Annals of General Psychiatry



Poster presentation



# Preclinical study on cognitive and antidepressant effects of chronic low-dose olanzapine

Marco Orsetti*[1], Pier Luigi Canonico[1], Luciana Colella[1], Anna Dellarole[1] and Piera Ghi[2]

Address: [1]Dipartimento Di Scienze Chimiche, Alimentari, Farmaceutiche e Farmacologiche (DiSCAFF), Universitá Del Piemon, Italy and [2]Dipartimento Di Anatomia, Farmacologia e Medicina Legale, Universitá Di Torino, Italy

* Corresponding author

*from* International Society on Brain and Behaviour: 2nd International Congress on Brain and Behaviour
Thessaloniki, Greece. 17–20 November 2005

Published: 28 February 2006

*Annals of General Psychiatry* 2006, **5**(Suppl 1):S181 doi:10.1186/1744-859X-5-S1-S181

## Background

Although in bipolar patients the main therapeutic indication of olanzapine (OLA) is the management of acute mania, several observations suggest that this agent may exert antidepressant as well as antimanic effects. However, in our knowledge, there are no preclinical studies supporting this hypothesis. Thus, the main goal of the present work was to evaluate the putative antidepressant effect of OLA (0.02–0.1 or 0.5 mg/kg/day), in comparison to amitriptyline (AMI) (5 mg/kg/day), haloperidol (HAL) (0.2 mg/kg/day) and sodium valproate (VPA) (5.0 or 30 mg/kg/day), in rats exposed to a protocol of chronic mild stress (CMS). The second aim of this project was to assess the efficacy of OLA, AMI, HAL and VPA in reverting the cognitive impairment produced by the anhedonic state. Both control and anhedonic rats will be subjected to two short-memory paradigms, the place recognition test and the object discrimination test, in order to evaluate the effects of the examined drugs on visuo- spatial memory.

## Materials and methods

One of the following stressors was administered daily (in random order) over a period of 3–4 weeks: crowding, by placing 8 animals in standard individual cages for 24 hours, food deprivation for 24 hours, 45° cage tilt for 5 hours, shaker stress (horizontal shakes at high speed) for 10 minutes, soiled cage (200 ml water in sawdust bedding), intermittent overnight illumination (light on and off every 3 hours), light on overnight (24 hours), tail pinch for 2 minutes, swimming in cold water (16°C) for 5 minutes. Sucrose consumption tests were performed 7, 14, 21 and 28 days after the beginning of the CMS procedure. In drug experiments, stress was continued throughout the treatment period (28 days) and weekly sucrose preference tests were carried out 24 hours after the last drug administration. Sucrose consumption tests were also performed 2, 5, 7, 14, 21 and 28 days after the end of the CMS administration in order to achieve detailed information about recovery from anhedonia. The spatial memory was evaluated by testing the ability of the rats to discriminate a familiar versus a novel environment, while the visual memory was assessed by testing the ability of the rast to discriminate familiar versus novel objects.

## Results

The repeated administration of low doses of OLA, in a rodent model of depression, has protective effects against the anhedonia induced by the CMS protocol. 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 four weeks, whereas the effect of OLA is evident already one week after the beginning of the chronic treatment. The administration of CMS protocol causes a memory impairment both in the place recognition and object discrimination test. In naive rats VPA, OLA 0.02 or 0.1 mg/kg/day and HAL cause no detectable modification of visual short-term memory in comparison to saline group, although they do not revert the impairment of cognitive performance of anhedonic rats. VPA 5 mg/kg/day or OLA 0.02 mg/kg/day do not modify spatial short-term memory in naive rats while the lowest dose of OLA reverts the stress-induced cognitive impairment of anhedonic rats.

## Discussion

The chronic administration of low-dose OLA causes rapid and sustained antidepressant-like effects, whereas all other antimanic treatments show loss of efficacy at three weeks. In addition, the chronic administration of low-dose OLA seems to be more effective than administration of VPA or HAL to prevent the CMS-related damage of visual and spatial short-term memories. Taken toghether, these observations support the hypothesis that OLA has a broader pharmacotherapeutic profile than solely as an antipsychotic or antimanic agent and that it has the potential to lead to substantial cognitive benefits in depressed patients.