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Morphine sensitization as a model of mania: Comparative study of the effects of repeated lithium or carbamazepine administration

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ABSTRACT

Repeated unavoidable stress induces in rats decreased reactivity to avoidable stressors and an anhedonia-like condition that are reverted by long-term antidepressant treatments and regarded as models of core symptoms of depression. Morphine-sensitized rats present resilience to stress-induced behavioral deficits and, if hyporeactivity to stress models a depressive symptom, stress resistance can be regarded as a manic symptom. This hypothesis is supported by the observation that long-term lithium administration reinstates sensitivity to stress in sensitized rats. The first aim of the study was to examine the effects of carbamazepine, a standard antimanic treatment, on the stress resilience of sensitized rats, to further characterize morphine sensitization as a model of manic symptom. Carbamazepine administration abolished stress resilience but did not interfere with the expression of sensitization. The second aim of the study was to assess whether repeated carbamazepine treatment affected the dopaminergic and behavioral responses to a natural reward, a palatable food (vanilla sugar, VS), in non food-deprived sensitized and control rats and compare these possible effects with those of repeated lithium administration. Control and sensitized rats showed increased extraneuronal dopamine levels in the nucleus accumbens shell after VS consumption and competence to acquire an instrumental VS-sustained appetitive behavior (VAB). Repeated carbamazepine treatment abolished the dopaminergic response to VS consumption and disrupted the competence to acquire VAB in control rats. Lithium-treated rats showed a dopaminergic response to VS and easily acquired the appetitive behavior. In sensitized rats, neither carbamazepine nor lithium administration interfered with the dopaminergic response to VS and the acquisition of VAB. In summary, the effect of carbamazepine on the stress resilience of sensitized rats further supported the hypothesis that morphine sensitization might model some symptoms of mania. Moreover, in control rats carbamazepine treatment elicited an anhedonia-like condition that clearly distinguished the effects of this drug from those of lithium.

1. Introduction

The neurobiological mechanisms underpinning mood disorders are still unresolved, unlike other medical conditions in which the physiopathology can be well defined. This fact, in addition to the wide spectrum of symptoms (none pathognomonic of a specific syndrome) that characterize psychiatric disorders is also reflected in the difficulty of mimicking psychopathologic symptoms or complex syndromes in experimental research. Two core symptoms of depression can be induced in rats by repeated exposure to unavoidable stress, a condition of hyporeactivity to avoidable stressors and an anhedonia-like condition (Gambarana et al., 2001; Willner et al., 1992). The latter is characterized by a blunted dopaminergic response to palatable food consumption in the shell portion of the nucleus accumbens (NAcS), measured by microdialysis, and the inability to acquire a palatable food-sustained appetitive behavior (Di Chiara and Tanda, 1997; Gambarana et al., 2003; Ghiglieri et al., 1997). Both conditions are responsive to long-term antidepressant treatments (Gambarana et al., 2001). Several approaches have also been taken to model reproducible manic-like behavioral modifications in rodents (Dencker and Husum, 2010; Einat and Manji, 2006; Flaisher-Grinberg et al., 2009; Gould and Einat, 2007; Roybal et al., 2007). One of the traits of mania, the modified reactivity to external stimuli, can be modeled in rats by the long-lasting condition of morphine sensitization (Gambarana et al., 2000). In fact, while in our experimental conditions >90% of rats develop an escape deficit (Gambarana et al., 2001) and this can be considered the "normal" pattern of behavioral response to unavoidable stress exposure, sensitized rats do not develop an escape deficit after acute or chronic

Abbreviations: NAcS, nucleus accumbens shell; VAB, vanilla sugar-sustained appetitive behavior; VS, vanilla sugar.

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unavoidable stress exposure (Scheggi et al., 2000; Scheggi, unpublished results). Since depression and mania can be considered to occupy extreme poles on an affective spectrum, if hyporeactivity to stress models a depressive symptom, resilience to develop stress-induced sequelae may configure a behavioral phenotype that conforms to face validity for a symptom of mania (Gambarana et al., 2000). A similar reasoning has been proposed for the behavioral response to the forced swimming test of different mice strains (Flaisher-Grinberg and Einat, 2009). In this case the hypothesis was that a low degree of immobility in this test could be the mirror image of the despair-like increased immobility usually shown by rodents and that it could represent the opposite, the increased vigor and goal-directed behavior facet of a manic-like behavior. Moreover, if stress resilience actually mimics a mania symptom, it should be reduced or abolished by classical anti-manic agents. Lithium, the gold standard medicament in the treatment of bipolar disorders and manic symptoms (Coryell, 2009; Kovacsics et al., 2009), abolishes this resilience since, after a 2–3 week administration, it induces hyporeactivity to aversive stimuli in control and sensitized rats (Gambarana et al., 2000). Interestingly, long-term lithium treatment does not interfere with the expression of morphine sensitization, in terms of stereotypies and locomotor activity (Gambarana et al., 2000). The first aim of this study was to further validate the condition of morphine sensitization as a model of manic symptoms by testing its sensitivity to a different anti-manic drug. Thus, the possible antagonistic activity of carbamazepine, an anticonvulsant clinically validated as an anti-manic and frequently used off-label as a mood stabilizer (Calabrese et al., 1995; Keck et al., 2002; Post et al., 1998a, 1998b), on sensitization-induced stress resilience was studied.

Mood stabilizers should selectively blunt and/or prevent the symptoms that identify the different phases of bipolar disorder while leaving unmodified the responsiveness to internal and environmental stimuli during the periods of "normal" mood (euthymia) (Bourin and Prica, 2007). Thus, the second aim of the study was to assess whether repeated carbamazepine treatment affected the responsiveness to a positive stimulus, a palatable food, in control and morphine-sensitized rats and to compare these possible effects with those of repeated lithium administration. Preliminary data demonstrated that morphine-sensitized rats are as competent as control rats in acquiring an instrumental appetitive behavior reinforced by a palatable food (Gambarana et al., 2010). Exposure to palatable food is widely used in experimental protocols since it elicits consistent behavioral and neurochemical responses, it is a validated index of hedonic responsiveness, and the two bottle choice test is commonly used for assessing hedonic reactions to sucrose (Willner et al., 1987). In order to study hedonic responsiveness, we used only non food-deprived rats since the emotional value of food has a prevalent hedonic component in these animals (Di Chiara, 2002). Rats are very fond of vanilla sugar (VS) and consumption of 4–5 small VS pellets increases dopaminergic transmission in discrete frontal mesolimbic areas, such as the medial prefrontal cortex and the NAcS (Masi et al., 2001). A correlation has been observed between this dopaminergic response after VS consumption and the ability to acquire an instrumental behavior based on the reinforcing properties of VS pellets (Gambarana et al., 2003), the earning of which is made contingent on the choice of one of the two divergent arms of a Y-maze (VS sustained appetitive behavior, VAB) (Ghiglieri et al., 1997). These neurochemical and behavioral paradigms can be used to investigate the possible effects of psychotropic drugs on the spontaneous responses to a natural reward in control and sensitized rats. Repeated lithium administration in rats has been shown to improve cognition (Sharifzadeh et al., 2007; Tsaltas et al., 2007a, 2007b; Vasconcellos et al., 2003) and to leave unmodified the expression of the dopaminergic response in the NAcS to a palatable food and the competence to acquire an instrumental appetitive behavior sustained by this food (Masi et al., 2000).

2. Materials and methods

2.1. Animals

Experiments were carried out on male Sprague-Dawley rats (Charles River, Calco, Italy) that were allowed at least 1 week of habituation to the animal colony and that weighed 200–225 g when the experimental procedures began. Animals were housed 5 per cage in an environment maintained at a constant temperature and humidity with free access to food and water. A 12 h reverse light/dark cycle (7:00 am lights off, 7:00 pm lights on) was used. Experiments were carried out from 9:00 a m to 5:00 pm under a red light and controlled noise conditions in a testing room separate from and adjacent to the main animal room. The procedures used were in accordance with the European legislation on the use and care of laboratory animals (EEC Council Directive 86/609) and were approved by the University of Siena Ethics Committee. All efforts were made to minimize the number of animals used and their suffering.

2.2. Induction of morphine sensitization

Sensitization was induced by administering morphine (10 mg/kg/day s. c.) for 7 days as previously described (Scheggi et al., 2004). After a 10-day washout the development of behavioral sensitization was assessed: rats were administered morphine (5 mg/kg s. c.) and their locomotor activity and stereotypies were recorded for 30 min (the first 5 min after injection were not taken into account). Locomotor activity was determined in motility cages that detected horizontal activity and rearings (Imetronic, Pessac, France). Stereotypies were scored by experimenters blind to the experimental conditions according to a published rating scale (Scheggi et al., 2000). A cumulative score reflecting stereotypy intensity during the 30 min observation period was assigned to each rat.

2.3. Escape deficit induction

Escape deficit was induced by the exposure of rats to an unavoidable shock session as previously described (Gambarana et al., 2001). Twenty-four h later, rats were exposed to a shock-escape test in an apparatus consisting of a Plexiglas cage (30×60×30 cm) divided into two equal chambers: a neutral chamber and an electrified chamber connected to a S48 Grass stimulator (Grass Instrument, Astro-Med Inc., West Warwick, RI). An electrode was applied to the tail and the animal was then placed in the electrified chamber and exposed to 30 consecutive shocks (1 mA×5 s) at 30 s intervals. Shocks were delivered, coinciding with a 5 s opening of the door connecting the electrified to the neutral chamber.

2.4. VS pellet preparation

VS pellets were made daily: standard food pellets (Harlan Italy, S. Pietro al Natisone, Italy) were crushed by mortar and pestle and the fragments were dampened with water and rolled in powdered vanilla sugar (Zucchero Vanigliato, Cannamela S.p.A., S. Lazzaro di Savena, Italy) to obtain pellets weighing approximately 150 mg.

2.5. Induction of VAB

A dark Plexiglas Y-maze (15×40×20 cm for each of the three arms) was used; a VS pellet was placed in a small tray at the end of one of the two divergent arms. Sessions of 10 trials with 15-min intervals between them were administered daily for a total of 10 sessions, as previously described (Ghiglieri et al., 1997). Either the

right or the left arm was designated correct, balanced among animals. If the empty arm was chosen (incorrect trial), the rat was returned to its cage for 15 min before the next trial. When the baited arm was chosen (correct trial) the rat was allowed to consume the VS pellet and then returned to its cage for 15 min before the next trial. A trial was defined as incomplete when the rat did not reach the end of one of the two diverging arms. In each session, the variables recorded were: number of correct, incorrect, incomplete trials, and number of VS pellets consumed.

2.6. Microdialysis procedure

Anaesthetized rats (pentobarbital 50 mg/kg, scopolamine 0.4 mg/kg, i. p.) were placed in a stereotaxic instrument and a concentric vertical probe was lowered into the NAcS (AP + 1.7 mm, L ± 1.2 mm from bregma, V − 8.0 mm from skull surface) according to (Paxinos and Watson, 1998). Microdialysis probes were made from semipermeable dialysis tubing (AN 69, Hospal, Bologna, Italy); the length of the permeable portion of the membrane was 2.0 mm. Probes were implanted in the left or right NAcS, balanced within the groups. After surgery, rats had 24 h of recovery before the beginning of microdialysis. Water and standard food pellets were available at this time and up to the end of the experiment. On the day of the experiment, Ringer's solution (147 mM NaCl, 2.2 mM $CaCl_2$, 4 mM KCl) was infused through the probe at a flow rate of 1 μl/min; dialysate samples were collected every 10 min and immediately analyzed by HPLC with electrochemical detection (ESA Coulochem II with a 5014 A analytical cell, ESA Inc., Chelmsford, MA, USA). The potential of the first electrode was set at + 275 mV, and that of the second, the recording electrode, at − 275 mV. The mobile phase consisted of an aqueous solution containing: 0.2 M sodium acetate, 0.1 mM Na_2EDTA, 10% methanol, pH 4.5. A flow-rate of 0.65 ml/min was used. Data were acquired by PC using EZChrom 6.6 software (Scientific Software Inc., San Ramon, CA, USA) and were quantified based on peak area by comparison with a standard curve run before and after each experiment. Microdialysis data was utilized only when probe placement was microscopically confirmed on cresyl violet-stained brain sections.

2.7. Drugs

Lithium chloride and morphine were dissolved in deionized/distilled water and injected at a volume of 1 ml/kg rat body weight; rats in the control groups received the same volume of saline. Carbamazepine was dissolved in 50% propylene glycol and 50% deionized/distilled water and injected at a volume of 1 ml/kg rat body weight; rats in the control groups received the same volume of vehicle. Pentobarbital was dissolved in a mixture of 12% ethanol, 38% propylene glycol and 50% deionized/distilled water (v/v) containing scopolamine, and was injected at a volume of 4 ml/kg body weight. Pentobarbital was purchased from Sigma Chemical Co. (St. Louis, MO, USA) and morphine from SALARS (Como, Italy). All other drugs and chemicals were purchased from commercial sources.

2.8. Experimental protocols

In each experiment, rats underwent the sensitization protocol, or received saline (1 ml/kg/day, s. c., for 8 days, *repeated saline*); in the *repeated saline* groups 5 additional rats were always included to serve as the control group in each sensitization test. After a 10-day washout, morphine-treated and 5 *repeated saline* rats were challenged with morphine (5 mg/kg, s. c.) to assess sensitization. In each experiment, morphine-treated rats that showed a sensitized response (i. e., stereotypy scores, locomotor activity counts and rearings significantly higher than the *repeated saline* group: *morphine-sensitized*) and morphine-naïve *repeated-saline* rats were used.

2.8.1. Experiment 1: effects of repeated carbamazepine treatment on the stress resilience of morphine-sensitized rats

In order to examine whether carbamazepine modified the response to unavoidable stress and whether this possible effect varied with treatment duration, a group of rats received vehicle (1 ml/kg i. p. twice a day) and was divided into two subgroups: one was exposed to the unavoidable stress session prior to the escape test (stress group, $n = 8$) and the other was only exposed to the escape test (naïve group, $n = 8$). Another group of rats received carbamazepine (6 mg/kg) i. p. twice a day for 5 ($n = 6$), 14 ($n = 6$), and 30 days ($n = 8$). Rats were exposed to an unavoidable stress session 18–20 h after the last treatment and to the escape test 24 h after the unavoidable stress exposure. Moreover, in order to verify whether a long-term carbamazepine treatment induced a spontaneous escape deficit (without previous unavoidable stress exposure) similar to that induced by long-term lithium administration (Gambarana et al., 1999a), rats received vehicle (1 ml/kg) or carbamazepine (6 mg/kg) i. p. twice a day for 14, 30 and 40 days and were tested for escape, after unavoidable stress exposure (*stress*) or without previous exposure to the stress session (*naïve* and *carbamazepine*), ($n = 8$–12 in each group).

The effect of repeated carbamazepine treatment on the response to unavoidable stress exposure in sensitized rats was then examined. Rats were divided into two groups: 25 rats received saline (1 ml/kg) and 16 rats received morphine (10 mg/kg) s. c. for 7 days. Twenty-four h after the assessment of sensitization, 20 saline and 16 sensitized rats were divided into subgroups: 12 of the repeated-saline and 8 of the sensitized rats received vehicle (1 ml/kg); 8 of the repeated-saline and 8 of the sensitized rats received carbamazepine (6 mg/kg) i. p. twice a day for 14 days. Eighteen to twenty hours after the last treatment, 6 vehicle-treated repeated-saline rats were tested for escape (*naïve*), 6 were exposed to the unavoidable stress session and 24 h later were tested for escape (*stress*); carbamazepine-treated repeated-saline rats (*carbamazepine*, $n = 8$), carbamazepine-treated sensitized rats (*morphine + carbamazepine*, $n = 8$) and vehicle-treated sensitized rats (*morphine*, $n = 8$) were exposed to the unavoidable stress session and 24 h later were tested for escape. The dose of carbamazepine was selected on the basis of previous studies (Ichikawa and Meltzer, 1999) and preliminary experiments showing that the repeated administration of 6 mg/kg of carbamazepine twice a day did not induce overt modifications in the spontaneous behavior of rats or neurological signs, while preventing electroconvulsive shock-induced convulsions (Masi and Grappi, unpublished results).

2.8.2. Experiment 2: effects of repeated carbamazepine administration on the dopaminergic response to palatable food consumption in the NAcS of saline-treated and morphine-sensitized rats

In order to study whether repeated carbamazepine treatment modified the response to a natural reward in repeated-saline or sensitized rats, the dopaminergic output in the NAcS was examined by microdialysis at baseline and after the consumption of a palatable food (VS pellets). Rats received saline (1 ml/kg, $n = 20$) or morphine (10 mg/kg, $n = 15$) s. c. for 7 days. Twenty-four h after the sensitization test, 15 saline and 15 sensitized rats were divided into four groups: 7 repeated-saline and 7 sensitized rats received vehicle (1 ml/kg, *control* and *morphine* groups, respectively), 8 repeated-saline and 8 sensitized rats received carbamazepine (6 mg/kg, *carbamazepine* and *morphine + carbamazepine* groups, respectively) i. p. twice a day for 10 days. Rats underwent surgery 18–20 h after the last treatment, received a vehicle or carbamazepine administration several hours after the surgery, and the following day, 18–20 h after the treatment, they underwent microdialysis.

Table 1
Behavioral responses to morphine challenge in *repeated saline* and *morphine-sensitized* rats.

Group	*n*	Stereotypy score	Rearings number	Horizontal locomotor activity
Experiment 1				
Repeated saline	5	0.96 ± 0.32	4.40 ± 2.67	12.20 ± 5.44
Repeated morphine	16	5.09 ± 0.08***	35.88 ± 8.19*	154.70 ± 27.39**
Experiment 2				
Repeated saline	5	1.10 ± 0.33	13.00 ± 6.34	19.60 ± 8.49
Repeated morphine	15	4.15 ± 0.20***	55.83 ± 6.03***	191.50 ± 27.57**
Experiment 3				
Repeated saline	5	0.43 ± 0.14	4.400 ± 0.92	14.20 ± 4.84
Repeated morphine	14	4.06 ± 0.17***	34.21 ± 5.8**	124.40 ± 26.36**
Experiment 4				
Repeated saline	5	0.66 ± 0.12	8.00 ± 4.51	12.80 ± 6.46
Repeated morphine	12	4.46 ± 0.28***	32.50 ± 4.76**	90.83 ± 10.05***
Experiment 5				
Repeated saline	5	0.49 ± 0.16	3.60 ± 2.87	18.20 ± 8.87
Repeated morphine	14	4.46 ± 0.17***	34.20 ± 4.96**	134.7 ± 14.78***

Morphine-sensitized rats repeated saline rats were challenged with morphine (5 mg/kg s. c.) after a 10-day washout. Data are expressed as the mean ± S.E.M. of stereotypy scores, rearings number and horizontal locomotor activity in a 30 min observation period. * $P<0.05$; ** $P<0.01$, *** $P<0.001$ versus the *Repetead Saline* group, *t* test.

2.8.3. Experiment 3: effects of repeated carbamazepine administration on the competence of saline-treated and morphine-sensitized rats to acquire VAB

The purpose of the experiment was to evaluate whether repeated carbamazepine treatment modified the spontaneous competence of saline-treated rats to acquire an instrumental appetitive behavior and whether it could affect this competence in sensitized rats. Rats received saline (1 ml/kg, $n=21$) or morphine (10 mg/kg, $n=14$) s. c. for 7 days. Twenty-four h after the sensitization test, 16 saline and 16 sensitized rats were divided into four groups: 8 repeated-saline and 8 sensitized rats received vehicle (1 ml/kg, *control* and *morphine* groups, respectively), 8 repeated saline and 8 sensitized rats received carbamazepine (6 mg/kg, *carbamazepine* and *morphine + carbamazepine* groups, respectively), i. p. twice a day for 10 days before the beginning and during the 10-day exposure to the Y-maze.

2.8.4. Experiment 4: effects of repeated lithium administration on the dopaminergic response to palatable food consumption in the NAcS of saline-treated and morphine-sensitized rats

In order to study whether repeated lithium treatment would modify the response to a natural reward in sensitized rats, dopaminergic output in the NAcS was examined by microdialysis at baseline and after the consumption of VS pellets. Rats received saline (1 ml/kg, $n=17$) or morphine (10 mg/kg, $n=12$) s. c. for 7 days. Twenty-four h after the sensitization test, 12 saline and 12 sensitized rats were divided into four groups: 6 repeated-saline and 6 sensitized rats received saline (1 ml/kg, *control* and *morphine* groups, respectively), 6 repeated-saline and 6 sensitized rats received lithium (0.8 mEq/kg, *lithium* and *morphine + lithium* groups, respectively) i. p. twice a day for 10 days. Rats underwent surgery 18–20 h after the last treatment, then received saline or lithium administration several hours after the surgery and the following morning, 2 h before the beginning of the microdialysis experiment. The dose of lithium was chosen on the basis of previously published results in order to obtain mean plasma lithium concentrations of 0.65–0.75 mEq/l (Gambarana et al., 1999a; Gambarana et al., 2000).

2.8.5. Experiment 5: effects of repeated lithium administration on the competence of morphine-sensitized rats to acquire VAB

The purpose of the experiment was to evaluate whether repeated lithium treatment would modify the competence of sensitized rats to acquire VAB. Rats received saline (1 ml/kg, $n=19$) or morphine (10 mg/kg, $n=14$) s. c. for 7 days. Twenty-four h after the sensitization test, 14 saline and 14 sensitized rats were divided into four groups: 7 repeated-saline and 7 sensitized rats received saline (1 ml/kg, *control* and *morphine* groups, respectively), 7 repeated-saline and 7 sensitized rats received lithium (0.8 mEq/kg, *lithium* and *morphine + lithium* groups, respectively), i. p. twice a day for 10 days before the beginning and during the 10-day exposure to the Y-maze.

2.9. Statistical analyses

Statistical analyses were performed on commercially available software (GraphPad Prism statistical package, GraphPad, San Diego, CA, USA). Motor response to acute morphine administration (horizontal locomotor activity counts, rearings and stereotypy scores) was analyzed by unpaired *t* test. The data on the number of escapes were subjected to one-way analysis of variance (ANOVA). Data from the microdialysis and VAB experiments were analyzed using two-way, mixed factorial, repeated-measures ANOVA (r-ANOVA) with group as the between-subject variable and the time or session as the within-subject variable. Post-hoc analyses were performed by Bonferroni's or Dunnett's test when $p<0.05$.

3. Results

The morphine-treated rats utilized in each experiment developed behavioral sensitization, as indicated by the higher stereotypy scores, compared to control rats, in response to a 5 mg/kg morphine dose (Table 1).

Table 2
Effect of repeated carbamazepine administration on the escape response.

Group	*n*	Unavoidable stress	Number of escapes
Naive	8	no	25.5 ± 0.9**
Stress	8	yes	1.3 ± 0.5
Carbamazepine 5 days	6	yes	26.8 ± 0.8**
Carbamazepine 14 days	6	yes	3.8 ± 1.3
Carbamazepine 30 days	8	yes	2.7 ± 0.6
Naïve	12	no	24.2 ± 0.9**
Stress	12	yes	1.8 ± 0.5
Carbamazepine 14 days	8	no	24.6 ± 1.5**
Carbamazepine 30 days	8	no	24.9 ± 1.2**
Carbamazepine 40 days	8	no	23.8 ± 1.1**

Data are expressed as the mean ± S.E.M. of the number of escapes. ** $P<0.01$ compared to the *stress* group, Dunnett's test.

3.1. Experiment 1: effects of repeated carbamazepine treatment on the stress resilience of morphine-sensitized rats

Before studying the possible effect of carbamazepine administration on the resilience of sensitized rats to develop behavioral sequelae after unavoidable stress exposure, we first examined the effect of repeated carbamazepine treatment on the response to a nociceptive stimulus in control rats. Analysis of numbers of escapes showed differences between the groups ($F_{4,35}=246.0$, $P<0.001$); post hoc analysis demonstrated that after unavoidable stress exposure, the *stress* group developed a clear-cut escape deficit; carbamazepine-treated rats were protected from the behavioral sequelae of acute stress after a short-term treatment (5 days), but gradually developed tolerance to this protective effect and after 14 and 30 days of treatment they showed an escape deficit similar to that of the *stress* group (Table 2). The effect of a long-term treatment with carbamazepine (14, 30 and 40 days) on the spontaneous escape response was then examined ($F_{4,49}=125.5$, $P<0.001$): carbamazepine-treated rats did not develop a spontaneous escape deficit (Table 2).

The effect of repeated carbamazepine treatment on the consequences of unavoidable stress exposure in sensitized rats was also examined. Twenty-four h after the sensitization test, rats were divided into subgroups: 12 of the repeated saline and 8 of the sensitized rats received vehicle (1 ml/kg); 8 of the repeated saline and 8 of the sensitized rats received carbamazepine (6 mg/kg) i. p. twice a day for 14 days. Analysis of numbers of escapes showed differences between groups ($F_{4,35}=117.3$, $P<0.001$); in particular, repeated carbamazepine administration reinstated the susceptibility to stress in sensitized rats, that is the *morphine + carbamazepine* group exposed to the unavoidable stress session developed an escape deficit similar to the *stress* and *carbamazepine* groups (Fig. 1). After the escape test, treatments (vehicle or carbamazepine) were resumed in the naïve, carbamazepine and morphine + carbamazepine groups; a week later the expression of sensitization was tested by challenging the animals with morphine (5 mg/kg, s. c.). Repeated carbamazepine administration did not modify the response to an acute morphine challenge in the *sensitized rats* ($F_{2,21}=117.7$, $P<0.001$) (Fig. 2). Thus, carbamazepine treatment abolished the stress resilience of sensitized rats without modifying the expression of the locomotor sensitization.

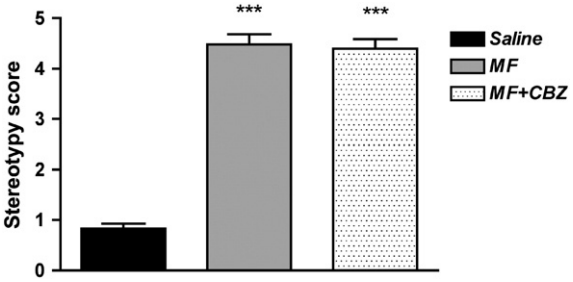

Fig. 2. Behavioral response to a morphine challenge in morphine-sensitized rats, treated or not with carbamazepine. After the escape test (Fig. 1), the vehicle-treated and carbamazepine-treated sensitized groups (*MF* and *MF + CBZ, respectively*) and a repeated-saline group (*Saline*) resumed treatments (vehicle or carbamazepine) and a week later they received a morphine challenge (5 mg/kg, s. c.). Values are expressed as the mean of stereotypy scores ± S.E.M. in the 30 min observation period. $^{***}P<0.001$ versus the *Saline* group (Bonferroni's test).

3.2. Experiment 2: effects of repeated carbamazepine administration on the dopaminergic response to palatable food consumption in the NAcS of saline-treated and morphine-sensitized rats

Extraneuronal dopamine values at baseline were different between groups (*control*: 5.0 ± 0.6 pg/10 µl, *carbamazepine*: 3.0 ± 0.5 pg/10 µl, *morphine*: 6.1 ± 0.5 pg/10 µl, *morphine + carbamazepine*: 6.0 ± 0.5 pg/10 µl, ANOVA $F_{3,28}=7.60$, $P<0.001$); in particular, they were lower in the *carbamazepine* group compared to levels in the other groups ($P<0.05$ versus the control group and $P<0.01$ versus the *morphine* and *morphine + carbamazepine* groups). Increases in dopamine levels after VS consumption were affected by group ($F_{3,200}=8.56$, $P<0.001$), time ($F_{8,200}=63.94$, $P<0.001$) and their interaction ($F_{24,200}=4.41$, $P<0.001$), as dopamine output increased in the *control, morphine*, and *morphine + carbamazepine* groups, but was not significantly modified in *the carbamazepine* group (Fig. 3).

3.3. Experiment 3: effects of repeated carbamazepine administration on the competence of saline-treated and morphine-sensitized rats to acquire VAB

This experiment was aimed at evaluating whether carbamazepine treatment would modify the natural competence of saline-treated rats

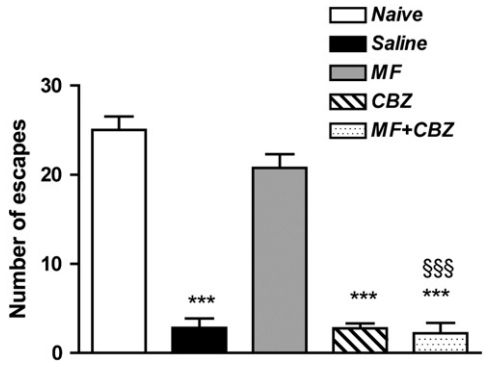

Fig. 1. Effect of repeated carbamazepine administration on the resilience to stress of morphine-sensitized rats. Repeated-saline and sensitized rats received vehicle (*Saline* and *MF*, respectively) or carbamazepine (*CBZ* and *MF + CBZ*, respectively) for 14 days before the experiment. Rats were exposed to the unavoidable stress and the following day they were tested for escape. A group of repeated-saline rats was tested for escape without unavoidable stress exposure (*Naïve*). Scores are expressed as the mean number of escapes ± S.E.M. in 30 consecutive trials. $^{***}P<0.001$ versus the *Naïve* and *MF* groups; $^{§§§}P<0.001$ versus the *MF* group (Bonferroni's test).

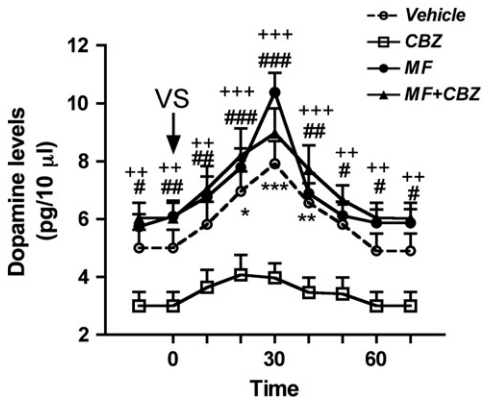

Fig. 3. Changes in extraneuronal dopamine levels in the NAcS in response to VS consumption in repeated-saline and morphine-sensitized rats, treated or not with carbamazepine. Repeated-saline and sensitized rats received vehicle (*Vehicle* and *MF*, respectively) or carbamazepine (*CBZ* and *MF + CBZ*, respectively) for 10 days before the experiment. After the assessment of baseline dopamine levels, five VS pellets were introduced in the microdialysis cage (arrow) and samples were collected. Values represent the mean ± S.E.M. of extraneuronal dopamine levels. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, *CBZ* versus *Vehicle* group; $^{\#}P<0.05$, $^{\#\#}P<0.01$, $^{\#\#\#}P<0.001$, CBZ versus *MF* group; $^{++}P<0.01$, $^{+++}P<0.001$, *CBZ* versus *CBZ + MF* group (Bonferroni's test).

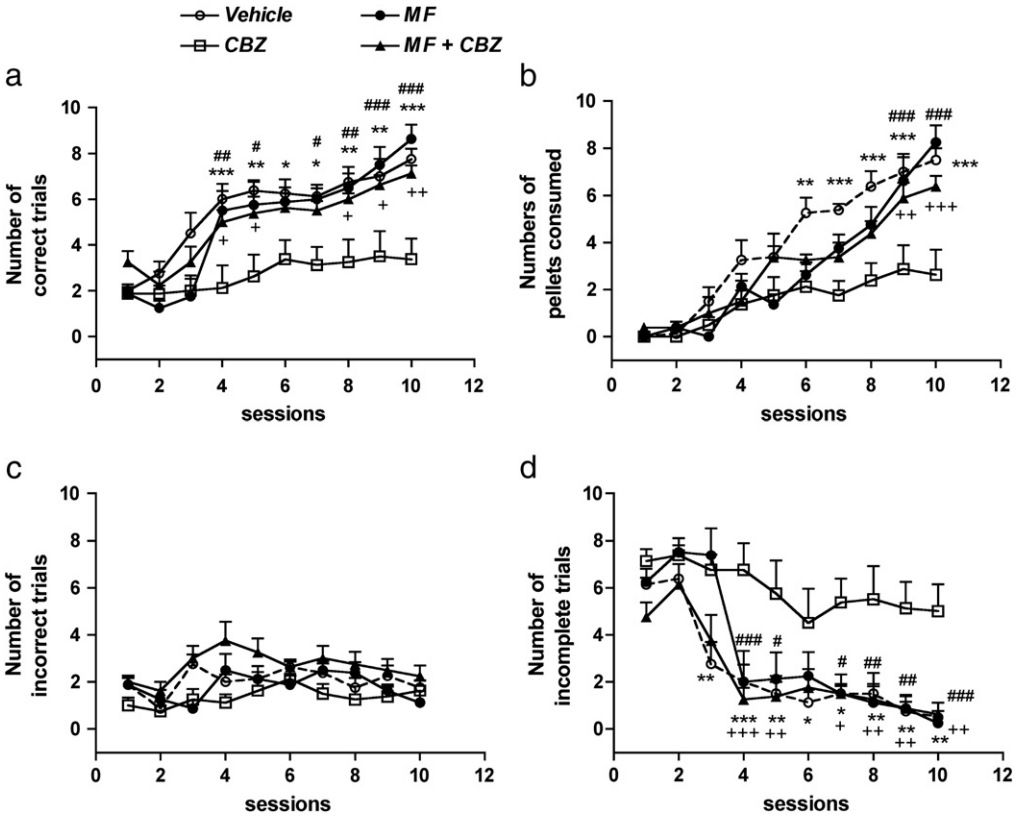

Fig. 4. Y-maze exposure for VAB acquisition in repeated-saline and morphine-sensitized rats, treated or not with carbamazepine. Repeated-saline and sensitized rats received vehicle (*Vehicle* and *MF*, respectively) or carbamazepine (*CBZ* and *MF + CBZ*, respectively) for 10 days before and during the 10-day Y-maze exposure. Data are presented as mean ± S.E.M. of the number of correct (a), incorrect (c) and incomplete trials (d), and number of pellets consumed (b). $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, *CBZ* versus *Vehicle* group; $^{\#}P<0.05$, $^{\#\#}P<0.01$, $^{\#\#\#}P<0.001$ CBZ versus *MF* group; $^{+}P<0.05$, $^{++}P<0.01$, $^{+++}P<0.0y01$ *CBZ* versus *CBZ + MF* group (Bonferroni's test).

to acquire VAB and whether it could affect this competence in sensitized rats. The number of correct trials performed and VS pellets consumed were affected by group (correct trials: $F_{3,\ 252}=8.07$, $P<0.001$; VS pellets consumed: $F_{3,\ 252}=7.93$, $P<0.001$), session (correct trials: $F_{9,\ 252}=37.76$, $P<0.001$; VS pellets consumed: $F_{9,\ 252}=69.23$, $P<0.001$), and their interaction (correct trials: $F_{27,\ 252}=2.73$, $P<0.001$; VS pellets consumed: $F_{27,\ 252}=3.65$, $P<0.001$). The *control* and *morphine* rats performed more correct trials and consumed more VS pellets with repeated sessions, while *carbamazepine* rats did not (Fig. 4a and b). Moreover, carbamazepine treatment did not modify the performance of sensitized rats (Fig. 4a and b). Analysis of the number of incorrect trials indicated an effect of group ($F_{3,\ 252}=5.75$, $P<0.01$) and session ($F_{9,\ 252}=3.73$, $P<0.001$); no statistical differences were demonstrated by post hoc comparisons (Fig. 4c). The number of incomplete trials was affected by group ($F_{3,\ 252}=8.38$, $P<0.001$), session ($F_{9,\ 252}=34.51$, $P<0.001$), and their interaction ($F_{27,\ 252}=2.42$, $P<0.001$). The number of incomplete trials was higher in *carbamazepine* than in *vehicle*, *morphine* and *morphine + carbamazepine* rats (Fig. 4d). This experiment indicates that carbamazepine administration reduced the competence to acquire VAB of repeated-saline rats, while leaving unmodified the competence of sensitized rats, as suggested by the results of the microdialysis experiment.

3.4. Experiment 4: effects of repeated lithium administration on the dopaminergic response to palatable food consumption in the NAcS of saline-treated and morphine-sensitized rats

The purpose of the experiment was to study whether repeated lithium treatment modified the response to a natural reward in sensitized rats. Baseline extraneuronal dopamine values were similar between groups (*control*: 5.8 ± 0.5 pg/10 μl, *lithium*: 7.5 ± 0.3 pg/10 μl, *morphine*: 7.6 ± 0.5 pg/10 μl, *morphine + lithium*: 6.2 ± 0.6 pg/10 μl). Increases in dopamine levels were affected by time ($F_{8,160}=52.13$, $P<0.001$), but not by group, as dopamine output increased in all groups after VS consumption (Fig. 5).

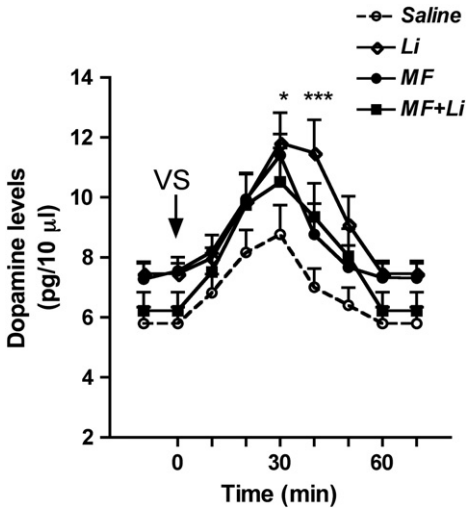

Fig. 5. Changes in extraneuronal dopamine levels in the NAcS in response to VS consumption in repeated-saline and morphine-sensitized rats, treated or not with lithium. Repeated-saline and sensitized rats received vehicle (*Vehicle* and *MF*, respectively) or lithium (*Li* and *MF + Li*, respectively) for 10 days before the experiment. After the assessment of baseline dopamine levels, five VS pellets were introduced in the microdialysis cage (arrow) and samples were collected. Values represent the mean ± S.E.M. of extraneuronal dopamine levels. $^{*}P<0.05$, $^{***}P<0.001$, *Saline* versus *Li* group (Bonferroni's test).

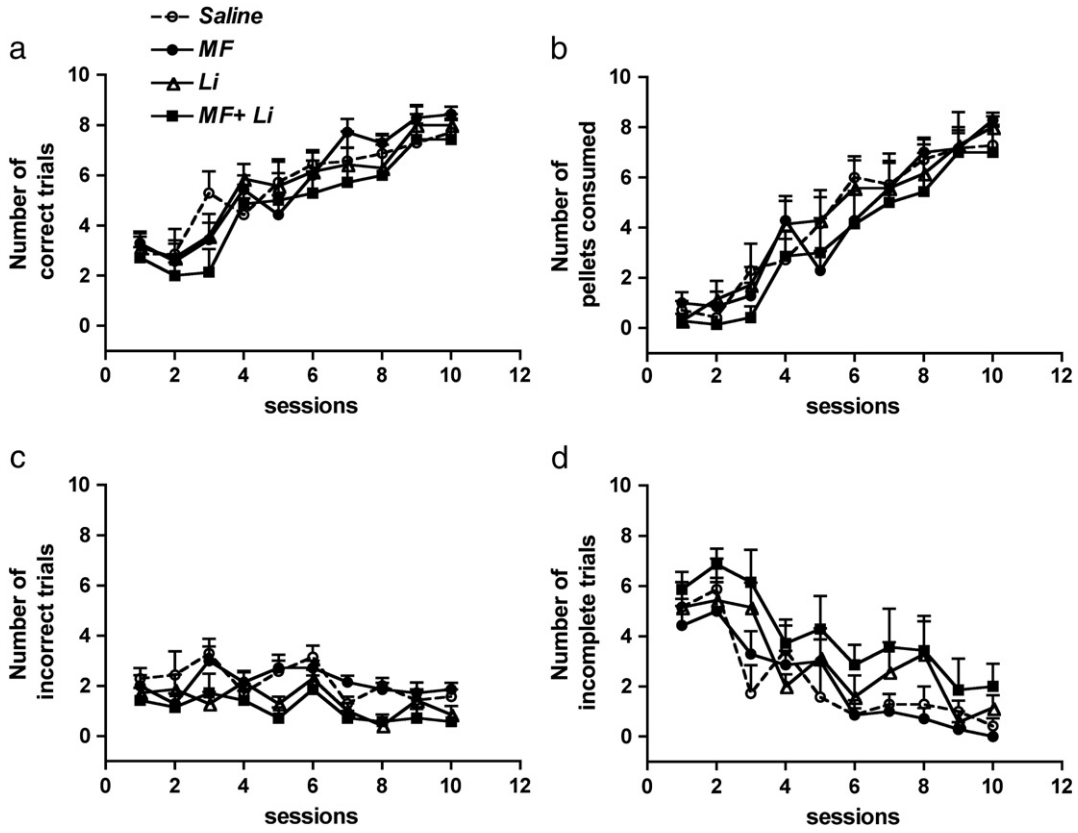

Fig. 6. Y-maze exposure for VAB acquisition in repeated-saline and morphine-sensitized rats, treated or not with lithium. Repeated-saline and sensitized rats received vehicle (*Vehicle* and *MF*, respectively) or lithium (*Li* and *MF + Li*, respectively) for 10 days before and during the 10-day Y-maze exposure. Data are presented as mean ± S.E.M. of the number of correct (a), incorrect (c) and incomplete trials (d), and number of pellets consumed (b).

Post-hoc analysis demonstrated that dopamine levels were higher in the *lithium* than in the *control* group 30 and 40 min after the VS meal (Fig. 5).

3.5. Experiment 5: effects of repeated lithium administration on the competence of morphine-sensitized rats to acquire VAB

The purpose of the experiment was to evaluate whether repeated lithium treatment, that does not modify the natural competence of saline-treated rats to acquire VAB (Masi et al., 2000), would affect VAB acquisition in sensitized rats. The number of correct trials performed and VS pellets consumed were affected only by session (correct trials: $F_{9,\ 216} = 38.46$, $P<0.001$; VS pellets consumed: $F_{9,\ 216} = 56.24$, $P<0.001$) (Fig. 6a, b). Analysis of the number of incorrect trials indicated an effect of treatment ($F_{3,\ 216} = 9.71$, $P<0.001$) and session ($F_{9,\ 216} = 4.63$, $P<0.001$); however, no statistical differences were demonstrated by post hoc comparisons (Fig. 6c). The number of incorrect trials was affected only by session ($F_{9,\ 216} = 26.22$, $P<0.001$) (Fig. 6d). These results indicate a similar competence to acquire VAB in the 4 groups of rats tested.

4. Discussion

In morphine-sensitized rats, carbamazepine administration reinstated sensitivity to the behavioral effects of unavoidable stress exposure, while it did not interfere with the sensitized motor response to a morphine challenge. In non-sensitized rats, carbamazepine treatment showed a biphasic effect on the escape response, since a short-term (5 days) administration prevented the development of an escape deficit induced by unavoidable stress, while tolerance to this protective effect developed after 14 days and was still present after 30 days of treatment. The susceptibility of sensitization-associated stress resilience to the repeated administration of an anti-manic drug, in addition to the demonstrated responsiveness to lithium (Gambarana et al., 2000), strengthens the hypothesis that the condition of morphine sensitization leads to relatively persistent behavioral modifications that conform to predictive validity criteria for a model of a manic symptom (McKinney and Bunney, 1969; Willner, 1995). However, this model is not endowed with a clear construct validity, as there are no evidences that sensitization to opioids develops in humans. The onset of the therapeutic effectiveness of carbamazepine is generally rapid in the treatment of seizure disorders, whereas it shows some lag in the treatment of mania, and it exhibits a longer lag in mood disorder treatment (Post, 1988). These time course variations suggest that different mechanisms might underlie the efficacy of carbamazepine in different neuropsychiatric syndromes. Biochemical and pharmacological data suggest that different neurotransmitters are involved in the effects of carbamazepine (Baf et al., 1994; Post, 1988; Waldmeier et al., 1995). The data on the dopaminergic modifications induced by carbamazepine treatments appear to be relatively inconsistent due to the different experimental conditions and techniques utilized (Baf et al., 1994; Elphick, 1989; Ichikawa et al., 2005; Ichikawa and Meltzer, 1999; Nibuya et al., 1991; Waldmeier et al., 1995). However, sufficient agreement exists on decreased dopaminergic transmission in the limbic areas of long-term carbamazepine treated rats (Basselin et al., 2008; Okada et al., 1997). Moreover, in bipolar patients carbamazepine administration decreases probenecid-induced accumulations of HVA and this effect is clearly related to subsequent better clinical outcomes (Post et al., 1986). In non-sensitized rats, repeated carbamazepine administration induced a decrease in basal extraneuronal dopamine levels, reduced the dopaminergic response to palatable food consumption in the NAcS, and disrupted the competence to acquire an appetitive behavior instrumental at earning that food. Sensitized rats showed basal levels of extraneuronal dopamine in the NAcS similar to those of control

animals, in agreement with previous results (Gambarana et al., 2000). Moreover, they presented a dopaminergic response to VS consumption in the NAcS and acquired VAB. Thus, the variables examined in this study do not indicate modifications in the reward seeking/motivation domain in morphine-sensitized rats. The *morphine + carbamazepine* group showed dopamine levels at baseline and after VS consumption similar to those in the *morphine* group and retained the competence to acquire VAB.

Several animal studies have demonstrated a depressogenic activity of lithium (Carrol and Sharp, 1971; Hines, 1986). Chronic lithium administration impairs (Geoffroy et al., 1991), or appears to be inactive on (Overstreet, 1993), the escape response of rats administered a previous unavoidable stress. However, lithium has also been reported to improve performance in some experimental models of depression, either induced by stress (Faria and Teixeira, 1993; Teixeira et al., 1995) or genetic (Aulakh et al., 1994), and to potentiate the effects of antidepressant drugs in the forced swimming test (Bourin et al., 1996; Nixon et al., 1994). Such discrepancies regarding lithium effects on animal models could be related to the different experimental conditions or the animal species or strain used. Conflicting results have also been found on the effects of chronic lithium administration on tissue and extraneuronal dopamine levels in discrete brain areas (Ferrie et al., 2008; Ho et al., 1970). Lithium administered systemically slowly enters the blood brain barrier and reaches equilibrium with plasma concentration within ~2 days (Kersten, 1987; Poust, 1987). In our experimental conditions, a 3-day lithium administration prevents the development of escape deficit produced by exposure to unavoidable stress, while after a 3-week treatments rats show a spontaneous escape deficit associated with decreased basal extraneuronal dopamine levels and dopamine output in the NAcS (Gambarana et al., 1999a). This biphasic effect likely represents an adaptive response to the initial lithium-induced perturbations. After a 3-week lithium administration rats show sensitivity to the incentive properties of a palatable meal in terms of intense NAcS dopaminergic response to VS consumption, regardless of their low baseline dopamine levels, and competence to acquire VAB (Masi et al., 2000). Moreover, once lithium-treated rats acquire VAB their levels of extraneuronal dopamine in the NAcS and their capacity to escape an avoidable stress are similar to those of control rats (Masi et al., 2000). The present study shows that after a 10-day lithium treatment, basal dopamine levels and the dopaminergic response to VS consumption in the NAcS were in the range of control values. Moreover, it confirms that under continuous lithium treatment rats retain the competence to acquire an appetitive instrumental behavior (Masi et al., 2000). In sensitized rats lithium treatment did not modify dopamine basal levels nor the dopaminergic response to a VS meal in the NAcS, or the competence to acquire VAB. Thus, the two treatments had rather similar effects in morphine-sensitized rats, as they abolished the stress resilience of sensitized rats but did not affect their hedonic/motivational competences, with the exception of the escape deficit which is spontaneous in lithium-treated rats (Gambarana et al., 1999a), whereas it developed only after unavoidable stress exposure in carbamazepine-treated rats. Conversely, when repeatedly administered to non-sensitized rats, carbamazepine and lithium showed quite different effect profiles. In fact, the effects observed after repeated carbamazepine administration appeared to some extent similar to those observed after chronic stress exposure (Gambarana et al., 1999b), since rats showed a blunted dopaminergic response to VS consumption and did not acquire VAB. In this context, the present results suggest that repeated carbamazepine administration induces a condition of reduced dopaminergic and behavioral response to a positive stimulus. Thus, a significant result of this study is the observation of the development of an anhedonia-like condition after repeated carbamazepine administration that distinguished the effects of this drug on "normal" rats from those of lithium. This observation may be correlated with the different clinical profile of carbamazepine and lithium. Anhedonia in humans is an established suicidal risk factor in depressed, bipolar and schizophrenic subjects (Leventhal and Rehm, 2005; Loas et al., 2000; Loas et al., 2009; Nock and Kazdin; 2002; Spijker et al., 2009). Lithium, the drug of reference for the treatment of bipolar disorder, also reduces the risk of attempted or completed suicide, while other drugs widely used as mood stabilizers, such as the anticonvulsants, lack substantial evidence of antisuicidal activity (Kovacsics et al., 2009). In clinical practice mood stabilizers are administered to bipolar patients with the aim of preventing or attenuating the intensity of manic or depressive episodes, and treatments are continued independently of the mood phases. The observation that morphine-sensitized rats were resistant to the anhedonia-inducing effect of carbamazepine suggests that, if the condition of morphine sensitization in rats models some of the traits of mania in humans, during a manic episode bipolar patients might be protected from carbamazepine-induced anhedonia. However, vulnerability to the possible anhedonia-inducing effect of carbamazepine may fluctuate, being negligible during manic phases and likely high during euthymic or depressive phases. The dysmodulation of motivation and reward is considered a core domain of bipolar disorder and conditions of increased reward seeking have been proposed to model this aspect of the manic phase of the disorder (Hasler et al., 2006). The mood stabilizers lithium and valproate reduce the increased sweet solution preference in one of these models (Flaisher-Grinberg et al., 2009). However, to our knowledge, the possible influence of these repeated treatments on the motivation/reward domain of control animals has not been previously characterized. Moreover, while the possible anti- or pro-anhedonic activity of drugs employed as mood stabilizers has not been specifically addressed by human studies, it may represent a critical determinant of the anti-suicidal activity of a drug. Lithium reduces the risk of attempted or completed suicide (Baldessarini et al., 2006; Cipriani et al., 2005; Collins and McFarland, 2008; Goodwin et al., 2003), while the anticonvulsants used as mood stabilizers lack substantial evidence of antisuicidal activity (Kovacsics et al., 2009). This difference does not correlate with the effects on two main suicidal risk factors, impulsivity and aggressiveness, that appear to be equally controlled in clinical practice by lithium and anticonvulsants administration (Kovacsics et al., 2009). Thus, the efficacy in controlling one or two risk factors does not necessarily imply that a drug that shows these effects is endowed with antisuicidal activity. Anticonvulsants, particularly sodium valproate and carbamazepine, are employed prophylactically in bipolar disorder, although the main regulatory agencies have denied this clinical indication to both of them. In particular, carbamazepine is only approved for acute mania and its inferiority as a mood stabilizer compared to lithium is well documented (Dardennes et al., 1995; Davis et al., 1999; Denicoff et al., 1997; Greil et al., 1997; Post, 2000; Post et al., 1998a, 1998b). Lithium is also approved as augmentation therapy in depressed patients resistant to standard antidepressants (Bauer et al. 2000). Thus, the observed divergent effects of lithium and carbamazepine on the acquisition of an appetitive behavior in rats suggest that the influence on the hedonic domain may be relevant to interpret the different effects of these two drugs in bipolar and depressed patients.

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References

Aulakh CS, Hill JL, Murphy DL. Enhanced anorexic responses to m-chlorophenylpiperazine during lithium administration to fawn-hooded rats. Pharmacol Biochem Behav 1994;49:759–62.

Baf MH, Subhash MN, Lakshmana KM, Rao BS. Alterations in monoamine levels in discrete regions of rat brain after chronic administration of carbamazepine. Neurochem Res 1994;19:1139–43.

Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. Bipolar Disord 2006;8:625–39.

Basselin M, Chang L, Chen M, Bell JM, Rapoport SI. Chronic carbamazepine administration attenuates dopamine D_2-like receptor-initiated signaling via arachidonic acid in rat brain. Neurochem Res 2008;33:1373–83.

Bauer M, Bschor T, Kunz D, Berghöfer A, Ströhle A, Müller-Oerlinghausen B. Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. Am J Psychiatry 2000;157: 1429–35.

Bourin M, Hascoet M, Colombel MC, Redrobe JP, Baker GB. Differential effects of clonidine, lithium and quinine in the forced swimming test in mice for antidepressants: possible roles of serotoninergic systems. Eur Neuropsychopharmacol 1996;6:231–6.

Bourin M, Prica C. The role of mood stabilisers in the treatment of the depressive facet of bipolar disorders. Neurosci Biobehav Rev 2007;31:963–75.

Calabrese JR, Bowden C, Woyshville MJ. Lithium and the anticonvulsants in the treatment of bipolar disorders. In: Bloom FE, Kupfer DJ, editors. Psychopharmacology: the Fourth Generation of Progress. New York: Raven Press Ltd; 1995. p. 1099–2011.

Carrol BJ, Sharp PT. Rubidium and lithium: opposite effects on amine-mediated excitement. Science 1971;172:1355–7.

Cipriani A, Pretty H, Hawton K, Geddes JR. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. Am J Psychiatry 2005;162:1805–19.

Collins JC, McFarland BH. Divalproex, lithium and suicide among Medicaid patients with bipolar disorder. J Affect Disord 2008;107:23–8.

Coryell W. Maintenance treatment in bipolar disorder: a reassessment of lithium as the first choice. Bipolar Disorders 2009;11(Suppl.2):77–83.

Dardennes R, Even C, Bange F, Heim A. Comparison of carbamazepine and lithium in the prophylaxis of bipolar disorders. A meta-analysis. Br J Psychiatry 1995;166:378–81.

Davis JM, Janicak PG, Hogan DM. Mood stabilizers in the prevention of recurrent affective disorders: a meta-analysis. Acta Psychiatr Scand 1999;100:406–17.

Dencker D, Husum H. Antimanic efficacy of retigabine in a proposed mouse model of bipolar disorder. Behav Brain Res 2010;207:78–83.

Denicoff KD, Smith-Jackson EE, Bryan AL, Ali SO, Post RM. Valproate prophylaxis in a prospective clinical trial of refractory bipolar disorder. Am J Psychiatry 1997;154: 1456–8.

Di Chiara G, Tanda G. Blunting of reactivity of dopamine transmission to palatable food: a biochemical marker of anhedonia in the CMS model? Psychopharmacology 1997;134:351–3.

Di Chiara G. Nucleus accumbens shell and core dopamine: differential role in behavior and addiction. Behav Brain Res 2002;137:75–114.

Einat H, Manji HK. Cellular plasticity cascades: genes-to-behavior pathways in animal models of bipolar disorder. Biol Psychiatry 2006;59:1160–71.

Elphick M. Effects of carbamazepine on dopamine function in rodents. Psychopharmacology 1989;99:532–6.

Faria MS, Teixeira NA. Reversal of learned helplessness by chronic lithium treatment at a prophylactic level. Braz J Med Biol Res 1993;26:1201–12.

Ferrie LJ, Gartside SE, Martin KM, Young AH, McQuade R. Effect of chronic lithium treatment on D2/3 autoreceptor regulation of dopaminergic function in the rat. Pharmacol Biochem Behav 2008;90:218–25.

Flaisher-Grinberg S, Einat H. A possible utilization of the mice forced swim test for modeling manic-like increase in vigor and goal-directed behavior. J Pharmacol Toxicol Meth 2009;59:141–5.

Flaisher-Grinberg S, Overgaard S, Einat H. Attenuation of high sweet solution preference by mood stabilizers: a possible mouse model for the increased reward-seeking domain of mania. J Neurosci Meth 2009;177:44–50.

Gambarana C, Ghiglieri O, Masi F, Scheggi S, Tagliamonte A, De Montis MG. The effects of long-term administration of rubidium or lithium on reactivity to stress and on dopamine output in the nucleus accumbens in rats. Brain Res 1999a;826:200–9.

Gambarana C, Masi F, Tagliamonte A, Scheggi S, Ghiglieri O, De Montis MG. A chronic stress which impairs reactivity in rats also decreases dopaminergic transmission in the nucleus accumbens: a microdialysis study. J Neurochem 1999b;72:2039–46.

Gambarana C, Mangiavacchi S, Masi F, Scheggi S, Tagliamonte A, Tolu P, et al. Long-term lithium administration abolishes the resistance to stress in rats sensitized to morphine. Brain Res 2000;877:218–25.

Gambarana C, Scheggi S, Tagliamonte A, Tolu P, De Montis MG. Animal models for the study of antidepressant activity. Brain Res Prot 2001;7:11–20.

Gambarana C, Masi F, Leggio B, Grappi S, Nanni G, Scheggi S, et al. Acquisition of a palatable-food-sustained appetitive behavior in satiated rats is dependent on the dopaminergic response to this food in limbic areas. Neuroscience 2003;121:179–87.

Gambarana C, Grappi S, Scheggi S, Marchese G, De Montis MG. Carbamazepine effects on the morphine-sensitization model of mania in rats. FENS Abstr 2010;5:017.13.

Geoffroy M, Tvede K, Christensen AV, Schou JS. The effect of imipramine and lithium on "learned helplessness" and acetylcholinesterase in rat brain. Pharmacol Biochem Behav 1991;38:93–7.

Ghiglieri O, Gambarana C, Scheggi S, Tagliamonte A, Willner P, De Montis MG. Palatable food induces an appetitive behaviour in satiated rats which can be inhibited by chronic stress. Behav Pharmacol 1997;8:619–28.

Goodwin FK, Fireman B, Simon GE, Hunkeler EM, Lee J, Revicki D. Suicide risk in bipolar disorder during treatment with lithium and divalproex. JAMA 2003;290:1467–73.

Gould TD, Einat H. Animal models of bipolar disorder and mood stabilizer efficacy: a critical need for improvement. Neurosci Biobehav Rev 2007;31:825–31.

Greil W, Ludwig-Mayerhofer W, Erazo N, Schöchlin C, Schmidt S, Engel RR, et al. Lithium versus carbamazepine in the maintenance treatment of bipolar disorders—a randomised study. J Affect Disord 1997;43:151–61.

Hasler G, Drevets WC, Gould TD, Gottesman II, Manji HK. Toward constructing an endophenotype strategy for bipolar disorders. Biol Psychiatry 2006;60:93–105.

Hines G. Effects of lithium on shock-induced changes in open-field activity. Psychopharmacology 1986;88:209–12.

Ho AKS, Loh HH, Craves F, Hitzemann RJ, Gershon S. The effect of prolonged lithium treatment on the synthesis rate and turnover of monoamines in brain regions of rats. Eur J Pharmacol 1970;10:72–8.

Ichikawa J, Meltzer HY. Valproate and carbamazepine increase prefrontal dopamine release by 5-HT1A receptor activation. Eur J Pharmacol 1999;380:R1–3.

Ichikawa J, Dai J, Meltzer HY. Lithium differs from anticonvulsant mood stabilizers in prefrontal cortical and accumbal dopamine release: role of 5-HT(1A) receptor agonism. Brain Res 2005;1049:182–90.

Keck Jr PE, McElroy SL, Richtand N, Tohen M. What makes a drug a primary mood stabilizer? Mol Psychiatry 2002;7:S8–S14.

Kersten L. The gastrointestinal system. In: Johnson FN, editor. Depression and mania. Modern Lithium Therapy. Oxford: IRL Press; 1987. p. 196–201.

Kovacsics CE, Gottesman II, Gould TD. Lithium's antisuicidal efficacy: elucidation of neurobiological targets using endophenotype strategies. Annu Rev Pharmacol Toxicol 2009;49:175–98.

Leventhal AM, Rehm LP. The empirical status of melancholia: implications for psychology. Clin Psychol Rev 2005;25:25–44.

Loas G, Perot JM, Chignague JF, Trespalacios H, Delahousse J. Parasuicide, anhedonia, and depression. Compar Psychiatry 2000;41:369–72.

Loas G, Azi A, Noisette C, Legrand A, Yon V. Fourteen-year prospective follow-up study of positive and negative symptoms in chronic schizophrenic patients dying from suicide compared to other causes of death. Psychopathology 2009;42:185–9.

Masi F, Scheggi S, Mangiavacchi S, Romeo A, Tagliamonte A, De Montis MG, et al. Acquisition of an appetitive behavior reverses the effects of long-term treatment with lithium in rats. Neuroscience 2000;100:805–10.

Masi F, Scheggi S, Mangiavacchi S, Tolu P, Tagliamonte A, De Montis MG, et al. Dopamine output in the nucleus accumbens shell is related to the acquisition and the retention of a motivated appetitive behavior in rats. Brain Res 2001;903:102–9.

McKinney Jr WT, Bunney Jr WE. Animal model of depression. I. Review of evidence: implications for research. Arch Gen Psychiatry 1969;21:240–8.

Nibuya M, Kanba S, Kinoshita N, Suzuki E, Yagi G, Nakaki T, et al. Effects of carbamazepine and ipsapirone on turnovers of monoamines in the rat brain. Jpn J Psychiatry Neurol 1991;45:127–8.

Nixon MK, Hascoet M, Bourin M, Colombel MC. Additive effects of lithium and antidepressants in the forced swimming test: further evidence for involvement of the serotoninergic system. Psychopharmacology 1994;115:59–64.

Nock MK, Kazdin AE. Examination of affective, cognitive, and behavioral factors and suicide-related outcomes in children and young adolescents. J Clin Child Adolesc Psychol 2002;31:48–58.

Okada M, Hirano T, Mizuno K, Chiba T, Kawata Y, Kiryu K, et al. Biphasic effects of carbamazepine on the dopaminergic system in rat striatum and hippocampus. Epilepsy Res 1997;28:143–53.

Overstreet DH. The Flinders sensitive line rats: a genetic animal model of depression. Neurosci Biobehav Rev 1993;17:51–68.

Paxinos G, Watson C. The Rat Brain in Stereotaxic Coordinates. New York: Academic Press; 1998.

Post RM, Rubinow DR, Uhde TW, Ballenger JC, Linnoila M. Dopaminergic effects of carbamazepine. Relationship to clinical response in affective illness. Arch Gen Psychiatry 1986;43:392–6.

Post RM. Time course of clinical effects of carbamazepine: implications for mechanisms of action. J Clin Psychiatry 1988;49(Suppl):35–48.

Post RM, Frye MA, Denicoff KD, Leverich GS, Kimbrell TA, Dunn RT. Beyond lithium in the treatment of bipolar illness. Neuropsychopharmacology 1998a;19:206–19.

Post RM, Denicoff KD, Frye MA, Dunn RT, Leverich GS, Osuch E, et al. A history of the use of anticonvulsants as mood stabilizers in the last two decades of the 20th century. Neuropsychobiology 1998b;38:152–66.

Post RM. Psychopharmacology of mood-stabilizers. In: Buckley PF, Waddington JL, editors. Schizophrenia and Mood Disorders: The New Drug Therapies in Clinical Practice. Boston: Butterworth-Heinemann; 2000. p. 127–54.

Poust RI. Kinetic and tissue distribution. In: Johnson FN, editor. Depression and mania. Modern lithium therapy. Oxford: IRL Press; 1987. p. 73–4.

Roybal K, Theobold D, Graham A, DiNieri JA, Russo SJ, Krishnan V, et al. Mania-like behavior induced by disruption of CLOCK. Proc Natl Acad Sci USA 2007;104:6406–11.

Scheggi S, Masi F, Tagliamonte A, Gambarana C, Tolu P, De Montis MG. Rats sensitized to morphine are resistant to the behavioral effects of an unavoidable stress. Brain Res 2000;853:290–8.

Scheggi S, Rauggi R, Gambarana C, Tagliamonte A, De Montis MG. Dopamine and cyclic AMP-regulated phosphoprotein-32 phosphorylation pattern in cocaine and morphine-sensitized rats. J Neurochem 2004;90:792–9.

Sharifzadeh M, Aghsami M, Gholizadeh S, Tabrizian K, Soodi M, Khalaj S, et al. Protective effects of chronic lithium treatment against spatial memory retention deficits induced by the protein kinase AII inhibitor H-89 in rats. Pharmacology 2007;80: 158–65.

Spijker J, de Graaf R, Ten Have M, Nolen WA, Speckens A. Predictors of suicidality in depressive spectrum disorders in the general population: results of the Netherlands

Mental Health Survey and Incidence Study. Soc Psychiatry Psychiatr Epidemiol 2009. Jul 19.
Teixeira NA, Pereira DG, Hermini AH. Chronic but not acute Li^{+} treatment prevents behavioral depression in rats. Braz J Med Biol Res 1995;28:1003–7.
Tsaltas E, Kontis D, Boulougouris V, Papakosta V-M, Giannou H, Poulopoulou C, et al. Enhancing effects of chronic lithium on memory in the rat. Behav Brain Res 2007a;177:51–60.
Tsaltas E, Kyriazi T, Poulopoulou C, Kontis D, Maillis A. Enhancing effects of lithium on memory are not by-products of learning or attentional deficits. Behav Brain Res 2007b;180:241–5.
Vasconcellos APS, Tabajara AS, Ferrari C, Rocha E, Dalmaz C. Effect of chronic stress on spatial memory in rats is attenuated by lithium treatment. Physiol Behav 2003;79:143–9.
Waldmeier PC, Baumann PA, Wicki P, Feldtrauer JJ, Stierlin C, Schmutz M. Similar potency of carbamazepine, oxcarbazepine, and lamotrigine in inhibiting the release of glutamate and other neurotransmitters. Neurology 1995;45:1907–13.
Willner P, Towell A, Sampson D, Sophokleous S, Muscat R. Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant. Psychopharmacology 1987;93:358–64.
Willner P, Muscat R, Papp M. Chronic mild stress-induced anhedonia. A realistic animal model of depression. Europ J Pharmacol 1992;296:129–36.
Willner P. Animal models of depression: validity and applications. Adv Biochem Psychopharmacol 1995;49:19–41.