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Short communication

Dizocilpine prevents the enhanced locomotor response to quinpirole induced by repeated electroconvulsive shock

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Abstract

Repeated administration of electroconvulsive shock, as expected, potentiated the locomotor stimulant response to quinpirole (0.3 mg/kg s.c.), a dopamine D_2-like receptor agonist. Chronic, but not acute, treatment with the NMDA receptor non-competitive antagonist dizocilpine (0.3 mg/kg i.p.) prevented electroconvulsive shock-induced potentiation of quinpirole locomotor response. These results suggest that NMDA receptor activation is necessary for the development of supersensitivity to dopamine receptor agonists produced by repeated electroconvulsive shock. The relevance of this observation in regard to the mechanism of electroconvulsive shock therapeutic effect is discussed. © 1997 Elsevier Science B.V.

Keywords: Dizocilpine; Dopamine receptor; Electroconvulsive shock; NMDA receptor; Supersensitivity

1. Introduction

A great deal of experimental evidence suggests that the NMDA subtype of glutamate receptor is involved in several forms of behavioural and neural plasticity. In particular, the NMDA receptor plays an important role in neuronal development, long-term potentiation, kindling, learning and memory (see McDonald and Johnston, 1990). Moreover, it has been reported that the non-competitive NMDA receptor antagonist dizocilpine (also known as MK-801) prevents the development of opiate tolerance and dependence (Trujillo and Akil, 1991), and interferes with the development of sensitization to dopamine receptor stimulant drugs (Wolf and Khansa, 1991), suggesting that NMDA receptors play a crucial role in the development of drug-induced changes in sensitivity to neurotransmitters. In line with this evidence, we have shown that dizocilpine prevents the potentiation of the locomotor response to the D_2-like dopamine receptor agonist quinpirole induced by chronic treatment with the antidepressant drug imipramine (D'Aquila et al., 1992).

The locomotor response to dopamine receptor agonists is attributed to the stimulation of dopamine receptors in the mesolimbic system (Kelly et al., 1975), which is a major anatomical substrate of reward related responses and pleasure-seeking behaviours (see Willner and Scheel-Krüger, 1991). The functional activation of this system, of which the potentiated locomotor response to dopamine agonists is an instance, is regarded as one of the mechanisms underlying the therapeutic effect of a variety of antidepressant drugs and of electroconvulsive shock, a highly effective treatment in depressive illness (see Serra et al., 1992).

In the present study, we examined the effect of dizocilpine on the potentiation of the locomotor response to quinpirole induced by repeated electroconvulsive shock. The results indicate that chronic, but not acute, treatment with dizocilpine prevents the development of electroconvulsive shock-induced supersensitivity.

2. Materials and methods

Experiments were performed on male Sprague-Dawley rats (Charles River, Como, Italy), initially weighing 160–180 g. The animals were housed 4 per cage in air-conditioned rooms (temperature: 22°C; humidity: 60–70%) with a 24 h light/dark cycle (light from 8.00 a.m. to 8.00 p.m.) and with water and a standard laboratory diet ad libitum. The animals were allowed 2 weeks of acclimatization to the colony after arrival.

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Quinpirole-HCl (Research Biochemicals International, Natick, MA, USA) and dizocilpine ((+)-5-methyl-10,11-dihydro-5-*H*-dibenzo-[*a*,*d*]-cyclohepten-5,10-imine maleate, Research Biochemicals International) were dissolved in saline.

Electroconvulsive shock (120 V, sinusoidal 50 Hz, for 1 s) was delivered through ear-clip electrodes to unanaesthetized rats. Control animals were handled in the same way but no current was applied.

The analysis of locomotor activity was performed by the Videotrack 512 System (Electronique Lyonnaise, Lyon, France). The total distance (cm) covered by the rats with ambulatory movements ('wide movements' according to VT 512 System User's Manual, pp. A.18–19) was considered as a measure of locomotor activity.

The animals were divided into four groups which received once daily for 8 days: (1) electroconvulsive shock followed by saline (5 ml/kg, intraperitoneally, i.p.); (2) electroconvulsive shock followed by dizocilpine (0.3 mg/kg, i.p.); (3) sham electroconvulsive shock followed by dizocilpine; (4) sham electroconvulsive shock followed by saline. Two additional groups of rats, which were given for 8 days either electroconvulsive shock or the sham treatment, received a single injection of dizocilpine after the last electroconvulsive shock or sham electroconvulsive shock. Dizocilpine was administered 15 min after electroconvulsive shock.

All electroconvulsive shock-treated animals responded with a tonic-clonic seizure, which lasted between 10 and 20 s. No difference was observed between animals in the saline and chronic dizocilpine groups.

Twenty-four hours after the last treatment, the animals were individually placed into the motility cages (40 × 40 cm). After 2 h of habituation, they were subcutaneously injected either with quinpirole (0.3 mg/kg) or with saline (1 ml/kg), and the locomotor activity was recorded for 45 min. Experiments were performed between 9.00 and 14.00 h in a sound-proof room.

Results were analyzed by analysis of variance, supplemented by tests of simple main effects and *F*-tests for contrasts, using the appropriate analysis of variance error term (Winer, 1971). Analysis involved three between-subjects factors: electroconvulsive shock (electroconvulsive shock-treated/controls), quinpirole (quinpirole/saline) and dizocilpine (saline/chronic dizocilpine/acute dizocilpine).

The present study has been carried out after approval of the Ethical Committee of the University of Cagliari.

3. Results

The spontaneous locomotor activity of animals, measured during the habituation period, did not differ between the different groups (*F* values relative to the factors electroconvulsive shock, dizocilpine and their interaction: < 1, not significant).

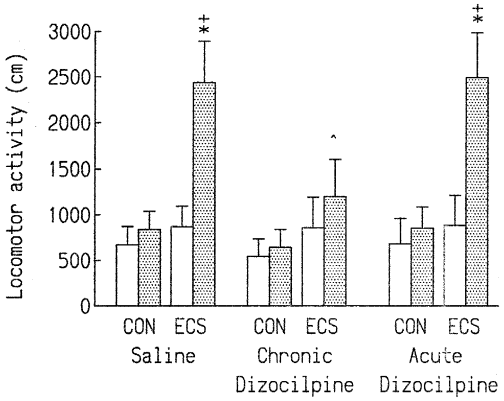

Fig. 1. CON, controls; ECS, repeated ECS; open columns, saline; stippled columns, quinpirole. Each value represents the mean ± S.E.M. of 6 animals per group. After 2 h of habituation to the motility cages, rats were injected with either quinpirole (0.3 mg/kg, s.c.) or saline (1 ml/kg, s.c.) and the locomotor activity was monitored for 45 min (* simple main effect of quinpirole, $P < 0.01$; $^{+}$ *F*-test for contrasts (effect of ECS), $P < 0.01$; $^{\wedge}$ simple main effect of dizocilpine, $P < 0.01$).

Analysis of variance showed a significant effect of electroconvulsive shock ($F(1,5) = 6.94$, $P = 0.04$) and quinpirole ($F(1,5) = 8.48$, $P = 0.03$), with an overall interaction between these two factors close to statistical significance ($F(1,15) = 6.94$, $P = 0.04$). However, the interaction between quinpirole and electroconvulsive shock was significant in saline-treated animals ($F(1,15) = 4,82$, $P < 0.05$) and in animals which received a single injection of dizocilpine ($F(1,15) = 5.11$, $P < 0.05$).

The administration of the D_2-like dopamine receptor agonist quinpirole (0.3 mg/kg s.c.) failed to increase locomotor activity in the control group ($F(1,15) = 0.15$, not significant), but increased locomotor activity in electroconvulsive shock-treated animals (simple main effect of quinpirole in electroconvulsive shock-treated rats: $F(1,15) = 13.79$, $P < 0.01$; simple main effect of electroconvulsive shock in quinpirole-treated rats: $F(1,15) = 13.68$, $P < 0.01$) (Fig. 1). The ability of quinpirole to increase locomotor activity is a well known phenomenon (see Serra et al., 1990); however, the magnitude of this effect is dependent upon experimental conditions and method of detection (e.g., photocell apparatus or video-tracking system). In this study we used a dose that in our experimental conditions is a subthreshold dose for this effect (see also D'Aquila et al., 1992): as a result, only animals whose sensitivity to quinpirole was enhanced by electroconvulsive shock did show an increased locomotor response.

The administration of the non-competitive NMDA receptor antagonist dizocilpine following each electroconvulsive shock session antagonized the potentiated behavioural response to quinpirole ($F(1,20) = 20.53$, $P < 0.01$) (Fig. 1). In contrast, a single injection after the last electroconvulsive shock failed to affect it (simple main effect of quinpirole on acute dizocilpine-electroconvulsive shock group: $F(1,15) = 14.55$, $P < 0.01$) (Fig. 1).

4. Discussion

The results confirm that repeated treatment with electroconvulsive shock potentiates the locomotor response to quinpirole, a D_2-like dopamine receptor agonist (Serra et al., 1990), and show that the non-competitive NMDA receptor antagonist dizocilpine, when administered after each electroconvulsive shock session, prevents the development of this potentiation.

Since acute dizocilpine administration fails to antagonize the locomotor stimulating effect of the indirect dopamine agonists amphetamine and cocaine (Wolf et al., 1994), it is unlikely that our results may be explained by a direct antagonism of the quinpirole locomotor effect. Consistently, a single injection of dizocilpine failed to influence the quinpirole locomotor response in our electroconvulsive shock-treated group. Moreover, although we are not aware of any study on dizocilpine pharmacokinetics after chronic treatment, due to its relatively short elimination half-life (brain 2.05 h; plasma 1.9 h; Vezzani et al., 1989), the interval of 24 h between the last dizocilpine injection and the quinpirole challenge should reasonably rule out the possibility of a direct interaction.

These results suggest that dizocilpine is able to prevent the development of behavioural supersensitivity to dopamine receptor agonists induced by repeated electroconvulsive shock, but not to suppress it after its development. This picture is similar to the one observed in chronic imipramine-treated rats, where chronic, but not acute, treatment with dizocilpine prevented the development of behavioural supersensitivity to quinpirole (D'Aquila et al., 1992).

The fact that dizocilpine prevents the development of behavioural supersensitivity to dopamine receptor agonists induced by two antidepressant treatments as different as imipramine and electroconvulsive shock, suggests that activation of NMDA receptors might be a necessary step in reaching the antidepressant clinical effect. This hypothesis is in apparent contrast with the observation that dizocilpine and other antagonists at the NMDA receptor have been shown to possess an antidepressant-like activity in both acute (Trullas and Skolnick, 1990) and chronic (Papp and Moryl, 1994) animal models of depression. However, Meloni et al. (1993) reported that acute administration of dizocilpine exerts an antidepressant-like effect in the learned helplessness model of depression, whereas the same drug, chronically administered through osmotic minipumps subcutaneously implanted, is able to antagonize the effect of chronic imipramine in the same model.

The present finding is consistent with the observation that repeated treatment with dizocilpine prevents the increased locomotor response to the dopamine agonist apomorphine induced by electroconvulsive shock in mice (Nomikos et al., 1992). Both ours and Nomikos' results show that the effect of dizocilpine in preventing the development of electroconvulsive shock-induced supersensitivity to dopamine agonists does not require the inhibition of the electroconvulsive shock-induced seizures, in that dizocilpine exerts its effect when administered after the electroconvulsive shock session. Carlsson and Carlsson (1990) suggested that electroconvulsive shock-induced potentiation of dopamine-mediated responses is due to a postictal excitotoxic damage of postsynaptic neurons in the basal ganglia, following the excessive release of excitatory amino acids occurring during the seizure. Since dizocilpine has been shown to prevent NMDA-mediated neurodegeneration (see Rothman and Olney, 1987), Nomikos et al. (1992) suggested that such protective effect might explain its ability to prevent the electroconvulsive shock effect.

Although this explanation might seem at odds with the fact that dizocilpine exerts a similar effect on imipramine-induced supersensitivity to dopamine receptor agonists (postictal excitotoxic damage could hardly be suspected as being responsible for imipramine effects), it has to be borne in mind that the increases in dopaminergic activity observed after either electroconvulsive shock or imipramine, although similar in many respects, appear to be dependent upon different underlying neural mechanisms (D'Aquila et al., 1997). Therefore, it may well be that dizocilpine affects the two through different mechanisms.

Alternatively, it is possible that chronic treatment with dizocilpine prevents the behavioural supersensitivity induced by electroconvulsive shock by desensitizing D_2-like receptors. In fact, chronic treatment with dizocilpine has been shown to reduce both the density of D_2 receptors and the locomotor response to quinpirole (Dall'Olio et al., 1992).

Regardless of the mechanisms involved, the observation that dizocilpine interferes with the effect of repeated electroconvulsive shock, along with our previous observation showing the same effect in rats chronically treated with imipramine, further suggests that the NMDA receptor could be considered both a target in the development of new antidepressant drugs and a focus in the study of the neural mechanisms of mood disorders.

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