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Olanzapine withdrawal/discontinuation-induced hyperthermia in rats

Andrew J. Goudie [a,*], Jon C. Cole [a], Harry R. Sumnall [b]

[a] School of Psychology, University of Liverpool, Eleanor Rathbone Building, Bedford Street North, Liverpool, L69 7ZA, UK
[b] Centre for Public Health, Liverpool John Moores University, Liverpool, UK

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Abstract

In female rats olanzapine (4 mg/kg b.i.d., i.p.) induced acute hypothermia, followed by very rapid full tolerance. With more prolonged treatment (over > 10 days) the hypothermic effect of olanzapine was reinstated. Subsequent withdrawal after 18 days of treatment induced very rapid onset (within 1 day) hyperthermia, which was time limited, dissipating completely over 3–4 days. These findings are similar to previous findings with clozapine [Goudie A Smith J Robertson A Cavanagh C (1999). Clozapine as a drug of dependence. Psychopharmacology; 142: 369–374.]. Although the mechanism(s) involved in the secondary hypothermic effect of olanzapine are, at present, unclear; the withdrawal hyperthermia observed represents the first report of a clear discontinuation effect of olanzapine. Such discontinuation effects are probably observed with many antipsychotic drugs. Since they have been suggested to facilitate relapse to psychosis and to interfere with subsequent clinical responses to antipsychotics, they merit further detailed analysis in both clinical and preclinical studies.

Keywords: Antipsychotic; Discontinuation; Olanzapine; Relapse; Tolerance; Withdrawal

1. Introduction

Some years ago we reported that in rats clozapine induces acute hypothermia, tolerance to such hypothermia with chronic treatment, and subsequent time-related withdrawal-induced hyperthermia (Goudie et al., 1999). We therefore reviewed the possible clinical significance of the clozapine withdrawal/discontinuation syndrome (Goudie, 2000), and suggested that clozapine discontinuation induces somatic withdrawal signs (such as hyperthermia), and that the "stress" experienced when such withdrawal signs occur may facilitate relapse to psychosis (see also Baldessarini et al., 1999a,b; Healy and Tranter, 1999). We suggested that it was important to study in much greater detail antipsychotic drug (APD) discontinuation syndromes both pre-clinically and clinically. Despite these findings, subsequent studies in this area have been relatively limited.

Moncrieff (2006) recently reviewed the literature on APD withdrawal and its possible relationship to relapse. She concluded that withdrawal effects in the clinic are more often observed following treatment with clozapine than with other APDs, and that some withdrawal effects are suggestive of responses which are not simply attributable to the return of an underlying disorder (e.g. psychotic symptoms in subjects with no psychiatric history). She therefore suggested that APD discontinuation may facilitate relapse above the level expected due to the underlying disorder. However, she stressed that the available data are limited and the underlying mechanisms unclear (see also Goudie, 2000). Moreover, she stressed that there is a need for further research in this area. This may be of particular importance given that there is some evidence that APD discontinuation may interfere with subsequent clinical responses to APDs (Grassi et al., 1999; Meltzer et al., 1996; Tollefson et al., 1999; Fernandez et al., 2005; Miodownik et al., 2006; although cf. Pickar and Bartko, 2003).

With these various considerations in mind, we set out to extend our work with clozapine, by examining the consequences of olanzapine withdrawal in rats. Specifically, we examined the effects of acute and chronic administration of olanzapine and

Abbreviations: APD, Antipsychotic drug; D_1, Dopamine$_1$ (receptor); D_2, Dopamine$_2$ (receptor); D_3, Dopamine$_3$ (receptor); 5-HT$_{1A}$, Serotonin$_{1A}$ (receptor); 5-HT$_{2A}$, Serotonin$_{2A}$ (receptor).

* Corresponding author. Tel.: +44 151 794 1124; fax: +44 151 794 2945.
E-mail address: ajg@liverpool.ac.uk (A.J. Goudie).

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subsequent olanzapine withdrawal, on the assumption that we might be able to observe acute olanzapine-induced hypothermia, tolerance to such hypothermia, and subsequent withdrawal/discontinuation-induced hyperthermia. Thus we set out to determine whether withdrawal/discontinuation effects of olanzapine can be detected in rats, in the hope that such studies will be of value in developing this important field of research.

2. Methods

The work reported was conducted in accord with The Animals (Scientific Procedures) Act 1986 under U.K. Home Office licensing.

2.1. Subjects

44 individually housed female Wistar rats (circa 300 g at the start of the study) were maintained in a temperature and humidity controlled room, on an ad lib diet of standard chow (Bantin and Kingman, Hull, U.K.). They had unlimited access to water, and were habituated to their housing for 7 days prior to the study. The 12:12 h light/dark cycle was set so that lights were on during the day.

2.2. Procedure

The study involved two phases. Chronic treatment (days 1–18) was followed by withdrawal (days 19–22). A control group ($n=14$) received vehicle both during the chronic treatment phase and during the withdrawal phase. An experimental group ($n=30$) received olanzapine during the chronic treatment phase and vehicle during the withdrawal phase. Initially we intended to run a dose/response study in which half of the drugged rats received 2 mg/kg of olanzapine and half 4 mg/kg. However, administration of these two specific doses on day 1 of the study (to 15 rats at each of the two doses) indicated that olanzapine at 4 mg/kg just failed to induce significant hypothermia relative to controls and olanzapine at 2 mg/kg had a smaller hypothermic effect (see Results). Thus on day 2 all 30 experimental rats received olanzapine at 4 mg/kg. This procedure was adopted in order to increase the power of the study to detect a significant hypothermic effect of olanzapine at 4 mg/kg. On day 2, olanzapine at 4 mg/kg induced significant hypothermia relative to vehicle treated controls (see Results), and this dose was therefore administered to all drugged rats on all subsequent treatment days (3–18). Olanzapine was administered b.i.d. as it has a short half life in rats (Aravagiri et al., 1999), and short duration behavioural effects in female rats after i.p injection in our laboratory (Goudie et al., 2007). During the chronic treatment phase olanzapine treated rats received their first daily dose in the morning (1000 h) and their second daily dose 4.5 h later. Controls received matched vehicle treatments. Body temperature recordings during the chronic treatment phase were always taken 1 h after the first daily injection of either olanzapine or vehicle. Body temperature recordings were taken in the withdrawal phase of the study at exactly the same time as during the chronic treatment phase, i.e. the first recording in this phase of the study was taken 20.5 h after the last drug or vehicle treatment, the next 24 h later, etc. Body temperatures were recorded in gently restrained rats in a temperature and humidity controlled room with a Comark™ microprocessor thermometer attached to a lubricated rectal probe. Temperature recordings were taken to the nearest 0.1 °C 20 s after insertion of the probe.

2.3. Statistics

Data from the two phases of the study were initially analysed separately. As the drugged rats received 4 mg/kg of olanzapine b.i.d. on days 2–18 only (see above), these chronic treatment data were subjected to a factorial (2) groups × (17) days repeated measures ANOVA. The withdrawal data obtained over days 19–22 were subjected to a similar factorial (2) groups × (4) days repeated measures ANOVA. Post hoc tests for pairwise comparisons between the two groups on each day involved *t*-tests with Bonferroni correction. All analyses were conducted with SPSS (v14.0).

2.4. Drugs

Olanzapine (Eli Lilly, UK) was administered i.p., dissolved in a few drops of 0.1 M HCl, diluted with distilled water and buffered back with NaOH to a pH around 5.5 and injected at a volume of 2 ml/kg.

3. Results

On day 1, when half the 30 drugged rats received 2 mg/kg of olanzapine and half 4 mg/kg (see Methods), the Mean (SE) body temperatures recorded in °C were:— Controls 37.121 (0.094), 2 mg/kg treated rats 36.927 (0.119), 4 mg/kg treated rats 36.807 (0.151). A *t* test indicated that the 4 mg/kg treated rats *just* failed to differ significantly from the Controls ($p=0.094$, two tailed). Thus on day 2, and on all following days, olanzapine was administered at the higher 4 mg/kg dose to all 30 drugged rats to enhance the power of the study, and thus ensure that we observed statistically significant olanzapine-induced hypothermia at the 4 mg/kg dose.

Group mean temperatures recorded throughout the rest of the study (i.e. from day 2 onwards) are shown in Fig. 1. For the chronic treatment phase of the study (days 2–18) there was a group × days interaction ($F(16, 672)=3.476$ $p=0.0001$). Subsequent post hoc tests revealed that olanzapine treated rats showed significant hypothermia on the first day of group treatment with olanzapine at 4 mg/kg (i.e. on day 2), and on intermittent days towards the end of treatment (see Fig. 1). The data show that olanzapine at 4 mg/kg induced significant initial hypothermia, to which full tolerance developed rapidly. This persisted until day 11. However, on day 12, and on intermittent following days, significant drug-induced hypothermia relative to controls returned. Olanzapine treated rats showed lower body temperatures than controls throughout days 12–18, even if the hypothermia was not actually significant on specific days (i.e. on days 15 and 16).

Group mean temperatures recorded throughout the withdrawal phase of the study (days 19–22 — see Fig. 1) revealed a