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Ondansetron Inhibits a Behavioural Consequence of Withdrawing From Drugs of Abuse

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COSTALL, B., B. J. JONES, M. E. KELLY, R. J. NAYLOR, E. S. ONAIVI AND M. B. TYERS. *Ondansetron inhibits a behavioural consequence of withdrawing from drugs of abuse.* PHARMACOL BIOCHEM BEHAV **36**(2) 339–344, 1990.—The ability of the selective 5-HT_3 receptor antagonist ondansetron to influence the behavioural consequences of withdrawal from chronic treatment with ethanol, nicotine or cocaine was investigated in the light/dark exploration test in the mouse and social interaction test in the rat. In both tests acute and chronic (7 days) treatments with ondansetron (0.01–1.0 $\mu g \cdot kg^{-1}$ IP) disinhibited suppressed behaviour; withdrawal from chronic treatment (0.1 mg/kg IP b.i.d.) did not exacerbate the behavioural suppression. Chronic treatment for 14 days with ethanol (8% w/v in the drinking water), nicotine (0.1 mg/kg b.i.d.) or cocaine (1.0 mg/kg b.i.d.) released suppressed behaviour in the mouse and rat tests. Behavioural suppression was increased following withdrawal from ethanol, nicotine and cocaine. The administration of ondansetron (0.01 mg/kg IP b.i.d.) during the period of ethanol, nicotine and cocaine withdrawal prevented the exacerbation in suppressed behaviour. It is concluded that ondansetron potently reduces behavioural suppression during acute and chronic treatments in the rodent models, does not cause a rebound exacerbation of behavioural suppression following withdrawal, and is a highly effective inhibitor of the increased behavioural suppression following withdrawal from the drugs of abuse: ethanol, nicotine and cocaine.

Ondansetron 5-HT_3 receptor Mouse aversive behaviour Drugs of abuse Withdrawal phenomena

WITHDRAWAL from drugs of abuse in man is associated with a variety of effects including dysphoria, craving, anxiety and somatic changes. The nature and intensity of the response is frequently related to the drug used and the degree of abuse. Anxiety is an important component of benzodiazepine withdrawal (20,22) and may contribute to the problems of withdrawal from other drugs. Thus, in rodent and primate models which measure the behavioural response of an animal to an aversive environment, the withdrawal from ethanol, nicotine and cocaine, as well as diazepam, results in suppressed behaviour (1,17). Whilst clinically the benzodiazepines may be used to reduce the severity of drug-induced withdrawal syndromes, their usefulness is compromised by their own abuse potential.

Recently, the acute administration of the 5-HT_3 receptor antagonist, ondansetron (4), has been reported to release suppressed behaviour in the mouse black and white test box model, the rat social interaction test, and in behavioural tests in the marmoset and cynomolgus monkey (21). The aims of the present study were to investigate in these mouse and rat models the effects of chronic administration and withdrawal from ondansetron, and the ability of ondansetron to prevent the behavioural consequences of withdrawing from chronic treatment with ethanol, nicotine and cocaine.

Preliminary results have been presented at the British Pharmacological Society (8,9).

METHOD

Experiments in the Mouse

Male albino BKW mice (Bradford strain), 25–30 g, were used throughout the studies. Mice were housed in groups of 10 in conditions of constant temperature (21°C) and controlled lighting (dark period 0700–1900 hr) and fed ad lib on a standard laboratory chow. Water was available in the living cages at all times, and water containing ethanol was available to mice receiving ethanol treatment.

Tests were conducted between 1300 and 1800 hr in a quiet darkened room illuminated with a red light. Mice were taken from a dark holding room in a dark container to the dark testing room where, after a 1-hour period of adaptation to the new environment, they were placed into the test box. The metal test box (45 × 27 × 27 cm high) was positioned on a bench 1 m above floor level. The box was open-topped and the base was lined into 9 cm

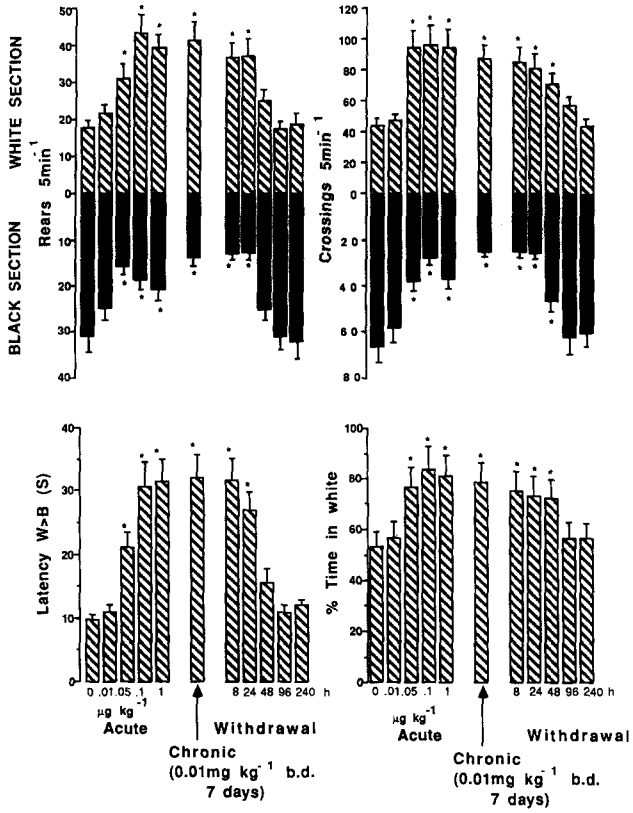

FIG. 1. The effect of ondansetron given acutely, chronically, or withdrawn from chronic treatment, in the light/dark exploration test in mouse. Testing was carried out 45 min after acute dosing, 45 min after the first dose on the 7th day of treatment (chronic), and then at five different times between 8 and 240 hr of withdrawal from chronic treatment. n = 8 per group. *$p<0.01$ compared to controls. Standard errors of the means are given: for % time spent in the light these were calculated from the original data.

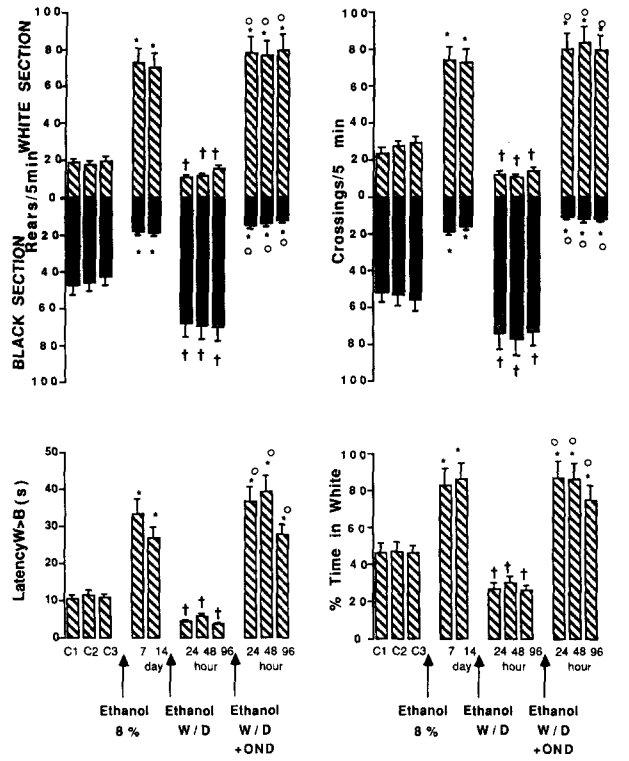

FIG. 2. The effects on mouse light/dark exploration of chronic (14 day) treatment with ethanol (8% w/v in drinking water), effects of withdrawing (W/D) from ethanol treatment, and influence of ondansetron (OND, 0.01 mg/kg IP b.i.d.) on the behavioural consequences of withdrawl from ethanol. C1 = control responses for days 7 and 14 of ethanol intake, C2 = control responses for measures of behaviour taken 24 to 96 hr after withdrawing ethanol, and C3 = control responses for behavioural effects of ethanol withdrawal in animals receiving treatment with ondansetron. n = 8 per group. *$p<0.01$ for redistribution of behaviour in favour of the light section, †$p<0.01$ for redistribution in favour of the dark, °$p<0.01$ for inhibition of the behavioural consequences of withdrawing from ethanol treatment. Standard errors of the means are given: for % time spent in the light these were calculated from the original data.

squares, two-fifths painted black and illuminated by red light (1 × 60 W, 0 lux) and partitioned from the remainder of the box which was painted white and brightly illuminated with a 1 × 60 W (400 lux) light source, the red and white lights being located 17 cm above the box. The compartments were connected by an opening 7.5 × 7.5 cm located at floor level in the centre of the partition. Mice were placed into the centre of the white, brightly lit area and the operator withdrew from the room. The mice were observed by remote video recording and four behaviours were noted: (a) the number of exploratory rearings in the white and black sections, (b) the number of line crossings in the white and black sections, (c) the time spent in the white and black areas and (d) the latency of the initial movement from the white to the black area.

Experiments in the Rat

Male Sprague-Dawley rats, 225–275 g, were normally housed in groups of five and kept on a 12 hr light/dark cycle with lights on at 0800 hr. Tests were conducted between 1300–1800 hr in an illuminated room. The apparatus used for the detection of changes in rat social interaction and exploratory behaviour consisted of an opaque white Perspex open-topped box (45 × 32 cm and 20 cm high) with 15 × 16 cm areas marked on the floor. Two naive rats, from separate housing cages, were placed into the box (with a 100-W bright white illumination 17 cm above) and their behaviour observed over a 10-min period by remote video recording. Two behaviours were noted: 1) social interaction between the animals was determined by timing (seconds) sniffing of partner, crawling under or climbing over partner, genital investigation of partner, following partner and 2) exploratory locomotion was measured as the number of crossings of the lines marked on the floor of the test box. Values for time spent in social interaction and moving around the observation cage were determined for individual animals. Naive animals were used in drug treated pairs in treatment groups of six, i.e., twelve animals.

Experimental Design

In the initial experiments mice and rats received acute and chronic administrations of nicotine (IP b.i.d.), cocaine (IP b.i.d.) or ethanol (administered in the drinking water) to determine dose regimens suitable for chronic administration and withdrawal studies [detailed dose response relationships have previously been established, see Costall *et al.* (8, 9, 13, 14), also unpublished data]. Ondansetron was administered as an acute treatment (45-min pretreatment) to establish dose regimes necessary to determine

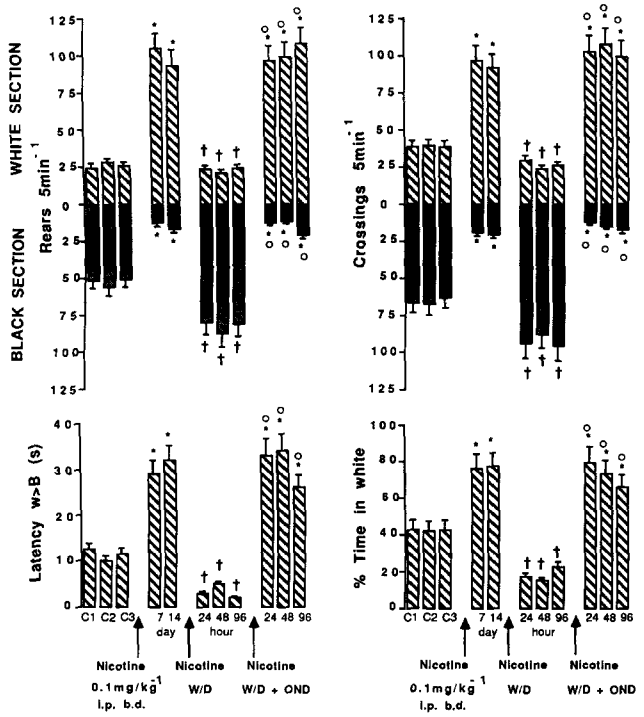

FIG. 3. The effects on mouse light/dark exploration of chronic (7 and 14 days) treatment with nicotine (0.1 mg/kg IP b.i.d.), effects of withdrawing (W/D) from 7-day nicotine treatment, and influence of ondansetron (OND, 0.01 mg/kg IP b.i.d.) on the behavioural consequences of withdrawal from nicotine. C1 = control responses for days 7 and 14 of nicotine treatment, C2 = control responses for measures of behaviour taken 24 to 96 hr after withdrawing nicotine treatment, and C3 = control responses for behavioural effects of nicotine withdrawal in animals receiving treatment with ondansetron. n = 8 per group. $*p<0.01$ for redistribution of behaviour in favour of the light section, $\dagger p<0.01$ for redistribution in favour of the dark, $^{\circ}p<0.01$ for inhibition of the behavioural consequences of withdrawing from nicotine treatment. Standard errors of the means are given: for % time spent in the light these were calculated from original data.

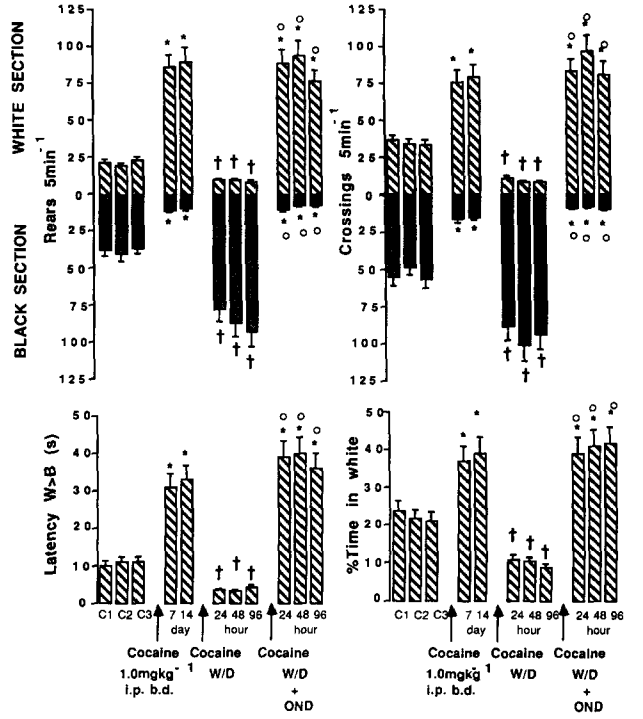

FIG. 4. The effects on mouse light/dark exploration of chronic (7 and 14 days) treatment with cocaine (1.0 mg/kg IP b.i.d.), effects of withdrawing (W/D) from 14-day cocaine treatment, and influence of ondansetron (OND, 0.01 mg/kg^{-1} IP b.i.d.) on the behavioural consequences of withdrawal from cocaine. C1 = control responses for days 7 and 14 of cocaine, C2 = control responses for measures of behaviour taken 24 to 96 hr after withdrawing cocaine, and C3 = control responses for behavioural effects of cocaine withdrawal in animals receiving treatment with ondansetron. n = 8 per group. $*p<0.01$ for redistribution of behaviour in favour of the light section, $\dagger p<0.01$ for redistribution in favour of the dark, $^{\circ}p<0.01$ for inhibition of behavioural consequences of withdrawing from cocaine treatment. Standard errors of the means are given: for % time spent in the light these were calculated from original data.

its effects during chronic administration and following withdrawal.

Subsequently, in the chronic drug administration and withdrawal experiments, groups of mice and rats received (a) no treatment, (b) vehicle, (c) ethanol, cocaine or nicotine for behavioural assessment during treatment and following withdrawal. On the day of withdrawal, mice that had received ethanol, nicotine and cocaine (the timing of the administrations was arranged to ensure that later measurements of the effects of drug withdrawal at 24, 48 or 96 hr occurred between 1300 and 1800 hr) were treated with ondansetron (0.01 mg/kg IP b.i.d.) on the same and following day and at 0800 on the 3rd day to cover the periods of drug withdrawal. In both the mouse and rat studies, naive animals were used on each test occasion. Experimenters remained blind to drug treatment throughout the studies, with the code only being broken after analyses were complete.

Analysis of Results

The results from the light/dark exploration and social interaction tests were analysed by analysis of variance followed by Dunnett's test for multiple comparisons.

Drugs

Drinking water containing ethanol (J. Burroughs Ltd.) was freshly prepared each day. Nicotine hydrogen tartrate, cocaine hydrochloride (BDH) and ondansetron (GR38032F) (1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl) methyl]-4H-carbazol-4-one, $HCl{\cdot}2H_2O$, Glaxo Group Research Ltd.) were prepared daily in distilled water. Doses are expressed as the base and with the exception of ethanol were administered in a volume of 1 ml/100 g body weight (mouse) or 1 ml/kg body weight (rat).

RESULTS

The Effects of Acute and Chronic Treatments With Ondansetron in the Mouse

The acute administration of ondansetron, 0.01–1.0 μg/kg IP, dose-dependently increased the proportion of time mice spent in the light section of the black and white test box. Line crossings and rears also correspondingly increased in the light section and decreased in the dark compartment. The latency to enter the dark compartment was also increased dose-dependently by ondansetron (Fig. 1).

In order to determine whether adverse effects could be elicited on withdrawal of ondansetron, a very high dose (0.01 mg/kg), which caused a maximal behavioural change on acute treatment,

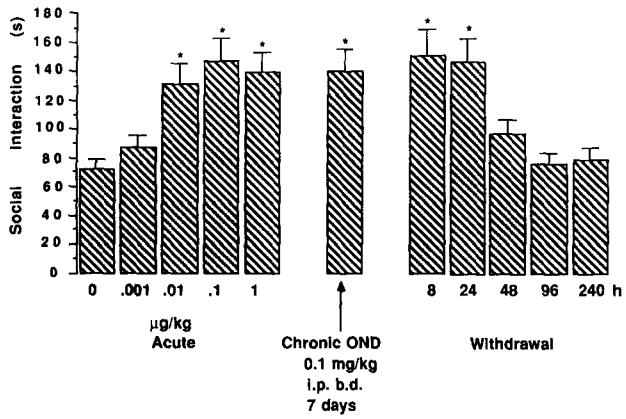

FIG. 5. The effects of ondansetron given acutely, chronically, or withdrawn from chronic treatment, on social interaction in rats. Testing was carried out 45 min after acute dosing, 45 min after the first dose on the 7th day of treatment (chronic), and then at five different times between 8 and 240 hr of withdrawal from chronic treatment. n=6 pairs per group. *$p<0.01$ compared to controls. Standard errors of the means are given.

was administered twice daily for 7 days. Mice tested on the 7th day of treatment showed the same redistribution of behaviour to the light area of the test box as observed in mice receiving acute treatment with lower doses (Fig. 1). Following withdrawal from a 7-day treatment, the preference for mice to explore the light area declined, values returning to control levels over a 4-day period. Even after a 10-day period of withdrawal, there was no evidence of a "rebound" response to preferentially explore the dark compartment (Fig. 1). In order to determine whether tolerance developed to the effects of ondansetron, a dose of 0.1 µg/kg IP was administered twice daily for 14 days. The behaviour of animals tested on days 1 and 14 was indistinguishable, mice spending 81 and 77% of their time respectively in the white compartment (n=8, $p>0.05$).

Under conditions where both compartments were illuminated with red light, mice distributed their behaviour in proportion to the size of the two compartments. This behaviour was not affected by ondansetron.

Chronic Treatment With Ethanol, Nicotine and Cocaine: Interaction With Ondansetron

Drug regimens of ethanool, 8% w/v in the drinking water for 14 days, nicotine, 0.1 mg/kg b.i.d. 7–14 days, and cocaine, 1.0 mg/kg b.i.d 14 days, were selected on the basis of previous work [see Costall *et al.* (13,14)] showing that their administration increased the proportion of time mice spent in the light area of the test chamber (Figs. 2, 3 and 4). Thus, the profile of behavioural change caused by such treatments was the same as recorded for treatment with ondansetron. However, the consequences of ceasing treatment with ethanol, nicotine and cocaine were quite different. Thus, following drug withdrawal the preference of mice to explore the light environment was reversed to preferential exploration of the dark section. Mice spent more time in the dark area associated with increased line crossings and rears, with a decrease in such activities in the light area. Furthermore, mice showed a reduced latency in initially moving from the light to the dark compartment. The changes caused by the withdrawal of ethanol, nicotine and cocaine were quantitatively similar (Figs. 2, 3 and 4) and were shown to persist for at least 96 hr. Ten days after withdrawal from ethanol, nicotine and cocaine the behaviour of animals was indistinguishable from vehicle treated controls [see also Costall *et al.* (14)].

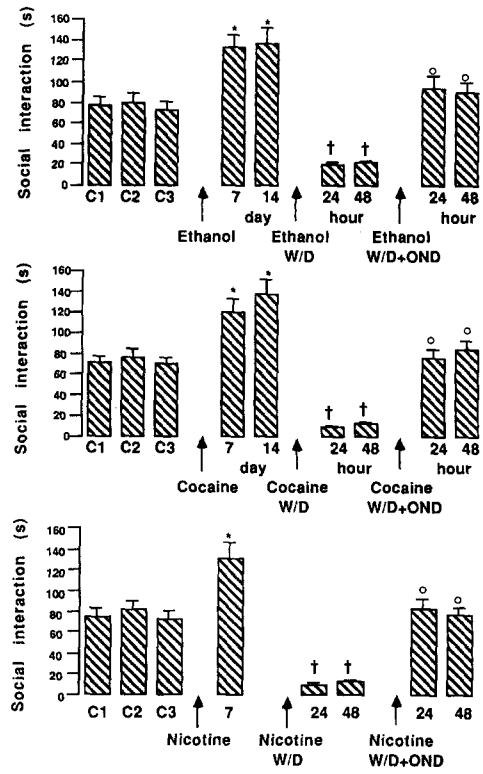

FIG. 6. The effects on social interaction in rats of chronic (7 and 14 day) treatment with ethanol (8% w/v in drinking water), cocaine (1.0 mg/kg IP b.i.d.) and nicotine (0.1 mg/kg IP b.i.d.) effects of withdrawing (W/D) from ethanol (14 day), cocaine (14 day) or nicotine (7 day) treatments, and influence of ondansetron (OND, 0.01 mg/kg IP b.i.d.) on the behavioural consequences of withdrawing from ethanol, cocaine or nicotine. C1 = control responses for days 7/14 of ethanol/cocaine/nicotine intake, C2 = control responses for measures of behaviour taken 24 to 48 hr after withdrawing ethanol/cocaine/nicotine, and C3 = control responses for behavioural effects of withdrawing ethanol/cocaine/nicotine in animals receiving treatment with ondansetron. n=6 pairs per group. *$p<0.01$ for increased social interaction, †$p<0.01$ for decreased social interaction, and °$p<0.01$ for inhibition of the decreased social interaction associated with withdrawing treatment with ethanol/cocaine/nicotine. Standard errors of the means are given.

The administration of ondansetron, 0.01 mg/kg IP b.i.d., during the period of withdrawal from ethanol, nicotine and cocaine prevented the profile of change caused by withdrawal from the drugs of abuse. Thus, animals withdrawn from ethanol, nicotine and cocaine but treated with ondansetron continued to show a preference for exploration in the light area (Figs. 2, 3 and 4).

Acute and Chronic Treatments With Ondansetron in the Rat

The acute and chronic administration of ondansetron (0.01–1.0 µg/kg IP acute, 0.1 mg/kg chronic) significantly increased social interaction under high light, unfamiliar conditions. On withdrawal from a 7-day treatment with the high dose of 0.1 mg/kg IP b.i.d. ondansetron, the increased values of social interaction returned to the level shown by control rats. It is important to note that the withdrawal from ondansetron was not associated with a reduction in social interaction to values below those recorded for control animals (Fig. 5). In separate experiments it was shown that 0.01 µg/kg IP ondansetron failed to modify social interaction of rats under low light familiar conditions.

Chronic Treatment With Ethanol, Nicotine and Cocaine: Interaction With Ondansetron

Drug regimens of ethanol (8% w/v in the drinking water for 14 days), nicotine (0.1 mg/kg IP b.i.d., 7 days) and cocaine (1.0 mg/kg IP b.i.d., 14 days) were selected on the basis of previous studies (Costall *et al.*, unpublished data) showing that their administration increased social interaction in the rat. However, following drug withdrawal social interaction decreased to levels below those of control rats (Fig. 6). The administration of ondansetron (0.01 mg/kg IP b.i.d.) during the period of withdrawal from ethanol, nicotine and cocaine prevented the decreases in social interaction. Locomotor activity, measured as crossings of lines marked on the test box floor, was not altered from control values in any experiment.

DISCUSSION

In the light/dark exploration test in the mouse, and in the social interaction test in the rat, the acute and chronic administration of ondansetron reinstated the behaviours suppressed by the aversive conditions. Ondansetron did not change the pattern of behaviour under conditions where the aversive factor was absent or minimal, indicating that in both test procedures the effect of ondansetron was to release suppressed behaviours. From a range of psychopharmacological agents tested, this profile of action has only been shown by anxiolytic agents; anxiogenic agents increase the behavioural suppression (2, 12, 15, 16). However, more recently it was shown that chronic treatments with ethanol, nicotine and cocaine reduced the suppression in the mouse and rat tests, but that this was followed by an exacerbation following their withdrawal (13,14). The administration and withdrawal of diazepam produced a similar profile of action (1), but the present studies indicate a fundamental difference between the consequences of withdrawal from a benzodiazepine and ondansetron since withdrawal from ondansetron failed to precipitate any behavioural disturbances. Thus, the present results provide evidence that ondansetron is a putative anxiolytic agent, the effects of which persist on repeated treatment and are not associated with withdrawal phenomena.

The administration of ondansetron during the period of ethanol, nicotine and cocaine withdrawal was shown to prevent the increase in behavioural suppression in both the mouse and rat tests, a response similar to that observed following the administration of ondansetron during withdrawal of chronic treatment of the marmoset with ethanol, nicotine or cocaine (9). The inhibitory effect of ondansetron probably reflects a 5-HT_3 receptor blockade since in preliminary studies we have established a similar effect for other 5-HT_3 receptor antagonists. One possible explanation of these results is that they are a manifestation of the anxiolytic properties of ondansetron and the other 5-HT_3 receptor antagonists. However, the findings that buspirone failed to prevent the development of withdrawal suppression following chronic diazepam (11) suggest that this is not the case. Furthermore, it was shown recently that ondansetron reduced alcohol consumption in alcohol habituated experimental animals (23) and the 5-HT_3 receptor antagonists MDL72222 and ICS205-930 inhibited place-preference conditioning in rats induced by morphine, nicotine (5) or d-amphetamine (7). Thus, 5-HT_3 receptor antagonists may inhibit craving for drugs of abuse, by influencing a fundamental process underlying drug dependence. The key factor is likely to be the influence of the 5-HT_3 receptor antagonists on the dopaminergic projections from the ventral tegmental area. This system has an important role in mediating the rewarding effects of drugs of abuse (3) and overactivity of the system can be inhibited by 5-HT_3 receptor antagonists (10,19). Thus, there is a sound rationale for the use of 5-HT_3 receptor antagonists in the treatment of drug dependence, both for reducing withdrawal effects and for maintaining abstinence.

To conclude from the present experiments, we have demonstrated that ondansetron can prevent or reverse some of the behavioural changes that occur following withdrawal from drugs of abuse. Furthermore, tolerance to ondansetron itself does not appear to develop and there is no evidence of dependence liability. Drug suppression of the abstinence syndrome resulting from withdrawal of a drug of abuse is generally taken as being indicative of abuse potential for the suppressing drug. However, this cannot be concluded for ondansetron, or other 5-HT_3 receptor antagonists, since they are unique in having the ability to suppress the behavioural effects induced by withdrawing several different classes of dependence-producing drugs. In this respect, the effects of ondansetron are analogous with the effect of clonidine on opiate abstinence.

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