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Short communication

Monoamine oxidase inhibitor sensitive site implicated in sensitization to quinpirole

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Abstract

Clorgyline (1.0 mg/kg/day) administered via osmotic minipumps blocked the development of locomotor sensitization to the dopamine receptor agonist quinpirole (0.5 mg/kg every 3 days for 8 injections). In male rats already well sensitized to quinpirole, the continuous infusion of clorgyline (1.0 mg/kg/day for 28 days) produced a progressive decline in locomotor activity, despite a continued regimen of quinpirole injections (0.5 mg/kg every 3 days). It is suggested that the development, as well as the maintenance, of locomotor sensitization to quinpirole is modulated by the activation of an monoamine oxidase inhibitor-sensitive site. This site may be a dopamine D_2 receptor-linked monoamine oxidase inhibitor-displaceable quinpirole binding site, the enzyme monoamine oxidase-A, or other clorgyline binding sites. © 1997 Elsevier Science B.V.

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1. Introduction

Repeated administration of the dopamine stimulants amphetamine (Segal and Schuckit, 1983), apomorphine (Mattingly and Gotsick, 1989), bromocriptine (Hoffman and Wise, 1992), and quinpirole (Szechtman et al., 1994b), results in behavioral sensitization; that is, a progressive augmentation of the motor response to subsequent injections (Robinson and Becker, 1986). Although the development and expression of sensitization appears to be related to an increase in the somatodentritic release of dopamine in the ventral tegmental area and of dopamine transmission in the striatum and nucleus accumbens (Kalivas and Stewart, 1991), a recent report has opened the possibility that, at least for quinpirole, a novel binding site may be implicated in the process of sensitization. Specifically, in vitro findings have demonstrated that monoamine oxidase inhibitors such as clorgyline inhibit the binding of quinpirole, but not that of the dopamine D_2 receptor antagonist, spiperone, in rat striatal membranes (Levant et al., 1993, 1996). These findings suggest that monoamine oxidase inhibitors possess a unique affinity for a novel binding site within the striatum that is either labeled by quinpirole or which modulates quinpirole binding at dopamine D_2-like receptors (Levant et al., 1993, 1996) and which, we suggest, may be involved in sensitization. Indeed, the present report demonstrates that chronic clorgyline not only blocks the development of locomotor sensitization to quinpirole, but also partially reverses sensitization, once established.

2. Materials and methods

Three groups of male hooded Long-Evans rats (Charles River, Canada; weighing 150–175 g at the start of the experiment) received 8 injections of quinpirole (0.5 mg/kg, s.c., every three days) according to a protocol that has been shown to reliably induce a stable level of locomotor sensitization (Szechtman et al., 1994a,b). Two of the three groups of rats received a continuous infusion of clorgyline (0.2 mg/kg/day, $n = 4$ or 1.0 mg/kg/day, $n = 6$) for 28 days via subcutaneously implanted Alzet 2ML4 osmotic minipumps (Alza, Palo Alto, CA), while the third group (quinpirole-Control group, $n = 6$) underwent sham surgery. Filling concentrations for the minipumps were determined using the method described by Greenshaw (1986). The 1

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mg/kg/day dose of clorgyline has been previously shown to inhibit monoamine oxidase-A activity by 100% and attenuate the acute behavioral effects of a low dose of quinpirole (Allison et al., 1995). Immediately following each quinpirole injection, animals were placed in automated activity monitors (Omnitech Electronics, Columbus, OH) and their locomotor activity recorded for 90 min. The osmotic minipumps were explanted after the 8th injection, and one week later all groups received a challenge injection of quinpirole (0.5 mg/kg, s.c.) and their locomotor activity was recorded for 90 min. Furthermore, a savings paradigm was employed to probe for any latent sensitization in the chlorgyline pretreated groups. All groups continued to receive injections of quinpirole (0.5 mg/kg, every three days), and the number of injections needed to bring the clorgyline pretreated animals to the sensitized level of locomotion was monitored.

To determine the effect of clorgyline on sensitized locomotion, quinpirole-sensitized rats received a subcutaneous infusion of clorgyline (1.0 mg/kg/day for 28 days, $n = 6$) and 8 injections of quinpirole, while a comparison group was administered quinpirole only ($n = 10$). Animals from the previous study were used, but reassigned into the appropriate groups and the experimental protocol remained unchanged.

3. Results

As shown in Fig. 1 (left), quinpirole produced robust sensitization in the quinpirole-Control group, as evidenced by a 5-fold increase in locomotor activity on injection 8, compared to the acute quinpirole injection. Moreover, although the low clorgyline dose was ineffective, the higher dose of clorgyline (1.0 mg/kg/day), fully blocked the induction of quinpirole sensitization.

A week following the explantation of the minipumps, all groups received an injection of quinpirole. The quinpirole-Control group locomoted significantly more than the group of rats previously treated with the high dose of clorgyline (548.2 ± 8.8 m vs. 144.5 ± 4.9 m, $p = 0.002$, *t*-test). Furthermore, animals pretreated with clorgyline required 8 to 9 additional quinpirole injections to reach the same level of sensitization as that shown by the quinpirole-Control group, which corresponds to the number of injections that naive rats require to achieve a stable level of locomotor sensitization (see Fig. 1; Szechtman et al., 1994a,b). Together, these findings suggest that clorgyline blocked the development of locomotor sensitization to quinpirole, and not merely its expression.

Fig. 1 (right) shows that clorgyline induced a decline in sensitized locomotion, but it took 19 days of clorgyline treatment (7th injection of quinpirole) before the level of locomotor activity was found to decrease significantly compared to the animals performance at the beginning of treatment.

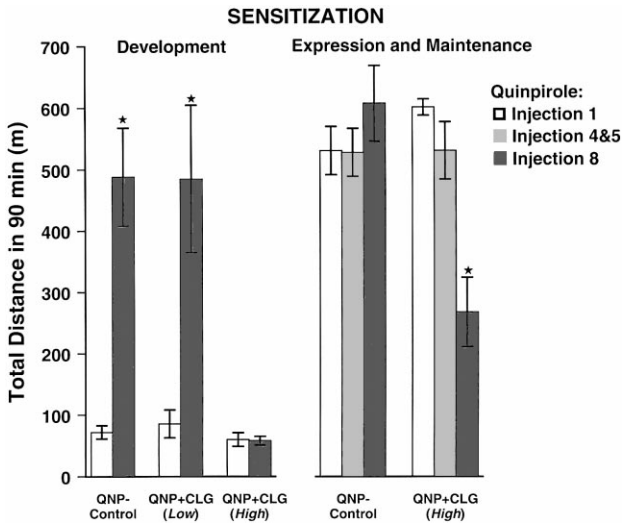

Fig. 1. The effect of chronic treatment with clorgyline on the development, expression and maintenance of locomotor sensitization induced by quinpirole. Clorgyline was continuously administered via osmotic minipumps at a dose of either 0.2 mg/kg/day (low) or 1 mg/kg/day (high). Injection 4&5 refers to the mean of performance on injections 4 and 5. Bars represent mean ± SEM. * $p < 0.05$ compared to performance at quinpirole Injection 1; *t*-test.

4. Discussion

The findings of this study demonstrate that the continuous administration of clorgyline not only blocked the development of locomotor sensitization to quinpirole, but also attenuated a well established sensitization. The fact that the latter effect of clorgyline was delayed and not immediate, suggests that the attenuation of sensitization was probably a time-dependent process induced by clorgyline and that the maintenance of sensitization to quinpirole is an active process. To our knowledge, a progressive reversal of locomotor sensitization has not been reported before.

The effects of clorgyline on locomotor sensitization may reflect an interaction with the monoamine oxidase inhibitor-displaceable quinpirole binding site identified by Levant et al. (1993, 1996). However, the present findings do not rule out the possibility that the critical action of clorgyline on sensitization may be via the inhibition of monoamine oxidase-A, or the down-regulation of imidazoline I_2-preferring receptors (Allison et al., 1995; Alemany et al., 1995; Lione et al., 1996) or other clorgyline binding sites (Levant et al., 1996). To distinguish among these possible sites of action, it will be necessary to investigate the effect of site-selective monoamine oxidase inhibitors on quinpirole-induced sensitization. Nevertheless, regardless of which alternative proves to be correct, the demonstration that a monoamine oxidase inhibitor-type drug

blocks the development and attenuates the expression/maintenance of quinpirole-induced locomotor sensitization, opens a potentially novel pathway to investigate the mechanism of sensitization.

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References

Allison, K., Ivanova, S., Greenshaw, A.J., 1995. Behavioral response to SKF 38393 and quinpirole following chronic antidepressant treatment. Eur. J. Pharmacol. 277, 139–144.

Alemany, R., Olmos, G., Garcia-Sevilla, J., 1995. The effects of phenelzine and other monoamine oxidase inhibitor antidepressants on brain and liver I2 imidazoline-preferring receptors. Br. J. Pharmacol. 114, 837–845.

Greenshaw, A.J., 1986. Osmotic mini-pumps: A convenient program for weight-adjusted filling concentrations. Brain Res. Bull. 16, 759–761.

Hoffman, D.C., Wise, R.A., 1992. Locomotor-activating effects of the D_2 agonist bromocriptine show environment-specific sensitization following repeated injections. Psychopharmacology 107, 277–284.

Kalivas, P., Stewart, J., 1991. Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res. Rev. 16, 223–244.

Levant, B., Grigoradis, D., DeSouza, E., 1993. Monoamine oxidase inhibitors inhibit [^{3}H]quinpirole binding in rat striatal membranes. Eur. J. Pharmacol. 246, 171–178.

Levant, B., Moehlenkamp, J., Morgan, K., Leonard, L., Cheng, C., 1996. Modulation of [^{3}H]quinpirole binding in brain by monoamine oxidase inhibitors: Evidence for a potential novel binding site. J. Pharmacol. Exp. Ther. 278, 145–153.

Lione, L., Nutt, D., Hudson, A., 1996. [^{3}H]2-(2-benzofuranyl)-2-imidazoline: A new selective high affinity radioligand for the study of rabbit brain imidazoline I2 receptors. Eur. J. Pharmacol. 304, 221–229.

Mattingly, B.A., Gotsick, J.E., 1989. Conditioning and experimental factors affecting the developments of sensitization to apomorphine. Behav. Neurosci. 103, 1311–1317.

Robinson, T., Becker, J., 1986. Enduring changes in brain and behavior produced by chronic amphetamine administration: A review and evaluation of animal models of amphetamine psychosis. Brain Res. 396, 157–198.

Segal, D.S., Schuckit, M.A., 1983. Animal models of stimulant-induced psychosis. In: Creese, I. (Ed.) Stimulants: Neurochemical, Behavioral and Clinical Perspectives. Raven Press, New York, pp. 131–167.

Szechtman, H., Dai, H., Mustafa, S., Einat, H., Sullivan, R.M., 1994a. Effects of dose and interdose interval on locomotor sensitization to the dopamine agonist quinpirole. Pharmacol. Biochem. Behav. 48, 921–928.

Szechtman, H., Talangbayan, H., Canaran, G., Dai, H., Eilam, D., 1994b. Dynamics of behavioral sensitization induced by the dopamine agonist quinpirole and a proposed central energy control mechanism. Psychopharmacology 115, 95–104.