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Effects of S 18986-1, a novel cognitive enhancer, on memory performances in an object recognition task in rats

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Abstract

(*S*)-2,3-dihydro-[3,4]cyclopentano-1,2,4-benzothiadiazine-1,1-dioxide (S 18986-1) is a new compound that facilitates post-synaptic responses by modulating α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor-mediated synaptic responses and thus promotes long-term potentiation and potentiates (*S*)-AMPA-induced release of noradrenaline in rat brain slices. In the present study, the effects of S 18986-1 were evaluated on cognitive functions by using a one-trial object-recognition test in the Wistar rat, a test which measures a form of episodic memory in rodents. Recognition was measured by the ability of treated rats to discriminate between a familiar and a new object after a 24-h retention delay. Oral administrations with S 18986-1 (0.3 to 100 mg/kg) 1 h before each session of the test improved object recognition at concentrations as low as 0.3 mg/kg. Under the same conditions, the nootropic drug aniracetam was active at a dose of 10 mg/kg by i.p. route. S 18986-1 was still effective on the object-recognition test when it was administered 4 h before each of the three sessions. Furthermore, subchronic oral pretreatment (7 days) with S 18986-1 (0.3 to 30 mg/kg) also increased the recognition of the familiar object indicating that the animals failed to develop tolerance to repeated administrations with S 18986-1. Finally, the recognition of the familiar object was improved when S 18986-1 was administered before the recognition trial whereas the rats failed to recognise the familiar object when S 18986-1 was administered before the sample presentation trial only. Taken together, the results indicated that S 18986-1 facilitated a form of episodic memory in the rat, by improving the recognition of a familiar information (retention). Furthermore, S 18986-1 was long-acting and demonstrated a good oral bioavailability. These data confer on S 18986-1, a potential role in improving episodic memory impaired in neurodegenerative diseases and during aging.

Keywords: AMPA receptor; Object recognition; Memory; (Rat); S 18986-1

1. Introduction

Facilitation of glutamatergic transmission promotes the formation of long-term potentiation, a type of synaptic plasticity hypothesised to be involved in the encoding of memory (Morris et al., 1986; Danysz et al., 1995). A considerable body of evidence suggests that the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor mediates the voltage-independent fast excitatory postsynaptic currents in the brain. The involvement of AMPA receptors in long-term potentiation formation is now well established (Bliss and Collingdridge, 1993). The induction of long-term potentiation by reduction of AMPA receptors desensitisation has been suggested to be a possible neural mechanism for improving learning and memory. In this context, two major classes of drugs that are able to positively modulate AMPA receptors responses, the pyrrolidones (aniracetam, and related compounds, such as Ampakines®) and the benzothiadiazides (cyclothiazide and 7-chloro-3-methyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine *S,S*-dioxide (IDRA-21)) have been described. (Arai et al., 1996a,b; Isaacson and Nicoll, 1991; Yamada and Turetsky, 1996). Aniracetam, at first discovered as a nootropic agent capable of improving the cognitive functions, was then shown to act as a positive allosteric modulator of AMPA selective glutamate receptors and to reduce the rate of rapid receptor autodesensitization that follows the transmitter gating of these channels, and to facilitate the induction of long-term potentiation (Ito et al., 1990; Isaacson and Nicoll, 1991; Tang et al., 1991). Recently, new centrally active drugs, the ampakine® family, which prolong the

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open time of the AMPA receptor channel and thereby enhance excitatory synaptic responses, were described (Arai et al., 1994,1996b; Staubli et al., 1994a). Behavioural studies indicated that members of this family, such as 1-(1,3-benzodioxol-5-ylcarbonyl)piperidine (1-BCP) and 1-(quinolalin-6-ycarbonyl)piperidine (CX-516), improved recent memory and long-term memory in adult and aged rats in various learning and memory paradigms (Staubli et al., 1994b,1996; Larson et al., 1995; Granger et al., 1996; Hampson et al., 1998). CX-516 also improved delayed recall in young adult (Lynch et al., 1997) and memory encoding in aged impaired humans (Ingvar et al., 1997). IDRA-21, which belongs to the family of benzothiadiazide compounds, also attenuates the rapid autodesensitization of AMPA receptors (Zivkovic et al., 1995) and facilitates the induction of long-term potentiation (Arai et al. 1996a). This compound improves performances of control rats and rats impaired by the administration of the AMPA receptor antagonist 1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[f]quinoxaline-7-sulfonamide (NBQX), the benzodiazepine drug alprazolam or by the muscarinic cholinergic antagonist scopolamine, in the water maze test and in the passive avoidance test (Zivkovic et al., 1995). IDRA-21 has also been shown to reverse the memory impairment induced by the administration of the amnesic drug alprazolam in monkeys (Thompson et al., 1995).

Extensive studies have linked the cognitive-enhancing effects of these compounds with the induction of long-term potentiation. However, the cognitive effects of these drugs could also be related to a regulation of the release of various brain neurotransmitters related to learning and memory, namely acetylcholine and noradrenaline. Indeed, AMPA has been shown to stimulate acetylcholine (Giovannini et al., 1998; Bonhomme et al., 1999) and noradrenaline (Cowen and Beart, 1998) release, and the positive modulators of AMPA-type receptors, such as cyclothiazide and 1-BCP have been demonstrated to potentiate (*S*)-AMPA-induced release of [^{3}H]-noradrenaline in rat hippocampal slices (Desai et al., 1995; Pittaluga et al., 1999).

Among a series of pyrrolo-benzothiadiazine derivatives, (*S*)-2,3-dihydro-[3,4]cyclopentano-1,2,4-benzothiadiazine-1,1-dioxide (*S* 18986-1) was selected as a new positive allosteric modulator of AMPA-type receptor. Electrophysiological studies demonstrated that S 18986-1 potentiated AMPA-induced current on *Xenopus laevis* oocytes injected with rat cortex mRNA (Desos et al., 1996). In vitro studies also indicated that S 18986-1 increased extracellular excitatory field potentials in the CA1 region after stimulation of the Schaffer collateral commissural projection in the rat hippocampal slices (Lepagnol et al., 1997). Moreover, in vivo experiments demonstrated that intraperitoneal (i.p.) treatment with S 18986-1 enhanced long-term potentiation in the dentate gyrus of anaesthetized rat after stimulation of the perforant path (Lepagnol et al., 1997). In vitro neurotransmitters release studies indicated that S 18986-1 potentiated the noradrenaline release induced by the application of AMPA in rat brain slices (Lockhart et al., 1998, in press). The present study was aimed at investigating the cognitive-enhancing properties of S 18986-1 in an object-recognition test in the rat. The one-trial object-recognition paradigm developed by Ennaceur and Delacour (1988) was employed and is based on spontaneous exploratory activity. The test does not involve rule learning or reinforcement and can be considered as a model of episodic memory in rodents. The object recognition in the rat is sensitive to the effects of ageing and to cholinergic dysfunction (Scali et al., 1994; Bartolini et al., 1996). Pharmacological studies indicated that nootropic drugs, such as aniracetam or piracetam and cholinesterase inhibitors (metrifonate), improve recognition memory in this test (Ennaceur et al., 1989; Bartolini et al., 1996; Scali et al., 1997). The cognitive-enhancing effects of S 18986-1 were investigated in the object-recognition test in the rat with a 24-h retention delay between the sample presentation and its recognition. In the same conditions, the effects of the nootropic drug, aniracetam, has also been studied. Some preliminary results have been already presented as abstract form (Lebrun et al., 1998).

2. Material and methods

2.1. Animals

The experiments were performed with male Wistar rats (Iffa Credo, France) weighing 270–310 g on the day of experiments. The animals were used for experimentation after adaptation to the laboratory conditions for at least 10 days and during 5 days before the beginning of memory testing, they were routinely handled by the experimenter. The rats were randomly allocated to the different experimental groups and were housed 2 in a cage at 21 ± 1°C, 60 ± 5% humidity, on 12 h light/dark cycle (light on from 0700 to 1900 h), with food and water ad libitum.

All the experiments were carried out according to the guidelines of the European Community's Council for Animals experiments (DL 116/92) with the permission of the local ethical committee at the Institut de Recherches Servier.

2.2. Apparatus

The apparatus used was an open box made of grey plexiglas ($65 \times 45 \times 42$ cm). It was placed in a sound-isolated room. A light provided a constant illumination of about 35 Lux at the level of the test apparatus. The objects to be discriminated were pyramids made of either red plastic or lead and existed in duplicate. They could not be displaced by the rats.

2.3. Behavioural testing

The object recognition was evaluated according to Ennaceur and Delacour (1988) with minor modifications. The day before testing the rats were allowed to explore the apparatus for a 2-min session of habituation. Twenty four hours later, testing began. On the day of the test, at the first 3-min sample trial (T1), two identical objects (termed as sample objects O1 and O2) were presented at the corners of the box. In the second 3-min choice trial (T2), one of the objects presented in T1 was replaced by a new object. With short delays between 1 min and 4 h between T1 and T2, rats were able to recognise the object presented in T1 as evidenced by increased exploration toward the new object (Ennaceur and Delacour, 1988). Since a cognitive-enhancing effect of S 18986-1 was expected, an increased interval of 24 h between T1 and T2 was used. In these conditions, control rats did not recognise the familiar object as evidenced by similar times of exploration of the new and familiar objects.

The basic measure was the time (in seconds) taken by the rats in exploring the objects in the two trials. Exploration was considered as directing the nose to the objects at a distance ≤ 2 cm to the objects and/or touching it with the nose. The times spent exploring the familiar (F) and the new object (N) during T2 were recorded separately and the difference between the two exploration times was taken as the discrimination index ($d = N - F$). For the sample trial T1, the discrimination index was $d' = \text{O2}-\text{O1}$ and expected to be around zero.

2.4. Drugs preparation and administration

S 18986-1 (Servier, France) and aniracetam (Sigma) were dissolved in either distilled water or saline for oral and i.p. administration, respectively. Administrations were in a volume of 5 ml/kg body weight. Control rats received Twen 80 with saline for i.p. injection or distilled water for oral administration. In the majority of the experiments, S 18986-1 was administered before each session of the test (habituation, T1 and T2). However, in an experiment aimed at studying the effects of S 18986-1 on the acquisition or on the recognition of the information, the compound was administered either before the session of habituation, or before T1 or before T2. For subchronic oral pretreatment, S 18986-1 was administered during 7 days before the beginning of the test then before each of the three respective sessions. The administrations were made 30 and 60 min before the test for i.p. and oral route, respectively. In a study aimed at investigating the duration of activity of S 18986-1, the drug was administered 1, 2, 3 or 4 h before the test.

2.5. Statistical analysis

One-way analysis of variances (ANOVA) and subsequent Dunnett test post hoc analyses for between groups comparisons were applied on the discrimination indexes d and d'. As no difference between groups was demonstrated for d', only the data for the discrimination index (d) recorded on the second trial (T2) were presented. Results are expressed as the means ± S.E.M.

3. Results

3.1. Effects of acute i.p. treatment with aniracetam

Aniracetam significantly increased the difference of exploration time between the new object and the familiar object in T2 ($F(4,53) = 19.89$; $P < 0.001$) in a dose-related fashion. As shown in Fig. 1, the doses of 10, 30 and 100 mg/kg induced a significant increase of the discrimination index ($P < 0.001$) whereas the dose of 3 mg/kg was without any effect.

3.2. Effects of acute oral treatment with S 18986-1

In an initial study conducted with low doses of S 18986-1 (from 0.3 to 10 mg/kg), the results indicated a significant effect of the compound on the object discrimination ($F(4,53) = 4.23$; $P = 0.005$), with doses of 0.3, 1 and 3 mg/kg being significantly different from controls (Fig. 2A). The same study conducted with higher doses (Fig. 2B) indicated a significant effect of increasing doses of S 18986-1 ($F(3,41) = 13.49$; $P < 0.001$) with discrimination indexes of 6 and 10 s for 30 and 100 mg/kg, respectively. The results presented in this second study confirmed the lack of effect for the dose of 10 mg/kg. It must also be noted that the administration of 30 and 100 mg/kg induced a significant decrease of the locomotion

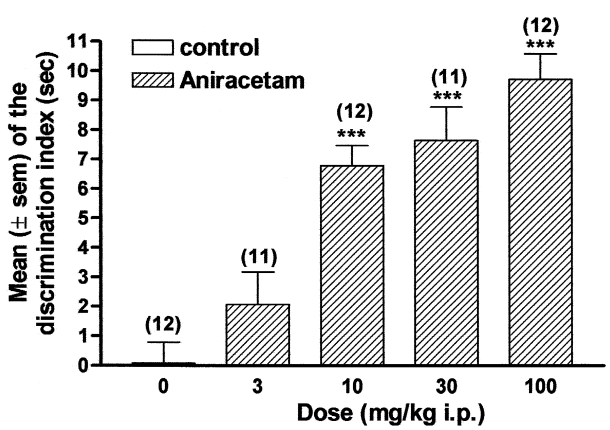

Fig. 1. Effects of treatment with Aniracetam in the object recognition test in rats. Aniracetam was administered by intraperitoneal route 30 min before each session. The discrimination index was the difference between the exploration times of the novel and familiar objects on the second trial (T2) which occurred 24 h after the first trial. Values are the means (±S.E.M.) with the number of animals/group in parentheses. *** $P \leq 0.001$ vs. control, ANOVA and Dunnett t-test.

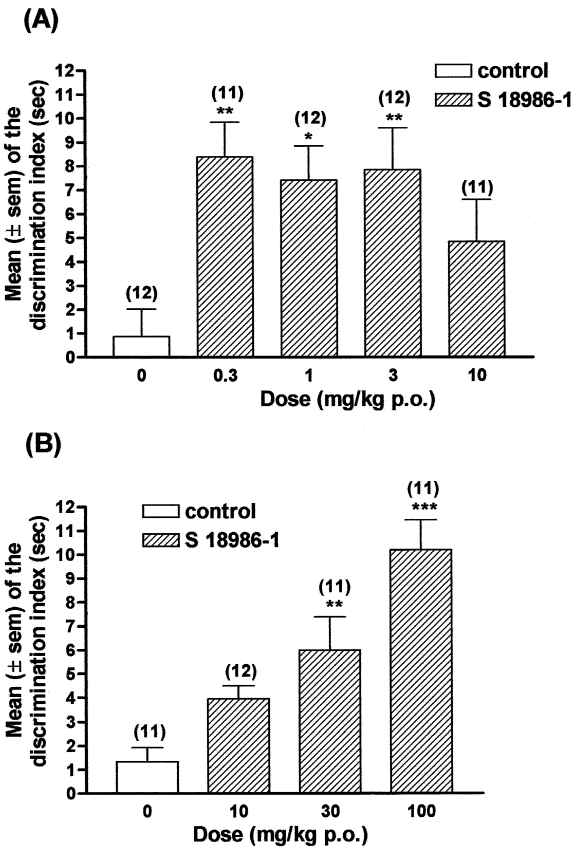

Fig. 2. Effects of oral treatment with S 18986-1 in the object recognition test in rats. S 18986-1 was administered by oral route 60 min before each session. A first study was conducted with low doses (A) and a second study investigated the effects of higher doses (B). The discrimination index was the difference between the exploration times of the novel and familiar objects on the second trial (T2) which occurred 24 h after the first trial. Values are the means (±S.E.M.) with the number of animals/group in parentheses. * $P \leq 0.05$; ** $P \leq 0.01$, *** $P \leq 0.001$ vs. control, ANOVA and Dunnett *t*-test.

recorded in the rats during the session of habituation (data not shown). But there was no significant decrease of the total exploration times of the two objects in T1 and T2.

3.3. Effects of subchronic oral treatment with S 18986-1

In an initial study, rats were chronically (7 days) pretreated with low doses of S 18986-1 (from 0.3 to 10 mg/kg). Results indicated a significant increase of the discrimination index ($F(4,85) = 4.91$; $P = 0.001$). As shown in Fig. 3A, the four doses tested are significantly different from the control group with a discrimination index comprised between 4.98 and 6.88 s. In a second study, a chronic pretreatment with a higher dose of S 18986-1 (from 3 to 30 mg/kg) also improved the discrimination between the familiar and the new object ($F(3,43) = 4.40$; $P = 0.009$). The doses of 3 and 30 mg/kg induced a significant increase of the discrimination index ($d = 8.63$ and $d = 6.97$ s for 3 and 30 mg/kg, respectively; Fig. 3B). As for acute treatment, the dose of 30 mg/kg decreased locomotion without changes in the total exploration of the two objects.

3.4. Effect of a delayed treatment with S 18986-1 on the object recognition

This study was aimed at studying the duration of activity of S 18986-1. The animals were treated with S 18986-1 at the dose of 1 mg/kg by oral route. The administrations were made either 1, 2, 3 or 4 h before each session of the test. The results presented in Fig. 4 indicated a significant increase of the discrimination index with a delay of 1 h ($d = 6.51$, $P < 0.001$) and 2 h ($d = 6.14$; $P < 0.001$) compared with the control group. Administered 3 or 4 h before the test, S 18986-1 was still efficacious in increasing object recognition ($d = 5.48$; $P < 0.05$ and $d = 4.99$; $P < 0.01$ for 3 and 4 h, respectively).

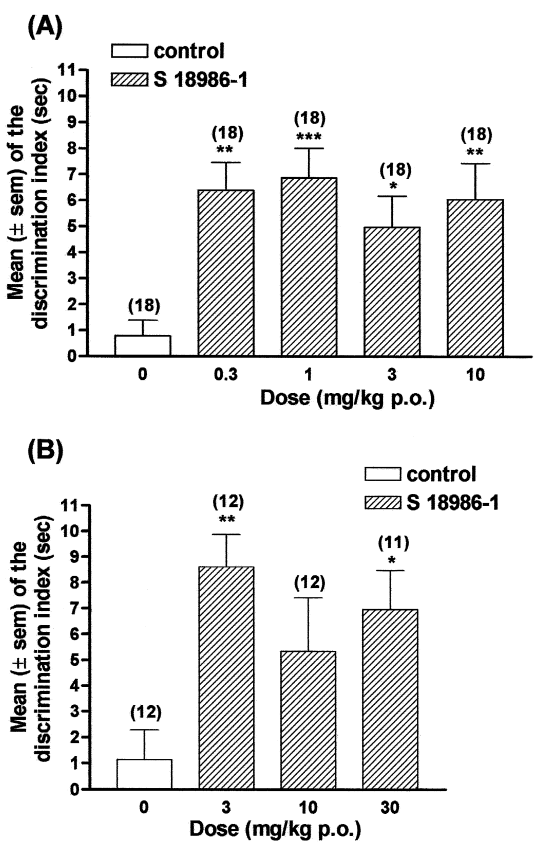

Fig. 3. Effects of chronic oral treatment with S 18986-1 in the object recognition test in rats. Animals were chronically pretreated (7 days) with S 18986-1 then 60 min before each session of the test. A first study was conducted with low doses (A) and a second study investigated the effects of higher doses (B). The discrimination index was the difference between the exploration times of the novel and familiar objects on the second trial (T2) which occurred 24 h after the first trial. Values are the means (±S.E.M.) with the number of animals/group in parentheses. * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$ vs. control, ANOVA and Dunnett *t*-test.

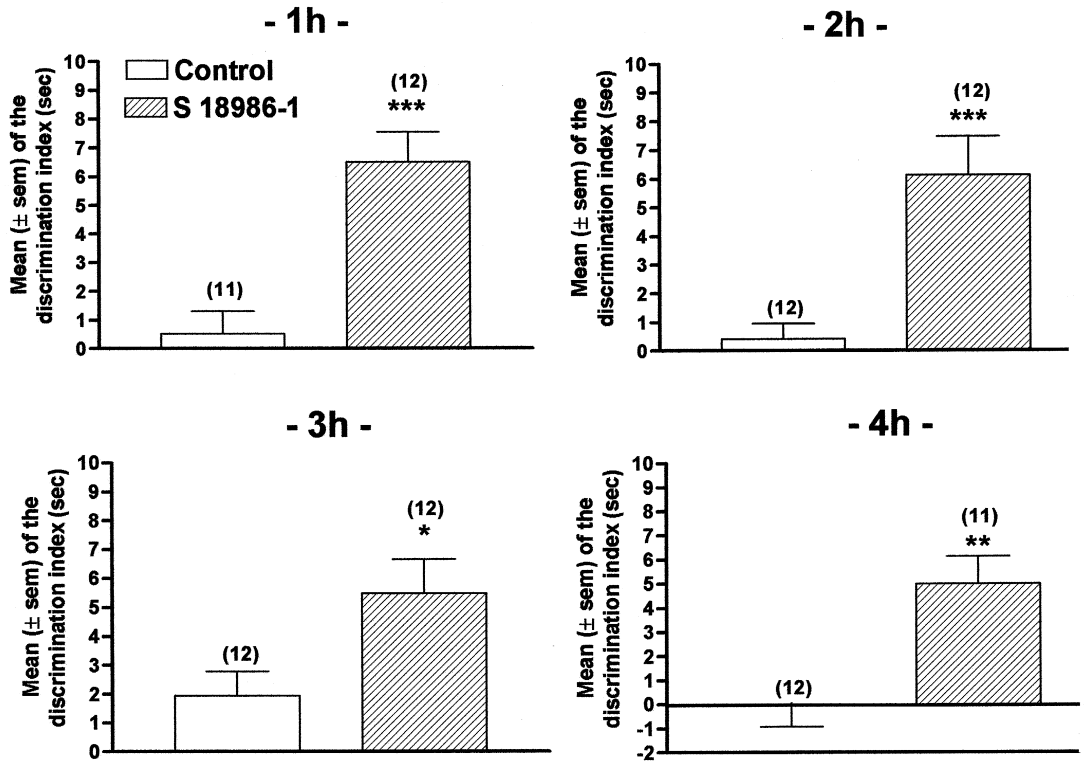

Fig. 4. Effects of delayed treatments with S 18986-1 in the object recognition test in rats. S 18986-1 was administered to the rats at the dose of 1 mg/kg by oral route. The administrations were made 1, 2, 3 or 4 h before each session of the test. The discrimination index was the difference between the exploration times of the novel and familiar objects on the second trial (T2) which occurred 24 h after the first trial. Values are the means (±S.E.M.) with the number of animals/group in parentheses. * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$ vs. control, one-way ANOVA.

3.5. Influence of the schedule of treatment with S 18986-1 on the object recognition

In order to further study the effects of S 18986-1 on the different stages of the test, the compound was administered at the dose of 0.3 mg/kg by oral route either before the habituation session, or before T1 or before T2 and compared to the three administrations condition (habituation + T1 + T2). A one-way analysis of variances indicated a significant effect of treatment ($F(4,55) = 5.27$; $P = 0.001$). As shown in Fig. 5, the administration of S 18986-1 60 min before T2 (recognition trial) induced a significant increase of the discrimination index ($d = 7.45$, $P < 0.01$) as compared with the control group ($d = 0.37$). A similar effect ($d = 6.72$, $P < 0.01$) was also observed when the drug was administered before each session. In contrast, a lack of effect of S 18986-1 on the object recognition was observed when the compound was administered only before the session of habituation or before T1 (sample presentation trial) (Fig. 5).

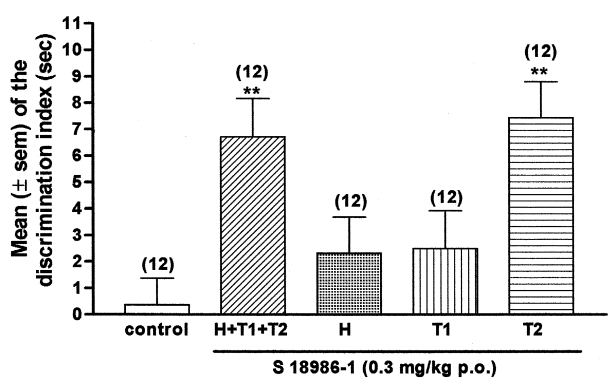

Fig. 5. Influence of the schedule of treatment with S 18986-1 in the object recognition test in rats. S 18986-1 was administered by oral route (0.3 mg/kg) either 60 min before each session (H + T1 + T2) or only before the session of habituation (H), before the acquisition trial (T1) or before the recognition trial (T2), the animals receiving the vehicle the two other days. The discrimination index was the difference between the exploration times of the novel and familiar objects on the second trial (T2) which occurred 24 h after the first trial. Values are the means (±S.E.M.) with the number of animals/group in parentheses. ** $P \leq 0.01$ vs. control, ANOVA and Dunnett *t*-test.

4. Discussion

The object-recognition test measures a nonspatial memory with the characteristics of episodic memory (Ennaceur and Delacour, 1988) assessed in nonhuman primates by the visual-recognition test. Young control rats recognise a familiar object with retention intervals between 1 min and 4 h. With a 24-h retention delay, the times spent in exploring the familiar and new objects were similar, indi-

cating that the rats no longer recognise the familiar object (Ennaceur and Delacour, 1988). In these conditions of forgetting, nootropic drugs, such as piracetam and pramiracetam, improved object recognition in young rats (Ennaceur et al., 1989). In the present study, we demonstrated that aniracetam, another nootropic drug, which has been shown to act as positive allosteric modulator of AMPA-type receptor (Ito et al., 1990; Isaacson and Nicoll, 1991; Tang et al., 1991), was also effective on the object recognition in adult rat after i.p. administrations. Some studies also indicated that oral administration with aniracetam improved the object recognition-impaired in aged rats and in rats injected with the cholinergic antagonist scopolamine with doses of aniracetam ranging from 50 to 100 mg/kg (Bartolini et al., 1996). In the present study, the positive effects obtained with i.p. injections of aniracetam were in the same range of doses (10 to 100 mg/kg). Rats that received S 18986-1, a new positive modulator at AMPA-type receptor, before each trial of the test were able to recognise the familiar object 24 h after. The effects of S 18986-1 were observed in a range of doses of 0.3 to 100 mg/kg and with a biphasic effect (0.3–1–3 mg/kg) and (30–100 mg/kg). The dose of 10 mg/kg did not modify significantly ($P > 0.05$) the object recognition. With the higher doses of 30 and 100 mg/kg, a decrease in the exploration recorded on the first session (habituation) was observed (data not shown). Nevertheless, during the sample presentation and the sample recognition trials, the total exploration of the two objects was not decreased by the drug regardless of the doses used, indicating that the decrease in motility observed during the habituation session was without consequences on the motivation to explore the objects on the subsequent trials. The minimal effective dose demonstrating cognitive-enhancing effects was 0.3 mg/kg. Indeed, lower doses (0.03 and 0.1 mg/kg) were not significantly active (data not shown). The results observed with S 18986-1 and aniracetam confirmed that drugs that positively modulate the postsynaptic currents generated by AMPA receptors (Ito et al., 1990; Isaacson and Nicoll, 1991; Tang et al., 1991; Lepagnol et al., 1997) may improve the cognitive function. However, it could not be excluded that the memory-enhancing effect observed with S 18986-1 on the recognition of the familiar object was related to the modulatory activity of the compound on the release of noradrenaline. S 18986-1 (30–1000 μM) was shown to modulate AMPA-evoked release of [^{3}H]-noradrenaline in rats hippocampal slices (Lockhart et al., 1998, in press). The biphasic dose–effect relationship observed with S 18986-1 was surprising. One possible hypothesis to explain this result is that S 18986-1 acts through different mechanisms operating at different doses. At low and high doses (1 and 100 mg/kg i.p., respectively), S 18986-1 increased long-term potentiation in anaesthetized rats (Lepagnol et al., 1997). On the other hand, at high dose (30 mg/kg i.p.), but not at lower doses, S 18986-1 decreased the dopamine turnover in various brain structures (data not shown). It is possible that at high doses (30 and 100 mg/kg p.o.) mechanisms other than AMPA modulation may influence memory performances of the rats.

Some experiments indicated that i.p. injections of S 18986-1 improved memory impairment induced by the muscarinic antagonist, scopolamine in the passive avoidance test in the rat (Lepagnol et al., 1997). In the present study, S 18986-1 was administered by oral route. The cognitive-enhancing activity observed with S 18986-1 in the object-recognition test indicated an excellent oral bioavailability for this compound. Improvement of memory in the object-recognition test was still observed with subchronic treatment (7 days) with S 18986-1, suggesting a lack of tolerance with repeated administrations of the compound. Moreover, the experiment aimed at studying the duration of activity of S 18986-1 demonstrated that the compound was still active when administered 4 h before the test. In other words, S 18986-1 was long-acting.

A last experiment was conducted in order to test whether S 18986-1 facilitated memory through acquisition or retention of the information. When administered before the first trial (acquisition trial) only, S 18986-1 failed to demonstrate an effect on the object recognition in the second trial. When an injection with S 18986-1 was made before the second trial and a saline treatment before the acquisition trial, S 18986-1 increased the recognition of the familiar object. Taken together, these results indicated that S 18986-1 exerted its cognitive-enhancing activity through recognition of the information and not by increasing acquisition of the information. *N*-methyl-D-aspartate (NMDA) and AMPA receptors, both implicated in long-term potentiation mechanism, may be differently involved in the time course of learning phases. There is evidence to suggest that NMDA receptors influence acquisition and encoding processes but not retrieval of information (Danysz et al., 1995). AMPA-type receptors might be involved in both acquisition and retrieval processes (Izquierdo, 1993; Danysz et al., 1995). The lack of effect with S 18986-1 on acquisition of the task might be related to the memory paradigm used. In the object-recognition test conducted with normal adult rats, acquisition that indicates encoding of the information, is probably at its optimal state. In this regard, forgetting of the familiar object, observed after a 24-h retention interval, would be associated with a defect of retrieval rather than with a time-dependent decay of the memory trace. It is possible that memory of the familiar object was still present but not accessible, and that this accessibility has been improved by facilitation of the glutamatergic transmission with S 18986-1 through positive modulation of AMPA-type receptor.

The object-recognition test has been developed as a model of episodic memory in the rat (Ennaceur and Delacour, 1988). This form of memory is sensitive to the effects of normal aging in human. In patients suffering from Alzheimer's disease, episodic memory is also im-

paired earlier in the disease. The object-recognition test conducted in the rat was shown to be sensitive to the effects of ageing and to cholinergic dysfunction (Scali et al., 1994; Bartolini et al., 1996). Some results indicated that S 18986-1 was also active in aged impaired rats in the object-recognition test (Lebrun et al., 1998). Taken as a whole, the cognitive-enhancing properties of S 18986-1 demonstrated in a rodent model of episodic memory indicated that the compound may be useful in the treatment of memory disorders, especially of episodic memory observed during aging and at the beginning of various chronic neurodegenerative diseases.

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References

Arai, A., Kessler, M., Xiao, P., Ambros-Ingerson, J., Rogers, G., Lynch, G., 1994. A centrally active drug that modulates AMPA receptor gated currents. Brain Res. 638, 343–346.

Arai, A., Guidotti, A., Costa, E., Lynch, G., 1996a. Effect of the ampa receptor modulator IDRA 21 on LTP in hippocampal slices. NeuroReport 7, 2211–2215.

Arai, A., Kessler, M., Rogers, G., Lynch, G., 1996b. Effects of a memory-enhancing drug on DL-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor currents and synaptic transmission in hippocampus. J. Pharmacol. Exp. Ther. 278, 627–638.

Bartolini, L., Casamenti, F., Pepeu, G., 1996. Aniracetam restores object recognition impaired by age, scopolamine, and nucleus basalis lesions. Pharmacol. Biochem. Behav. 53, 277–283.

Bliss, T.V.P., Collingdridge, G.L., 1993. A synaptic model of memory: long term potentiation in the hippocampus. Nature 361, 31–39.

Bonhomme, N., Grève, P., Favale, D., Lestage, P., 1999. Control of acetylcholine release by AMPA receptors in rat prefrontal cortex. In: Rollema, H., Abercrombie, E., Sulzer, D., Zackheim, J. (Eds.), Monitoring Molecules in Neurosciences. Pfizer, New York, pp. 220–221.

Cowen, M.S., Beart, P.M., 1998. Cyclothiazide and AMPA receptor desensitization: analyses from studies of AMPA-induced release of [^{3}H]-noradrenaline from hippocampal slices. Br. J. Pharmacol. 123, 473–480.

Danysz, W., Zajaczkowski, W., Parsons, C.G., 1995. Modulation of learning processes by ionotropic glutamate receptor ligands. Behav. Pharmacol. 6, 455–474.

Desai, M.A., Valli, M.J., Monn, J.A., Schoepp, D.D., 1995. 1-BCP, a memory-enhancing agent, selectively potentiates AMPA-induced [^{3}H]noradrenaline release in rat hippocampal slices. Neuropharmacology 34, 141–147.

Desos, P., Serkiz, B., Morain, P., Lepagnol, J., Cordi, A., 1996. Enantioselective synthesis of a pyrrolo-benzothiadiazine derivative S 18986, a new ampa receptor positive modulator. Bioorg. Med. Chem. Lett. 6, 3003–3008.

Ennaceur, A., Delacour, J., 1988. A new one-trial test for neurobiological studies of memory in rats: I. Behavioral data. Behav. Brain Res. 31, 47–59.

Ennaceur, A., Cavoy, A., Costa, J.C., Delacour, J., 1989. A new one-trial test for neurobiological studies of memory in rats: II. Effects of piracetam and pramiracetam. Behav. Brain Res. 33, 197–207.

Giovannini, M.G., Rakovska, A., Della Corte, L., Bianchi, L., Pepeu, G., 1998. Activation of non-NMDA receptors stimulates acetylcholine and GABA release from dorsal hippocampus: a microdialysis study in the rat. Neurosci. Lett. 243, 152–156.

Granger, R., Deadwyler, S., Davis, M., Moskovitz, B., Kessler, M., Rogers, G., Lynch, G., 1996. Facilitation of glutamate receptors reverses an age-associated memory impairment in rats. Synapse 22, 332–337.

Hampson, R.E., Rogers, G., Lynch, G., Deadwyler, S.A., 1998. Facilitative effects of the ampakine CX516 on short-term memory in rats: correlations with hippocampal neuronal activity. J. Neurosci. 18, 2748–2763.

Ingvar, M., Ambros-Ingerson, J., Davis, M., Granger, R., Kessler, M., Rogers, G.A., Schehr, R.S., Lynch, G., 1997. Enhancement by an ampakine of memory encoding in humans. Exp. Neurol. 146, 553–559.

Isaacson, J.S., Nicoll, R.A., 1991. Aniracetam reduces glutamate receptor desensitization and slows the decay of fast excitatory synaptic currents in the hippocampus. Proc. Natl. Acad. Sci. 88, 10936–10940.

Ito, I., Tanabe, S., Kohda, A., Sugiyama, H., 1990. Allosteric potentiation of quisqualate receptors by nootropic drug aniracetam. J. Physiol. 424, 533–543.

Izquierdo, I., 1993. Long term potentiation and mechanisms of memory. Drug Dev. Res. 30, 1–17.

Larson, J., Lieu, T., Petchpradub, V., LeDuc, B., Ngo, H., Rogers, G., Lynch, G., 1995. Facilitation of olfactory learning by a modulator of AMPA receptors. J. Neurosci. 15, 8023–8030.

Lebrun, C., Roger, A., Pillière, E., Albinet, K., Krentner, M., Lestage, P., 1998. S 18986-1, positive modulator of AMPA-type glutamate receptors a novel cognitive enhancing agent. Soc. Neurosci. Abstr. 24, 44.10.

Lepagnol, J., Lebrun, C., Pillière, E., Thomas, J.Y., Desos, P., Cordi, A., Lestage, P., 1997. Neuroexcitatory and cognition enhancing effects of S 18986-1, a positive allosteric modulator of glutamate AMPA receptors. Soc. Neurosci. Abstr. 23, 717.6.

Lockhart, B., Iop, F., Bonhomme, N., Lestage, P., 1998. S 18986-1, a new positive modulator of AMPA-type glutamate receptors, potentiates AMPA-mediated [^{3}H]-noradrenaline release from rat hippocampal slices. Soc. Neurosci. Abstr. 24, 44.9.

Lochkart, B., Iop, F., Closier, M., Lestage, P., in press. (*S*)-2,3-dihydro-[3,4]cyclopentano-1,2,4-benzothiadiazine-1,1-dioxide (S 18986-1): a positive modulator of AMPA-receptors enhances (*S*)-AMPA-mediated [^{3}H]noradrenaline release from rat hippocampal and frontal cortex slices. Eur. J. Pharmacol.

Lynch, G., Granger, R., Ambros-Ingerson, J., Davis, C.M., Kessler, M., Schehr, R., 1997. Evidence that a positive modulator of AMPA-type glutamate receptors improves delayed recall in aged humans. Exp. Neurol. 145, 89–92.

Morris, R.G.M., Anderson, E., Lynch, G.S., Baudry, M., 1986. Selective impairment of learning and blockage of long-term potentiation by *N*-methyl-D-aspartate receptor antagonist, AP5. Nature 319, 774–776.

Pittaluga, A., Bonfanti, A., Arvigo, D., Raiteri, M., 1999. Aniracetam, 1-BCP and cyclothiazide differentially modulate the function of NMDA and AMPA receptors mediating enhancement of noradrenaline release in rat hippocampal slices. Naunyn-Schmiedeberg's Arch. Pharmacol. 359, 272–279.

Scali, C., Casamenti, F., Pazzagli, M., Bartolini, L., Pepeu, G., 1994. Nerve growth factor increases extracellular acetylcholine levels in the parietal cortex and hippocampus of aged rats and restores object recognition. Neurosci. Lett. 170, 117–120.

Scali, C., Giovannini, M.G., Bartolini, L., Prosperi, C., Hinz, V., Schmidt, B., Pepeu, G., 1997. Effect of metrifonate on extracellular brain acetylcholine and object recognition in aged rats. Eur. J. Pharmacol. 325, 173–180.

Staubli, U., Perez, Y., Xu, F.B., Rogers, G., Ingvar, M., Stone-Elander, S., Lynch, G., 1994a. Centrally active modulators of glutamate receptors facilitate the induction of long-term potentiation in vivo. Proc. Natl. Acad. Sci. 91, 11158–11162.

Staubli, U., Rogers, G., Lynch, G., 1994b. Facilitation of glutamate receptors enhances memory. Proc. Natl. Acad. Sci. 91, 777–781.

Staubli, U., Izrael, Z., Xu, F.B., 1996. Remembrance of odors past: enhancement by central facilitation of AMPA receptors. Behav. Neurosci. 110, 1067–1073.

Tang, C.M., Shi, Q.Y., Katchman, A., Lynch, G., 1991. Modulation of the time course of fast EPSCs and glutamate channel kinetics by aniracetam. Science 254, 288–290.

Thompson, D.M., Guidotti, A., DiBella, M., Costa, E., 1995. 7-Chloro-3-methyl-3,4-dihydro-2*H*-1,2,4 benzothidiazine *S,S*-dioxide (IDRA 21), a congener of aniracetam, potently abates pharmacologically induced cognitive impairments in patas monkeys. Proc. Natl. Acad. Sci. 92, 7667–7671.

Yamada, K.A., Turetsky, D.M., 1996. Allosteric interactions between cyclothiazide and AMPA/kainate receptor antagonists. Br. J. Pharmacol. 117, 1663–1672.

Zivkovic, I., Thompson, D.M., Bertolino, M., Uzunov, D., DiBella, M., Costa, E., Guidotti, A., 1995. 7-Chloro-3-methyl-3,4-dihydro-2*H*-1,2,4 benzothidiazine *S,S*-dioxide (IDRA 21): a benzothiadiazine derivative that enhances cognition by attenuating DL-α-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid (AMPA) receptor desensitization. J. Pharmacol. Exp. Ther. 272, 300–309.