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The neurotensin receptor antagonist, SR48692, attenuates the expression of amphetamine-induced behavioural sensitisation in mice

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Abstract

The effects of acute administration of the neurotensin receptor antagonist, SR48692 (2-{[1-(7-chloroquinolin-4-yl)-5-(2,6-dimethoxyphenyl)-1H-pyrazol-3-carbonyl]amino}adamantane-2-carboxylic acid), on amphetamine-induced behavioural sensitisation were studied with the locomotor activity of mice in an open-field as an experimental parameter. The animals were repeatedly pretreated with saline or amphetamine (2.0 mg/kg, i.p. once a day, every other day for 13 days) and 2, 9 and 16 days after the last injection they received an acute i.p. administration of saline or 0.3 mg/kg SR48692 15 min before a challenge i.p. injection of 2.0 mg/kg amphetamine. Locomotor activity of the amphetamine-challenged mice was significantly higher in amphetamine-pretreated animals than in saline-pretreated mice on days 9 and 16 after withdrawal. SR48692 prevented the expression of this behavioural sensitisation. In addition, in saline-pretreated mice, the first two challenge injections of amphetamine sufficed to induce a sensitized locomotor response to the third challenge injection of the drug. SR48692 administration before amphetamine challenge injections prevented the development of this challenge injection-induced sensitisation in saline-pretreated mice but not in amphetamine-pretreated animals. In order to determine the effects of SR48692 on the expression of amphetamine-induced behavioural sensitisation in the absence of this challenge injection-induced sensitisation, the experiment was redone with a single challenge test 9 days after pretreatment. Once again, SR48692 prevented the expression of amphetamine-induced behavioural sensitisation. These results suggest that neurotensinergic transmission has a critical role in both the initiation and expression of locomotor sensitisation to amphetamine. © 2001 Published by Elsevier Science B.V.

Keywords: Neurotensin; Dopamine; Motivation; Locomotor activity; Open-field

1. Introduction

Chronic intermittent administration of amphetamine to animals produces a progressive and enduring increase in hyperactivity and stereotyped behaviour (Bellot et al., 1996; Kalivas and Stewart, 1991; Nelson and Ellison, 1978). This phenomenon, called behavioural sensitisation, has been widely recognized as an animal model of lasting susceptibility to exacerbation of psychostimulant-induced psychosis (Robinson and Becker, 1986). As regards sensitisation to the locomotor stimulatory effects of amphetamine, this model has also been suggested to be useful for studying mechanisms underlying drug craving in humans (Robinson and Berridge, 1993). Indeed, whereas substantial evidence links the locomotor-stimulating effects of addictive drugs to their positive reinforcing properties (Wise and Bozarth, 1982), most drugs of abuse stimulate locomotion in rodents and induce sensitisation (Kalivas and Stewart, 1991).

It has been hypothesized that activation of mesolimbic dopaminergic pathways—from the ventral tegmental area to the nucleus accumbens—is related to both the reinforcing and locomotor-stimulating properties of drugs of abuse (Wise and Bozarth, 1987). Sensitisation to the locomotor-stimulating effects of amphetamine also appears to require alterations within the mesoaccumbens dopamine system. Indeed, a variety of data shows that the initiation of behavioural sensitisation to psychostimulants occurs in the ventral tegmental area, whereas the neuronal events associated with the expression of the phenomenon are centered in a collection of interconnected limbic nuclei, among which dopamine transmission in the nucleus accumbens seems to play a critical role (Pierce and Kalivas, 1997).

Neurotensin is an endogenous tridecapeptide which is mainly localized in regions containing either cell bodies or terminals of dopamine neurons, including the mesolimbic dopamine system (Kasckow and Nemeroff, 1991). Microinjection of neurotensin into the ventral tegmental area

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enhances dopamine release in the nucleus accumbens (Kalivas and Duffy, 1990) and increases locomotion of rats (Kalivas et al., 1983). Conversely, when injected into the nucleus accumbens, neurotensin inhibits the release of dopamine (Tanganelli et al., 1994) and decreases the behavioural responses induced by dopamine agonists (Kalivas et al., 1984; Nemeroff et al., 1983; Ervin et al., 1981). After repeated injections with neurotensin, the locomotor-activating effect of the ventral tegmental area is increased (Kalivas and Duffy, 1990; Elliot and Nemeroff, 1986; Kalivas and Taylor, 1985). In this context, a growing body of evidence suggests the involvement of neurotensin in locomotor sensitisation to psychostimulants. Thus, whereas repeated intracerebroventricular (i.c.v.) injections of neurotensin enhance the locomotor-stimulating effect of a challenge i.p. injection of amphetamine (Rompré, 1997), repeated i.p. injections of the dopamine uptake inhibitor, GBR12783 (1-[2-(diphenylmethoxy)ethyl]4-(3-pnehyl-2-(propenyl)-piperazine), increase the locomotor-stimulating effect of a challenge i.c.v. injection of [D-Trp^{11}]neurotensin, a neurotensin derivative resistant to peptidase inactivation (Boulay et al., 1996). In addition, previous repeated administration of the neurotensin receptor antagonist, SR48692 (2-{[1-(7-chloroquinolin-4-yl)-5-(2,6-dimethoxyphenyl)-1H-pyrazol-3-carbonyl]amino} adamantane-2-carboxylic acid), produces an attenuating effect on the development of sensitisation to the locomotor-activating effect of cocaine in rats (Horger et al., 1994). In contrast, co-treatment with SR48692 30 or 60 min before cocaine or amphetamine injection, respectively, failed to produce an antagonistic effect on the development of cocaine sensitisation (Horger et al., 1994), but inhibited the development of amphetamine sensitisation (Rompré and Perron, 2000).

To date, the involvement of neurotensin transmission blockade in the expression of behavioural sensitisation to psychostimulants in mice has not been explored. To address this question, the primary purpose of this study was to investigate the effects of acute SR48692 administration on the expression of locomotor sensitisation to amphetamine in mice.

2. Materials and methods

2.1. Subjects

Three-month-old female Swiss mice ranging in weight from 25 to 30 g at the beginning of the experiment were used in this study. The animals were housed in groups and maintained in an environment with controlled temperature (22 ± 1 °C) and a 12 h light/dark cycle (lights on at 06:30 h). The mice had free access to food and water. All procedures were performed in strict accordance with the guidelines of the Committee on Animals of the Colégio Brasileiro de Experimentação Animal (COBEA) and the Committee on Care and Use of Laboratory Animal Resources, National Research Council, USA.

2.2. Drugs

SR48692, kindly provided by Dr. Danielle Gully, Sanofi Recherche, France, was initially suspended with a drop of Tween 80 and further diluted in 0.9% NaCl. D-amphetamine sulfate (Sigma) was diluted in distilled water. Saline (0.9% NaCl) was used as control solution. All solutions were administered intraperitoneally (i.p.) in a volume of 10 ml/kg body weight.

2.3. Open-field procedure

The open-field arena was a circular wooden box (40 cm in diameter and 30 cm high) with an open top, and a floor divided into 18 squares. A circle was marked in the center of the field. Locomotor activity was scored by trained observers blind to experimental conditions and was recorded as the number of lines crossed by the animal during 5 min sessions. This period of time has been used before in behavioural sensitisation studies and was reported to be sufficient to reveal this phenomenon (Bellot et al., 1996, 1997). All animals were habituated to the open-field arena before the drug pretreatments started. The habituation process consisted of letting the mouse explore the open-field arena for two 5-min sessions, 24 h apart. The last habituation session was held 1 day before amphetamine or saline long-term pretreatment started.

2.4. Experimental procedures

2.4.1. Experiment 1

Various doses of SR48692 were tested for effects on open-field behaviour. Thirty-nine mice were randomly divided into four groups and treated acutely with three SR48692 i.p. doses (0.03; 0.1; 0.3 mg/kg) or saline 30 min before being tested in an open-field for locomotor activity as described above.

2.4.2. Experiment 2

The mice were divided randomly and equally into four groups ($n = 13$): Saline–Saline (long-term treated and acutely challenged with saline), Saline–SR48692 (long-term treated with saline and acutely challenged with SR48692), Amphetamine–Saline (long-term treated with amphetamine and acutely challenged with saline) and Amphetamine–SR48692 (long-term treated with amphetamine and acutely challenged with SR48692). The animals received an injection of saline followed by another injection of saline or of 2.0 mg/kg amphetamine 30 min later, every other day for 13 days. The pretreatment drug was injected in the home cages and thus the animals were not

Table 1
Effects of acute SR48692 treatment on locomotor activity of mice

	Groups (mg/kg)			
	Saline	0.03 SR48692	0.1 SR48692	0.3 SR48692
Locomotor activity	93 ± 9.9 (10)	92 ± 9.2 (10)	82 ± 19.9 (10)	92 ± 17.9 (9)

Mice received i.p. injections 30 min before being placed in the open-field arena for a 5-min observation test. Data are means ± S.E.M. Number of animals are in parentheses.

exposed to the test environment during this experimental phase. On days 2, 9 and 16 following the cessation of pretreatment, the animals received a challenge injection of saline or 0.3 mg/kg SR48692 followed by an injection of 2.0 mg/kg amphetamine after 15 min. Fifteen minutes after the amphetamine challenge injection, they were individually placed in the center of the open-field arena and locomotor activity was recorded for 5 min. Amphetamine was injected every other day because it has been suggested that such a schedule of pretreatment is more effective to produce behavioural sensitisation than daily injections (Betancur et al., 1998). The dose of 2.0 mg/kg amphetamine was chosen because it induces locomotor-stimulant effects in mice under our experimental conditions. The dose of SR48692 was determined in experiment 1. Since neurotensinergic transmission has also been related to several other physiological effects, such as muscle relaxion, hypothermia and hypotension, which can, to some extent, attenuate locomotor activity (Nemeroff, 1986), we chose the highest acute dose of SR48692 that does not itself modify spontaneous open-field behaviour. Since behavioural sensitisation may be modified by stress (Piazza et al., 1990), the same number of injections (two) was used both in repeated pretreatment and in challenge procedures.

2.4.3. Experiment 3

This experiment was conducted exactly as experiment 2, except that a single challenge test was performed 9 days after saline or amphetamine pretreatment.

2.5. Statistical analysis

In the first experiment, one-way analysis of variance (ANOVA) was used to analyze the effect of SR48692 single administration on locomotor activity. In the second experiment, three-way ANOVA was used to analyze locomotor activity, to determine the pretreatment (amphetamine or saline) and challenge (SR48692 or saline) effects and repeated measures effects, as well as the interactions between these variables. In the third experiment, two-way ANOVA was used to analyze locomotor activity, to determine the pretreatment (amphetamine or saline) and challenge (SR48692 or saline) effects, as well as the interaction between these variables. Post hoc Duncan's multiple range tests were performed for specific group comparisons. $P < 0.05$ was used as the criterion for statistical significance.

3. Results

3.1. Experiment 1

None of the three acute SR48692 doses induced significant changes in locomotor activity (Table 1). Thus, we decided to use the highest SR48692 dose (0.3 mg/kg) to study the possible effect of neurotensin receptor blockade on the amphetamine-induced sensitisation phenomenon.

3.2. Experiment 2

Statistical analysis showed a significant main effect of pretreatment ($F(1,48) = 20.16$; $P < 0.0001$), challenge

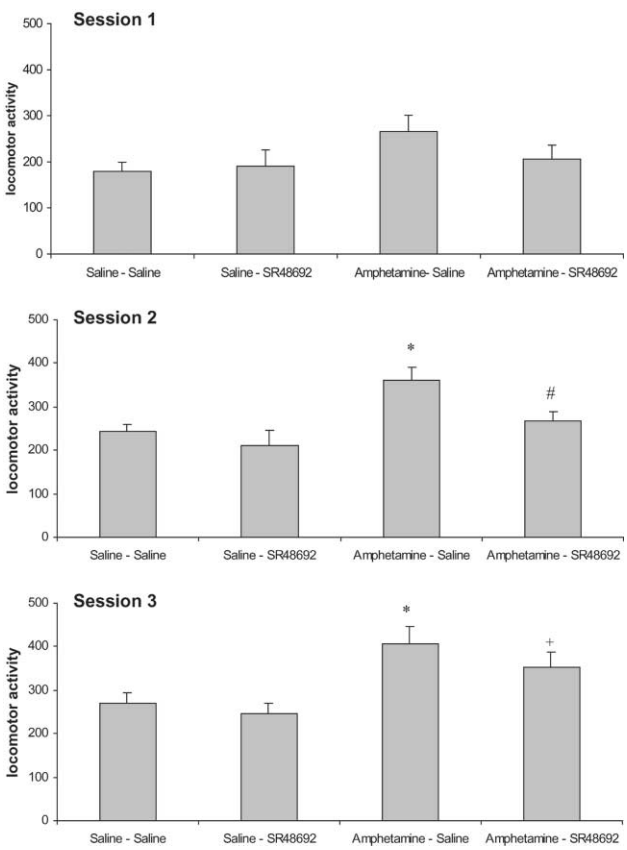

Fig. 1. Effect of challenge with saline or 0.3 mg/kg SR48692 and 2.0 mg/kg amphetamine on locomotor activity, after chronic pretreatment with saline or 2.0 mg/kg amphetamine. Mice received two injections of saline and saline or amphetamine every other day, for 13 days. Two days after the end of pretreatment (session 1), they were injected with saline or SR48692, followed 15 min later by amphetamine. Their locomotor activity was then measured for a period of 5 min, 15 min after amphetamine injection. This procedure was repeated 9 (session 2) and 16 (session 3) days after discontinuation of pretreatment. Means ± S.E.M. of data from 13 animals per group. $^{*}P < 0.05$ compared to Saline–Saline group $\#P < 0.05$ compared to Amphetamine–Saline group $+P < 0.05$ compared to Saline–SR48692 group. Three-way ANOVA, Duncan.

($F(1,48) = 4.65$; $P < 0.05$) and session ($F(2,96) = 13.77$; $P < 0.0001$) on locomotor activity. The interactions between these factors were not significant. As can be seen in Fig. 1, no changes in locomotor activity were recorded during the first session, performed 2 days following discontinuation of the drug pretreatment schedule. For session 2, held 7 days after the first session, the post hoc test revealed significant enhancement of locomotion in the Amphetamine-Saline group, as compared to the Saline–Saline and Amphetamine–SR48692 groups. The locomotor activity of the Saline–SR48692 group was not significantly different from that of the Saline–Saline or Amphetamine–SR48692 groups. For session 3, performed 7 days after the second session, we verified that locomotion was enhanced in the Amphetamine–Saline as compared to that in the Saline–Saline group. Once again, the locomotor activity of animals of the Saline–SR48692 group was not significantly different from that of mice in the Saline–Saline group, but was lower than that of the Amphetamine–SR48692 group.

With respect to the main effect of session (Fig. 2), the Saline–Saline, Amphetamine–Saline and Amphetamine–SR48692 groups had significantly higher locomotor activity in the third session than in the first. The Saline–SR48692 group did not show statistically significant changes between sessions.

3.3. Experiment 3

Experiment 3 aimed to determine the effects of SR48692 on the expression of amphetamine-induced behavioural sensitisation in the absence of the challenge injection-induced sensitisation described above (experiment 2). Statistical analysis showed a significant effect of pretreatment ($F(1,34) = 28.75$; $P < 0.0001$), challenge ($F(1,34) = 7.53$; $P < 0.05$) and interaction between pretreatment and challenge ($F(1,34) = 5.66$; $P < 0.05$) on locomotor activity. Multiple pairwise comparisons revealed significant enhancement of locomotion in the Amphetamine–Saline group as compared to the Saline–Saline, Saline–SR48692 and Amphetamine–SR48692 groups, as can be seen in Fig. 3.

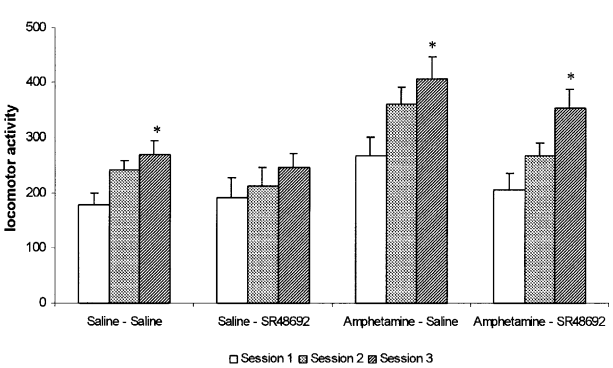

Fig. 2. Comparison of locomotor activity in sessions 1, 2 and 3 of mice pretreated and challenged as described in Fig. 1. $^{*}P < 0.05$ compared to session 1 data for the same group. Three-way ANOVA, Duncan.

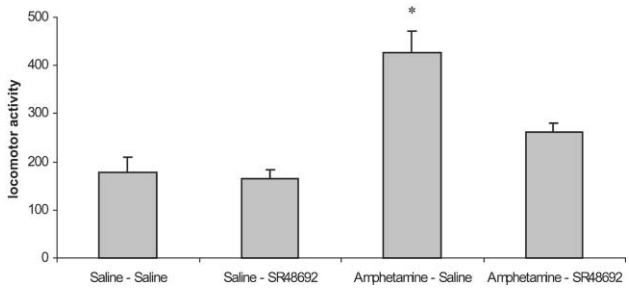

Fig. 3. Effect of challenge with saline or 0.3 mg/kg SR48692 and 2.0 mg/kg amphetamine on locomotor activity, after chronic pretreatment with saline or 2.0 mg/kg amphetamine. Mice received two injections of saline and saline or amphetamine every other day, for 13 days. Nine days after the end of pretreatment, they were injected with saline or SR48692, followed 15 min later by amphetamine. Their locomotor activity was then measured for a period of 5 min, 15 min after amphetamine injection. Means ± S.E.M. of data from 9–10 animals per group. $^{*}P < 0.05$ compared to Saline–Saline, Saline–SR48692 and Amphetamine–SR48692 groups. Two-way ANOVA, Duncan.

4. Discussion

The major findings of the present study were that: (1) the neurotensin antagonist, SR48692, prevented the expression of amphetamine-induced locomotor sensitisation but did not modify its acute locomotor-stimulating effect, (2) two challenge injections of amphetamine in saline-pretreated mice were sufficient to induce a sensitized locomotor response to a third challenge injection of the psychostimulant, (3) this (extra) sensitized response was also observed in amphetamine-pretreated animals, (4) SR48692 administration before the amphetamine challenge injections prevented the development of this challenge injection-induced sensitisation in saline-pretreated mice but not in the previous amphetamine-sensitized animals.

The lack of effects of acute injection of SR48692 on the locomotor activity of mice acutely injected with amphetamine agrees with data reported by Betancur et al. (1998). These investigators demonstrated that acute i.p. administration of SR48692 did not modify the locomotor activity elicited by cocaine. These results seem to be at variance with the above mentioned increased locomotion induced by microinjection of neurotensin in the ventral tegmental area (Kalivas et al., 1983). However, neurotensin, as mentioned earlier, when injected into the nucleus accumbens, decreases the behavioural responses induced by dopamine agonists such as amphetamine or apomorphine (Kalivas et al., 1984; Nemeroff et al., 1983; Ervin et al., 1981). Thus, the absence of effects of i.p. injection of SR48692 on locomotor activity in mice acutely treated with amphetamine may be related to simultaneous blockade of neurotensin receptors in both ventral tegmen-

tal area and nucleus accumbens, where neurotensin has opposite effects. On the other hand, it is worth pointing out that neurotensin exerts its effects by interacting with at least two distinct receptor subtypes, a high-affinity receptor (NTS1) and a low-affinity receptor (nts2), sensitive to levocabastine, a histamine H_1 receptor antagonist (Chalon et al., 1996; Tanaka et al., 1990; Schotte et al., 1986). SR48692 displays higher affinity for NTS1 than for nts2 receptors (Gully et al., 1993). Thus, since NTS1 receptors, nts2 receptors or other subtypes yet to be identified may be differently involved in the neurotensin/dopamine interaction in the mesolimbic pathway (Azzi et al., 1998), the effects of a systemic injection of SR48692 are not necessarily supposed to be the opposite of the effects of neurotensin.

The above concern notwithstanding, the ability of SR48692 to prevent the expression of the sensitized locomotor response to amphetamine seems to be consistent with data reported by Boulay et al. (1996). These investigators found that rats which develop an enhanced locomotor response to the specific dopamine uptake inhibitor, GBR12783, after its repeated administration are also sensitized to the stimulant motor effect of an acute i.c.v. injection of [D-Trp^{11}]neurotensin. According to Boulay et al. (1996), their findings could be related to a cross-sensitisation phenomenon (since, as mentioned above, repeated neurotensin exposure is also able to induce sensitisation to its stimulant effects). Alternatively, this could indicate that changes in neurotensinergic transmission contribute to drug-induced sensitisation. Our data lend support to the latter possibility, suggesting that neurotensinergic transmission has a critical role in the expression of amphetamine-induced locomotor sensitisation. Within this context, chronic cocaine has been shown to induce divergent effects on neurotensin density in different mesocortical regions in the rat (Pilotte et al., 1991). Indeed, whereas in these latter experiments, repeated cocaine administration decreased neurotensin binding in the ventral tegmental area, there was an increase in the prefrontal cortex and the nucleus accumbens was unaffected. Thus, further work is clearly required to characterize the specific substrates related to the neurotensinergic role in the development and expression of psychostimulant-induced behavioural sensitisation.

In the present study, a sensitized locomotion-activating response to a challenge amphetamine injection was observed on days 9 and 16, but not on day 2 following the discontinuation of repeated amphetamine pretreatment. In this respect, it has been demonstrated that biochemical alterations in the mesolimbic dopaminergic system associated with early psychostimulant withdrawal may mask some of the changes underlying behavioural sensitisation (Pierce and Kalivas, 1997). Interestingly, only two challenge injections of amphetamine were sufficient to induce a sensitized locomotor response to a third challenge injection of the drug in both saline- and amphetamine-pretreated mice. It is important to note that these challenge injections were followed by open-field exposures. In this respect, sensitisation can be classified as conditioned and unconditioned and the influence of learning and conditioning has been discussed (Camarini et al., 2000; Stewart and Vezina, 1988). Accordingly, it has been suggested that environmental cues might be conditioned stimuli for drug-like conditioned responses, potentiating the development of behavioural sensitisation (Pierce and Kalivas, 1997)—although sensitisation to the locomotor-activating effect of amphetamine and other drugs of abuse was observed when drug injections were not paired with the observation environment (Bellot et al., 1996, 1997).

Importantly, SR48692 administration prior to amphetamine challenge injections prevented the development of this "challenge injection-induced sensitisation" in saline-pretreated mice but not in amphetamine-pretreated animals, which had already developed unconditioned behavioural sensitisation. Interestingly, Haracz et al. (1995) suggested that the conditioned component of sensitisation would be NMDA receptor-dependent, whereas the unconditioned component would be NMDA receptor-independent. In this context, Rompré (1997) suggested that repeated neurotensin treatment produces sensitisation to the locomotion-stimulating effect of an acute amphetamine injection via activation of neurotensin receptors in the medial prefrontal cortex efferents to the ventral midbrain, which contain glutamate and/or aspartate (Christie et al., 1985), neurotransmitters that can modulate subcortical dopamine neurotransmission (Kalivas and Duffy, 1995). Thus, although highly speculative, the possibility is raised that SR48692 specifically prevented the conditioned component of behavioural sensitisation by blocking neurotensin receptors in the medial prefrontal cortex. In further support of this assumption, activation of neurotensin receptors in this region was found to stimulate midbrain dopamine cell firing (Rompré and Boye, 1994).

Finally, it should be noted that the ability of SR48692 to prevent the development of challenge amphetamine injections-induced sensitisation apparently contradicts the findings reported by Horger et al. (1994), showing that co-treatment with SR48692 1 h before cocaine injection failed to prevent the development of cocaine sensitisation to the locomotor-activating response in rats. However, these drug pretreatments were administered in the home cage and not paired with the apparatus. In another experiment in their study, Horger et al. (1994) found that SR48692 pretreatment for 5 days delayed the development of cocaine-induced locomotor sensitisation. Although differences in SR48692 treatment schedule (co-administration vs. previous administration) have been suggested to be associated with these contradictory effects, it is interesting to note that in this second experiment, cocaine injections were paired with the observation environment. In this context, the attenuating effect of SR48692 co-treatment on the development of amphetamine-induced sensitisation re-

ported by Rompré and Perron (2000) was observed in an experimental situation in which amphetamine injections were paired with the observation environment.

In conclusion, the results of the present study strongly indicate that the blockade of neurotensin receptors attenuates both the initiation and the expression of amphetamine-induced locomotor sensitisation. These findings suggest that both acute and long-term treatments with selective neurotensin receptor antagonists could be of potential clinical usefulness in the treatment of neuropsychiatric disorders supposedly related to the behavioural sensitisation phenomenon.

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