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Short communication

Chronic lithium chloride fails to prevent imipramine-induced sensitization to the dopamine D_2-like receptor agonist quinpirole

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Abstract

Lithium salts, an effective antimanic treatment, are able to prevent the development of the dopaminergic behavioural supersensitivity induced by chronic treatment with neuroleptics, by denervation of the dopaminergic terminal fields and by rapid eye movements (REM) sleep deprivation, which is considered a model of mania. We have studied the effect of a lithium (LiCl) diet, inducing a lithium serum level in the range of therapeutic efficacy, on the development of the supersensitivity to the locomotor effect of the dopamine D_2-like receptor agonist, quinpirole, induced by chronic treatment with the antidepressant drug, imipramine. The results show that lithium is not able to prevent the development of such behavioural supersensitivity. The present data suggest that antidepressant-induced dopaminergic supersensitivity might provide a useful model of those manic states induced by (or subsequent to) antidepressant treatments. Moreover, the finding is consistent with the view that antidepressant-induced dopaminergic supersensitivity might play a role in the therapeutic effect of these drugs (which is known to be augmented by lithium, and not antagonised). Finally, the results show that the dopaminergic supersensitivity induced by imipramine is qualitatively different from that induced by neuroleptics or denervation of the dopaminergic terminal fields.

Keywords: Antidepressant drug; Imipramine; Lithium chloride; Locomotor activity; Mania

1. Introduction

Lithium salts are widely used in psychiatry for their antimanic and mood stabilising efficacy (Baldessarini, 1996). As to the antimanic therapeutic effect, it has been suggested that it might be due, at least in part, to the ability of lithium salts to interfere with dopaminergic neurotransmission. Preclinical studies have shown the ability of lithium salts to antagonise behaviours mediated by the stimulation of dopamine receptors and to prevent (or to reduce) the development of the dopaminergic behavioural supersensitivity induced either by chronic treatment with neuroleptic drugs or by denervation of the dopaminergic terminal fields in the brain. In particular, lithium salts have been reported to antagonise apomorphine-induced pecking in pigeons (Dehpour et al., 1998) and apomorphine-induced penile erection in rats (Dehpour et al., 1995), but not amphetamine-induced stereotypy, hyperactivity and hypothermia (Ebstein et al., 1980). Moreover, lithium salts prevent the development of the behavioural supersensitivity to amphetamine (Pittman et al., 1984) and apomorphine (Bloom et al., 1983) induced by chronic treatment with the dopamine receptor antagonist, haloperidol, and the development of the behavioural supersensitivity to apomorphine induced by lesioning of dopaminergic terminal fields (Gruenthal, 1984; Swerdlow et al., 1985). Lithium salts are also effective to prevent the increased locomotor response to amphetamine (Arriaga et al. 1988) and apomorphine (Das Chagas Rodrigues et al., 1985) induced by rapid eye movement (REM) sleep deprivation, a behavioural manipulation that is used to model mania in animals (Gessa et al., 1995). On the contrary, lithium salts do not antagonise the dopaminergic behavioural supersensitivity induced by repeated amphetamine administration (Rubin and Wooten, 1984).

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Behavioural dopaminergic supersensitivity can also be induced by chronic treatment with antidepressant drugs (see Serra et al., 1992). Since the antidepressant-induced dopaminergic behavioural supersensitivity has been suggested, on the one hand, to play a role in the therapeutic effect of these drugs (see Serra et al., 1992), with which lithium salts are often given (Baldessarini, 1996), and, on the other hand, to be a model of the antidepressant-induced switch to mania (Serra et al., 1990), which is resistant to lithium salt therapy (see Koukopoulos et al., 1995), it was of some interest to know whether its development might be prevented by lithium chloride.

To address this issue, we investigated the effect of the simultaneous chronic administration of lithium chloride and the tricyclic antidepressant, imipramine, on the locomotor response to the dopamine D_2-like receptor agonist, quinpirole.

2. Materials and methods

2.1. Subjects

The experiments were performed on male Sprague–Dawley rats (Charles River, Como, Italy) that initially weighed 160–180 g. They were housed four per cage in air-conditioned rooms. The rooms were lit between 0800 and 2000 h and maintained at a temperature of 22°C and humidity of 60–70%. The animals had water and the standard laboratory diet (except for the LiCl-treated group, see below) ad libitum.

2.2. Drugs and treatments

The animals were divided into four groups ($n = 8$): (1) control diet plus vehicle, (2) control diet plus imipramine, (3) ''lithium'' diet plus vehicle, (4) ''lithium'' diet plus imipramine. Imipramine treatment and lithium diet were given for 4 weeks and the animals were challenged with quinpirole and tested for locomotor activity 24 h after the end of this drug regimen.

Quinpirole HCl and imipramine HCl (Sigma, St. Louis, USA) were dissolved in distilled water. Imipramine was administered intraperitoneally in daily injections, at the dose of 20 mg/kg in a volume of 1 ml/kg. Lithium-treated rats were fed the ''lithium'' diet (pellets with 60 mEq/kg LiCl) and their average serum lithium level was 0.76 ± 0.1 mEq/l at the end of the 4-week period. Quinpirole was administered subcutaneously (s.c.) at the dose of 0.15 mg/kg in a volume of 1 ml/kg.

2.3. Locomotor activity

Locomotor activity was measured by placing the animals individually in motility cages (M/P 40 Fc Electronic Motility Meter, Motron Products, Stockholm). Each cage had 40 photoconductive sensors placed in the floor area (21×32 cm) at a fixed distance of 4 cm. The sensors were lit uniformly by an incandescent lamp mounted 60 cm above the floor. Motor activity was defined as the number of interruptions of a beam. Experiments were performed between 0900 and 2100 h in a soundproof room. After 1-h habituation to the motility cages, all the rats were s.c. injected with 0.15 mg/kg quinpirole and the locomotor response was recorded for the next 45 min.

2.4. Statistics

The results were analysed by analysis of variance (ANOVA), supplemented by *F*-tests for contrasts, using the appropriate ANOVA error term (Winer, 1971). The analysis involved two between-subjects factors: lithium chloride and imipramine.

3. Results

3.1. Habituation

ANOVA showed a significant main effect both of lithium chloride [$F(1,28) = 4.29$; $P < 0.05$] and of imipramine [$F(1,28) = 7.72$; $P < 0.01$], with no significant interaction between the two factors [$F(1,28) = 0.63$; not significant]. These effects were due to the ability of both lithium chloride and imipramine treatment to induce a slight reduction in the locomotor activity of the rats (Fig. 1).

3.2. Quinpirole challenge

ANOVA showed a significant main effect of imipramine [$F(1,28) = 24.41$; $P < 0.001$]. Neither a significant effect of lithium chloride [$F(1,28) = 0.02$; not significant] nor a significant interaction between imipramine and lithium [$F(1,28) = 0.4$; not significant] was revealed. *F*-tests for

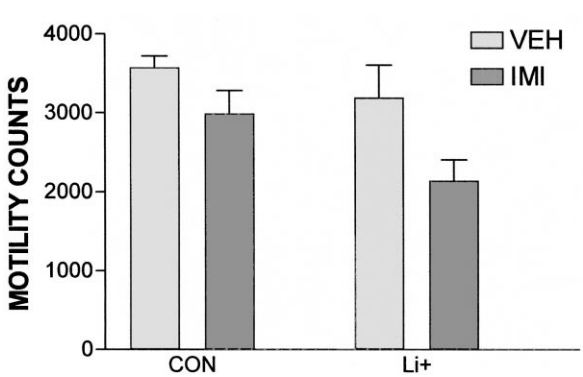

Fig. 1. Habituation. Veh: vehicle; IMI: imipramine. CON: controls; Li+: lithium. Each value represents the mean ± S.E.M. from eight rats. Locomotor activity was recorded for 60 min after placing the animals into the motility cages.

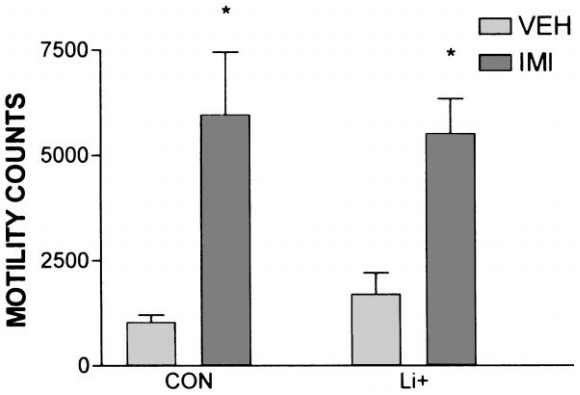

Fig. 2. Quinpirole-induced locomotor activity. Veh: vehicle; IMI: imipramine. CON: controls; Li+: lithium. Each value represents the mean ± S.E.M. from eight subjects. After 60-min habituation to the motility cages, locomotor activity was recorded for 45 min following a 0.15 mg/kg s.c. quinpirole injection. $^{*}P < 0.01$: Effect of imipramine (ANOVA followed by *F*-test for contrasts).

contrasts showed that chronic treatment with imipramine potentiated the quinpirole locomotor response both in controls [$F(1,28) = 15.52$; $P < 0.01$], and in ''lithium''-treated animals [$F(1,28) = 9.29$; $P < 0.01$] (Fig. 2).

4. Discussion

The results show that chronic treatment with lithium does not prevent behavioural supersensitivity to quinpirole induced by chronic treatment with imipramine.

This observation is consistent with our previous suggestion that antidepressant-induced dopaminergic behavioural supersensitivity might model manic states induced by antidepressant treatments (Serra et al., 1990), which are known to be resistant to lithium salts (see Koukopoulos et al., 1995).

Responsivity to lithium salts in bipolar patients may vary depending upon the pattern of switches (see Koukopoulos et al., 1995). In particular, patients showing a manic episode followed by depression and a ''well'' interval show a high responsiveness to lithium salt treatment, whereas patients showing depression switching into mania followed by a ''well'' interval are more likely to be resistant. Another group of bipolar patients, which are resistant to lithium salts, are ''rapid cyclers'', i.e. patients with four or more episodes per year. (It has been suggested that rapid cycling might be the consequence of repeated exposure of susceptible patients to antidepressants.) What emerges from these observations is that resistance to lithium salts is far more likely to be observed in those groups of patients who have received (or in which most are likely to have received) antidepressant drugs before lithium salts (Koukopoulos et al., 1995).

On the basis of these considerations, antidepressant-induced increased sensitivity to dopamine agonists might be proposed as a model of these lithium-resistant manic syndromes. Lithium-resistant manic episodes are likely to be successfully treatable with neuroleptic drugs (see Koukopoulos et al., 1995). Consistently, L-sulpiride, a dopamine D_2 receptor antagonist and an antipsychotic drug, is effective in antagonising the dopaminergic behavioural supersensitivity induced by chronic treatment with imipramine (Serra et al., 1990). Interestingly, the dopamine D_1 receptor antagonist SCH 23390, ((*R* +)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine), does not antagonise the dopamine behavioural supersensitivity induced by imipramine (Serra et al., 1990) but is effective in that induced by electroconvulsive shock (D'Aquila et al., 1997). It has been reported that this drug is devoid of antimanic properties (Gessa et al., 1991). It should be interesting to see whether SCH 23390 would exert a therapeutic effect in patients selected as not having a past history of antidepressant treatments.

The observation that lithium chloride does not prevent the antidepressant-induced dopaminergic behavioural supersensitivity is also consistent with the view that such supersensitivity might play a role in the therapeutic effect of these drugs, since lithium salts are often given with antidepressants to augment their therapeutic effect (Baldessarini, 1996) and have been shown to increase the effect of subthreshold doses of antidepressants in the forced swimming test, an animal model of depression (Nixon et al., 1994).

Finally, the present data suggest that behavioural supersensitivity induced by imipramine is qualitatively different from that induced by either denervation or dopamine receptor blockade, both of which are sensitive to the lithium chloride inhibitory effect.

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