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SGS742: the first $GABA_B$ receptor antagonist in clinical trials

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Abstract

The $GABA_B$ receptor antagonist SGS742 (CGP36742) displays pronounced cognition enhancing effects in mice, young and old rats and in *Rhesus* monkeys in active and passive avoidance paradigms, in an eight-arm radial maze and a Morris water maze and in a social learning task. SGS742 blocks the late inhibitory postsynaptic potential and the paired-pulse inhibition of population spikes recorded from CA1 pyramidal neurons of the hippocampus of rats in vitro and in vivo. SGS742 significantly enhances the release of glutamate, aspartate, glycine and somatostatin in vivo. Chronic administration of SGS742 causes an up-regulation of $GABA_B$ receptors in the frontal cortex of rats. Single doses cause a significant enhancement of the mRNA and protein levels of NGF and BDNF in the cortex and hippocampus of rats. The observed antidepressant effects of SGS742 in rats may be explained by these findings.

SGS742 was well tolerated in experimental animals as well as in young and elderly human volunteers with an absolute bioavailability in humans of 44%.

In a Phase II double-blind, placebo-controlled study in 110 patients with mild cognitive impairment (MCI), oral administration of SGS742 at a dose of 600 mg t.i.d. for 8 weeks significantly improved attention, in particular choice reaction time and visual information processing as well as working memory measured as pattern recognition speed. A second Phase II clinical trial in 280 Alzheimer's disease patients is underway.

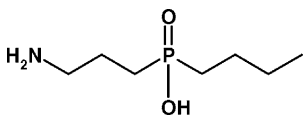
Keywords: $GABA_B$; Alzheimer's disease; Mild cognitive impairment

1. Introduction

Several $GABA_B$ receptor antagonists have been found to improve cognitive performance in a variety of animal models, such as the low affinity compounds, CGP35348 and CGP36742 (SGS742) or the high affinity compounds CGP55845A, CGP56433A, CGP61334, CGP62349 and CGP71872 (for a comprehensive review see [1]). Here we review the preclinical findings on SGS742 and present first results of a clinical trial in patients afflicted with mild cognitive impairment (MCI).

2. Material

SGS742 is 3-aminopropyl-*n*-butyl phosphinic acid, an achiral molecule, with molecular weight of 179.19 of the following structure:



The compound was synthesized in large scale at IRIX Pharmaceuticals.

3. Characterization of SGS742 in vitro

3.1. Selectivity of interactions with $GABA_B$ receptors

SGS742 interacts with $GABA_B$ receptors with IC_{50} of 38 μM (inhibition of binding of [^{3}H]CGP27492 to $GABA_B$

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receptors of rat cortex membranes [2]), with IC_{50} of 62 μM with $GABA_C$ receptors (inhibition of the response of 1 μM GABA using human ρ1 mRNA expressed in *Xenopus* oocytes [3]) and with IC_{50} of 508 μM with $GABA_A$ receptors (inhibition of binding of [^{3}H]muscimol to rat brain membranes measured according to [4]). It does not interact with 18 other receptors present in the CNS at a concentration of 1 mM (receptors: benzodiazepine, muscarinic acetylcholine (CMD and QNB), alpha$_1$-, alpha$_2$- and beta-adrenergic, 5HT$_1$, 5HT$_2$, 5HT$_3$, histamine$_1$, histamine$_2$, adenosine$_1$, μ-opiate, NMDA, glycine, quisqualate, kainate and NK1; [2]).

3.2. Antagonism at $GABA_B$ receptors

This was shown in the following electrophysiological experiment.

Hippocampal slices from adult male Sprague–Dawley rats were superfused at 33 °C with gassed artificial cerebrospinal fluid. Penicillin-induced epileptic-like discharges were strongly and reversibly depressed by 6 μM baclofen. SGS742 antagonizes the depressant action of 6 μM baclofen at concentrations of 10 μM by about 50%, and 100 μM by about 100% (Fig. 1).

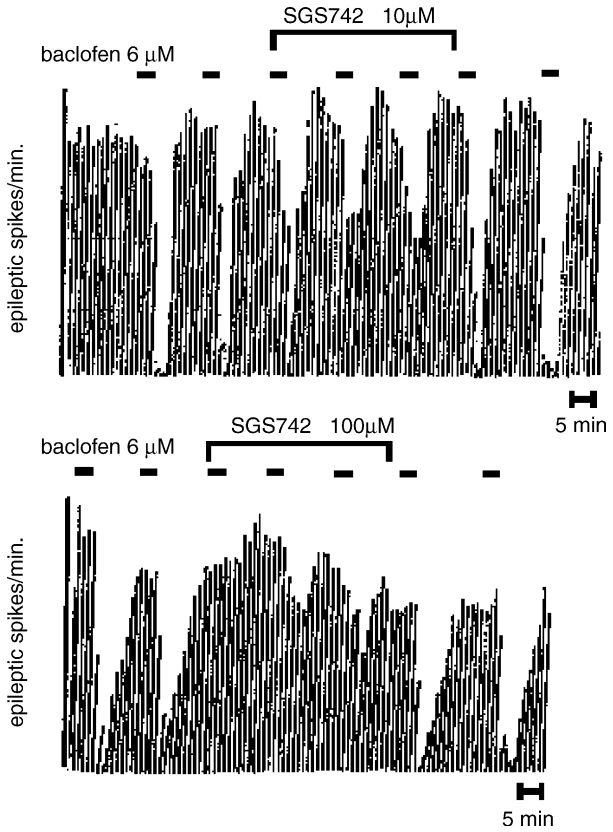

Fig. 1. The depressant action of 6 μM baclofen on penicillin-induced epileptic-like discharges in hippocampal slices is reversibly reduced by 10 and 100 μM of SGS742. Baclofen and SGS742 were bath-applied.

3.3. Effects at postsynaptic $GABA_B$ receptors

Postsynaptic $GABA_B$ receptors activate inwardly rectifying Kir3 potassium channels. Stimulation of Schaffer collateral/commissural fibers evoked the late inhibitory postsynaptic potential. SGS742 reduced the late i.p.s.p. at a threshold concentration of 10 μM and effects a full blockade at 1 mM [5].

3.4. Effects at presynaptic $GABA_B$ receptors

Activation of presynaptic $GABA_B$ receptors causes an inhibition of neurotransmitter release from both inhibitory and excitatory terminals. SGS742 enhanced the release of GABA in electrically stimulated rat cerebral cortex slices. The EC_{150} (concentration, which caused a 50% increase of GABA release) was 38 μM ([2]).

The separate populations of presynaptic receptors can be activated by endogenously released GABA. The level of activation of each population, however, critically depends upon the pattern of afferent input. As a result activation of presynaptic $GABA_B$ receptors strongly influences the balance of excitatory to inhibitory synaptic input and thereby the excitability of the postsynaptic neuron. In this respect paired-pulse stimulation causes an increase in the duration of the second field excitatory postsynaptic potential (fEPSP) relative to the first fEPSP and this effect was abolished by the $GABA_B$ receptor antagonist SGS742 (30–300 μM; Fig. 2) [6].

SGS742 antagonized the (−)-baclofen-induced inhibition of the release of somatostatin evoked by K^+-depolarization of synaptosomes from rat cerebral cortex with an IC_{50} of 0.14 μM. The effect of 10 μM of (−)-baclofen was completely prevented by 3 μM of SGS742 [7]. It appears that disinhibition of somatostatin release is mediated by the sst5 subtype of somatostatin receptors [8]. SGS742 increased the basal outflow of [^{125}I]somatostatin from hippocampal synaptosomes with an EC_{50} value of 0.2 μM [9].

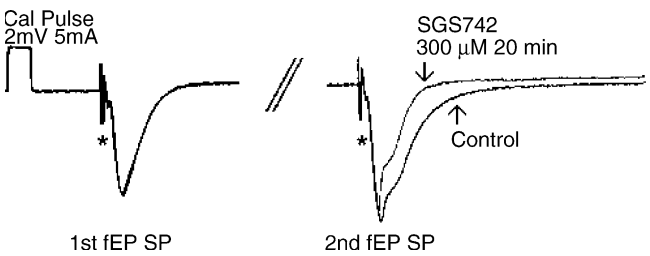

Fig. 2. $GABA_B$ receptor antagonists like SGS742 reverse paired-pulse depression. Field EPSPs (fEPSP) were recorded in the *stratum radiatum* of area CA1 in hippocampal slices. Pairs of fEPSP (first fEPSP and second fEPSP) were evoked stimulating the Schaffer collateral/commissural pathway with an inter-stimulus interval of 200 ms. In the control situation the fEPSP following the second pulse is much longer relative to the first fEPSP. SGS742 (300 μM) abolished this effect. The point of each stimulus is indicated with an asterisk.

4. Characterization of SGS742 in vivo

4.1. Antagonism at $GABA_B$ receptors

When baclofen was administered iontophoretically near spontaneously active cortical neurons in chloral hydrate-anaesthetized rats, it induced a transient but pronounced firing depression. SGS742 partially reduced this depressant effect at 10 mg/kg i.v. and completely reduced the effect at 30 mg/kg i.v. In experiments where GABA and baclofen were administered alternately, SGS742 did not antagonize the effects of GABA, because the latter were mostly $GABA_A$ receptor mediated, as has been shown earlier in experiments using the $GABA_A$ receptor antagonist bicuculline methiodide [23] (Fig. 3).

4.2. Up-regulation of $GABA_B$ receptors

Chronic administration of SGS742, 100 mg/kg i.p. once daily for 21 days, caused an increase of $GABA_B$ receptor binding in the outer laminar region of the frontal cortex by 55% [10].

4.3. Effects at presynaptic $GABA_B$ receptors

Population spikes of CA1 pyramidal neurons were induced in chloral hydrate anaesthetized rats by stimulation of the Schaffer collateral/commissural fibers. SGS742 dose dependently reduced paired-pulse inhibition. Pronounced effects were seen at a dose of 10 mg/kg i.v. at interstimulus intervals of 150–170 ms [6].

When a solution of 1 mM of SGS742 in ACSF was dialyzed into the ventrobasal thalamus of freely moving rats a two- to three-fold increase of extracellular glutamate, aspartate and glycine was observed after 20 and 60 min due to influx of transmembrane Ca^{2+} ions [11].

Local application of 5 mM of SGS742 via the microdialysis probe to the hippocampus of halothane-anaesthetized rats increased the extracellular concentration of somatostatin by 150% in the hippocampus 200 min after drug application [9].

4.4. Facilitation of memory

Increased release of the excitatory neurotransmitters L-glutamate and aspartate, suppression of the late inhibitory postsynaptic potential, facilitation of the induction of LTP (which was shown with the prototypical $GABA_B$ receptor antagonist CGP 35348 in vitro and in vivo [12]) may lead to an amplification of neurotransmission and to improved signal processing in the brain and could produce positive effects on cognitive functions after treatment with $GABA_B$ receptor antagonists. This hypothesis was confirmed in several experiments showing improvement of different aspects of learning and memory functions in experimental animals.

4.4.1. Facilitation of memory in mice

When administered orally 60 min before the learning trial SGS742 at doses between 1 and 100 mg/kg improved retention performance of mice after a retention interval of 24 h in a passive avoidance paradigm [13]. At lower doses, a trend but no significant effects were observed (Fig. 4, upper panel). The duration of action is at least 5 h: when administered 5 h before the learning trial SGS742 at doses of 0.3, 3 and 30 mg/kg p.o. significantly improved retention performance of mice 24 h later (data not shown).

The processes of memorization are thought to outlast the training experience, i.e. the fixation process continues after the termination of the learning experience. Hence, memorization can be affected by drugs even if they are administered immediately after the learning trial (''post-trial''). SGS742 at doses of 0.3, 3 and 30 mg/kg i.p., given within 10 s after the learning trial, significantly improved retention performance of mice 24 h later under such conditions (Fig. 4, lower panel). The memory-enhancing effects of a

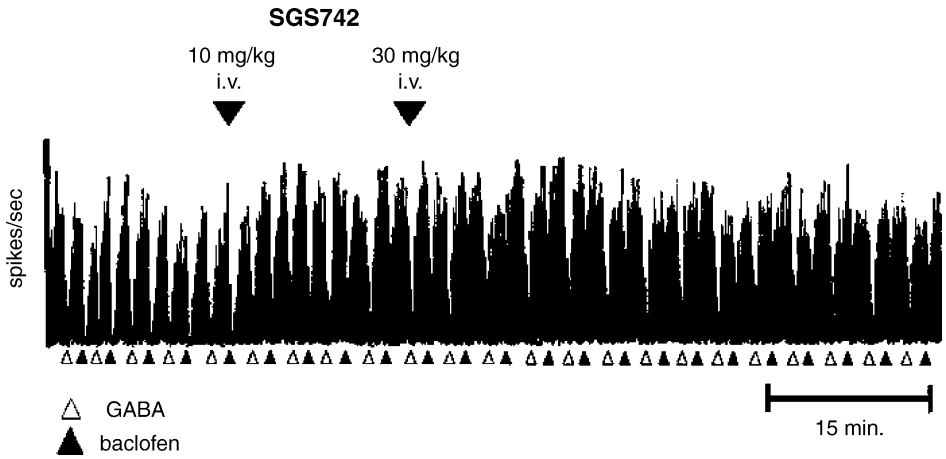

Fig. 3. Intravenously applied SGS742 antagonized the depressant effects of iontophoretically applied baclofen on cortical neurons in vivo. The drug did not antagonize the effects of GABA.

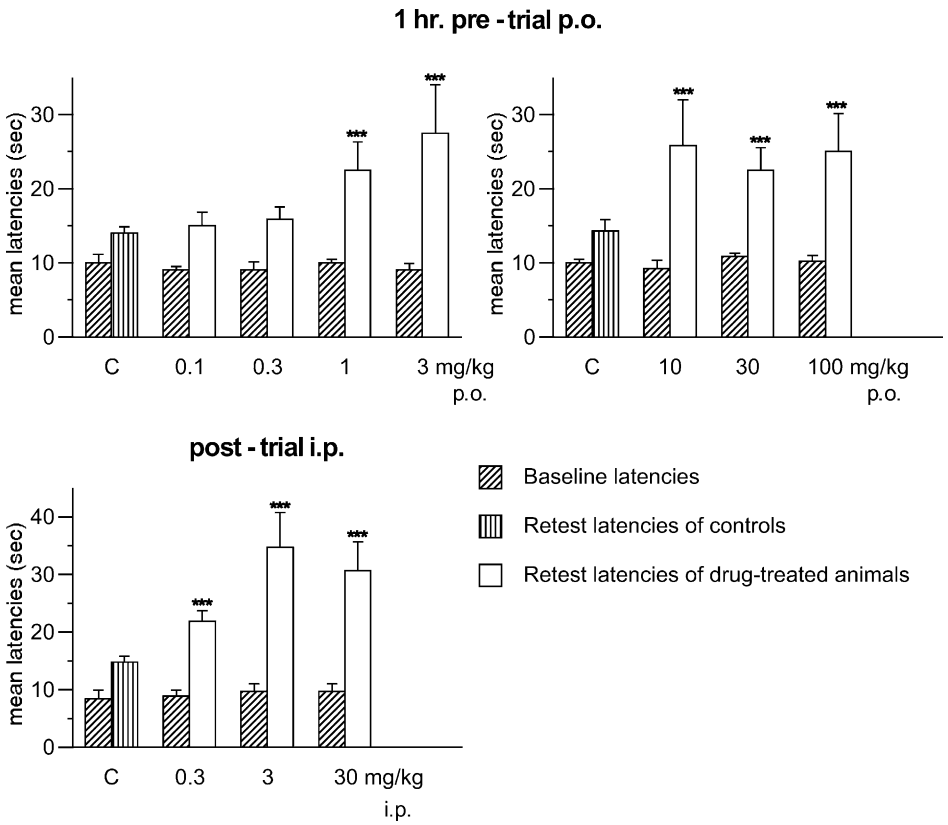

Fig. 4. Step-down passive avoidance (data from three independent experiments). SGS742 administered orally 60 min before (upper panel) or i.p. immediately after the learning trial (lower panel). Histograms depict the mean baseline and retest latencies (±S.E.M.) of pre-experimental and control groups. Longer retest latencies indicate better learning ($N = 25$/group). $^{***}P < 0.001$; generalized two-tailed Wilcoxon test (reproduced from [13] with permission from Elsevier).

single treatment with 10 mg/kg i.p. of SGS742 given immediately after a learning experience remain detectable for at least 4 months thereafter indicating facilitation of the formation of long-term memory traces [14].

The memory enhancing effect of 30 mg/kg p.o. SGS742 was counteracted by pretreatment with 3 mg/kg p.o. (but not 0.3 or 1 mg/kg) of the $GABA_B$ receptor agonist (±)-baclofen in the step-down passive avoidance paradigm in mice. This strongly suggests that the memory facilitation induced by SGS742 is mediated by $GABA_B$ receptors (Fig. 5).

Memory facilitation could also be observed in an eight-arm radial maze task in male CD1 mice (8 per group) tested on each of 10 consecutive days after i.p. administration of 10 and 100 mg/kg, but not of 1 mg/kg of SGS742. They displayed significantly enhanced performance by 17–34 and 20–31%, $P < 0.05$, respectively, in comparison to control animals 5–10 days after commencement of the study. By contrast, 2 and 4 mg/kg i.p. of (−)-baclofen induced a significant impairment of performance (by 16–20 and 20–30%, $P < 0.05$, respectively). This depressant effect was completely reversed by pretreatment (15 min before) with SGS742. At 2 and 4 mg/kg i.p. (−)-baclofen did not produce a significant muscle relaxant effect, which may have contributed to its apparent amnesic action [15].

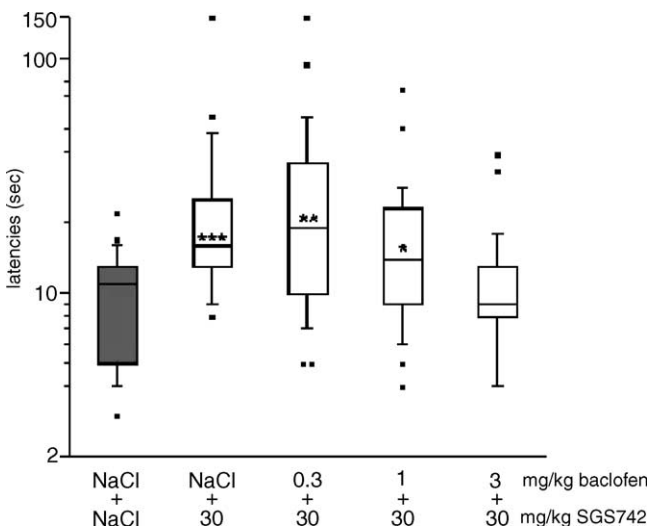

Fig. 5. The effects of (±)-baclofen on memory facilitation induced by 30 mg/kg p.o. SGS742. (±)-baclofen at doses of 0.3, 1 or 3 mg/kg p.o. was administered 2 h before the learning trial, SGS742 (30 mg/kg p.o.) 1 h thereafter, i.e. 1 h before the learning trial. The boxplots indicate the retest latencies of the various experimental and the control groups after a retention interval of 24 h. Dark gray box: saline treated control; light gray box: treated with 30 mg/kg p.o. SGS742; open boxes: groups receiving 0.3, 1 or 3 mg/kg p.o. (±)-baclofen prior to SGS742. Higher latencies are indicative of better learning ($N = 25$/group). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs. saline-treated controls (Mann–Whitney U-test, two tailed).

4.4.2. Facilitation of memory in young and old rats

SGS742 at doses of 10 and 30 mg/kg p.o. significantly attenuated the baclofen- and scopolamine-induced deficits in a Morris water maze task in rats. Rats were given four training trials per day with a submerged platform at a fixed location in the maze for 4 days. On day 4, the rats were required to swim in the pool without the platform after the fourth training trial. Intaperitoneal injection of baclofen (4 mg/kg) or scopolamine (0.3 mg/kg) significantly increased the escape latency to reach the platform and decreased the duration in the quadrant where the platform had been originally located [16].

In a social learning paradigm in rats, treatment with SGS742 facilitated recollection of an already encountered partner. A dose of 3 mg/kg p.o. of SGS742 1 h before the first meeting with a partner shortened the time spent in scrutinizing the partner at a second meeting 24 h later. No curtailment was observed if a new partner is presented [13,17] (Fig. 6).

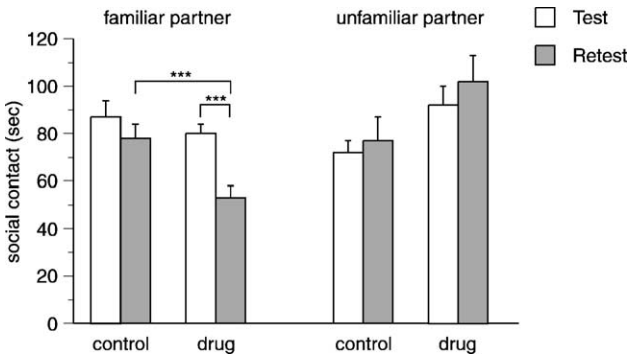

Fig. 6. The effects of SGS742 (3 mg/kg p.o.) on social learning in rats. Pairs of adult (age 3 months) and juvenile (age 4 weeks) animals were used. The duration of the active approach response of the adult animal was recorded during a baseline period on day 1 and a retest period 24 h later. The compound was given orally 1 h before the first encounter. The histograms represent the cumulative mean duration of scrutiny (in seconds) during the 5-min baseline test and retest observation periods. Left panel: encounter with the familiar partner. Right panel: encounter with an unfamiliar partner. Shorter scrutiny indicates better memory. $N = 20$ rats/group. $^{***}P < 0.001$, Student's t-test. (reproduced from [13] with permission from Elsevier).

In an active avoidance paradigm with negative reinforcement Wistar rats treated with saline made more escapes on the fifth day than on day 1. Rats treated with 100 mg/kg i.p. of SGS742 made fewer escapes on the third, fourth and fifth days ($P < 0.05$) compared to saline-treated control animals. In Genetic Absence Epilepsy Rats of Strasbourg (GAERS) SGS742 treated animals made significantly fewer escapes on days 2 ($P < 0.05$), 3, 4, and 5 ($P < 0.01$) compared with the saline group [18].

Similarly to humans a decline of the ability to acquire and to make use of information can be observed in aging animals. Aged rats show a marked loss of the ability to "learn", i.e. to perform tasks that require retention. SGS742 at daily doses of 0.3, 3 and 30 mg/kg p.o. improved learning performance of 27 months old rats in a multiple trial one-way active avoidance test: the animals always had to jump from compartment A to compartment B in order to avoid a foot shock in compartment A. If after a number of trials (two trials per day) reaching criterion (five consecutive avoidances), aged rats are placed in the safe compartment B (passive avoidance test), they are very likely to jump to compartment A, i.e. to perform the acquired reaction ("reaction learning"). In contrast, young animals tend to remain in compartment B, remembering that compartment B is safe; they show "place-learning". Aged rats, daily treated with SGS742, behaved like young rats: if being put directly into the safe compartment, they displayed place-learning (Fig. 7).

4.4.3. Facilitation of memory in Rhesus monkeys

In a series of tasks of increasing complexity, Rhesus monkeys had to learn that a reward of peanuts was concealed under one out of three beakers depending on its color and position. A yellow beaker contained the reward only if it was in the middle, a blue one only if it was on the right, and a red one only if it was on the left. At each daily session, the monkey had 16 chances to earn its reward. As soon as it had scored 12 out of 16 correct choices, the degree of complexity of the task was raised. Five degrees of difficulty were used. If no signs of improvement were evident after five sessions at a given level of complexity, the experiment was stopped.

One series lasted 14 days at the most. In total, three series were carried out. Each series was followed by a wash-out period of 2 weeks. In each of the three series the same procedure was followed, with one exception: in the second series the colors of the beakers were changed to brown, green and orange, and in the third black beakers with white markings (cross, circle, stripes) were used. In each series the animals were randomly divided into two groups. One hour before each session SGS742 (0.5 mg/kg) or placebo (milk powder) was administered orally in capsules. When the scores attained by the individual monkeys under the influence of the drug and placebo where ranked, it emerged clearly that they performed best after treatment with the drug (Fig. 8). These data bear out the assumption that SGS742 has positive effects on cognitive functions [13].

4.5. Potential antidepressant effects of SGS742

Rats were treated with 100 mg/kg i.p. of SGS742 once daily for 14 days. On day 14 the rats were subjected to 90 inescapable electrical shocks (1 mA) of 10 s duration with a 2 s inter-shock interval. On day 15 the rats received a 40-trial escape test. The inescapable shocks increased escape failures in the escape test. SGS742 significantly improved the escape failures. Baclofen (4 mg/kg i.p.) attenuated the escape failures, improving effect of SGS742 [19].

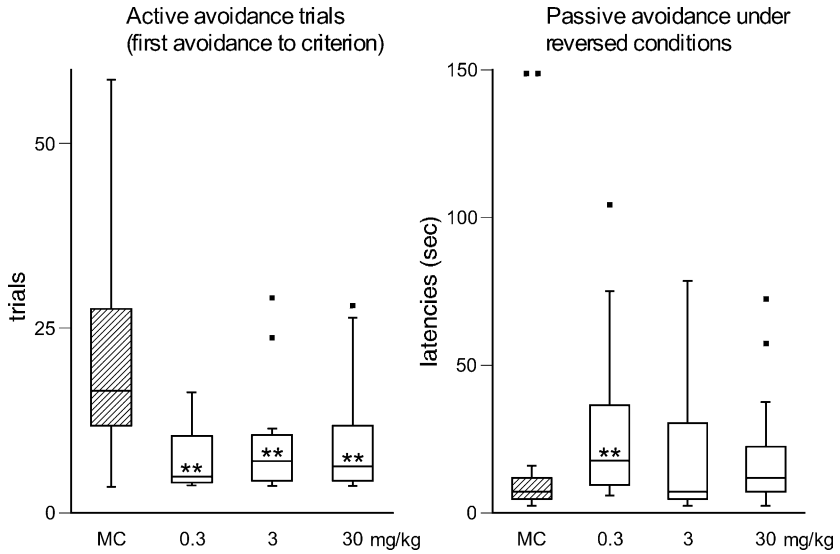

Fig. 7. Active and passive avoidance in 27 months old rats. The boxplots on the left panel depict the number of trials needed to reach the criterion of five consecutive active avoidances (fewer trials indicate better learning). After meeting the criterion of five consecutive active-avoidance reactions, the animals were placed directly into the safe compartment. The boxplots on the right panel represent the step-through latencies, i.e. the time before the animals enter the "dangerous" compartment A. Higher latencies (in comparison with vehicle-treated controls) indicate better memory. MC: methocel-treated controls. $N = 13$–15 animals/group. $^{**}P < 0.01$ (Mann–Whitney U-test, one tailed).

4.6. Effects on the release of NGF and BDNF

A single dose of 600 mg/kg i.p. of SGS742 was administered to GAERS and the levels of NGF and BDNF mRNA were measured after 6 and 24 h in cortex, hippocampus and spinal cord (Fig. 9). The NGF mRNA level rose to ~ 200% in cortex and spinal cord after 6 h. The levels of BDNF mRNA rose to ~270% in hippocampus after 6 h and 24 h. The increase of BDNF mRNA in spinal cord amounted to ~200% after 24 h. With the high affinity $GABA_B$ receptor antagonist CGP56999A, a single dose of 1 mg/kg i.p. elicited increases of NGF and BDNF proteins exceeding 200%. Peak values were reached after 72 h [20].

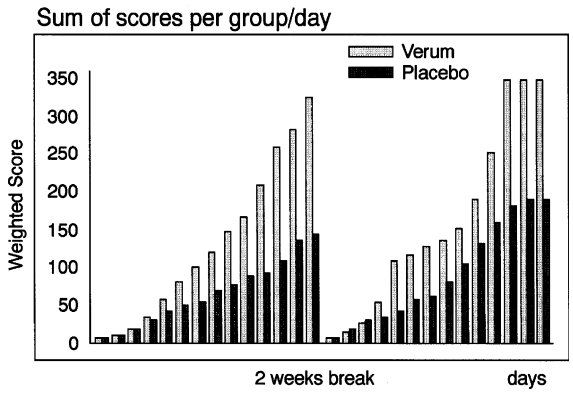

Fig. 8. Learning of increasingly complex tasks over 2 weeks in 20 Rhesus monkeys treated once daily with a dose of 0.5 mg/kg of SGS742. After a 2 weeks washout a crossover was implemented and treatment continued in the two groups for additional 2 weeks.

5. ADME studies in animals

Absorption and distribution studies were performed in rats (30 mg/kg i.v. and 30–2000 mg/kg p.o.) and dogs (30 mg/kg i.v. and 30–600 mg/kg p.o.). Orally administered drug was incompletely absorbed, but the absorbed fraction was completely bioavailable. Absorption in dogs was higher than in rats (29–53% versus 12–31%, respectively) [21]. Orally administered SGS742 was absorbed rapidly with little accumulation. Among all species tested, peak plasma concentrations were generally reached within 1–4 h after doses of up to 2000 mg/kg. Repeated administration of SGS742 for up to 3 months did not affect the drug's pharmacokinetic parameters. SGS742 was rapidly distributed throughout the body. Five minutes after intravenous administration, concentrations of SGS742 in most organs and tissues except kidney were lower than that in plasma. The lowest levels were found in the brain. A qualitatively similar pattern was seen with oral dosing.

The drug was rapidly eliminated from the body. Twenty-four hours after oral dosing concentrations of SGS742 in all tissues examined were <1 nmol/g. Levels of drug in tissues of rats that were repeatedly dosed (30 mg/kg p.o. × 10 days) were two to three times higher than when measured 24 h after a single oral dose. Levels in the brain were slightly more pronounced than those in plasma. This higher accumulation could reflect a slow passage of the compound across the blood–brain barrier [21].

SGS742 is apparently not metabolized, as the fraction of the dose absorbed was excreted almost exclusively in the urine as unchanged compound. The bulk of the absorbed dose was recovered within 8–24 h in rats and within 24–

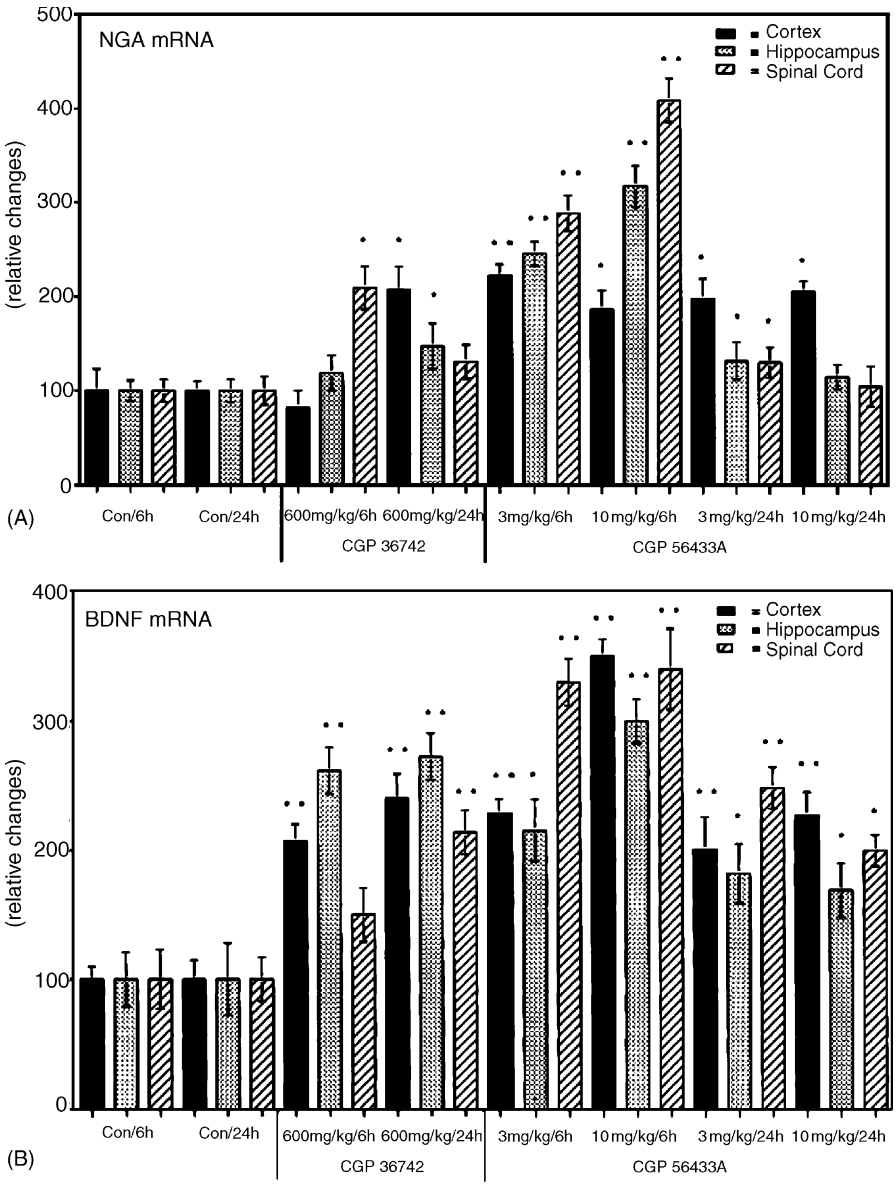

Fig. 9. CGP36742 (SGS742) and CGP56433A-elicited increases in NGF mRNA (A) and BDNF mRNA (B) in cortex, hippocampus and spinal cord of adult male rats. Rats were decapitated at the indicated times after single i.p. injections of 600 mg/kg of SGS742 or 3 or 10 mg/kg of CGP56433A. The amount of NGF and BDNF mRNA was estimated by Northern blot hybridization analysis. Arbitrary units were calculated as described. The values for control rats at the two time points (6 and 24 h) were set equal to 100% and experimental data are expressed as relative changes. Data are the mean ± S.E.M.; $N = 4$ for each group. Con: controls. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. the respective control groups (ANOVA) (reproduced from [20] with permission from Elsevier and the principal investigator).

48 h in dogs. Seven days after rats were given a single dose, residual concentrations of [^{14}C]-SGS742 in all tissues were very low or below detectable limits [21].

6. Preclinical safety studies

6.1. Genotoxicity

In tests for genotoxicity, SGS742 produced no mutagenic, clastogenic or aneugenic effects [21].

6.2. Reproductive toxicity

In teratology studies, SGS742 was not teratogenic in rats or rabbits, however, slight maternal effects were seen at the highest doses (2000 and 600 mg/kg, respectively). In peri/postnatal and reproduction studies in rats, pup toxicity (reduced pup survival, increased resorptions, stillborns and postimplantation losses) was seen only at doses causing maternal toxicity (2000 mg/kg). At lower doses, where no maternal toxicity occurred, no adverse effects were noted [21].

6.3. Repeated dose toxicity

Oral administration of SGS742 or its fumarate salt (SGS742M) for up to 12 months produced no overt signs of toxicity at doses of up to 1200 mg/kg in rats and at doses of up to 300 mg/kg in dogs. In 6/12-month oral toxicity studies, the clear ''no observable effect'' level in dogs was 100 mg/kg; in rats, the only observation was a slight reduction in body weight gain in males at 200 and 600 mg/kg. This finding was considered to be of minimal toxicologic significance [21].

7. Clinical studies with SGS742

7.1. Phase I studies

Initial data on the safety and tolerability of SGS742 were derived from 10 Phase I trials involving a variety of dosing configurations. Some of these studies included elderly male and female healthy volunteers. In Phase I there were no reported serious adverse events or drug-related effects on cardiovascular or laboratory variables. One of two subjects who received the highest dose of drug tested suffered moderate to severe headache, moderate drowsiness, and severe nausea and vomiting. Mild to moderate nonspecific and non-dose-related adverse events reported by subjects included headache, tiredness, sleepiness and dizziness. All adverse events resolved fully and spontaneously. Neither the amount nor the rate of absorption after single and repeated doses was significantly different in elderly and young volunteers. Renal clearance was approximately 20% lower in elderly subjects, probably because of an age-related physiologic decrease in kidney function. There was a gender effect on systemic availability, the AUC being 40% higher in women. However, this difference was related to body weight [21].

7.2. Phase II study in patients with MCI

The effects of SGS742 on cognition were investigated in a double-blind, placebo-controlled study undertaken as the first assessment of the efficacy of SGS742 in 110 patients age 59–85 years with MCI. The study was conducted at 13 US centers. Patients were treated for 8 weeks with either oral SGS742 600 mg t.i.d. (n = 75) or placebo (n = 35). Efficacy was evaluated by analyzing results from cognitive tests performed at baseline and at weeks 2, 5 and 8. The results showed significant improvement in working memory, psychomotor speed and attention with SGS742 as compared with placebo. SGS742 appeared to be safe and well tolerated in this study [22].

The results from these exploratory analyses demonstrate that SGS742 has activities in various cognitive domains. Therefore, additional clinical studies exploring the use of SGS742 as a treatment for disorders associated with cognitive impairment are warranted.

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