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Withdrawal-Like Behaviour Induced by Inhibitors of Biogenic Amine Reuptake in Rats Treated Chronically with Δ^9-Tetrahydrocannabinol

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Abstract. The effects of the biogenic amine reuptake inhibitors fluoxetine, clomipramine and imipramine on the behaviour of rats after chronic treatment with Δ^9-tetrahydrocannabinol (Δ^9-THC) for 5 and 10 days were examined. Rats with permanently in-dwelling IV cannulae were injected twice daily with doses of Δ^9-THC (2 – 6 mg/kg). Δ^9-THC treatment reduced the rate of body weight gain and induced the typical biphasic modifications of behaviour. Tolerance developed to both of these effects. On days 6 and 11 of the experiment, rats were injected IP with 15 mg/kg imipramine HCl, clomipramine HCl or fluoxetine HCl, and behaviour, consisting of writhes, backward kicks, jumps and wet shakes, was observed for the next 30 min. Each of the amine reuptake inhibitors induced changes in behaviour, the severity of which appeared to correlate with their ability to inhibit the reuptake of 5-hydroxytryptamine (5-HT). It is suggested that tryptaminergic mechanisms are involved in the production of a withdrawal-like behaviour after chronic Δ^9-THC treatment.

Key words: Δ^9-Tetrahydrocannabinol – Withdrawal-like behaviour – Body weight – Food consumption – Imipramine – Clomipramine – Fluoxetine

Chronic administration of Δ^9-tetrahydrocannabinol (Δ^9-THC), the major psychoactive constituent of cannabis, results in the development of tolerance in both laboratory animals (Anderson et al., 1975; Paton, 1975; Taylor and Fennessy, 1978a) and man (Jones and Benowitz, 1976). In rats, tolerance has been shown to develop to physiological parameters such as hypothermia and reduction in body weight, while in man, tolerance develops to some of the cardiovascular and intoxicating effects. Despite such observations, numerous studies have indicated that physical dependence does not develop and that abstinence signs are not observed in rats (Snyder, 1971; Leite and Carlini, 1974) pigeons (McMillan et al., 1970) or monkeys (Harris et al., 1974) after chronic administration of Δ^9-THC or cannabis extracts. On the other hand, a number of studies have shown abstinence signs following the cessation of chronic administration of Δ^9-THC to monkeys (Kaymakcalan, 1972) and man (Jones, 1971; Jones and Benowitz, 1976). It is obvious that the lack of a specific antagonist to Δ^9-THC has hindered progress in this area. However, there have been reports of naloxone precipitated withdrawal in rats chronically treated with Δ^9-THC (Hirschhorn and Rosecrans, 1974; Kaymakcalan et al., 1977). In addition, Fennessy and Taylor (1978) have shown that clomipramine, a potent inhibitor of the reuptake of 5-hydroxytryptamine (5-HT), inhibits some of the acute effects of Δ^9-THC. When clomipramine was administered to rats chronically treated with Δ^9-THC, quantifiable behavioural changes were observed (Taylor and Fennessy, 1978b). It has been suggested these behavioural changes may be manifestations of a withdrawal-like syndrome from Δ^9-THC and that these observations may provide evidence for physical dependence on Δ^9-THC.

These results, and those from previous investigations which implicate the involvement of a tryptaminergic mechanism in some of the actions of Δ^9-THC (Sofia et al., 1971; Taylor and Fennessy, 1977), prompted us to further investigate the effects of biogenic amine reuptake inhibitors on the behaviour of rats chronically treated with Δ^9-THC. To examine this, the behavioural effects induced by amine reuptake inhibitors with different specificities for neuronal reuptake mechanisms were compared in rats which were treated with Δ^9-THC twice daily for 5 or 10 days. The behavioural effects observed included writhing, back-

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ward kicking of the hind legs, jumping and wet shakes. In addition, body weight and food consumption were monitored throughout the experimental period. The agents used were imipramine, an inhibitor of the reuptake of noradrenaline which has minimal effect on 5-HT reuptake mechanisms, clomipramine, an inhibitor of 5-HT reuptake mechanisms which has minimal effect on noradrenergic reuptake mechanisms and fluoxetine, which has a greater potency and selectivity for the inhibition of tryptaminergic reuptake mechanisms than does either imipramine or clomipramine (Fuller and Wong, 1977).

Materials and Methods

Male albino Wistar rats (220 – 290 g) were used. Food and water were available ad libitum. Rats received standard laboratory food (Clark King GR2 + pellets). All experiments were performed in a room with an ambient temperature of 21 ± 1° C and a 12-h light-dark cycle. Cannulae were implanted into the external jugular veins of individually caged rats according to the method of Fennessy and Taylor (1977). Animals were allowed 48 h to recover from surgery before being randomly assigned into two groups which received IV injections of either Δ^9-THC or the vehicle, polyvinylpyrrolidone (PVP), for 5 or 10 days. The schedule of doses of Δ^9-THC and PVP is shown in Table 1.

Behaviour. On days 6 and 11 of the experimental period, when the next dose of Δ^9-THC was due (i.e. after 5 or 10 days of chronic treatment, respectively), the groups of rats were further divided into groups of five and individually placed in 10 l opaque plastic buckets. After 15 min each rat was injected IP with either normal saline (0.9 % NaCl w/v), imipramine HCl (15 mg/kg), clomipramine HCl (15 mg/kg) or fluoxetine HCl (15 mg/kg). They were then returned to their buckets and behaviour was observed for the following 30 min. During this observation period overt behaviour such as writhes, backward kicks, wet shakes and jumps were quantified. In addition, other responses, more difficult to quantify, such as front paw tremor, fine body tremor, chewing movements, ptosis, squealing, yawning, excessive grooming and ataxia were also recorded. All behavioural observations were made by individuals who were unaware of the treatment the rats had received. The body weight of each animal was recorded just prior to injection on all days of the experiment and only morning body weight was used in the analysis of this parameter. Daily food consumption of each animal was measured by weighing the amount of food consumed in the 24-h period before the morning injection of Δ^9-THC or PVP.

Preparation of Δ^9-THC. For IV administration, Δ^9-THC was suspended in saline by the use of PVP following the method of Fenimore and Loy (1971).

Analysis of Results. Student's unpaired *t*-test was used for the analysis of body weight and food consumption results. Behavioural results were analysed by use of the χ^2-test. Lines were fitted by linear regression using the least squares method, and, for testing significance of the difference between slopes, a *t*-distribution was used.

Drugs. The following drugs were used: Clomipramine HCl (Anafranil, Geigy), fluoxetine HCl (Lilly), imipramine HCl (Tofranil, Geigy), PVP (Kollidon 25, BASF) and (–)trans-Δ^9-THC (Batch C770701X, NIDA). All drugs were administered in normal saline in a volume of 1 ml/kg.

Table 1. Schedule of Δ^9-THC and polyvinylpyrrolidone (PVP) dosage

Day	Dose (mg/kg)			
	Δ^9-THC		PVP	
	a.m.	p.m.	a.m.	p.m.
1	2	2	40	40
2 – 4	4	4	80	80
5	4	6	80	120
6 – 10	6	6	120	120

Results

Body Weight. The initial mean body weight of the 5-day PVP-treated animals (255 ± 7 g) was not significantly different ($P > 0.1$) from that of the corresponding Δ^9-THC-treated group (271 ± 6 g). Also the initial mean body weight of the 10-day PVP-treated animals (236 ± 7 g) and those treated with Δ^9-THC for 10 days (231 ± 8 g) were not significantly different ($P > 0.1$). The percentage change in body weight of animals treated with Δ^9-THC or PVP over the 10-day experimental period is shown in Fig. 1. During this period, the mean body weight of the PVP-treated group increased in a linear manner. The mean body weight of the Δ^9-THC-treated group was significantly lower than that of the PVP-treated group on each corresponding day of the experiment ($P < 0.05$). Growth of the Δ^9-THC-treated animals was retarded for the first 5 days of the experiment. However, this group appeared to gain weight in a linear manner from day 6 onwards.

The lines fitted to the body weight values obtained from day 6 to day 11 of the PVP- and Δ^9-THC-treated rats do not depart significantly from parallelism ($P > 0.05$). Such a result indicates that after day 5 the rate of increase in body weight is the same for both groups.

Daily Food Consumption. The daily food consumption of the Δ^9-THC-treated animals was significantly lower ($P < 0.05$) than that of the PVP-treated group on each corresponding day of the experiment (Fig. 2). The daily food consumption of the PVP-treated group generally remained constant throughout the experimental period. On the other hand, the daily food consumption of the Δ^9-THC-treated animals increased from day 2 onwards and by day 5 was significantly greater ($P < 0.05$) than that on day 2. From then onwards (i.e. from day 5 – 11) the daily food consumption of the Δ^9-THC-treated group remained constant; however, it was still significantly lower than that of the PVP-treated group.

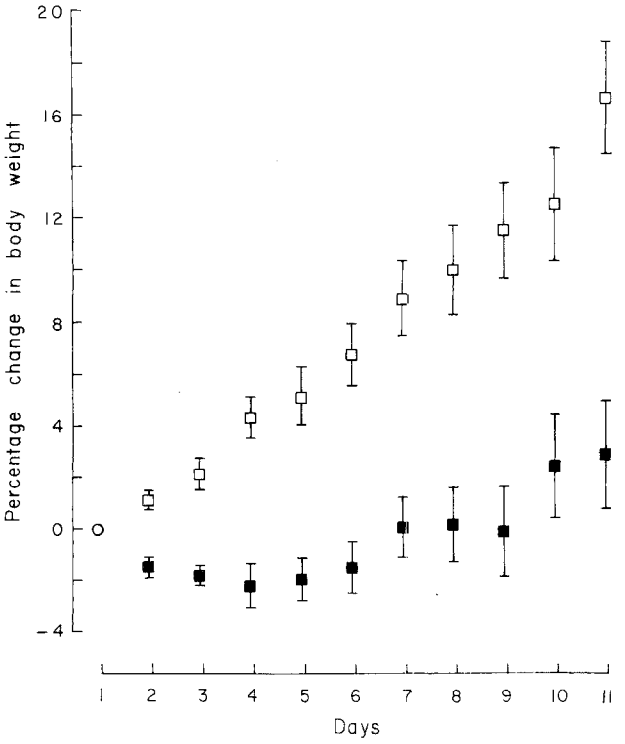

Fig. 1. Effect of twice daily IV injections of increasing doses of PVP (40–120 mg/kg), (□) or Δ^9-THC (2–6 mg/kg), (■) on the body weight of rats treated for 10 days. The body weight is expressed as the percentage change from the body weight on day 1 and each value represents the mean change ± SE of 20 rats. The body weight of the PVP-treated group increased in a linear manner ($r > 0.36$) from days 2–11. The body weight of the Δ^9-THC treated group increased in a linear manner from day 6 ($r > 0.19$). The lines drawn (from day 6 for each group) do not depart significantly from parallelism ($P > 0.05$)

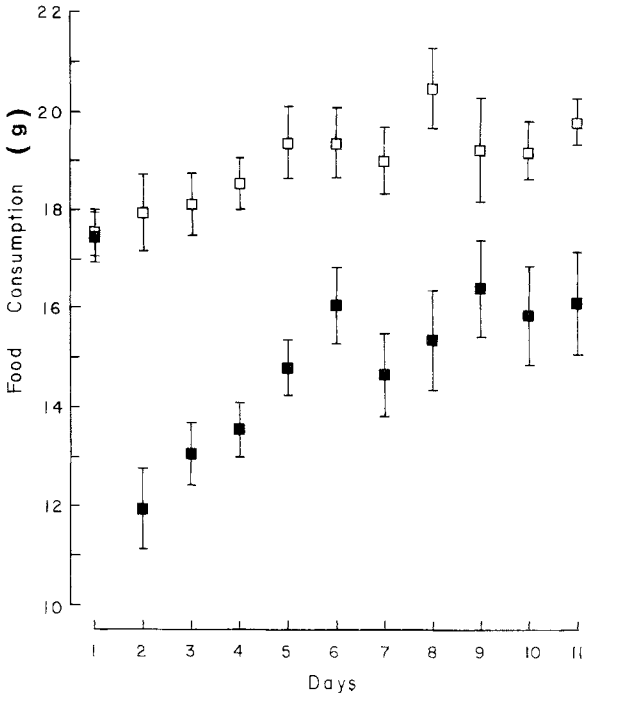

Fig. 2. Effect of twice daily IV injections of increasing doses of PVP (40–120 mg/kg), (□) or Δ^9-THC (2–6 mg/kg), (■) on daily food consumption (g) measured on days 1–11. The values represent the mean ± SE of 20 rats

Behaviour During Chronic Treatment. IV injections of PVP did not modify the behaviour of the animals over the experimental period. IV administration of Δ^9-THC produced a characteristic biphasic modification of behaviour (Taylor and Fennessy, 1978a) which consisted of a period of hyperactivity (increased motor activity and spontaneous jumping) lasting about 15 min, followed by depression which lasted for at least 2 h. The animals began to exhibit tolerance to these Δ^9-THC effects by day 2 and the injection of the morning dose on day 5 had little effect on behaviour. However, administration of the higher dose of Δ^9-THC (6 mg/kg) on the evening of day 5 again produced the characteristic behavioural response. Tolerance to this dose of Δ^9-THC also developed and was quite marked by day 10.

Behaviour After Administration of Biogenic Amine Reuptake Inhibitors. The biogenic amine reuptake inhibitors induced quantifiable behavioural changes (writhes, backward kicks, jumps, and wet shakes) when administered to rats chronically treated with Δ^9-THC for 5 or 10 days.

The total number of jumps and wet shakes observed after the administration of saline, imipramine, clomipramine or fluoxetine in groups of five rats treated for 5 and 10 days with either PVP or Δ^9-THC are shown in Figs. 3a and b. The number of jumps observed in each group was low. Fluoxetine induced a significant number ($P < 0.05$) of jumps after 5 days of Δ^9-THC treatment, whereas imipramine induced a significant number ($P < 0.05$) of jumps in the animals treated for 10 days. Injection of rats treated for 10 days with Δ^9-THC with saline, imipramine and fluoxetine induced a significant number ($P < 0.05$) of wet shakes. However, saline induced a significant number ($P < 0.05$) of wet shakes in animals treated with PVP for 5 days.

Figure 4 shows the total number of backward kicks observed in each group of five rats treated with PVP and Δ^9-THC for 5 or 10 days, after injection with saline, imipramine, clomipramine of fluoxetine. After 5 days of chronic treatment, a significant number ($P < 0.05$) of backward kicks was induced only by injection of clomipramine and fluoxetine in rats treated with Δ^9-THC. Each of the amine reuptake inhibitors induced a significantly greater number ($P < 0.05$) of backward kicks in rats treated for 10 days with Δ^9-THC than did

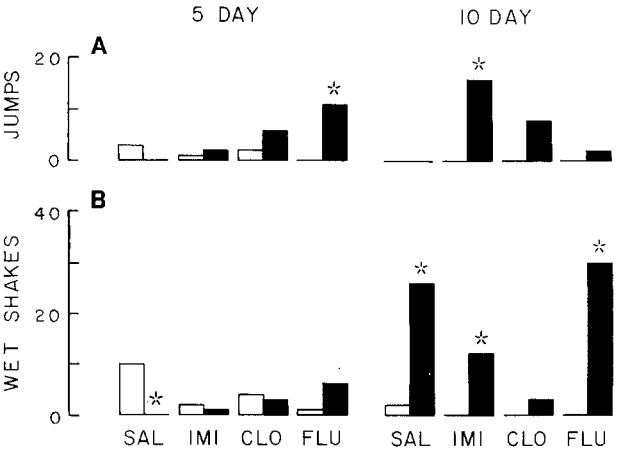

Fig. 3. Effect of amine reuptake inhibitors on (**A**) jumping and (**B**) wet shake behaviour in rats chronically treated with PVP (40–120 mg/kg) (open columns) or Δ^9-THC (2–6 mg/kg) (filled columns) IV for 5 and 10 days. The inhibitors were imipramine (*IMI*), clomipramine (*CLO*) and fluoxetine (*FLU*). These drugs were injected IP in doses of 15 mg/kg when the next dose of Δ^9-THC or PVP was due, and behaviour was recorded for the next 30 min. Saline (*SAL*) was injected as a control. Each value represents the total number of jumps or wet shakes in groups of five animals. * $P < 0.05$ compared to PVP (Chi-squared test)

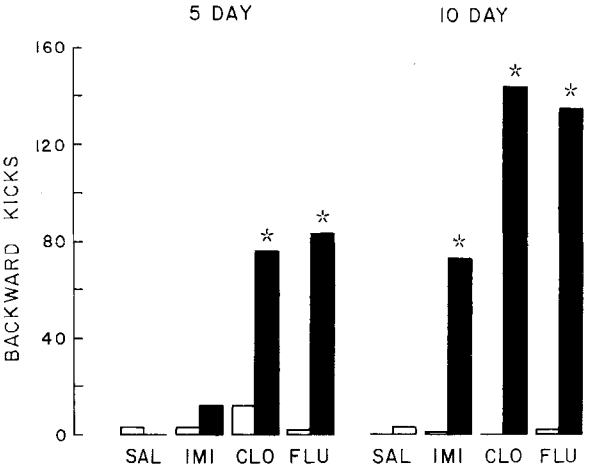

Fig. 4. Effect of amine reuptake inhibitors on backward kicking behaviour in rats chronically treated with PVP (40–120 mg/kg) (open columns) or Δ^9-THC (2–6 mg/kg) (filled columns) IV for 5 and 10 days. The inhibitors were imipramine (*IMI*), clomipramine (*CLO*) and fluoxetine (*FLU*). These drugs were injected IP in doses of 15 mg/kg when the next dose of Δ^9-THC or PVP was due and behaviour was recorded for the next 30 min. Saline (*SAL*) was injected as a control. Each value represents the total number of backward kicks in groups of five animals. * $P < 0.05$ compared to the corresponding PVP value (Chi-squared test)

saline. In addition, these drugs induced a significantly greater number ($P < 0.05$) of backward kicks in rats treated for 10 days with Δ^9-THC than in rats treated with PVP. The number of backward kicks induced by clomipramine and fluoxetine in rats treated for 10 days with Δ^9-THC was significantly greater ($P < 0.05$) than that induced by imipramine.

The total number of writhes observed in each group of five rats treated with Δ^9-THC and PVP for 5 or 10 days after injection with saline, imipramine, clomipramine and fluoxetine is shown in Fig. 5. After 5 days of chronic treatment imipramine, clomipramine and fluoxetine induced a significantly greater number ($P < 0.05$) of writhes in Δ^9-THC-treated animals than in PVP-treated animals. In Δ^9-THC-treated rats the number of writhes induced by clomipramine and fluoxetine was significantly greater ($P < 0.05$) than the number induced by imipramine, which was greater than that induced by saline. After 10 days of chronic treatment, saline, imipramine, clomipramine and fluoxetine induced a significantly greater number ($P < 0.05$) of writhes in Δ^9-THC-treated rats than in PVP-treated rats. The number of writhes induced by the amine reuptake inhibitors was significantly greater ($P < 0.05$) than the number induced by saline in Δ^9-THC-treated rats. Fluoxetine induced a greater number of writhes than did clomipramine or imipramine.

The non-quantified behavioural signs (front paw tremor, fine body tremor, chewing, ptosis, squealing,

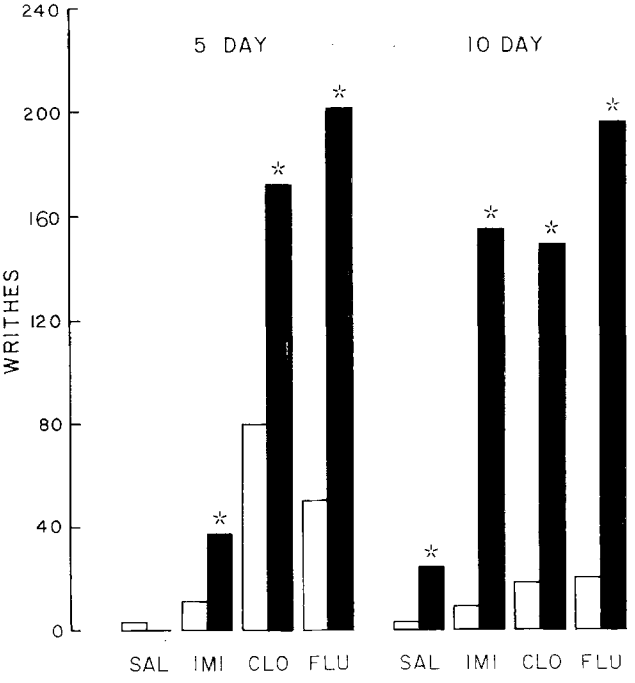

Fig. 5. Effect of amine reuptake inhibitors on writhing behaviour in rats chronically treated with PVP (40–120 mg/kg) (open columns) or Δ^9-THC (2–6 mg/kg) (filled columns) IV for 5 and 10 days. The inhibitors were imipramine (*IMI*), clomipramine (*CLO*) and fluoxetine (*FLU*). These drugs were injected IP in doses of 15 mg/kg when the next dose of Δ^9-THC or PVP was due and behaviour was recorded for the next 30 min. Saline (*SAL*) was injected as a control. Each value represents the total number of writhes in groups of five animals. * $P < 0.05$ compared to corresponding PVP value (Chi-squared test)

yawning, excessive grooming and ataxia) were observed only in animals treated with Δ^9-THC after injection of the amine reuptake inhibitors. These signs were not observed in animals treated with PVP nor in animals treated with Δ^9-THC after injection with saline. These behavioural signs were quite marked after injection with clomipramine and fluoxetine but not after imipramine in the rats treated for 5 days with Δ^9-THC. However, after 10 days of Δ^9-THC treatment, the administration of each of the reuptake inhibitors resulted in the exhibition of these signs.

Discussion

The present results confirm our previous finding that clomipramine induces a behavioural response which may be indicative of withdrawal in rats chronically treated with Δ^9-THC (Taylor and Fennessy, 1978b). Furthermore, it is apparent that other biogenic amine reuptake inhibitors will also induce this response. From the behavioural observations made in this study, it is suggested that there is a relationship between the 5-HT reuptake inhibiting activity of these compounds and their ability to induce the behavioural response in Δ^9-THC-treated animals. It appears that fluoxetine is the most effective in producing these behavioural changes. Clomipramine is less potent, but is, in turn, more potent than imipramine.

The body weight results show that PVP-treated animals gain weight in a linear manner and that Δ^9-THC-treated animals initially lose weight and, after day 5, begin to gain it at a rate similar to that of the control animals. These results are consistent with the findings of other workers and our own previous observations (Kaymakcalan et al., 1977; Taylor and Fennessy, 1978a, b) in that Δ^9-THC treatment results in a reduction in body weight. However, the present results show that tolerance develops to this effect, since from days 6 – 11 the rate of increase in body weight of the Δ^9-THC-treated animals is not different from that of the PVP-treated animals. This fall in body weight may be explained by the observation that the Δ^9-THC-treated animals had consumed less food than the vehicle-treated animals. This observed anorexigenic effect of Δ^9-THC confirms our earlier observations (Taylor and Fennessy, 1978b) and those of other workers (Sofia and Barry, 1974; Miczek, 1979). Although water intake was not measured in this study, this parameter has been reported to be reduced during chronic Δ^9-THC treatment (Sjöden et al., 1973; Miczek, 1979) and may also be a contributory factor to the reduction in body weight. Presumably, reduced food and water consumption are consequences of the general central nervous system depressant effects of Δ^9-THC.

The acute biphasic behavioural changes observed during the periods of Δ^9-THC administration confirm our previous observations (Taylor and Fennessy, 1978a). The present results also confirm that animals treated chronically with Δ^9-THC develop tolerance to these acute behavioural effects. This was further evidenced by the re-establishment of some of the acute behavioural changes when the dose of Δ^9-THC was increased from 4 to 6 mg/kg. Consistent with these observations are those of body weight and food consumption. The food consumption of the Δ^9-THC-treated animals was significantly greater on day 5 compared to that on day 2. Food consumption then remained relatively constant for the remainder of the experiment. However, it was still significantly less than that of the PVP-treated animals. Body weight of the Δ^9-THC-treated animals began to increase in a linear manner after day 5 and the rate of increase in body weight was similar to that of the control animals. These findings suggest that tolerance develops to Δ^9-THC, a phenomenon which was quite marked by day 10 of administration.

The behavioural changes occurring after the administration of the reuptake inhibitors indicate that these drugs induce a withdrawal-like syndrome in rats chronically treated with Δ^9-THC for 5 or 10 days. The jumping and wet shakes behaviour were low in number and no consistent trend was obvious. It is concluded that there parameters are not reliable indices of the behavioural changes induced by biogenic amine reuptake inhibitors in Δ^9-THC-treated rats. In contrast, the writhing and backward kicking behaviours appear to be more representative of the behaviour, both quantified and non-quantified, induced by these drugs. It would appear that clomipramine and fluoxetine induce a greater number of backward kicks in Δ^9-THC-treated animals than does imipramine. It is also interesting to note that the number of backward kicks induced by any of the biogenic amine inhibitors increases with the duration of Δ^9-THC administration. The writhing behaviours are more frequent after fluoxetine and clomipramine than after imipramine in the 5-day Δ^9-THC-treated rats. In addition, after 10 days of chronic treatment, fluoxetine is more effective in inducing writhes than either clomipramine or imipramine.

The non-quantified behavioural changes are also in good agreement with the incidence of the backward kicking and writhing behaviour. The behavioural changes are not observed in PVP-treated rats and appear to be more marked when the incidence of writhes and backward kicks is high.

A precise order of potency of the reuptake inhibitors in inducing behavioural changes cannot be accurately assessed for our results, because only a single dose of

each inhibitor was used. However, since approximately equimolar doses of the inhibitors were used, it appears reasonable to suggest that the order of potency of these agents in inducing behavioural changes is fluoxetine > clomipramine > imipramine. The dose of each amine reuptake inhibitor used in this experiment (15 mg/kg) was chosen on the basis of the data reported by Lidbrink et al. (1971). These authors showed that clomipramine (15 mg/kg) caused minimal blockade of noradrenaline (NA) reuptake with only a slight potentiation of the L-dopa-induced effect on the flexor reflex activity in the rat. However, clomipramine was found to potentiate the 5-hydroxytryptophan-induced increase in the extensor reflex and also to inhibit the reuptake of 5-HT in rat brain tryptaminergic neurones. In addition, Fennessy and Taylor (1978) reported that this dose of clomipramine antagonised the Δ^9-THC-induced hypothermia and changes in brain monoamines of the rat. Fuller and Wong (1977) compared the potency of fluoxetine, clomipramine and imipramine in inhibiting the reuptake of monoamines and they found that the order of potency for the inhibition of NA reuptake was imipramine > clomipramine > fluoxetine, whereas that for 5-HT reuptake was fluoxetine > clomipramine > imipramine. Since the apparent order of potency of these agents in inducing the behavioural changes observed in our experiments parallels the order of potency for inhibiting the reuptake of 5-HT, it appears that the ability to inhibit the reuptake of 5-HT may be an important criterion of agents that will elicit these behavioural changes. However, the mechanism by which these drugs act is unknown. Δ^9-THC appears to modify tryptaminergic function in the brain acutely with a resultant increase in the brain level of the acid metabolite of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA). This effect is presumably due to release of 5-HT from tryptaminergic neurones (Fennessy and Taylor, 1977). Since tolerance appears to develop to this effect of Δ^9-THC (Taylor and Fennessy, 1978a), drugs such as 5-HT reuptake inhibitors may affect an already compromised central tryptaminergic function.

The marked increase in the incidence of writhing and backward kicking induced by imipramine after 10 days of Δ^9-THC treatment compared with the 5 day observation suggests that additional neurotransmitter systems may be associated with the longer periods of Δ^9-THC administration. Kaymakcalan et al. (1977) observed a naloxone-induced abstinence syndrome in rats treated with Δ^9-THC for 35 days, the abstinence syndrome being qualitatively similar to that observed in rats withdrawing from the opiates. Using the dosage regime outlined in Table 1, naloxone was found to be in-effective in inducing abstinence signs in rats treated with Δ^9-THC for 10 days (Taylor and Fennessy, unpublished observations). This tends to support the view that no single neurotransmitter system is responsible for the actions of Δ^9-THC and may reflect the multiplicity of Δ^9-THC effects.

In conclusion, twice daily IV injections of Δ^9-THC (2–6 mg/kg) over a 10-day period induced a state of what appears to be physical dependence in rats. The behavioural signs, consisting mainly of writhing and backward kicking, were precipitated by IP injections of biogenic amine reuptake inhibitors. The potency of the inhibitors in inducing the different behavioural signs was fluoxetine > clomipramine > imipramine. Since the apparent order of potency of these agents in precipitating the behavioural changes after chronic Δ^9-THC treatment is the same as the order of potency and selectivity for the inhibition of 5-HT repuptake mechanisms, it is suggested that tryptaminergic mechanisms are involved. However, since imipramine is an inhibitor of NA reuptake and clomipramine and imipramine antagonise central histamine H_2-receptors, the involvement of other neurotransmitter systems cannot be excluded.

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