5-HT₃ antagonists reduce morphine self-administration in rats

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- 1 The effects of the 5-HT₃ receptor antagonists, ondansetron and tropisetron, on morphine consumption were studied in naive and morphine-dependent rats.
- 2 The administration of ondansetron (1 µg kg⁻¹, i.p. twice daily) 7 days prior to, and during a 21-day period of, morphine availability (increasing concentration from 0.1 to 0.4 mg ml⁻¹) in 5% sucrose solution reduced opiate intake from the 9th day of morphine treatment.
- 3 The administration of ondansetron (0.1 µg kg⁻¹, i.p. twice daily) or tropisetron (0.1 µg kg⁻¹, i.p. twice daily) on the 14th day of the 21-day period of morphine treatment failed to reduce opiate consumption. Administration of the larger doses of tropisetron (1 µg kg⁻¹) or ondansetron (1 µg kg⁻¹) reduced morphine consumption.
- 4 After receiving 21 days of treatment with morphine alone or with the ondansetron or tropisetron regimens identified above, the sucrose solutions were substituted with tap water for 7 days. These detoxified rats were then allowed a free choice of sucrose or morphine for 10 days. Animals that had received concomitant treatment with ondansetron or tropisetron showed reduced morphine intake when compared with the controls treated with morphine only or with vehicle-treated controls.
- 5 The administration of cyproheptadine (100 or 250 µg kg⁻¹, i.p. twice daily) on the 14th day of 21-day morphine treatment failed to modify morphine intake and also failed to influence the subsequent intake of the opiate in the free choice situation.
- 6 It is concluded that ondansetron and tropisetron can reduce morphine intake in both naive and morphine-dependent rats.

Keywords: Morphine intake; ondansetron; tropisetron; cyproheptadine; rats; self administration

Introduction

Drugs of abuse are thought to activate mesolimbic dopaminergic systems (Di Chiara & Imperato, 1988). Indeed, dopamine is considered to play an important role in the process of reward and reinforcement, and in place preference conditioning studies. It has been demonstrated that heroin reward is dependent on a dopaminergic substrate (Bozarth & Wise, 1981). Lesioning of the nucleus accumbens, using the neurotoxin 6-hydroxydopamine or kainic acid, has been shown to disrupt heroin place-preference conditioning (Spyraki *et al.*, 1983), to increase significantly intravenous morphine self-administration (Smith *et al.*, 1985) and to reduce cocaine and heroin self-administration in rats (Zito *et al.*, 1985). Evidence for 5-HT₃ receptor involvement in the regulation of limbic dopamine function has come from both behavioural and biochemical studies. Thus, the locomotor hyperactivity induced by the injection or infusion of dopamine or amphetamine into the nucleus accumbens or amygdala is exacerbated by the 5-HT₃ receptor agonist, 2-methyl-5-hydroxytryptamine (2-methyl-5-HT) and inhibited by the 5-HT₃ receptor antagonist, ondansetron (Costall *et al.*, 1987). Discrete activation of midbrain dopamine cells also causes an increase in activity and release of forebrain dopamine which is antagonized by ondansetron or tropisetron (Hagan *et al.*, 1987; 1990). Such evidence indicates that activation of 5-HT₃ receptors will enhance dopamine function; limbic dopamine release is indeed reported to be increased following activation of 5-HT₃ receptors (Jiang *et al.*, 1990; Chan *et al.*, 1991). The ability of 5-HT₃ receptors to influence dopamine release suggests that 5-HT₃ receptor antagonists may be useful in the treatment of some aspects of drug abuse in man.

Recent evidence has shown that ondansetron, tropisetron and MDL 72222 are able to prevent the induction of place preference to nicotine or morphine (Carboni *et al.*, 1988; Koob & Goeders, 1989; Higgins *et al.*, 1991). Furthermore,

ondansetron has been shown to reduce alcohol consumption in the rat and marmoset (Oakley *et al.*, 1988; Sellers *et al.*, 1988) and to prevent the exacerbation in behavioural response to an aversive situation following withdrawal from alcohol, cocaine, nicotine or diazepam (Costall *et al.*, 1990). The aim of the present study was to investigate the influence of ondansetron and tropisetron on morphine intake in naive and morphine-dependent rats.

Methods

General

Male Sprague-Dawley rats (weighing 140–160 g) were used. The animals were kept in groups of 6 per cage in a rat battery. Room temperature was maintained at 22 ± 1°C and relative humidity at 60–70%. The rats were exposed to a daily cycle of 12 h light and 12 h darkness, with lights on at 06 h 00 min to 18 h 00 min. They were allowed free access to a standard balanced laboratory diet of rat pellets (Ralston Purina Co., U.S.A.) and drinking water containing either 5% sucrose (Taikoo, Hong Kong) (w/v) or morphine sulphate (Macfarlan Smith Ltd., U.K.) prepared in a 5% sucrose solution. The drinking solutions were freshly prepared daily. Morphine was given in increasing concentrations of 0.1, 0.2, 0.3 and finally 0.4 mg ml⁻¹ at 48 h intervals. The final concentration of morphine was maintained until the end of the 3 week induction period. All animals were permitted to drink *ad libitum*.

Experimental design

Rats were randomly divided into a control sucrose-treated group and a morphine-treated group which received the treatments for 21 days. The sucrose or morphine solutions were then withdrawn for 7 days, the drinking solutions being

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replaced by tap water. For the following 10 days, both groups of rats were allowed a free choice between drinking morphine or sucrose solutions. During the entire experimental period (38 days), the body weight of each animal and the volume of the drinking fluid consumed were recorded daily. Although the total volume measured daily was for 6 rats in the cage, the actual amount drunk by each animal was calculated in proportion to its daily body weight. The daily volume consumed by each rat was, therefore, calculated on an individual basis and not derived by dividing the total consumed volume by the 6 animals. In order to ensure that tolerance and dependence had developed in these animals given 21 day morphine treatment, the naloxone-precipitated withdrawal syndrome (wet-dog shakes, head shakes, diarrhoea, ptosis, chattering teeth, writhing, chewing, paw tremor and irritability to touch and handling) and responses to the tail-flick test were evaluated as described previously (Dai *et al.*, 1984); both assessments were carried throughout the 21 day induction period. These tests were also used to demonstrate that morphine-treated rats after withdrawal for 7 days were detoxified and did not respond to naloxone; the naloxone-precipitated syndrome was absent and tail-flick times were normal in these animals. A similar regimen of tests for addiction was repeated in other groups of sucrose-treated or morphine-treated rats given ondansetron (Glaxo) (0.1 or $1 \mu\text{g kg}^{-1}$, i.p. twice daily), tropisetron (Sandoz) (0.1 or $1 \mu\text{g kg}^{-1}$, i.p. twice daily) or cyproheptadine (Sigma) (100 or $250 \mu\text{g kg}^{-1}$, i.p. twice daily) 2 weeks after sucrose or opiate treatment. A higher dose of ondansetron ($1 \mu\text{g kg}^{-1}$, i.p. twice daily) was also given to other groups of animals 7 days before sucrose or opiate treatment. All injections were made twice daily at 09 h 00 min and 16 h 00 min and were continued until the end of the experiment (day 38).

Drugs

All drugs were freshly prepared before use. Morphine sulphate, expressed as its salt, was dissolved in 5% sucrose solution. Ondansetron, tropisetron or cyproheptadine hydrochloride, expressed as the base, was dissolved in a solution of 0.9% NaCl.

Statistical analysis

Values are given as means $\pm$ s.e.means. Where relevant, statistical analyses were carried out using Student's unpaired *t* test. Differences were considered significant at the 0.05 level.

Results

General observations

Throughout the 3 week induction period, the daily intake of morphine solution was similar to that of sucrose (Figure 1). The body weights of the rats in both groups increased steadily during the first 13 days, with no significant differences between the two treatments. Measurements taken on days 17, 19 and 21 indicated that the body weights of the morphine-treated rats were slightly but significantly less than those of the sucrose-treated groups (Figure 1). The morphine-treated rats exhibited naloxone-precipitated withdrawal changes (wet-dog shakes, head shakes, diarrhoea, ptosis, chattering teeth, writhing, chewing, paw tremor and irritability to touch and handling) and prolonged reaction times in the tail-flick test starting from the 7th day of opiate treatment and persisting up to day 21 (data not shown). When the drinking solution was replaced by tap water, these morphine-dependent animals no longer responded to the naloxone and tail-flick tests by the 7th day of opiate withdrawal (data not shown).

Figure 1 Daily fluid consumption and body weights of rats receiving sucrose (○) or morphine (●) (0.1 mg ml^{-1} days 1 and 2, 0.2 mg ml^{-1} days 3 and 4, 0.3 mg ml^{-1} days 5 and 6, 0.4 mg ml^{-1} days 7 to 21) for 21 days. Each value is the mean $\pm$ s.e.mean of 24 animals. * $P < 0.05$; ** $P < 0.001$, compared to sucrose-treated controls.

Figure 2 (a) Sucrose intake during the 21 day treatment period in rats treated with sucrose only (○); sucrose + ondansetron $0.1 \mu\text{g kg}^{-1}$, i.p. twice daily (Δ) and sucrose + ondansetron $1 \mu\text{g kg}^{-1}$, i.p. twice daily (▲) when given from the 14th day of sucrose administration, or with sucrose + ondansetron $1 \mu\text{g kg}^{-1}$, i.p. twice daily given 7 days prior to sucrose treatment (◆). Each value is the mean of 24 rats. (b) Morphine intake during the 21 day treatment period in rats treated with morphine only (○); morphine + ondansetron $0.1 \mu\text{g kg}^{-1}$, i.p. twice daily (Δ) and morphine + ondansetron $1 \mu\text{g kg}^{-1}$, i.p. twice daily (▲) when given from the 14th day of morphine administration, or with morphine + ondansetron $1 \mu\text{g kg}^{-1}$, i.p. twice daily given 7 days prior to morphine treatment (◆). Each value is the mean $\pm$ s.e.mean of 24–36 rats. * $P < 0.05$; ** $P < 0.02$, compared to morphine-treated controls.

Figure 3 (a) Sucrose intake during the 21 day treatment period in rats treated with sucrose only (O); sucrose + tropisetron $0.1 \mu\text{g kg}^{-1}$, i.p. twice daily (Δ) and sucrose + tropisetron $1 \mu\text{g kg}^{-1}$, i.p. twice daily ($\blacktriangle$), given from the 14th day of sucrose administration. (b) Morphine intake during the 21 day treatment period in rats treated with morphine only (O); morphine + tropisetron $0.1 \mu\text{g kg}^{-1}$, i.p., twice daily (Δ) and morphine + tropisetron $1 \mu\text{g kg}^{-1}$, i.p., twice daily ($\blacktriangle$), given from the 14th day of morphine administration. Each value is the mean $\pm$ s.e.mean of 24 rats. * $P < 0.05$; ** $P < 0.001$, compared to morphine-treated controls.

Effects of ondansetron or tropisetron on sucrose or morphine intake in rats during 21 day sucrose- or morphine-treatment

Ondansetron (0.1 or $1 \mu\text{g kg}^{-1}$, i.p.) given twice daily, commencing either 7 days prior to or 14 days after starting sucrose treatment did not have any significant effect on sucrose intake (Figure 2a). Similarly, ondansetron (0.1 or $1 \mu\text{g kg}^{-1}$), starting on day 14 of morphine treatment, did not affect opiate consumption in morphine-treated rats during days 14 to 20. However, at day 21, the higher dose of ondansetron ($1 \mu\text{g kg}^{-1}$) significantly reduced morphine intake (Figure 2b). When ondansetron treatment was started 7 days before the morphine regimen, there was a significant reduction in morphine consumption from the 9th day which persisted until the 21st day of the opiate-treatment period (Figure 2b).

The administration of tropisetron (0.1 or $1 \mu\text{g kg}^{-1}$, i.p. twice daily) starting at day 14 of sucrose treatment did not change the volume of sucrose intake (Figure 3a). However, the administration of the higher dose of tropisetron ($1 \mu\text{g kg}^{-1}$), starting on the 14th day of morphine treatment, significantly reduced morphine intake from days 17 to 21 of

Table 1 Morphine consumption (ml/rat day^{-1}) in previously sucrose- or morphine-treated rats during the 10 day drinking preference period

	1	2	3	4	5	6	7	8	9
Previously sucrose-treated	3.6 ± 1.5	4.5 ± 0.7	5.3 ± 0.9	7.8 ± 3.1	7.3 ± 3.4	5.2 ± 1.1	4.8 ± 0.4	5.3 ± 1.3	4.1 ± 0.5
Previously morphine-treated	$23.8 \pm 0.4^*$	$26.1 \pm 2.3^{**}$	$27.4 \pm 1.7^{**}$	$27.7 \pm 2.0^{**}$	$31.7 \pm 2.2^{**}$	$28.1 \pm 1.9^{**}$	$29.3 \pm 1.7^{**}$	$32.0 \pm 2.0^{**}$	$28.2 \pm 2.2^{**}$

Each value is the mean $\pm$ s.e.mean of 24 rats. * $P < 0.01$; ** $P < 0.001$, compared to the corresponding previously sucrose-treated controls.

Table 2 Effect of ondansetron, tropisetron or cyproheptadine on sucrose or morphine consumption in rats observed for 10 days after 7 day withdrawal from sucrose or opiate treatment

<i>Treatment</i>	<i>Morphine intake (ml/rat day⁻¹)</i>	<i>Sucrose intake (ml/rat day⁻¹)</i>
<i>Previously sucrose-treated rats</i>		
Saline 2 ml kg ⁻¹ , i.p. b.d.	5.6 ± 0.7	30.1 ± 0.2
Ondansetron given from 14th day of treatment		
0.1 µg kg ⁻¹ , i.p. b.d.	3.1 ± 0.7*	28.7 ± 2.1
1.0 µg kg ⁻¹ , i.p. b.d.	3.3 ± 0.3*	30.6 ± 0.5
Ondansetron given 7 days prior to treatment		
1.0 µg kg ⁻¹ , i.p. b.d.	3.0 ± 0.5*	31.2 ± 0.2
Tropisetron given from 14th day of treatment		
0.1 µg kg ⁻¹ , i.p. b.d.	4.7 ± 0.8	32.3 ± 3.4
1.0 µg kg ⁻¹ , i.p. b.d.	1.2 ± 0.2**	30.7 ± 0.2
Cyproheptadine given from 14th day of treatment		
100 µg kg ⁻¹ , i.p. b.d.	7.1 ± 2.4	31.0 ± 1.2
250 µg kg ⁻¹ , i.p. b.d.	7.0 ± 2.9	29.0 ± 2.5
<i>Previously morphine-treated rats</i>		
Saline 2 ml kg ⁻¹ , i.p. b.d.	30.8 ± 1.0†	25.1 ± 3.1
Ondansetron given from 14th day of treatment		
0.1 µg kg ⁻¹ , i.p. b.d.	21.2 ± 2.4*	29.2 ± 1.0
1.0 µg kg ⁻¹ , i.p. b.d.	17.4 ± 4.3**	28.4 ± 1.4
Ondansetron given 7 days prior to treatment		
1.0 µg kg ⁻¹ , i.p. b.d.	17.0 ± 4.3**	25.4 ± 2.6
Tropisetron given from 14th day of treatment		
1.0 µg kg ⁻¹ , i.p. b.d.	20.5 ± 3.3**	26.8 ± 3.0
1.0 µg kg ⁻¹ , i.p. b.d.	20.4 ± 3.0	25.3 ± 4.3
Cyproheptadine given from 14th day of treatment		
100 µg kg ⁻¹ , i.p. b.d.	33.5 ± 1.9	31.4 ± 3.4
250 µg kg ⁻¹ , i.p. b.d.	29.1 ± 1.2	32.1 ± 1.1

Each value is the mean ± s.e.mean derived from the total 10 day consumption of 24 rats in each group. * $P < 0.05$; ** $P < 0.02$, compared to their own sucrose- or morphine-treated controls. † $P < 0.001$, compared to previously sucrose-treated saline controls.

treatment. The lower dose of tropisetron (0.1 µg kg⁻¹) was without effect on morphine consumption (Figure 3b).

Effect of ondansetron or tropisetron on sucrose or morphine intake in rats previously treated for 21 days with sucrose or morphine

Table 1 shows the morphine intake in rats which had previously received 21 day treatment with morphine or sucrose and had been withdrawn for 7 days; they were then allowed access for 10 days to a choice between sucrose or morphine. Throughout the 10 day drinking preference period, rats that were previously morphine-dependent showed a clear preference for morphine intake which was significant from the 1st day until the last day of the free choice period (Table 1). The volume of opiate solution intake in the previously morphine-dependent rats observed for 10 days following opiate withdrawal was approximately five fold higher than that of their previously sucrose-treated controls (Table 2). In contrast, the volume of sucrose solution intake was similar in both groups. This marked increase in morphine intake was significantly reduced in the groups of rats that had received ondansetron (0.1 or 1 µg kg⁻¹, i.p., twice daily) or tropisetron (0.1 or 1 µg kg⁻¹, i.p., twice daily) from day 14 of the morphine regimen and in the group which had received ondansetron 7 days before and during the 21 day period of morphine administration (Table 2).

In rats that had previously received sucrose, the intake of morphine was reduced in those animals that had received concomitant ondansetron (0.1 or 1 µg kg⁻¹ from day 14 of treatment or 7 days before and during treatment) or tropisetron (1 µg kg⁻¹ from day 14 of treatment) (Table 2). The sucrose solution intake during the 10 day period was similar in the previously sucrose- or morphine-treated groups given ondansetron or tropisetron.

Effect of cyproheptadine on sucrose or morphine intake in rats previously treated for 21 days with sucrose or morphine

During the 21 day treatment with sucrose or morphine, the administration of cyproheptadine (100 or 250 µg kg⁻¹, i.p., twice daily) given from day 14 of treatment, did not affect the volume of sucrose or opiate solution intake in either group of animals. Sucrose intake during the 21 day sucrose treatment period before and after cyproheptadine treatment was 54.2 ± 5.9–63.8 ± 3.3 and 54.0 ± 6.3–60.2 ± 5.7 ml/rat day⁻¹, respectively. Morphine intake during the 21 day morphine treatment period before and after cyproheptadine treatment was found to be 43.3 ± 5.6–50.9 ± 8.7 and 41.2 ± 5.3–55.2 ± 6.9 ml/rat day⁻¹, respectively.

During the 10 day drinking preference period after 21 day treatment with sucrose or morphine, the administration of cyproheptadine (100 or 250 µg kg⁻¹, i.p. twice daily) failed to modify either sucrose or morphine intake when compared to control values (Table 2).

Discussion

Previous studies in our laboratory have shown that a gradual increase in the concentration of morphine in sucrose drinking water can produce physical dependence and a relapse after successful opiate withdrawal and detoxification (Dai *et al.*, 1984). Preliminary data have also indicated that morphine-dependence, as manifested by the naloxone-precipitated withdrawal signs and morphine tolerance as well as by the reaction time in response to pain using the tail-immersion test, starts to develop at the 7th day after morphine treatment. These effects are found to be fully established from the 14th day of opiate treatment and persist until the end of the 21 day treatment period (data not shown in this paper). In order to

study the effect of 5-HT₃ antagonists on morphine consumption in morphine-dependent rats, administration of 5-HT₃ antagonists was, therefore, started on day 14 of morphine treatment when the animals had already been shown to have developed dependence and tolerance to the opiate. The purpose of using the other dosage regimen in which the administration of 5-HT₃ antagonists was started 7 days before morphine treatment, was to investigate whether 5-HT₃ antagonists would affect morphine consumption in rats before they received opiate treatment and became opiate-dependent. Naloxone treatment had no effect on the volume of sucrose drunk daily by the sucrose-drinking controls given ondansetron or tropisetron (Figures 2a, 3a), nor did it influence the volume consumed daily by morphine-addicted rats which were subsequently not given the 5-HT₃ receptor blockers (Figures 2b, 3b). Bradley *et al.* (1986) have illustrated the pharmacological characteristics of the 5-HT₃ receptor site and have indicated that one of the criteria is that the 5-HT₃ receptor should be blocked selectively by low concentrations of MDL 72222, ICS 205-930, granisetron or ondansetron. Hence, in the present study, two relatively low doses (0.1 and 1 µg kg⁻¹) of ondansetron and tropisetron were selected in order to verify whether the effect of these 5-HT₃ antagonists on morphine consumption could be mediated via the 5-HT₃ receptors. Indeed, the two doses of ondansetron and tropisetron used in this study have been demonstrated by other researchers to be effective in inhibiting the increased behavioural suppression following withdrawal from treatment with diazepam and other drugs of abuse (Costall *et al.*, 1989; 1990), and in reducing raised mesolimbic dopaminergic activity in the rat and marmoset (Costall *et al.*, 1987). Using such a dosage regimen in the present study, a dependency to morphine was established over a 21 day period, and 7 days after successful opiate withdrawal these detoxified rats showed a clear preference for morphine intake in a free choice situation. The total fluid intake in the detoxified rats was about 57% greater than their controls; the main reason for this difference was the increased intake of morphine solution, with only a small decrease in sucrose solution consumption. There is no clear explanation for this at present. It is possible that animals showing a relapse, under the experimental conditions studied, may tend to drink more morphine solution without a commensurate decrease in the volume of the non-drug solution which they also consume. Further detailed studies are needed. The major finding of the study was that ondansetron or tropisetron when administered prior to and during morphine intake significantly reduced the amount of morphine consumed. The effects of such treatments using ondansetron or tropisetron were also evident after discontinuing the drug regimens. Thus, in a free choice situation the animals that had previously received ondansetron or tropisetron showed a reduced intake of morphine when compared to those that had previously received morphine alone. The common pharmacological action of ondansetron and tropisetron is 5-HT₃ receptor blockade (Richardson *et al.*, 1985; Butler *et al.*, 1987). Since low doses of both compounds were effective in antagonizing morphine intake, their effects can reasonably be attributed to 5-HT₃ receptor antagonism.

Evidence which indicates an influence of morphine-like drugs and a role for opioid peptides in positive reinforcement effects comes from the phenomenon of opiate self-administration as exemplified by the present data, opiate-induced place preference and facilitation of operant self-stimulation behaviour (see reviews by Carr *et al.*, 1989; Bradshaw & Szabadi, 1989; Koob & Goeders, 1989). Whereas no single neural mechanism has been found to be responsible for the

control of behaviour by positive reinforcers, evidence of limbic dopamine involvement comes from the reinforcement effects of psychostimulants and their antagonism by neuroleptic agents as well as lesions of the dopamine pathways (see Carr *et al.*, 1989; Bradshaw & Szabadi, 1989). Dopamine may also play a role in mediating the reinforcing effects of morphine because conditioned place preference is inhibited by neuroleptics, intraventricular 6-hydroxydopamine lesions and catecholamine synthesis inhibition (Schwartz & Marchok, 1974; Smith *et al.*, 1985; Di Chiara & Imperato, 1988; see also Carr *et al.*, 1989). However, there are other studies in which neuroleptic treatment or dopamine neurone destruction has no effect on morphine self-administration (Ettenberg *et al.*, 1982; Pettit *et al.*, 1984). In all such experiments the treatment, in order to be successful, must overcome both rewarding and conditioning effects.

It is unlikely that the rewarding and conditioning effects are mediated via a single brain system. Thus, morphine and other opiate peptides cause self-administration/conditioned place preference following injection into the hypothalamus (Stein & Olds, 1977), the nucleus accumbens (Olds, 1982; Goeders *et al.*, 1984; 1985) and ventral tegmental area (Bozarth, 1983). Kainic acid lesions of the nucleus accumbens of intra-accumbens injection of the opiate receptor antagonist methyl naloxonium inhibits opiate self-administration (Zito *et al.*, 1985; Vaccarino *et al.*, 1985) to indicate the importance of this limbic area. Within the nucleus accumbens, drugs abused by man, including morphine, are known to increase dopamine concentrations in freely moving rats (Di Chiara & Imperato, 1988) and to decrease dopamine release following drug withdrawal (Rossetti *et al.*, 1992). Thus, a raised limbic dopamine function is likely to be an important factor in reinforcement effects, but other systems may play a major or modulatory role. The intraventricular or intra-accumbens injection of neurotoxins selective for the 5-HT neurone, attenuate morphine-conditioned place preference (Schwartz & Marchok, 1974; Nomikos *et al.*, 1986), electrolesions of the raphe nuclei shift the dose-effect function for morphine to the right (Glick & Cox, 1977) and lesioning of the 5-HT projection to the nucleus accumbens increases self-administration of morphine in dependent rats (Smith *et al.*, 1987).

From the above perspectives, it can be hypothesized that the ability of ondansetron and tropisetron to reduce morphine intake involves 5-HT₃ receptor antagonism and, therefore, an inhibition of 5-HT function causing the known reduction in limbic dopamine activity (Costall *et al.*, 1987; Hagan *et al.*, 1990). This is supported by the ability of tropisetron to reduce dose-dependently dopamine release in the nucleus accumbens induced by morphine, nicotine or ethanol (Carboni *et al.*, 1989). The ability of the 5-HT₃ receptor antagonists to prevent the exacerbation in aversive responses following withdrawal from treatment with drugs of abuse may contribute to the effects. Therefore, the reported ability of ondansetron to reduce the intake of alcohol (Oakley *et al.*, 1988; Sellers *et al.*, 1988) has been extended to the control of morphine intake, tropisetron being shown to have a similar effect. However, the site(s) of action of the 5-HT₃ receptor antagonists that reduce morphine self-administration remains to be investigated.

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