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European Journal of Pharmacology 416 (2001) 107–111

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Carbamazepine prevents imipramine-induced behavioural sensitization to the dopamine D_2-like receptor agonist quinpirole

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Received 7 December 2000; received in revised form 22 February 2001; accepted 26 February 2001

Abstract

Chronic treatment with antidepressants potentiates the behavioural sensitivity to the administration of dopamine receptor agonists. Such supersensitivity might be involved in the mechanism of action of antidepressant drugs, but it has also been suggested to play a role in the mechanisms underlying antidepressant treatment-related mania (i.e. antidepressant-induced mood switch and rapid cycling). Consistently to this hypothesis, we have recently shown that lithium salts, which are poorly effective in antidepressant-related mania, fail to prevent the development of imipramine-induced supersensitivity to the locomotor effect of the dopamine D_2-like receptor agonist quinpirole. In the present paper, we report the ability of carbamazepine, an anticonvulsant with antimanic and mood stabiliser properties, to prevent the development of supersensitivity to the locomotor response to quinpirole induced by chronic treatment with imipramine. The present results, together with the results of our previous study, might contribute to explain the different responsiveness to lithium and carbamazepine observed in some manic patients, and are consistent with the clinical data suggesting that carbamazepine might be more effective than lithium in antidepressant-related mania.

Keywords: Bipolar disorder; Carbamazepine; Dopamine; Imipramine; Mania; Motor activity; Quinpirole

1. Introduction

The stimulation of dopamine receptors in the nucleus accumbens, which is part of the mesolimbic dopamine system (see Willner et al., 1991), elicits an increase in motor activity (Kelly et al., 1975). Chronic treatments with antidepressant drugs potentiate this behavioural response, and such potentiation appears to be mediated by an increased sensitivity of postsynaptic dopamine D_2-like receptors in this area (Collu et al., 1997; D'Aquila et al., 1992, 1997a,b,c; Maj et al., 1989; Serra et al., 1979, 1990; Spyraki and Fibiger, 1981). The involvement of the mesolimbic dopamine system in the control of reward-related behaviours and motivation (see Willner and Scheel-Krüger, 1991), which are impaired in depression (American Psychiatric Association, 1994), suggested the hypothesis that such supersensitivity might play an important role in the mechanism of action of the therapeutic effect of this class of drugs (D'Aquila et al., 2000b; Serra et al., 1992).

Moreover, on the basis of experimental evidence suggesting a relationship between mania and increased dopaminergic neurotransmission (see Jimerson, 1987), it might be suggested that antidepressant-induced dopaminergic behavioural supersensitivity might be one of the neurobiological substrates underlying antidepressant-related mania, such as antidepressant-induced switch from depression to mania and rapid cycling, which has been suggested to be a consequence of repeated antidepressant treatment in bipolar depression (see Koukopoulos et al., 1995).

We have recently shown that treatment with lithium salts fails to prevent the behavioural dopaminergic supersensitivity induced by chronic treatment with imipramine (D'Aquila et al., 2000a). Refractoriness to lithium salts in bipolar patients is particularly frequent in rapid cycling and antidepressant-induced switch from depression to mania (see Koukopoulos et al., 1995). Therefore, the inability of lithium to prevent the antidepressant-induced dopaminergic supersensitivity provides support to the hypothesis that such supersensitivity might be considered a model of

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0014-2999/01/$ - see front matter
PII: S0014-2999(01)00876-7

antidepressant-related mania (D'Aquila et al., 2000a; Serra et al., 1990).

As an alternative to lithium in refractory patients, anticonvulsants such as carbamazepine, valproate or lamotrigine are often used with success (Soares, 2000). In particular, carbamazepine has been reported to be as effective as lithium in the treatment of mania (Brown et al., 1989; Emrich et al., 1985; Klein et al., 1984; Luznat et al., 1988; Okuma et al., 1979, 1990; Small et al., 1991). Moreover, clinical evidence suggests that it might be effective in the treatment of rapid cyclers (Joyce, 1988; Post et al., 1983, 1984, 1987).

In the framework of the hypothesis that antidepressant-induced dopaminergic supersensitivity might constitute one of the neurobiological mechanisms underlying antidepressant-related mania (D'Aquila et al., 2000a; Serra et al., 1990), it is of interest to determine whether treatment with carbamazepine is able to prevent the development of such supersensitivity. To this end, we investigated the effect of chronic treatment with carbamazepine on the locomotor response to the dopamine D_2-like receptor agonist quinpirole in animals treated with chronic imipramine.

2. Materials and methods

The present study was carried out in accordance to the Italian law, which allows experiments on laboratory animals only after submission of a research project to the competent authorities, and in accordance to the "Principles of laboratory animal care" (NIH publication no. 85–23, revised 1985).

2.1. Subjects

Experiments were performed on male Sprague–Dawley rats (Charles River, Como, Italy) weighing initially 130–200 g. They were housed two to three 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 60–70%. The animals had water and the standard laboratory diet (except for the carbamazepine-treated group, see below) ad libitum.

2.2. Drugs and treatments

The animals were divided into four groups: (1) control diet plus vehicle ($n = 10$); (2) control diet plus imipramine ($n = 10$); (3) "carbamazepine" diet plus vehicle ($n = 10$); and (4) "carbamazepine" diet plus imipramine ($n = 7$). Imipramine treatment and carbamazepine diet were given for 3 weeks and the animals were challenged with quinpirole and tested for motor 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. Carbamazepine-treated rats were fed the "carbamazepine" diet (pellets with 5 g/kg carbamazepine). Quinpirole was administered subcutaneously at the dose of 0.15 mg/kg in a volume of 1 ml/kg.

2.3. Motor activity

Motor activity was measured by an apparatus consisting of a mobile rack (height 180 cm, width 100 cm and depth 60 cm) with eight compartments (h 40 cm, w 45 cm, d 50 cm), into which a transparent perspex cage (height 19 cm, floor area 23×33 cm^2) was placed (Imetronic, Pessac, France). Motor activity is detected by a system of photocell infrared beams, dividing the cage area into two sectors, rear and front sector. In particular, the interruption of two photocell beams belonging to two different sectors is recorded as a "long movement" motility count. The interruption of two photocell beams belonging to the same sector is recorded as a "short movement" motility count. A "barrier" of infrared photocell beams, placed at the height of 15 cm, detects rearing activity. The apparatus was connected to a personal computer by an electronic interface.

Experiments were performed between 0900 and 1500 h. After 1-h habituation to the motility cages, all the rats were s.c. injected with 0.15 mg/kg quinpirole and the motor response was recorded for the following 45 min. Data have been collected in 5-min time bins.

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). Habituation and quinpirole challenge data have been analysed separately. The analysis involved two between groups factors, carbamazepine (with two levels: control and carbamazepine) and imipramine (with two levels: vehicle and imipramine), and a within group factor, time (habituation, 12 levels and quinpirole challenge, 9 levels, with each level corresponding to a 5-min time bin).

3. Results

3.1. Habituation

3.1.1. Long movements

ANOVA showed a significant main effect of time [$F(11,363) = 47.21$; $P < 10^{-6}$] (Table 1), due to a reduction in activity during habituation in all groups, with no significant main effect of carbamazepine [$F(1,33) = 0.038$; n.s.] and of imipramine [$F(1,33) = 0.97$, n.s.].

Table 1
Habituation. Each value represents the mean ± S.E.M. from 7 to 10 rats. Long movements, rearing and short movements were recorded for 60 min after placing the animals into the motility cages

		Vehicle	Imipramine
Long movements	Control	47.6 ± 5.22	38 ± 7.14
	Carbamazepine	42.8 ± 4.8	40.43 ± 6.52
Rearing	Control	192.2 ± 19.3	126.2 ± 17.06***
	Carbamazepine	189.2 ± 17.28	94 ± 13.4***
Short movements	Control	293.7 ± 24.9	246 ± 30.86
	Carbamazepine	301.9 ± 23.47	328.57 ± 40.06

*** $P < 0.001$: main effect of imipramine (ANOVA).

3.1.2. Rearing

ANOVA showed a significant main effect of imipramine [$F(1,33) = 20.57$; $P = 0.00007$], due to a reduced activity in the animals treated with imipramine regardless of carbamazepine treatment, and of time [$F(11,363) = 42.66$; $P < 10^{-6}$], due to a reduction in activity during habituation in all groups (Table 1).

3.1.3. Short movements

ANOVA showed a significant main effect of time [$F(11,363) = 74.30$; $P < 10^{-6}$], due to a reduction in activity during habituation in all groups (Table 1).

3.2. Quinpirole challenge

3.2.1. Long movements

ANOVA showed a significant main effect of carbamazepine [$F(1,33) = 6.71$; $P = 0.014$], and time [$F(8,264) = 4.69$; $P = 0.00002$], with no significant main effect of imipramine [$F(1,33) = 2.43$; n.s.]. Moreover, a significant interaction between carbamazepine, imipramine and time was revealed [$F(8,264) = 2.43$; $P = 0.015$] (Fig. 1A). Further analysis (F-tests for contrasts) showed an increased level of activity in the animals treated with imipramine with respect to their control group in the time bins between 10 and 35 min after quinpirole challenge (Fig. 1B). Moreover, the group treated with carbamazepine and imipramine displayed a statistically significant reduction of activity with respect to the group treated with imipramine alone in the time bins between 10 and 40 min after quinpirole challenge (Fig. 1B).

3.2.2. Rearing

ANOVA showed a significant main effect of carbamazepine [$F(1,33) = 15.6$; $P = 0.0004$] and time [$F(8,264) = 6.64$; $P < 10^{-6}$], no effect of imipramine

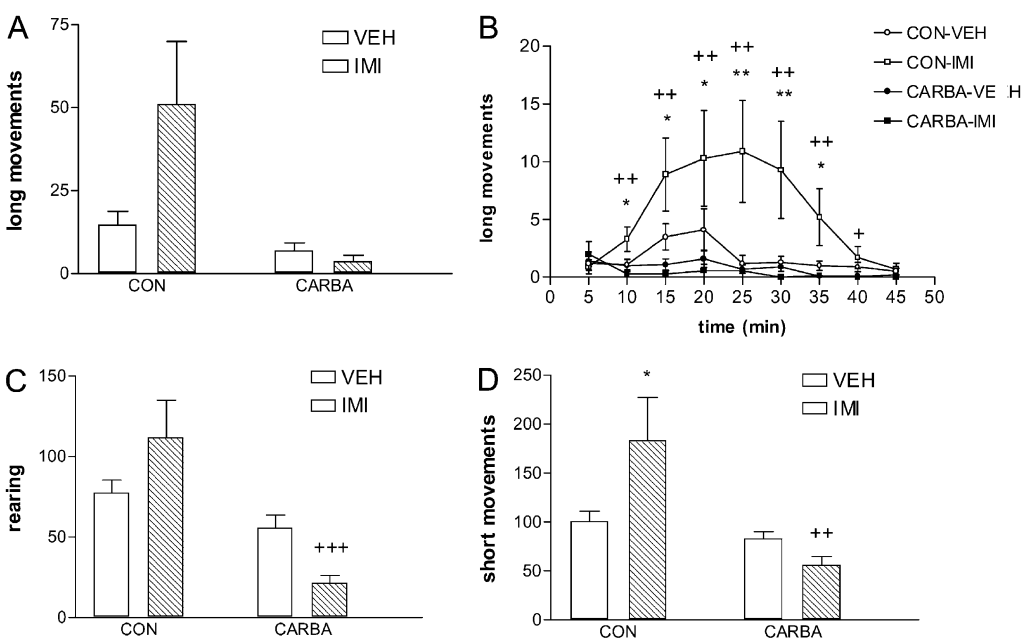

Fig. 1. Quinpirole challenge. CON: controls; CARBA: carbamazepine; VEH: vehicle; IMI: imipramine. Each value represents the mean ± S.E.M. from 7 to 10 rats. After 60-min habituation to the motility cages, long movements (panel A and B), rearing (panel C) and short movements (panel D) were recorded for 45 min following a 0.15-mg/kg s.c. quinpirole injection. (A, C, D) * $P < 0.05$, effect of imipramine; ++ P < 0.01, +++ P < 0.001, effect of carbamazepine (ANOVA followed by Newman–Keuls test). (B) * $P < 0.05$, ** $P < 0.01$, effect of imipramine; + $P < 0.05$, ++ $P < 0.01$, effect of carbamazepine (ANOVA followed by F-tests for contrasts).

[$F(1,33) = 0.00016$ n.s.], and a significant interaction between the factors carbamazepine and imipramine [$F(1,33) = 5.8$; $P = 0.02$] (Fig. 1C), due to the different effect of imipramine depending on carbamazepine treatment. Indeed, further analysis (Newman–Keuls test) revealed a statistically significant reduction of activity induced by carbamazepine in the animals treated with imipramine.

3.2.3. Short movements

ANOVA showed a significant main effect of carbamazepine [$F(1,33) = 8.14$; $P = 0.007$], time [$F(8,264) = 5.73$; $P = 0.000001$] and a significant interaction between carbamazepine and imipramine [$F(1,33) = 4.72$; $P = 0.037$], and carbamazepine, imipramine, and time [$F(8,264) = 2.49$; $P = 0.013$] (Fig. 1D). Further analysis (Newman–Keuls test) has shown an increased activity in the imipramine-treated group with respect to its control group, and a decreased activity in the group treated with carbamazepine and imipramine with respect to the group treated with imipramine alone.

4. Discussion

Chronic treatment with imipramine, as previously reported by a number of studies (see D'Aquila et al., 2000b), potentiated the locomotor response to quinpirole, as shown by an increase both of the "long movements" and of the "short movements" motility counts in the animals treated with imipramine after quinpirole challenge. Such a potentiation was prevented by carbamazepine treatment. Similar results, although less compelling, were obtained measuring rearing.

Carbamazepine is known to cause liver enzymatic induction, thus increasing both its own metabolism and that of concurrently administered medications (McNamara, 1996). It has been reported that the administration of carbamazepine to antidepressant-treated patients can reduce antidepressant plasma levels down to 40–50% with respect to control values (Leinonen et al., 1991). To overcome this problem, we used a particularly high dose of imipramine, 20 mg/kg/day, four times the dose necessary to induce dopaminergic supersensitivity (Papp et al., 1992).

Treatment with imipramine induced a decrease of rearing counts in the habituation period, both in control animals and in animals receiving the carbamazepine diet. This observation shows that the likely reduction of imipramine levels in carbamazepine-treated animals is not sufficient to prevent imipramine effects.

In the present study, we have shown that the development of imipramine-induced dopaminergic supersensitivity, which had been previously shown to be unaffected by treatment with lithium salts (D'Aquila et al., 2000a), is prevented by treatment with carbamazepine. According to the view that antidepressant-induced potentiation of dopaminergic transmission might constitute one of the neurobiological mechanisms underlying antidepressant-related mania, of which rapid cycling is an instance (Koukopoulos et al., 1995), the present results are consistent with the observation that carbamazepine has been shown to be effective in the treatment of rapid cyclers in uncontrolled studies and small controlled studies (Joyce, 1988; Post et al., 1983, 1984, 1987), although it must be pointed out that there are no controlled trials showing that carbamazepine is more effective than lithium in this category of patients (see Soares, 2000). Moreover, it might be predicted that the addition of carbamazepine to antidepressants in the treatment of bipolar depression should prevent both antidepressant-induced switch from depression to mania and rapid cycling in bipolar patients treated with antidepressant medications. This prediction is consistent with clinical data showing that addition of antidepressant drugs to mood stabilisers in bipolar mania does not result in an increase of mood switches (Boerlin et al., 1998), although it should be stressed that, no systematic comparison between lithium and carbamazepine has been performed in this study.

In our studies, we have shown a different responsivity to lithium and carbamazepine only in animals rendered supersensitive to dopamine agonists by treatment with imipramine. Further studies dealing with dopaminergic behavioural supersensitivity induced by different antidepressant drugs (and also electroconvulsive shock) are necessary in order to better evaluate the relevance of these findings.

Acknowledgements

This study has been supported by the Regione Autonoma della Sardegna and the Ministero per l'Università e la Ricerca Scientifica, Italia. The authors wish to thank Dr. M.L. Chessa, Dr. M.L. Cottino, Mr. C. Cabras, Ms. C. Grixoni, Ms. F. Panin and Ms. A. Ventroni for their skilful help in performing the experiments.

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