Effects of chronic administration of olanzapine, amitriptyline, haloperidol or sodium valproate in naïve and anhedonic rats

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Abstract
Although in bipolar patients the main therapeutic indication of atypical antipsychotics is the management of acute mania, several observations suggest that these agents may exert antidepressant as well as anti-manic effects. The main goal of the present work was to evaluate the putative antidepressant effect of chronic olanzapine (Ola) (0.02–0.1 or 0.5 mg/kg . d), in comparison to haloperidol (Hal) (0.2 mg/kg . d) and sodium valproate (VPA) (5 or 30 mg/kg . d), in rats exposed to a protocol of chronic mild stress. The tricyclic compound amitriptyline (Ami) (5 mg/kg . d) was used as reference drug. The results indicate that Ola, in a rodent model of depression, has protective effects against the stress-induced anhedonia. Compared to Hal and VPA, Ola shows a greater antidepressant activity and is as effective as Ami in preventing the anhedonic state. The effects of Ola and Ami, however, have a different time-course. A full reversion of the anhedonia by Ami appears after a latency of 4 wk, whereas the effect of Ola is already evident 1 wk after the beginning of the chronic treatment. Moreover, the recovery from anhedonia at the end of the stress protocol and after drug cessation was more rapid in groups of rats pretreated with Ola or VPA than in the group of saline-pretreated rats. In conclusion, these observations support the hypothesis that Ola has a broader pharmacotherapeutic profile than solely as an antipsychotic or anti-manic agent.

Key words: Anhedonia, chronic mild stress, olanzapine, rat.

Introduction
Bipolar disorder is characterized by periods of elevated mood referred to as hypomania or mania that usually alternate with episodes of depression or periods of euthymia. The mainstay of managing bipolar disorder is mood stabilization using lithium carbonate, although this drug may not be effective in an estimated 40–50% of cases. Considering the high percentage of poor or non-responders, as well as patients that are intolerant to the side-effects of lithium, it becomes very important that new treatment alternatives be identified. Mood-stabilizing anticonvulsants are the first alternative as long-term agents for the treatment of bipolar patients refractory to lithium. Other possible alternatives also include antipsychotics, benzodiazepines and calcium antagonists. The availability of atypical antipsychotic drugs, like olanzapine (Ola), risperidone, quetiapine and clozapine as alternatives to the classical drugs is an important challenge to the pharmacotherapy of bipolar disorder. Although in bipolar patients the main therapeutic indication of atypical antipsychotics is the management of acute mania, several observations suggest that these agents may exert antidepressant as well as anti-manic effects. A recent retrospective study of Sokolski and Denson (2003) reported significant improvements in clinician-rated bipolar severity scores for mania, depression and overall bipolar illness after administration of low doses of quetiapine in patients with incomplete

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response to mood stabilizers. Compared to haloperidol (Hal), the same drug (8 wk treatment, 600 mg/d) produced a greater reduction of depressive symptoms in schizophrenic patients with a history of partial refractoriness to conventional antipsychotics (Emsley et al., 2003). The efficacy of quetiapine and risperidone against depressive symptoms in psychotic patients has been investigated by Sajatovic et al. (2002). Although both agents produced improvements in mean Hamilton Rating Scale for Depression scores, quetiapine (mean dose 318 mg/d) showed greater efficacy than risperidone (mean dose 4.4 mg/d) in all patients.

As far as Ola is concerned, several clinical studies have confirmed the acute anti-manic efficacy of the drug. A 12-wk randomized controlled trial comparing the efficacy of this novel antipsychotic vs. Hal in the treatment of bipolar mania indicated that Ola did not differ from Hal in achieving overall remission of manic symptoms (Tohen et al., 2003a). However, median time to symptomatic mania remission was significantly shorter and overall mania improvement was greater for Ola (5–20 mg/d) than for divalproex (0.5–2.5 g/d) in another 47-wk study of acute bipolar mania (Tohen et al., 2003b). In particular, Ola seems to be slightly more effective than valproate (VPA) and as efficacious as Hal in the treatment of manic or mixed bipolar patients and, compared to Hal, Ola appears to be superior in treating depressive symptoms.

A retrospective study of Ghaemi et al. (2000) reported that a dosage of Ola in the 2.5–30 mg/d range appeared effective in treating the depressive phase of mood disorders in combination with antidepressants. This finding added further evidence to the previous clinical trials suggesting a moderate decrease of depressive symptoms in schizophrenic patients after Ola administration (Tollefson et al., 1997; Zarate et al., 1998). A recent paper of Tohen et al. (2003c) reporting a double-blind, 8-wk controlled trial on the efficacy of Ola and Ola + fluoxetine combination in the treatment of bipolar depression, confirms the putative antidepressant properties of this atypical antipsychotic. Although clinical reports seem to indicate that some novel antipsychotics might be used to treat depressive symptoms, at present no data are available on the effectiveness of these compounds to revert anhedonia in animal models of depression.

The main goal of the present work was to evaluate the putative antidepressant effect of Ola, in comparison to Hal, a typical neuroleptic drug mainly used to treat psychotic depression and VPA, a mood stabilizer widely used in monotherapy or combined with lithium, antidepressants or antipsychotics to treat bipolar patients, in rats exposed to a protocol of chronic mild stress (CMS). The tricyclic compound amitriptyline (Ami) was used as reference drug. CMS is a naturalistic paradigm of a hostile environment which models anhedonia, a core symptom of depression defined as the diminished preference by rats for palatable sweetened solution (sucrose solution) in a free choice trial with water. The animal model of anhedonia has proven to be especially successful in the functional identification of antidepressant drugs and, therefore, has a high degree of predictive validity (Ferretti et al., 1995; Ghi et al., 1995; Papp et al., 1996; Przegalinski et al., 1995). In our study saline, Ola, Hal, Ami and VPA were injected every day during the administration of the CMS protocol and the putative antidepressant effect of the selected drugs was checked by measuring sucrose preference both during the induction of anhedonia and, after the end of CMS protocol, during the recovery from the anhedonic state.

**Methods**

**Animals**

A total of 255 adult male albino rats (Charles River Laboratories Italia, Lecco, Italy) of the Wistar strain were used. Prior to starting the CMS protocol, the rats were housed in a temperature-controlled colony room (22 ± 2 °C) with free access to food and water, were maintained four per cage under standard laboratory conditions and were submitted to daily handling for at least 2 wk. The weight of the animals at the beginning of the experiments was 180–200 g. Each rat was weighed once a week both during CMS protocol and the following recovery period to verify the influence of CMS and/or drug administration on weight gain. All experiments were carried out in accordance with the European Communities Council Directive of 24 November 1986 and D.L. of 27 January 1992 no. 116 (86/609/EEC). All efforts were made to minimize animal suffering and to reduce the number of animals used.

**Sucrose preference training and testing**

Animals were housed individually with two 50-ml graduate tubes containing either 1% sucrose solution or tap water with standard laboratory chow continuously available. They were allowed 24 h to adapt to these two bottles and, within this period, the sucrose consumption was evaluated every 2 h from the beginning of the experiment. Both the water and sucrose intakes were measured by weighing the pre-weighed bottles containing the respective solutions. For each
animal, the basal sucrose preference after the training procedure was evaluated as

\[ S_{\text{Int}} \times 100 \]

\[ \frac{(S_{\text{Int}} + W_{\text{Int}})}{W_{\text{Int}}} \]

where \( S_{\text{Int}} \) = sucrose intake (g) = [(weight of bottle containing sucrose solution at 24 h) – (weight of bottle containing sucrose solution at 26 h)]; \( W_{\text{Int}} \) = water intake (g) = [(weight of bottle containing water at 24 h) – (weight of bottle containing water at 26 h)].

Figure 1 illustrates a representative experiment showing the learning procedure adopted to assess the basal sucrose preference.

Subsequently, the sucrose preference was monitored individually under similar conditions (two-bottle test, 2-h periods) at selected intervals both during and after the administration of the CMS protocol. Finally, in order to minimize the differences among individuals, the sucrose preference during both the CMS and recovery periods was calculated as percent difference vs. basal value. During the CMS protocol, the sucrose preference test was carried out at least 16 h after the conclusion of the stress session.

CMS protocol

Twenty-four hours after the evaluation of the basal sucrose preference, the rats were subjected to the procedure of CMS for the induction of anhedonia. The CMS protocol was designed to maximize the unpredictable nature of the stressors. One of the following stressors was administered daily (in random order) over a period of 3–4 wk: crowding, by placing eight animals in standard individual cages for 24 h; food deprivation for 24 h; 45° cage tilt for 5 h; shaker stress (horizontal shakes at high speed) for 10 min; soiled cage (200 ml water in sawdust bedding) for 5 h; intermittent overnight illumination (light on and off every 3 h for 24 h); light on overnight; tail pinch for 2 min; swimming in cold water (16°C) for 5 min. In developing our CMS protocol, we have made changes to the procedure previously described by Katz (1982), since the severity of the stressors employed was greatly reduced. Indeed, the individual stressors we have used do not include elements like intense foot-shock, restraint stress or 48 h water/food deprivation. In this respect, our CMS protocol is similar to the procedure of CMS adopted by Willner et al. (1987).

However, the choice of stressful stimuli, the intensity of each stressor, the order of administration and the duration of the whole protocol were validated in our laboratory in order to achieve a stable reduction (~50% vs. basal intake) of sucrose preference 2 wk after the beginning of the experiments. Immediately after the conclusion of each stress session, the animals were returned to the colony room and maintained in standard conditions until the next stress session of the CMS regime. Sucrose preference tests were performed 7, 14, 21 and 28 d after the beginning of the CMS procedure and never the day after food deprivation. In the drug experiments, stress was continued throughout the treatment period and weekly sucrose preference tests were carried out 24 h after drug administration. Sucrose preference tests were also performed 2, 5, 7, 14 and 21 d after the end of the CMS administration in order to achieve detailed information about recovery from anhedonia.

Drug administration

In the present work the following drugs have been tested: amitriptyline hydrochloride (Sigma-Aldrich Srl, Milano, Italy), 2-propyl-pentanoic acid sodium salt (sodium valproate, Sigma-Aldrich), haloperidol hydrochloride (Tocris Cookson Ltd, Bristol, UK) and olanzapine (synthesized at Eli Lilly and Co., Indianapolis, IN, USA). Eight groups of unstressed animals (\( n = 15 \) rats/group) were treated intraperitoneally with saline (28-d administration), Ami 5 mg/kg.d (28-d administration), VPA 5 and 30 mg/kg.d (21-d administration), Hal 0.2 mg/kg.d (21-d administration) or Ola 0.02–0.1 and 0.5 mg/kg.d (21-d administration). Two separate groups of control rats (\( n = 15 \)) were subjected to a 21- or 28-d period of both CMS and saline administration. One group of rats (\( n = 15 \)) was subjected to a 28-d period of both CMS
The naive-saline group is a group of naive rats (n=15) not subjected to CMS protocol. The other groups are those shown in Figure 3. CMS protocol, saline and Ola were administered from 0 to 21 d. Weekly comparisons between Ola-treated rats and naive-saline or saline groups indicate no statistical significant difference (Student’s t test for unpaired data). and 5 mg/kg.d Ami administration, whereas six groups of rats (n=15) were subjected to a 21-d period of CVS+VPA (5 or 30 mg/kg.d) or Hal (0.2 mg/kg.d) or Ola (0.02–0.1 or 0.5 mg/kg.d) administration. Saline or drug administration was carried out every day (from 15:00 to 16:00 hours) at the end of each stress session, except when the duration of the session was 24 h.

Statistical analysis
Sucrose preference data concerning the induction of anhedonia were analysed by a two-factor, mixed designed analysis of variance (ANOVA). Post-hoc comparisons were performed by Scheffé test, when appropriate. Student’s t test for unpaired data was used to compare data concerning different experimental groups. In all cases a value of p<0.05 was considered to be significant.

Results
Mean food consumption of saline-treated rats during the period of exposure to CMS was 26.6±1.4 g/d. During the same period, the mean food intake of the saline-naive group was 27.4±0.9 g/d. Global ANOVA applied to data of saline-treated rats revealed no significant effect of stress [F(1,28)=0.01, p=0.91], week [F(2,56)=0.22, p=0.8] and no significant interaction between these factors [F(2,56)=0.45, p=0.63]. Similar results were obtained for drug-treated groups. The analysis of weight gain was performed once a week during both the CMS and recovery periods. No significant effect of stress [F(1,28)=0.08, p=0.95] and stress x week interaction [F(6,168)=0.99, p=0.42] but a significant effect of the week factor [F(6,168)=2.6, p=0.019] was observed in saline-treated rats. These data clearly indicate that, in our experimental conditions, the increase of body weight was comparable in stressed and control rats. Moreover, no significant difference in weight gain was observed between saline-treated rats and rats treated with VPA [treatment: F(2,42)=0.24, p=0.78; week: F(6,252)=2.93, p=0.008; interaction: F(12,252)=0.36, p=0.97], Ami [treatment: F(1,28)=0.11, p=0.74; week: F(7,196)=2.47, p=0.018; interaction: F(7,196)=0.29, p=0.95], Ola [treatment: F(3,56)=0.082, p=0.97; week: F(6,336)=4.25, p<0.001; interaction: F(18,336)=0.74, p=0.75] (see Table 1) or Hal [treatment: F(1,28)=0.002, p=0.95; week: F(6,168)=2.25, p=0.04; interaction: F(6,168)=0.24, p=0.96]. In the final test, prior to the beginning of the CMS protocol, the mean basal sucrose intake was 13.3±1.1 g. In saline-treated stressed rats the sucrose intake fell to 6.38±0.74 g or 6.25±0.58 g after 3 or 4 wk respectively, whereas the intake remained at the same level in the naive-saline group (12.7±1.3 g).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Days</th>
<th>0/7</th>
<th>7/14</th>
<th>14/21</th>
<th>21/28</th>
<th>28/35</th>
<th>35/42</th>
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<tbody>
<tr>
<td>Naive-saline</td>
<td></td>
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<tr>
<td>Saline</td>
<td>10.7±1.9</td>
<td>11.8±1.8</td>
<td>11.0±0.9</td>
<td>11.9±1.8</td>
<td>14.6±2.7</td>
<td>9.4±1.8</td>
<td>6.0±1.5</td>
</tr>
<tr>
<td>Ola (0.02 mg/kg.d)</td>
<td>12.4±2.6</td>
<td>14.3±2.1</td>
<td>11.7±2.1</td>
<td>15.9±2.3</td>
<td>9.2±2.1</td>
<td>6.1±1.3</td>
<td>6.2±1.1</td>
</tr>
<tr>
<td>Ola (0.1 mg/kg.d)</td>
<td>12.8±1.7</td>
<td>14.6±2.1</td>
<td>11.2±2.1</td>
<td>12.7±2.8</td>
<td>10.5±2.6</td>
<td>7.3±1.6</td>
<td>9.5±1.9</td>
</tr>
<tr>
<td>Ola (0.5 mg/kg.d)</td>
<td>11.6±2.8</td>
<td>12.2±3</td>
<td>13.5±3.1</td>
<td>9.3±2</td>
<td>10.3±2.9</td>
<td>8.4±2.4</td>
<td>8.2±1.8</td>
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Table 1. Weight gain (grams, mean ±S.E.M.) of control and Ola-treated rats during the period of induction and recovery from anhedonia

In our experimental conditions, the evaluation of the antidepressant effect of the drugs examined is founded first on the comparison with the efficacity of Ami to revert the CMS-induced reduction of sucrose intake. To integrate our analysis, however, a second criterion has been established, i.e. the duration of the protective effect against anhedonia. In this respect, the most effective antidepressant may be considered the agent that maintains the euthymic state over the entire period of CMS administration.

In a separate saline-treated group and in the group of rats treated with Ami, the period of CMS administration was extended to 4 wk in order to attain a complete reversion of the anhedonia by the tricyclic
of treatment after the drug cessation, during the following period of recovery from anhedonia. The antidepressant action of Ami has a slow onset, since it appears ~ 3 wk after the beginning of the treatment and the rats pretreated with Ami returned to the euthymic state more rapidly than the saline-pretreated rats. *p < 0.05 vs. saline.

Chronic VPA administration

The effects of daily administration of saline or VPA on sucrose preference of stressed rats are shown in Figure 3. A two-way ANOVA applied to these data yielded a significant effect of treatment [F(2, 42) = 8.11, p < 0.001] and sucrose testing day [F(2, 84) = 18.6, p < 0.001] and no significant interaction between these two factors [F(4, 84) = 1.71, p = 0.15]. The following contrast analysis revealed a significant difference of saline vs. the 30 mg/kg, d VPA group [F(1, 42) = 16.1, p < 0.001]. The lower dose of VPA (5 mg/kg, d) had no effect [F(1, 42) = 2.88, p = 0.096]. Only the higher dose of VPA (30 mg/kg, d) employed in our experiments seems to have protective effects against the anhedonia induced by CMS. The action of VPA has a rapid onset, lasts ~ 15 days and disappears during the last week of CMS administration. The VPA administration over a period of 21 d on sucrose preference of naive rats is ineffective [treatment: F(2, 42) = 0.91, p = 0.41; testing day: F(2, 84) = 0.58, p = 0.56; interaction: F(4, 84) = 1.24, p = 0.29] (Table 2). The pattern of sucrose preference concerning the 21-d period following the end of CMS protocol and the cessation of VPA treatment is illustrated in Figure 3. A statistical significant effect of the treatment [F(2, 42) = 19.0, p < 0.001], sucrose testing day [F(4, 168) = 19.8, p < 0.001] and a significant interaction between the two factors [F(8, 168) = 14.2,
CMS administration. *pyonset, lasts anhedonia induced by CMS. The action of VPA has a rapid onset, during the following period of recovery from anhedonia. Only the higher dose of VPA (30 mg/kg . d) seems to have protective effects against the recovery from anhedonia. Only the higher dose of VPA after the drug cessation, during the following period of preference tests have also been performed 2, 5, 7, 14 and 21 d after the end of CMS administration.

**Figure 3.** Effect of chronic administration of VPA (* – , 5 mg/kg . d; – , 30 mg/kg . d) and saline (– ○ – ) on sucrose preference of rats exposed to a 21-d period of CMS. Sucrose preference tests have also been performed 2, 5, 7, 14 and 21 d after the drug cessation, during the following period of recovery from anhedonia. Only the higher dose of VPA (30 mg/kg . d) seems to have protective effects against the anhedonia induced by CMS. The action of VPA has a rapid onset, lasts ~15 d and disappears during the last week of CMS administration. * p < 0.05 vs. saline.

$p < 0.001$] indicated that rats pretreated with VPA returned to the euthymic state more rapidly than saline-pretreated rats. The contrast analysis applied to our data yielded significant differences between VPA (5 mg/kg . d) and saline groups $[F(1, 42) = 37.7, p < 0.001]$ and VPA (30 mg/kg . d) and saline groups $[F(1, 42) = 12.1, p = 0.001]$. Therefore, the recovery from anhedonia following CMS administration is accelerated by previous treatment with VPA. This finding seems to strengthen the hypothesis that repeated administration of high doses of VPA (30 mg/kg . d) has beneficial effects both during and after the application of unpredictable stressors.

**Chronic Ola administration**

The effects of daily administration of saline or Ola on sucrose preference of stressed rats are shown in Figure 4. The two-way ANOVA applied to these data yielded a significant effect of treatment $[F(3, 55) = 42.5, p < 0.001]$ and sucrose testing day $[F(2, 110) = 21.1, p < 0.001]$ and a significant interaction between the two factors $[F(6, 110) = 6.65, p < 0.001]$. A significant difference of saline vs. each of the three Ola-treated groups [saline vs. 0.02 mg/kg . d: $F(1, 55) = 117, p < 0.001$; saline vs. 0.1 mg/kg . d: $F(1, 55) = 46, p < 0.001$; saline vs. 0.5 mg/kg . d: $F(1, 55) = 12.4, p = 0.001]$, was observed. However, at the end of CMS administration, only the lowest dose of Ola had protective effects against anhedonia $(p < 0.05$ vs. saline group, Student’s t test). Within the first period of application of the CMS protocol, the repeated administration of Ola seems effective in contrasting the induction of anhedonia. However, the analysis of the whole results indicate that this effect is dose-dependent. In our experimental conditions, the most active dose of Ola is 0.02 mg/kg . d. The Ola administration on sucrose preference of naive rats is ineffective [treatment: $F(3, 55) = 1.18, p = 0.32$; testing day: $F(2, 110) = 0.12, p = 0.88$; interaction: $F(6, 110) = 1.37, p = 0.29]$ (Table 2). The pattern of sucrose preference concerning the 21-d period following the end of CMS protocol and the cessation of Ola treatment is shown in Figure 4. A significant effect of the treatment $[F(3, 55) = 24.4, p < 0.001]$, of the interaction between treatment and sucrose testing day $[F(12, 220) = 3.81, p < 0.001]$ but not of the sucrose testing day factor $[F(4, 220) = 0.49, p = 0.74]$ indicated that the pretreatment with Ola caused a stabilization of sucrose preference in stressed rats. In fact, the contrast analysis applied to our data yielded significant differences of the saline vs. 0.02 mg/kg . d Ola [saline vs. 0.02 mg/kg . d Ola: $F(1, 55) = 67.9, p < 0.001$, saline vs. 0.1 mg/kg . d Ola: $F(1, 55) = 35.8, p < 0.001$, saline vs. 0.5 mg/kg . d Ola groups: $F(1, 55) = 15.4, p < 0.001]$. Thus, the recovery from anhedonia following CMS administration is
accelerated by previous treatment with 0.02–0.1 or 0.5 mg/kg/d Ola. In addition, our data suggest also that the repeated administration of low doses of Ola (0.02 mg/kg/d) has beneficial effects both during and after the application of unpredictable stressors.

**Chronic Hal administration**

The effects of repeated administration of saline or Hal on sucrose preference of CMS rats are shown in Figure 5. A two-way ANOVA applied to these data yielded a significant effect of treatment \( F(1, 28) = 58.1, p < 0.001 \) and sucrose testing day \( F(2, 56) = 39.8, p < 0.001 \) and a significant interaction between the two factors \( F(2, 56) = 17.9, p < 0.001 \). Thus, our data indicate a weak protective effect against the CMS-induced anhedonia after chronic administration of 0.2 mg/kg/d Hal. The Hal administration on sucrose preference of naive rats is ineffective [treatment: \( F(1, 28) = 0.12, p = 0.72 \); testing day: \( F(2, 56) = 0.61, p = 0.54 \); interaction: \( F(2, 56) = 0.73, p = 0.48 \)] (Table 2).

The time-course of sucrose preference concerning the 21-d period following the end of the CMS protocol and the cessation of Hal treatment is illustrated in Figure 5. Statistical significant effects of treatment \( F(1, 28) = 7.9, p = 0.008 \) and sucrose testing day \( F(4, 112) = 13, p < 0.001 \) and a significant interaction between these two factors \( F(4, 112) = 3.1, p = 0.017 \) indicated that rats pretreated with Hal returned to the euthymic state more rapidly than saline-pretreated rats.

**Discussion**

The doses of Ola employed as an antipsychotic or anti-manic agent range from 5 to 20 mg/d. The recommended initial doses to treat schizophrenia or a bipolar episode of mania are 10 mg/d and 15 mg/d (monotherapy) or 10 mg/d (combined therapy) respectively. In addition, the available controlled clinical studies specifically evaluating depressed mood-disorder subjects indicate that the three doses of Ola exposed to a 21-d period of CMS. Although the recovery from anhedonia following CMS administration is accelerated by previous treatment with Hal, the drug shows negligible antidepressant effects. \( * p < 0.05 \) vs. saline.

Ola displayed a significantly greater sucrose preference in comparison to saline-treated rats, at the end of the CMS protocol only the lowest dose of Ola was effective. In addition, animals pretreated with 0.02 mg/kg/d Ola maintained a sucrose preference over the basal value, also after drug cessation, during the following 21-d period of recovery from anhedonia.

These findings might represent the first demonstration of the antidepressant-like effect of Ola in a rodent model of anhedonia. Higher efficacy has been obtained at doses below 0.1 mg/kg/d, corresponding to the lower end of the range of Ola therapeutical doses. At the most active dose (0.02 mg/kg/d), the effect of Ola has a rapid onset, beginning at week 1, and seems to cause a long-lasting stabilization of sucrose preference. Moreover, it should be emphasized that the effects of Ola reported here, like that of the other drugs, are preventative, not therapeutic, since both drug treatment and CMS administration occurred at the same time. The results of the present work are supported by recent literature concerning the addition of low-dose Ola to ongoing treatment with SSRIs. In particular, Shelton et al. (2001) have demonstrated that relatively low doses of the drug augment the effects of fluoxetine in depressed patients refractory to SSRI monotherapy. Two recent papers extend these clinical data, suggesting that the Ola + fluoxetine combination shows rapid and sustained improvement in depressive symptoms in patients with major depressive disorder, including treatment-resistant patients (Corya et al., 2003) and that the same drug combination is effective in the treatment of bipolar I depression.
(Tohen et al., 2003c). It is unlikely that the modifications of sucrose intake observed in the present work could be due to an effect on appetite. It is possible that weight gain is a side-effect of Ola in humans. In this perspective, we have carefully monitored both the food consumption and the time-course of rat body weight over the whole period of drug administration. The data indicate no significant differences in both food consumption and weight gain between saline- and Ola-treated rats.

Our results indicate also that Ami and the higher dose of VPA have protective effects against anhedonia induced by the CMS protocol. The antidepressant effects of the two drugs, however, have different magnitude and a different time-course. A full reversion of the anhedonia by Ami appeared only 4 wk after the beginning of the chronic treatment, whereas the VPA effects had a rapid onset but disappeared 2 wk later. In this respect, the patterns of antidepressant effect of Ola and VPA were quite similar, even though Ola, administered at doses below 0.1 mg/kg.d, exhibited greater efficacy than the anticonvulsant drug. Moreover, the recovery from anhedonia at the end of the CMS protocol was more rapid in groups of rats pretreated with the two doses of VPA than in the group of saline-pretreated rats. These findings are in line with previous studies reporting that VPA may be an effective treatment in patients who met the DSM-IV criteria for major depressive disorder (Davis et al., 1996) or in patients with bipolar II depression (Winsberg et al., 2001).

More recently, the results of a double-blind, placebo-controlled clinical trial, demonstrated the efficacy of VPA in reducing the symptoms of depression in bipolar I patients (Davis et al., 2005). Of note, two other anti-manic agents like lithium (Sluzewska and Szczawinska, 1996) and carbamazepine (Sluzewska and Nowakowska, 1994) were effective in reverting the CMS-induced reduction of sucrose preference. In our experiments, Hal showed weak protective effects against the anhedonic state induced by the CMS protocol. In contrast, Papp et al. (1996) reported that both Hal and chlorprothixene were devoid of antidepressant properties in the CMS model. The apparent discrepancy between our results and those of Papp et al. (1996) can be explained, at least in part, taking into account that different doses of Hal have been employed (0.2 mg/kg.d in the present study vs. 1.0 mg/kg.d). Interestingly, in a separate study, Papp and Wieronska (2000) reported that the CMS-induced decrease of sucrose consumption was rapidly reversed (within 2 wk) by administration of 5 or 10 mg/kg of the antipsychotic amisulpride, whereas higher doses of the drug were ineffective. As indicated by other authors (Lecrubier et al., 1988, 1997), the antidepressant effects of amisulpride appeared in a dose range lower than that used to treat schizophrenia and probably reflect the selective blockade of presynaptic dopamine receptors. Thus, the weak antidepressant effects of low-dose Hal observed in the present study and the ineffectiveness of higher doses of the same drug reported by Papp et al. (1996) in the CMS model may be explained in the light of these considerations.

Another difference between the present study and that of Papp et al. (1996) that could account for the different effect of Hal was that a prophylactic, not therapeutic, drug administration has been used in our experiments. This is an important general issue since Hal, Ola and VPA all have anxiolytic effects which could be relevant to a prophylactic effect in the CMS model. There is evidence in the literature that anxiolytics are not therapeutic in the CMS model (Muscat et al., 1992), but their prophylactic effects have not been examined in detail. In the learned helplessness model, however, chlordiazepoxide has prophylactic but not therapeutic effects (Drugan et al., 1984).

As reported by Kapur et al. (1998), atypical antipsychotics have high ratios of 5-HT2A/D2 receptor affinity, which may account for their efficacy on negative symptoms of schizophrenic patients and for their low propensity to produce extrapyramidal side-effects. At low doses (5–10 mg/d) Ola occupies over 90% of 5-HT2 sites and ~50% of D2 receptors. By increasing the doses, Ola loses the atypical profile, achieving a receptor blockade of up to 80% of D2 sites and no further antagonism at 5-HT2 receptors. Therefore, in the light of these considerations, the antidepressant effect observed in our study after repeated administration of Ola might be ascribed to the high ratio of 5-HT2/D2 antagonism that the drug exhibits at low doses. This is in agreement with previous findings of Muscat et al. (1992). The authors, indeed, reported that the acute pretreatment with raclopride, a D2-receptor antagonist, reversed the antidepressant effect of fluoxetine or maprotiline in rats subjected to the CMS protocol. In addition, Ola is a potent antagonist particularly at 5-HT2A and 5-HT2B receptor subtypes (Bymaster et al., 1999) and blockade of 5-HT2A receptors has been suggested by Stefanski and Goldberg (1997) to be involved in antidepressant activity. Thus, 5-HT2A antagonism might be responsible for the anti-anhedonic effect of Ola reported here.

In conclusion, although further experimental work is needed to confirm the results of the present study (i.e. by employing hedonic measures different from sucrose preference or animal models of depression
different from CMS), our findings clearly indicate that Ola has protective effects against CMS-induced anhedonia. The chronic administration of low-dose Ola (0.02 mg/kg . d) causes rapid and sustained antidepressant-like effects, whereas all other antimanic treatments show loss of efficacy at 3 wk. Although Ola is as effective as Ami in preventing the anhedonic state, the effects of Ola and Ami, have a different time-course: a full reversion of the anhedonia by the tricyclic compound appears after a latency of 4 wk, whereas the effect of Ola is already evident 1 wk after the beginning of the chronic treatment. Taken together, these observations support the hypothesis that Ola has a broader pharmacotherapeutic profile than solely as an antipsychotic or anti-manic agent.

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Statement of Interest

None.

References


