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The effect of oxcarbazepine on behavioural despair and learned helplessness

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Abstract

The effect of oxcarbazepine was evaluated in two tests of depression (forced swimming and learned helplessness) and in the open-field test. Acute (three times over 24 h) oxcarbazepine 80 mg/kg (but not 40 mg/kg) decreased immobility time in the forced swimming test. In the learned helplessness test, 4 days of treatment with oxcarbazepine 80 mg/kg reversed the deficits induced by foot-shock in rats submitted to the two-way active avoidance test. Oxcarbazepine 80 mg/kg did not modify the behaviour of rats in the open-field test, an indication that, at this dose, oxcarbazepine did not show a locomotor stimulatory effect. Thus, the data of the present study suggest that oxcarbazepine has a potential antidepressive effect. © 1998 Elsevier Science B.V.

Keywords: Animal model; Depression; Forced swimming; Learned helplessness; Open-field; Oxcarbazepine

1. Introduction

Carbamazepine, a widely used anticonvulsant drug, has an anxiolytic and antidepressant effect in animal models. In the animal models of anxiety, carbamazepine has an anticonflict effect in the Geller–Seifter conflict test (Almeida and Leite, 1990) and increases the percentage of time spent, and the percentage of arm entries in the open arms (Zangrossi et al., 1992). Carbamazepine reduces immobility time in the behavioural despair test (Maj et al., 1985; Barros and Leite, 1987), an animal model of depression. Results of clinical studies have confirmed these effects both in depressed patients (Post et al., 1996; Dilsaver et al., 1996) and in normal volunteers submitted to an experimental anxiogenic situation (Sartori et al., 1993).

Oxcarbazepine, the keto-homologue of carbamazepine, seems to share a similar profile of anticonvulsant activity in both screening test and clinical trials (Grant and Faulds, 1992). However, oxcarbazepine has a different biotransformation pathway and lacks of enzyme induction. These features explain the reports that oxcarbazepine induces fewer side-effects and has a lower potential for drug interactions than carbamazepine. These differences appear to result from a lack of epoxide derivate formation following oxcarbazepine metabolism (Grant and Faulds, 1992; Emrich, 1994). There is thus a suggestion that if the use of carbamazepine presents problems oxcarbazepine could be used instead (Emrich, 1990). However, some clinically relevant effects of carbamazepine could be due to its epoxide (Post et al., 1984). The psychotropic effect of oxcarbazepine could therefore differ from that of carbamazepine. Clinical data about the use of oxcarbazepine in affective disorders are scarce and mainly concern maniac episodes (Emrich, 1990, 1994; Post et al., 1996). However, study of the effect of oxcarbazepine on depressive episodes has been limited to a few case reports on bipolar patients, when doubtful results were obtained (Wildgrube, 1990). Thus the present study was performed to determine the effect of oxcarbazepine in two animal models of depression: the behavioural despair (or forced swimming test) and the learned helplessness test. The open-field test was used to evaluate general motor activity (Kelly, 1993).

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2. Materials and methods

2.1. Animals

Male Wistar rats 90 to 120 days old were used. The animals were housed in groups of five in polypropylene cages with wood shavings as bedding, under controlled conditions of light (12 h light–dark cycle, light on at 7:00 AM) and temperature (22°C). The animals had free access to water and food throughout the experiment.

2.2. Drugs

Oxcarbazepine (Novartis Biociências, Brazil) was dissolved in Tween 80 (1%, v/v) and distilled water. The control group received the vehicle. The injected volume for all experiments was 2.0 ml/kg of rat body weight, administered intraperitoneally.

2.3. Procedures

To minimize possible influences of circadian fluctuations on emotionality (Eidman et al., 1990), behavioural observations were made at the same time of the day (9:00–13:00).

2.3.1. Behavioral despair

The procedure was a modification of the Porsolt et al. (1978) method. Rats were placed in a glass aquarium ($20 \times 20 \times 40$ cm^3) containing 15 cm deep cold water (24 ± 1°C) for 15 min followed by a 5-min retest (test session) 24 h later. Immobility time was recorded during the test session: the rat was judged immobile whenever it stopped swimming and remained floating in the water, with its head just above water level (Borsini and Meli, 1988). The water was changed after each rat to avoid the influence of alarm substance (Abel and Bilitzke, 1990). Following the test, the animals were dried in a heated enclosure. The vehicle or oxcarbazepine was administered three times (24, 5 and 1 h) before a test session.

2.3.2. Learned helplessness

The Gemini Active Avoidance System (San Diego, CA, USA) was used. This apparatus is an automated shuttle box with two compartments of equal size ($20 \times 10 \times 19$ cm^3) separated by a wall with a central open door (6×6 cm^2) and equipped with a grid floor made of stainless steel bars. Half the rats were placed on one side of the shuttle box, with the door closed, and submitted to 60 inescapable foot-shocks (1.0 mA, 10 s) given according to a variable time schedule with a mean interval of 60 s (range from 20–100 s). The other half of the rats underwent the same manipulations except that no shock was given. Four days later, all animals were tested in a two-way avoidance test procedure in the Gemini Active Avoidance System. The testing session consisted of 30 trials, in which the rat was required to cross from one side to another to escape the shock. Shock was preceded by a 5-s conditioned stimulus tone, which remained until shock was terminated. If the rat failed to escape, the shock was terminated after 10 s and another trial was initiated. During testing, the shock intensity was 1.0 mA, delivered at random intervals (mean of 60 s and range from 20–100 s). After a training session, the animals were injected with vehicle or oxcarbazepine and injections were repeated twice daily for 4 days until 1 h before the two-way avoidance test.

2.3.3. Open-field test

The open-field apparatus is a circular arena (1 m diameter), divided into central and peripheral units, with a bright light. The rats were placed individually in the centre of the open-field and behaviour was evaluated for 5 min. Peripheral and central locomotion (number of units crossed) and rearing, time spent in grooming and immobility, and number of faecal boli were recorded (Kelly, 1993). The open-

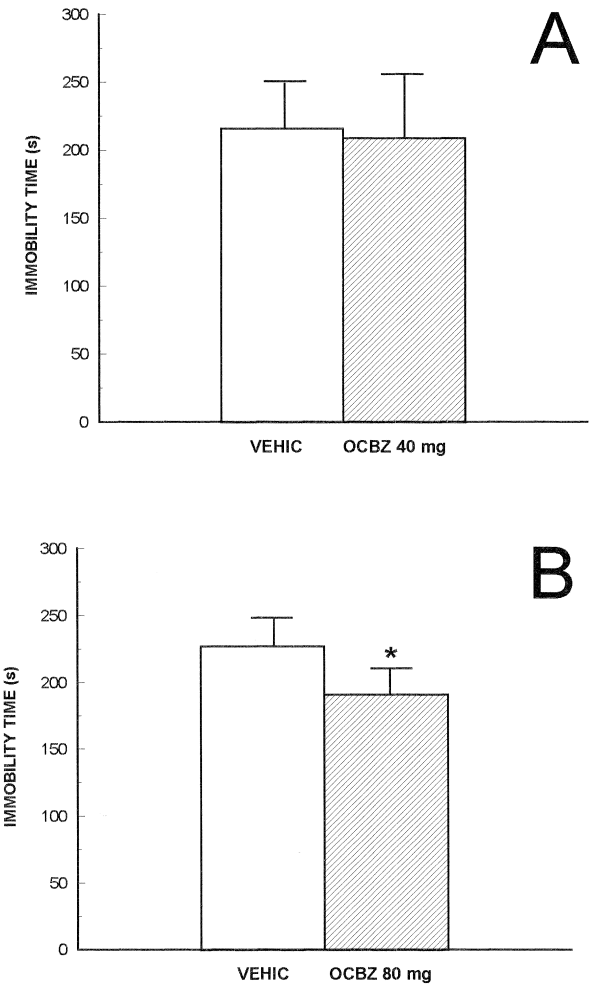

Fig. 1. Effect of subacute administration of oxcarbazepine 40 mg/kg (OCBZ, $n = 10$) or vehicle (VEIC, $n = 10$) (A) and oxcarbazepine 80 mg/kg (OCBZ, $n = 7$) or vehicle (VEIC, $n = 7$) (B) on the immobility time (mean ± S.D.) of rats submitted to the forced swimming test. * Significantly different from vehicle, Student's *t*-test.

Table 1
Effect of oxcarbazepine (80 mg/kg) and vehicle on learned helplessness induced by foot-shock in rats

Treatment	Block			Trial			
	1–5	6–10	11–15	16–20	21–25	26–30	
Vehicle	+non-shock	5.2 ± 1.7	5.6 ± 0.4	5.5 ± 0.4	5.2 ± 0.4	4.8 ± 0.6	4.6 ± 0.8
	+shock[a]	8.3 ± 2.3	8.5 ± 3.4	8.4 ± 4.1	7.6 ± 3.0	7.4 ± 3.0	6.0 ± 1.3
OCBZ (80 mg/kg)	+non-shock	6.9 ± 2.5	6.6 ± 1.3	5.5 ± 0.9	5.9 ± 1.7	5.0 ± 1.1	5.2 ± 1.1
	+shock	8.8 ± 3.5	8.0 ± 2.1	6.1 ± 3.5	7.7 ± 3.6	7.1 ± 4.1	5.83.4

Data represent mean escape latency ± S.D. (s). Drugs were administered i.p. twice daily for 4 days, $n = 8$/group.
[a]Significantly different from non-shocked vehicle treated rats, Newman–Keuls test.

field was washed with a water–alcohol (10%) solution before behavioural testing to avoid possible bias due to odors and/or residues left by rats tested earlier. Animals were tested 1 h after acute drug administration (oxcarbazepine or vehicle).

2.4. Statistical analysis

The results were evaluated by means of parametric analysis when appropriate and by non-parametric tests when the data did not fit parametric assumptions. Thus Student's *t*-test for independent groups was used to compare oxcarbazepine treated rats with control animals in the forced swimming test. The learned helplessness data were evaluated by two-way analysis of variance (ANOVA) with drug treatment as the first factor and block trial as a second factor. This was followed by a post-hoc Newman–Keuls test for individual group comparisons. The open-field parameters were analysed by Student's *t*-test (locomotor activity and immobility time) or Mann–Whitney *U*-test (rearing, grooming and faecal boli). Differences were considered statistically significant when $P < 0.05$.

3. Results

The effect of subacute treatment with oxcarbazepine on the behavioural despair model is shown in Fig. 1. The higher dose of oxcarbazepine (80 mg/kg) significantly decreased immobility time ($t = 2.780$, $P < 0.02$) when compared to the control, while the lowest dose (oxcarbazepine 40 mg/kg) did not modify immobility time ($t = 0.11$, $P > 0.10$) relative to the control.

The effect of 4 days treatment with oxcarbazepine on learned helplessness is shown in Table 1. Two-way analysis of variance revealed that there were significant effects for treatment ($F(3,28) = 4.36$, $P < 0.02$) and block trial factors ($F(5,140) = 3.75$, $P < 0.01$), but not for interaction ($F(15,140) = 0.57$, $P > 0.10$). Post-hoc analysis showed that rats previously exposed to uncontrollable and unpredictable shock and treated with vehicle had a marked learning deficit (longer response time) when compared to non-shocked rats (Table 1). On the other hand, no difference was seen between shocked and non-shocked animals treated with oxcarbazepine (80 mg/kg). Moreover, non-shocked animals treated with oxcarbazepine did not differ from non-shocked rats treated with vehicle (Table 1).

No significant differences were found for open-field behaviours between vehicle ($n = 8$) and oxcarbazepine 80 mg/kg ($n = 9$) treated rats: central locomotor activity: 5.4 ± 5.8 vs. 7.2 ± 6.8 (mean ± S.D., $t = -0.598$); peripheral locomotor activity: 39.4 ± 21.9 vs. 38.4 ± 15.7, (mean ± S.D., $t = 0.101$); central rearing: 3.0 ± 0.75 vs. 4.0 ± 2.25 (median ± semi-interquartile range (S.I.R.), $U = 27.50$); peripheral rearing: 14.0 ± 7.00 vs. 15.0 ± 4.75, (median ± S.I.R., $U = 33.00$); grooming: 18.5 ± 25.0 vs. 18.0 ± 7.0 (median ± S.I.R., $U = 34.50$); immobility time: 80.8 ± 7.6 vs. 83.0 ± 52.7 (mean ± S.D., $t = .055$); faecal boli: 1.5 ± 1.5 vs. 4.0 ± 1.75 (median ± S.I.R., $U = 17.50$) (Table 2).

Table 2
Open-field behaviour of rats acutely treated with oxcarbazepine 80 mg/kg ($n = 9$) or vehicle ($n = 8$)

	Open-field parameters						
	Locomotor activity[a]		Rearing[b]		Grooming[b]	Immobility time[a]	Faecal boli[b]
	Central	Peripheral	Central	Peripheral			
Vehicle	5.4 ± 5.8	39.4 ± 21.9	3.0 ± 0.75	14.0 ± 7.00	18.5 ± 25.0	80.8 ± 7.6	1.5 ± 1.5
OCBZ 80 mg/kg	7.2 ± 6.8	38.4 ± 15.7	4.0 ± 2.25	15.0 ± 4.75	18.0 ± 7.0	83.0 ± 52.7	4.0 ± 1.75
t	−0.598	0.101				0.055	
U			27.50	33.00	34.50		17.50

[a]Data represent mean ± S.D.
[b]Data represent median ± S.I.R. Rats were treated i.p. 1 h before the test.

4. Discussion

The results of learned helplessness showed that oxcarbazepine (80 mg/kg) reverses the learning deficits caused by uncontrollable and unpredictable shocks, an effect similar to that of antidepressant treatments (Sherman et al., 1982). In addition, this antidepressant-like activity is also seen in the behavioural despair test, in which the higher oxcarbazepine dose (80 mg/kg) reduces immobility time, an effect that was seen with antidepressants such as tricyclics, monoamine oxidase inhibitors, electroshock or paradoxical sleep deprivation (Borsini and Meli, 1988). Moreover, it appears that these effects are not due to an increase in locomotor activity (Sherman et al., 1982; Borsini and Meli, 1988) since oxcarbazepine (80 mg/kg) did not change open-field behaviour. Although no single animal model of depression has a generally accepted predictive power for clinical effectiveness and given that the magnitude of the effects was modest (particularly for learned helplessness), these results clearly suggest that oxcarbazepine has potential antidepressant clinical activity.

Interestingly, the oxcarbazepine effective dose in the forced swimming test now found was higher than the effective dose of carbamazepine (40 mg/kg) found previously with the same procedure (Maj et al., 1985; Barros and Leite, 1987). A similar relationship was seen between oxcarbazepine and carbamazepine in clinical trials for an anticonvulsant effect (Schwabe, 1994).

Although there is a discrepancy between the treatment length (1 or 4 days) used in the present study and the time lag needed to observe the clinical effect of antidepressant drugs (3–4 weeks), this approach has proved adequate for screening potential antidepressant drugs (Borsini and Meli, 1988; Willner, 1984). Moreover, the short treatment length used in the experimental models in the present study may explain the relatively high dose needed to demonstrate the antidepressant-like effect of oxcarbazepine (Barros and Leite, 1986; Willner, 1995).

Carbamazepine has multiple effects on neurotransmission (Post, 1987), but its antidepressive effect could be at least partially related to its dopaminergic actions. Carbamazepine releases [^{3}H]dopamine from striatal slices and enhances apomorphine-induced stereotypy (Barros et al., 1986; Barros and Leite, 1986), although decreases in dopamine turnover have been observed (Post, 1987). Moreover, the antidepressive-like actions of carbamazepine in the forced swimming test can be blocked by haloperidol (Barros and Leite, 1987). Oxcarbazepine thus may have a similar dopaminergic effect which can contribute to its potential antidepressive action. These dopaminergic effects could however be restricted to carbamazepine, making additional studies necessary to establish the mechanism of the oxcarbazepine antidepressive effect.

In conclusion, the present results indicated that oxcarbazepine has an antidepressive-like effect in animal models of depression without changes in the general activity level of the animals. Thus it is suggested that oxcarbazepine has a potential clinical antidepressive action.

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