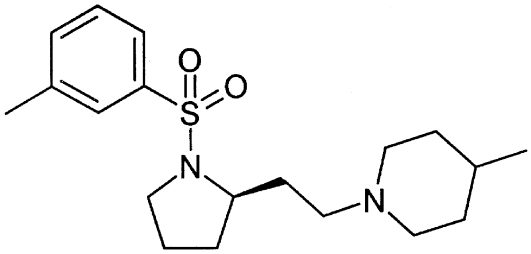

Fig. 1. Chemical structure of SB-258741.

phenol) (29,36,68), and SB-258719 ((*R*)-3,*N*-Dimethyl-*N*-[1-methyl-3-(4-methyl-piperidin-1-yl)propyl]benzenesulfonamide) (24,69), being the most potent and specific among them. The specificity of these three compounds is very similar. SB-269970 appears to be the most specific for the 5-HT_7 receptor, although it demonstrates some affinity for the 5-HT_{5A} receptor (36). SB-258741 has, however, been the subject of more intensive pharmacological investigation. As such, it is better suited to allow a more thorough examination of the potential pharmacological and clinical interest in 5-HT_7 receptor ligands (10).

The 5-HT_7 receptor is well conserved across species, and is located centrally in humans (6) and rodents (14,28,68,70,71), as well as peripherally (18). It has been suggested (see 10 for a review) that 5-HT_7 receptor ligands could be useful in the therapy of various clinical disorders, such as sleep disorders (29,38), schizophrenia (54), depression (33,61), cardio-vascular problems (65), pain (44), epilepsy (10), and migraine (67). Often these suggestions have not been supported by appropriate pharmacological studies. We demonstrated, for example, that in animal models of schizophrenia, the effects of the non-specific 5-HT_7 receptor antagonist, risperidone, were substantially different from those of the specific 5-HT_7 receptor antagonist, SB-258741 (51). Thus, the antipsychotic action of risperidone is probably not a consequence of its action at the 5-HT_7 receptor. Consequently, it is of interest to review relevant pharmacological data generated with the specific and potent 5-HT_7 receptor antagonist, SB-258741 (36). This compound is the first 5-HT_7 receptor antagonist described to be highly selective for these receptors. In this article the author reviews pharmacological findings with this compound, and attempts to relate them to the potential therapeutic efficacy. The available safety pharmacology data are discussed in an attempt to predict the potential side effects of SB-258741 and of similar specific and potent 5-HT_7 receptor antagonists.

CHEMISTRY

SB-258741, *R*-(+)-1-(Toluene-3-sulfonyl)-2-[2-(4-methylpiperidin-1-yl)ethyl]-pyrrolidine (Compound "13" in 36,37), was synthesized in the laboratories of GlaxoSmithKline Pharmaceuticals, from a SAR based on a piperidine structure. Its chemical structure is shown in Fig. 1. It has a molecular weight of 350 (base) and it is water soluble. Its empirical chemical formula is $C_{19}H_{30}N_2O_2S$.

Originally, a series of sulfonamides has been identified from a high-throughput screening (HTS) of the GlaxoSmithKline Pharmaceuticals compound bank as ligands for the cloned human 5-HT_7 receptors (37). The first HTS-identified selective 5-HT_7 receptor antagonist, SB-258719, had only a moderate affinity for the 5-HT_7 receptors (pK_i = 7.5; Table 1) (24,37). Optimization of this lead compound led to a series of compounds with a piperidine structure. SB-258741 (37) and SB-269970 (29,36,67) were among them. As compared with SB-258719, both affinity (pK_i = 8.5 and 8.9 respectively) and selectivity of these compounds improved considerably.

IN VITRO PHARMACOLOGY

As shown in Table 1, SB-258741 is a high affinity 5-HT_7 ligand with a pK_i of 8.5. It has a 200-fold selectivity over a large number of other 5-HT, dopaminergic, or adrenergic receptors (Compound "13" in 36,37). SB-258741 appears to be more selective and potent than the formerly published ligand, SB-258719 (24). It is also claimed to be more selective than SB-269970, which has high affinity for the 5-HT_{5A} receptors (36). The affinity of SB-258741 for the 5-HT_{5A} receptors was, however, not determined, so that with the respect to these receptors, these two compounds cannot be compared.

It has been suggested that 5-HT_7 receptor is an autoreceptor at 5-HT neurons, and that it potentiates 5-HT efflux (53). These claims were not confirmed, however, when the authors investigated whether SB-269970 could inhibit 5-HT efflux induced by unspecific 5-HT_7 agonist, 5-CT, or the partial agonist 8-OH-DPAT (53).

IN VIVO PHARMACOLOGY

Sleep Disorders

The suprachiasmatic nucleus (SCN) of the hypothalamus is a structure that is considered to be the primary site of regulation of the mammalian circadian clock, and is known to be under considerable control by the 5-HT system (52). The 5-HT_7 receptor is highly expressed in the SCN of the rat, giving rise to the suggestion that an antagonist of this receptor may alter the control of circadian rhythms (38,61,80). It has

TABLE 1. Receptor binding profiles and selectivity of the three leading 5-HT_7 receptor antagonists. Adapted from (24,36,37)

Ligands	5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	5-HT_{1E}	5-HT_{1F}	5-HT_{2A}	5-HT_{2B}	5-HT_{2c}	5-HT_4	5-HT_{5A}	5-HT_6	5-HT_7	α_{1b}	D_2	D_3	Selectivity
SB-258719	<5.1	<5.3	5.5	<4.8	<5.2	<4.8	<5.3	<4.8	<5.0	ND	<4.8	7.5	<4.8	5.4	5.4	100
SB-258741	6.0	5.8	5.5	<5.0	<5.0	<5.3	<5.6	<5.3	<5.0	ND	ND	8.5	<5.5	5.8	5.9	300
SB-269970	<5.0	6.0	5.8	<5.2	<5.5	<5.0	5.0	<5.0	5.9	7.2	5.2	8.9	<5.0	6.5	5.6	100

ND: No Data.

also been recently reported that the non-specific 5-HT_{1A}/5-HT_7 receptor agonist, 8-OH-DPAT, infused into the SCN of the hamster, induces phase advances in behavioral circadian phase resetting, and that this effect can be antagonized by either non-specific or specific 5-HT_7 receptor antagonists (22). Moreover, SB-269970, a 5-HT_7 receptor antagonist similar to SB-258741, has been shown to reduce the duration of paradoxical sleep in rats (29). The authors of these studies have subsequently suggested that this receptor might, therefore, control sleep, leading to the postulate that specific receptor ligands may have the capacity to effectively treat sleep disorders. Moreover, as a consequence of improvement of sleep, it has also been suggested that 5-HT_7 receptor antagonists might be useful in the treatment of depression, a mental disorder characterized by a profound alteration in sleep pattern (see below). Presently, there is a lack of preclinical and clinical investigations to support this postulate, but SB-258741 and similar compounds remain of considerable interest for the treatment of sleep disorders (37) and depression.

Schizophrenia

The localization of the 5-HT_7 receptor at the level of various limbic structures (14,28, 55,70,71,74) suggests that a ligand of this receptor might be of interest for the treatment of schizophrenia (54). Functional assays utilizing SB-258719 have shown that the 5-HT_7 receptor is positively coupled to adenylyl cyclase in the hippocampus of the guinea pig (70), a limbic structure whose dysfunction has been associated with schizophrenia (12,30).

Moreover, it is known that the 5-HT_7 receptor is targeted by several second generation antipsychotics such as clozapine, risperidone, and zotepine, and, with a lower affinity, by olanzapine and sertindole (5,21,54). However, it should be noted that not all antipsychotics have affinity for 5-HT_7 receptors (54), and that some compounds, that are devoid of antipsychotic properties, have affinity for this receptor.

In order to clarify the potential role of specific 5-HT_7 receptor antagonists in the treatment of schizophrenia, we tested SB-258741 in three animal models (51) related to the positive (and negative) symptoms of schizophrenia, and which are considered predictive of antipsychotic action. We used *d*-amphetamine-induced hyperactivity (3,4), and *d*-amphetamine- (23,47) or phencyclidine- (PCP) (7,8,39,78) antagonized prepulse inhibition (PPI) in the models in rats. We also tested this compound in a putative model for negative symptoms, PCP-disrupted social interaction (SIT) in rats (19,56–58). Induction of side effects by this compound was evaluated by testing its potency to reduce spontaneous motility, and to induce catalepsy in rats (2). SB-258741 had a significant effect in two models: *d*-amphetamine-induced hyperactivity in rats, and PCP-disrupted PPI. However, in both cases this effect might be a consequence of a modification of locomotor activity induced by SB-258741. SB-258741 dose-dependently antagonized *d*-amphetamine-induced hyperactivity, but also reduced spontaneous activity of rats at similar doses. Consequently, the effect of SB-258741 in this model is inconclusive. SB-258741 also dose-dependently normalized the effect of PCP in PCP-disrupted PPI in rats. However, SB-258741 also normalized the reduction of startle amplitude induced by PCP. This means that the positive effect of SB-258741 in this model is probably not related to a sensory gating process (64). Consequently, the beneficial effect of SB-258741 in the PCP-disrupted PPI model should be viewed with caution; it seems difficult to predict an antipsychotic action for SB-258741 based on the activity in this model (51). In *d*-amphetamine-disrupted PPI, SB-258741 did not reverse the effect of *d*-amphetamine. Thus, ac-

cording to the results obtained in these three models, the probability that SB-258741 alone can be effective in the treatment of positive symptoms in schizophrenic patients, seems low. In the model indicative of an effect on negative symptoms of schizophrenia, i.e. PCP-disrupted SIT in rats, SB-258741 had no beneficial effect. It even enhanced the disruptive effect of PCP on active social interaction instead of reducing it. At doses tested SB-258741 did not induce any sign of catalepsy.

We cannot exclude the possibility that a combination of a 5-HT_7 receptor antagonist and dopamine or an antagonist of another 5-HT receptor subtype would change the pattern of results obtained in models predictive of antipsychotic action or models predictive of side effects. We tested, therefore, SB-258741 in combination with the dopaminergic D_2 receptor antagonist remoxipride, and with the 5-HT_{2A} receptor antagonist, MDL-100151, in another model predictive of antipsychotic action, PCP-induced hyperactivity in mice (27). We did not find any enhancement of the beneficial effect of these two compounds by SB-258741 (H. Lundbeck A/S; unpublished data). These findings suggested that we should not expect any antipsychotic action with SB-258741.

Depression

It has been proposed that the 5-HT_7 receptor may be involved in the pathophysiology of depression (33,61). This hypothesis has been based on various studies. Measurement of c–Fos expression in the hypothalamus after acute treatment with antidepressants, and its inhibition by a non-specific 5-HT_7 receptor antagonist (33), led the authors to suggest that the 5-HT_7 receptor is implicated in the mechanism of action of antidepressants. Moreover, the 5-HT_7 receptor is targeted by several antidepressants, like mianserin or amitriptyline (21,45,62). The treatment of rats with fluoxetine (5 mg/kg/day, p.o.) for 21 days reduced the number of hypothalamic 5-HT_7 receptor binding sites. This result led the authors to suggest that hypothalamically-expressed 5-HT_7 receptor is downregulated as a result of chronic elevation of synaptic 5-HT (63). This hypothesis would support an antidepressant effect for a 5-HT_7 receptor antagonist. It has also been suggested that in the hippocampus, the 5-HT_7 receptor is under the inhibitory regulation of circulating adrenal steroids (32,79). This would indicate that the 5-HT_7 receptor is to some degree dependent upon the activity of the hypothalamic-pituitary-adrenocortical (HPA) axis, an axis that is widely acknowledged to be involved in the etiology of depression (9). Finally, this receptor has been implicated in the regulation of circadian rhythms (38). This finding further supports the hypothesis that 5-HT_7 receptor antagonists may be useful potential antidepressants, since disturbance of circadian rhythmicity is one of the recognized core symptoms of clinical depression (DMSIV) (31,61,77). However, no preclinical study supporting this hypothesis has been published with a specific 5-HT_7 receptor antagonist in a validated animal model for depression.

In this context, it has been reported that by intracerebroventricular (i.c.v.) administration 5-HT_7 antisense oligonucleotide does not affect exploratory or locomotor activity of rodents in the elevated plus-maze model (a predictive model for antidepressants/anxiolytics) (16). Moreover, preliminary investigations performed in our laboratories with SB-258741 in a set of models predictive of antidepressant-like or anxiolytic-like effects [reduced vocalization in rats (59,72), and forced-swimming test in mice (49,50)], did not demonstrate a robust antidepressant property of this compound (H. Lundbeck A/S; unpublished data). On the other hand, SB-258741, at 2.3 mg/kg s.c., significantly inhibited

isolation-induced aggressive behavior in mice (42). This effect was observed at 30 min, but not at 2 h after pretreatment (H. Lundbeck A/S; unpublished data). The lack of information on pharmacokinetic properties of SB-258741 prevented any firm conclusion regarding the therapeutic potential of this compound. However, the results may be explained by only a weak effect of this 5-HT_7 receptor antagonist in this model.

In conclusion, the results of our own studies together with the results reported in the literature, suggest that SB-258741 may have weak antidepressant, antiaggressive and/or anxiolytic effects, but that further studies are needed to confirm this.

Vascular Effects

Since 5-HT_7 receptor is expressed in adrenal glomerulosa of rats, it could be expected that a 5-HT_7 receptor antagonist might also have peripheral effects (18). Since the *zona glomerulosa* is the layer of adrenal cortex that is specifically involved in the synthesis of mineralocorticoids such as aldosterone, it is reasonable to expect that 5-HT_7 receptor antagonists may interfere in some way with the synthesis and/or release of this steroid hormone. Altered synthesis and metabolism of aldosterone in the clinic is associated with a variety of pathological symptoms, including changes in the Na^+ and/or K^+ excretion (1), which can alter osmoregulation and produce concomitant cardiovascular abnormalities (73). In addition, 5-HT_7 receptor is known to be expressed in the vascular smooth muscle (21,34,60,75). The non-specific 5-HT_7 receptor antagonists are known to antagonize the relaxing effect of 5-HT or 5-CT (20,65,67) suggesting a regulatory role in vasoconstriction. It has been subsequently postulated that this receptor could be an appropriate target for the treatment of migraine (66,67,76) or heart disease (65). The localization of this receptor in the brain as well as in the periphery suggests that a beneficial central vasoconstrictor effect of a 5-HT_7 receptor antagonist could be associated with peripheral side effects (see below).

Pain

The dorsal root ganglion is a relay for transmission of nociception (41). The 5-HT system has been shown to be involved in the nociceptive activity of this structure and ascending pain pathways (11,41). Consequently, SB-258741 could also be of interest as an analgesic due to the localization of the 5-HT_7 mRNA receptor in the dorsal root ganglion in rats or humans (44,48). However, this hypothesis has, until now, never been confirmed or contradicted in relevant animal models or clinical observations.

Epilepsy

Non-selective 5-HT_7 receptor antagonists were shown to protect DBA/2J mice from intense auditory stimulation-induced seizures (13). These data suggest that antagonism of 5-HT_7 receptors may protect against audiogenic seizures (13), and it has been speculated that 5-HT_7 receptor antagonists could be used for treatment of epilepsy (10). However, preliminary studies performed in our laboratories with SB-258741, at doses up to 9 mg/kg s.c., using the maximal electroshock (15) and pentetrazole (PTZ) (15,46) models in mice, did not demonstrate any beneficial effect of this compound in these models (H. Lundbeck

A/S; unpublished data). Consequently, on the basis of our investigations, we do not believe that SB-258741 should be expected to be of interest in treatment of epilepsy.

Cognition

Based on a study with non-specific ligands, it has been suggested that the 5-HT_7 receptor could be involved in memory consolidation processes (43). These authors claimed that blockade of this receptor may be beneficial "in reversing learning deficits associated with decreased cholinergic and/or glutamatergic neurotransmission". Thus, a 5-HT_7 receptor antagonist might be of interest in the treatment of cognitive dysfunction. In our own studies, we observed that SB-258741 normalized PCP-disrupted PPI in rats (51). Although the PPI model is not considered to be a classic model of cognition, there is no doubt that SB-258741 normalized some aspects of the dysfunction induced by PCP. It can, therefore, be hypothesized that, SB-258741 could reverse "cognitive dysfunction" associated with glutamatergic hypofunction. To confirm this hypothesis, it would be of interest to test SB-258741 or similar compounds, against scopolamine or a NMDA receptor antagonist, in an appropriate model of cognitive function.

SAFETY PHARMACOLOGY

No toxicological studies have been published with SB-258741 or any other specific 5-HT_7 receptor antagonist. However, the localization of the 5-HT_7 receptor in the arteries and veins (21,34,60,65,75), along with studies discussed earlier suggests that vascular side effects may be associated with administration of the 5-HT_7 receptor antagonists. In addition, it has been suggested that the 5-HT_7 receptor may serve to modulate the direct vasoconstrictor effects of the 5-$HT_{1B/1D}$ and 5-HT_{2A} receptor (75). To date, no appropriate cardiovascular safety studies have been published with regards SB-258741 or similarly specific ligands. Nevertheless, it has been suggested that the 5-HT_7 receptor could directly or indirectly regulates cardiac rhythmicity (76).

CLINICAL POTENTIAL

The original patent (25) covering SB-258741, as well as patents covering other selective 5-HT_7 receptor antagonists (26,35), claimed SB-258741 as a treatment of schizophrenia, sleep disorders, depression, and, more generally, CNS disorders. With respect to schizophrenia, the preclinical studies performed in our laboratories (51) suggest that SB-258741, or compounds with a similar receptor profile, will not have antipsychotic action in the clinic. We can not, however, exclude the possibility that SB-258741 might enhance the antipsychotic action of compounds with a specific affinity for other 5-HT or dopaminergic receptors. This conceivable add-on effect of SB-258741 in the treatment of schizophrenia was not supported, however, by a preliminary study conducted in our laboratory. When tested in combination with the dopamine D_2 receptor antagonist, remo-

xipride, or the 5-HT_{2A} receptor antagonist, MDL-100151, in a model predictive of antipsychotic efficacy, SB-258741 did not enhance beneficial effects of either of these two drugs. Consequently, the clinical antipsychotic potential of SB-258741 is not very strong.

According to the recent literature on the role of the 5-HT_7 receptor in the regulation of circadian rhythmicity, the indication for SB-258741 in the treatment of sleep disorders appears to be promising. Moreover, the recently discovered 5-HT_7 receptor antagonist, SB-269970, has been shown to reduce the duration of paradoxical sleep (REM) in rats (29). These authors have subsequently suggested that this ligand might be useful in the clinical control of sleep. However, there is still a lack of clinical trials with SB-258741, or similar compounds, in the treatment of sleep disorders.

With respect to the use of SB-258741 in the treatment of depression, there is no relevant preclinical or clinical data to support this claim. The interest in a 5-HT_7 receptor antagonist in the treatment of depression is predominantly associated with the finding that this receptor has been implicated in the regulation of circadian rhythms (38). As we have discussed above, disturbance of circadian rhythms and sleep patterns are commonly observed in depressed patients as well as in patients suffering from anxiety (31,61,77). It is entirely feasible that SB-258741 or similar compounds might prove beneficial in amelioration of the symptoms of depression as a consequence of improving sleep, and not by directly addressing the major underlying etiologies of the depressive disorder itself. This could, nevertheless, be claimed as an important treatment paradigm in depression, especially when considering the evidence that various treatments known to selectively and specifically affect sleep pattern (such as sleep deprivation) are at least acutely antidepressant (17,40). It can be concluded, therefore, that clinical studies with SB-258741 and/or other 5-HT_7 antagonists in the treatment of depression are warranted.

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