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Time-course of the effects of chronic Δ^9-tetrahydrocannabinol on behaviour, body temperature, brain amines and withdrawal-like behaviour in the rat

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The effects of clomipramine HCl (15 mg kg^{-1} i.p.) on behaviour, body temperature and brain amines were investigated in rats that had been chronically treated twice daily with increasing doses of Δ^9-tetrahydrocannabinol (Δ^9-THC, 2–6 mg kg^{-1} i.v.). Δ^9-THC produced a biphasic change in behaviour, stimulation followed by depression, and a pronounced hypothermia. Tolerance developed rapidly to these effects of Δ^9-THC. Chronic treatment with Δ^9-THC reduced the levels of homovanillic acid, 5-hydroxytryptamine and noradrenaline. The level of dopamine was not altered with chronic treatment and tolerance appeared to develop to the increased level of 5-hydroxyindoleacetic acid induced by Δ^9-THC. Injection of clomipramine, 12–14 h after 2, 5 or 10 days of Δ^9-THC treatment induced characteristic changes in the rats behaviour which consisted of writhes, backward kicking, wet shakes, jumps, ataxia and front paw and whole body tremor. The severity of the behavioural changes appeared to be dependent on the period of Δ^9-THC administration and they were not accompanied by a change in body temperature or consistent changes in brain amines or metabolites. The results indicate that physical dependence on Δ^9-THC may occur since clomipramine is able to precipitate changes in behaviour, indicative on an abstinence syndrome, in rats chronically treated with Δ^9-THC. It is suggested that tryptaminergic mechanisms are altered during chronic Δ^9-THC treatment and that clomipramine induces the behavioural changes by interacting with an altered tryptaminergic system.

The existence of physical dependence on cannabis has been a controversial issue. We have previously reported that clomipramine, a potent inhibitor of 5-hydroxytryptamine (5-HT) uptake, induced behavioural changes in rats chronically treated for 10 days with increasing doses of Δ^9-tetrahydrocannabinol (Δ^9-THC, Taylor & Fennessy 1978a). It was suggested that, since clomipramine attenuated some of the acute actions of Δ^9-THC (Fennessy & Taylor 1978) and precipitated withdrawal-like symptoms in rats chronically treated with Δ^9-THC, physical dependence on Δ^9-THC may occur. On the other hand, the development of tolerance to the effects of Δ^9-THC or cannabis extracts has been well documented (Adams et al 1976; Anderson et al 1975; Lomax 1971; Paton 1975; Taylor & Fennessy 1978b). During the development of tolerance to the Δ^9-THC-induced hypothermia, a correlation between some of the effects of Δ^9-THC and changes in brain tryptaminergic mechanisms was observed (Taylor & Fennessy 1978b).

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The present study was undertaken to extend the previous ones and examine possible correlations between the period of Δ^9-THC administration and the development of tolerance or the ability of clomipramine to induce behavioural changes (withdrawal) in rats. This was done at various times after twice daily treatment with increasing doses of Δ^9-THC for up to 10 days. Similar studies investigated changes induced by clomipramine on the behaviour, body temperature and brain amines of rats after various periods of chronic Δ^9-THC treatment. The study therefore further examines the existence of physical dependence on Δ^9-THC.

METHODS

Animals

Male albino Wistar rats, 200–265 g, were housed, and the experiments conducted in rooms maintained at an ambient temperature of 21 ± 1 °C with a 12 h light-dark cycle. For intravenous injections, polyethylene (PE10) cannulae were inserted into the external jugular veins (Fennessy & Taylor 1977). Before surgery the rats were kept in group cages, but

for the 48 h of recovery and during the experimental period they were kept in individual cages.

Experimental design

The experiments lasted from 1 to 11 days during which time the rats received daily two intravenous injections of either Δ^9-THC, which was suspended in 0·9% NaCl (saline) by use of polyvinylpyrrolidone (PVP) according to Fenimore & Loy (1971), or the vehicle, PVP.

The dose schedule used was:

	Dose (mg kg^{-1})			
	Δ^9-THC		PVP	
Day	am	pm	am	pm
1	2	2	40	40
2–4	4	4	80	80
5	4	6	80	120
6–10	6	6	120	120

Before each injection, each rat was weighed and the loose end of the cannula cut to allow entry of a 30-gauge needle. Δ^9-THC or PVP was injected, washed in with pyrogen-free saline, and the cannula then heat-sealed to maintain its integrity to allow for the administration of the next injection. Groups of 5 rats were injected intraperitoneally with 15 mg kg^{-1} clomipramine HCl or saline following 2, 5 or 10 days of treatment with Δ^9-THC or PVP. This clomipramine challenge was administered on the morning of the third, sixth or eleventh days when the next injection of Δ^9-THC was due. Fifteen min before the injection of clomipramine, each rat was placed in a 10 litre opaque plastic bucket to which it was returned after the injection of clomipramine.

Behavioural studies

For the duration of the experiment (up to 11 days) the behaviour of the Δ^9-THC-treated and PVP-treated rats was observed. For the 30 min following the injection of clomipramine or saline (on the third, sixth or eleventh days), the behaviour of the rats was recorded by trained observers who were unaware of the animals' pretreatments. During this period the number of writhes, backward kicks, wet shakes and jumps displayed by the rats were counted. In addition, other behavioural changes which included whole body and front paw tremor, ptosis, excessive grooming, yawning, vocalization and ataxia characterized by a listing of the animal to one side were noted.

Body temperature studies

The time-course of the effect of Δ^9-THC on the body temperature of each conscious rat was monitored by means of a thermistor probe which was inserted 6–7 cm into the rectum 1 h before, and continuously for 2 h after, the injection of Δ^9-THC. The effect of Δ^9-THC on body temperature was recorded each morning of the experimental period.

The body temperature during the withdrawal induced by clomipramine (Taylor & Fennessy 1978a) was recorded intermittently in rats which had been treated twice daily for 10 days with Δ^9-THC. In this study, body temperature was recorded continuously, beginning 1 h before and for 2 h following the administration of clomipramine.

Brain amine determinations

Groups of at least 5 rats were used for the determination of the whole brain levels of noradrenaline (NA), dopamine (DA), homovanillic acid (HVA), 5-HT and 5-hydroxyindole acetic acid (5-HIAA). At the time of, and 15 or 30 min after the injection of clomipramine, rats were decapitated, the brains rapidly removed, blotted free of excess blood, frozen in liquid nitrogen and stored at −20 °C. All rats were killed in the morning. After ion-exchange column chromatography (Bio-Rex 70) the amines and 5-HIAA were assayed spectrophotofluorimetrically as previously described (Taylor & Fennessy 1977). HVA was assayed fluorimetrically according to Andén et al (1963) after extraction using n-butyl acetate. The fluorescence developed was determined with an Aminco-Bowman spectrophotofluorimeter. The concentrations of brain amines were determined in terms of the free base or acid.

Analysis of results

Results were determined as means ± standard error of the mean (s.e.m.) in body temperature and brain amine studies. For testing the statistical significance of differences between means, Student's unpaired *t*-test was used. In behavioural studies, the behaviours were counted and the total number for 5 rats treated with Δ^9-THC or PVP compared using a Chi-squared test (Seigel 1956).

Drugs used

All drugs were dissolved or suspended in saline and were injected in a volume of 1 ml kg^{-1}. The drugs used were clomipramine HCl (Anafranil, Ciba-Geigy), polyvinylpyrrolidone (Kollidon 25, BASF) and (−)-*trans*-Δ^9-THC (Batch SSC 81896, NIDA). All reagents used for extraction and assay were of analytical grade.

RESULTS

Behaviour during chronic Δ⁹-THC treatment

The first administration of 2 mg kg^{-1} Δ⁹-THC resulted in a biphasic change in behaviour. This consisted of an excitatory behaviour superimposed on a state of depression. The excitatory behaviour consisted of an exploratory type of behaviour accompanied by spontaneous jumping. The depression was manifested as sedation, catatonia, depressed respiration, splayed rear legs and vocalization. These behavioural changes became evident 10 min after the injection of Δ⁹-THC. The excitatory behaviour lasted for up to 1 h, whereas the depression was evident up to 4 h later. The second injection of 2 mg kg^{-1} Δ⁹-THC in the evening of day 1, resulted in similar behavioural changes, although they appeared to be reduced in intensity. On the second day when the dose was increased to 4 mg kg^{-1}, Δ⁹-THC induced the same behavioural changes as on the first day. Tolerance developed further to these behavioural changes and was marked on the fifth day. When the dose of Δ⁹-THC was further increased to 6 mg kg^{-1}, only minor alterations in behaviour were observed and tolerance had developed to this dose by the eighth day.

Body temperature studies during chronic Δ⁹-THC treatment

Δ⁹-THC (2 mg kg^{-1}, i.v.) produced a pronounced hypothermia on the first day (Fig. 1). The drop in body temperature reached a maximum (−2·2 °C) 1 h after the injection of Δ⁹-THC. On the second day the increased dose of Δ⁹-THC (4 mg kg^{-1}) resulted in a similar decrease in body temperature. Tolerance developed to the hypothermic effect of Δ⁹-THC whereby the maximum dose of Δ⁹-THC (6 mg kg^{-1}) did not markedly alter body temperature. Throughout the experimental period the initial body temperatures of the Δ⁹-THC-treated rats and those of the PVP-treated rats were not statistically different ($P > 0.05$) and PVP did not alter the animals body temperature.

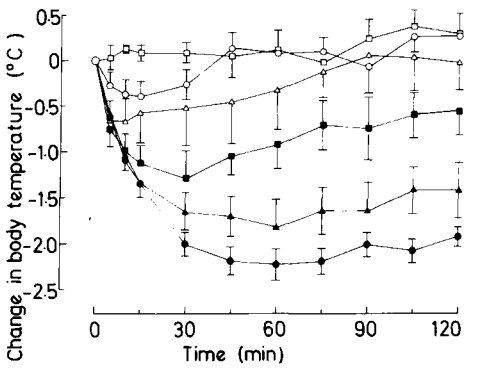

FIG. 1. The change in body temperature induced by Δ⁹-THC injected intravenously twice daily for 10 days recorded for the 2 h following the morning injection on days 1 (2 mg kg^{-1}, ●), 2 (4 mg kg^{-1}, ▲), 3 (4 mg kg^{-1}, ■), 5 (4 mg kg^{-1}, ○), 6 (6 mg kg^{-1} △) and 10 (6 mg kg^{-1}, □). Each point represents the mean ± s.e.m. from 6 rats.

Brain amines during chronic Δ⁹-THC treatment

Administration, twice daily of Δ⁹-THC for 2 or 5 days, increased the whole brain levels of 5-HIAA compared with PVP-treated rats. In addition, after 5 days the level of HVA was decreased. After 10 days, the brain levels of NA, HVA and 5-HT were reduced in Δ⁹-THC-treated rats (Table 1).

Behaviour induced by clomipramine after chronic Δ⁹-THC treatment

After chronic Δ⁹-THC treatment, clomipramine, injected intraperitoneally, induced characteristic changes in behaviour that were not observed in animals injected with saline. The changes were of

Table 1. Effect of chronic treatment with PVP or Δ⁹-THC on the whole brain levels of noradrenaline (NA), dopamine (DA), homovanillic acid (HVA), 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) of rats injected intravenously twice daily for up to 10 days.

	Brain level (μg g^{-1} wet wt)					
	Number of days of treatment					
	2		5		10	
Amine or metabolite	PVP	Δ⁹-THC	PVP	Δ⁹-THC	PVP	Δ⁹-THC
NA	0·576 ± 0·016	0·540 ± 0·019	0·605 ± 0·035	0·616 ± 0·010	0·574 ± 0·051	0·424 ± 0·018*
DA	0·761 ± 0·031	0·843 ± 0·026	0·778 ± 0·057	0·785 ± 0·027	0·817 ± 0·027	0·742 ± 0·061
HVA	0·072 ± 0·012	0·063 ± 0·011	0·077 ± 0·004	0·063 ± 0·004*	0·079 ± 0·009	0·032 ± 0·005*
5-HT	0·496 ± 0·018	0·510 ± 0·014	0·512 ± 0·012	0·467 ± 0·041	0·515 ± 0·009	0·437 ± 0·028*
5-HIAA	0·804 ± 0·029	0·908 ± 0·024*	0·847 ± 0·020	0·985 ± 0·038*	0·834 ± 0·037	0·931 ± 0·054

The levels were determined when the next injection of PVP or Δ⁹-THC was due. Each group was of at least 5 animals.
* $P < 0.05$ compared with PVP (control), Student's *t*-test.

two types: (i) quantifiable, and (ii) those more difficult to quantify. The quantifiable changes included writhing, backward kicking movements, wet shaking and jumping. In groups of 5 rats that had received chronic PVP treatment, no backward kicks, jumps or wet shakes were observed in the 30 min following injection of clomipramine. The numbers of wet shakes and jumps induced by clomipramine in rats chronically treated with Δ^9-THC were low (Fig. 2). The number of wet shakes after 5 days chronic Δ^9-THC treatment and the number of jumps after 10 days treatment were significantly different from

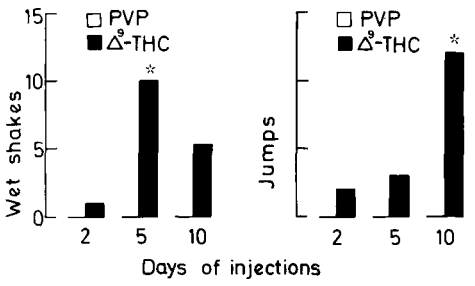

FIG. 2. Effects of clomipramine HCl (15 mg kg^{-1}, i.p.) on the wet shake and jumping behaviour of rats treated for up to 10 days with twice daily injections of PVP (40–120 mg kg^{-1}) or Δ^9-THC (2–6 mg kg^{-1}). PVP results are baseline. Each column represents the total number of wet shakes or jumps observed in groups of 5 rats during the 30 min following injection of clomipramine. *$P < 0.05$ compared with PVP, Chi-squared test.

those of the PVP-treated group ($P < 0.05$, Chi-squared test). Clomipramine induced a greater number of writhes and backward kicks in animals treated chronically with Δ^9-THC than in animals treated with PVP (Fig. 3). In addition, the number of backward kicks or writhes induced by clomipramine in Δ^9-THC-treated rats appeared to be dependent on the period of chronic Δ^9-THC treatment. The numbers after 10 days of Δ^9-THC were greater than those after 5 days of Δ^9-THC and the number of writhes induced after 5 days was greater than after 2 days treatment.

The severity of the clomipramine-precipitated behavioural changes in Δ^9-THC-treated rats that were more difficult to quantify was also dependent on the period of treatment. These behavioural changes included fine body and front paw tremor, vocalization, excessive yawning and ataxia which was characterized by a listing of the animals to one side. Clomipramine did not induce these behavioural changes in rats that had been chronically treated with PVP.

Body temperature following clomipramine after chronic Δ^9-THC treatment

On the morning of the 11th day (i.e. 12 h after 10 days of chronic twice daily treatment), the body temperature of PVP-treated rats (38·58 ± 0·34 °C, n = 6) was not different to that of Δ^9-THC-treated rats (38·23 ± 0·13 °C, n = 6, $P > 0.05$). Although clomipramine induced the characteristic changes in behaviour as described above in Δ^9-THC-treated rats, but not in PVP-treated rats, clomipramine did not markedly alter the body temperature of PVP- or Δ^9-THC-treated rats (Fig. 4).

Brain amines following clomipramine after chronic Δ^9-THC treatment

Clomipramine did not induce consistent alterations in the whole brain levels of the amines or acid

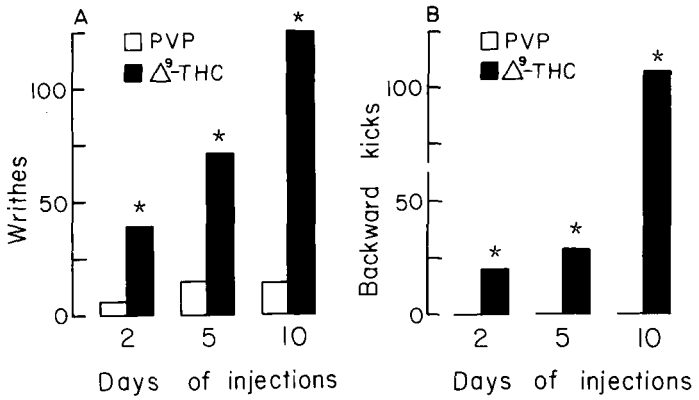

FIG. 3. Effects of clomipramine HCl (15 mg kg^{-1}, i.p.) on (A) writhing (B) backward kicking behaviour of rats treated for up to 10 days with twice daily injections of PVP (40–120 mg kg^{-1}, □) or Δ^9-THC (2–6 mg kg^{-1}, ■). PVP results are baseline in (B). Each column represents the total number of writhes or kicks observed in groups of 5 rats during the 30 min following the injection of clomipramine. *$P < 0.05$ compared with PVP, Chi-squared test.

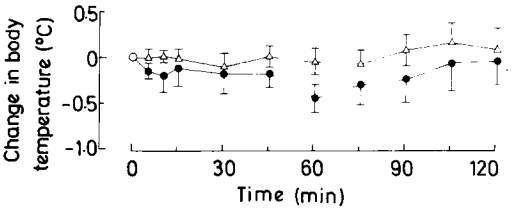

FIG. 4. The change in body temperature induced by clomipramine HCl (15 mg kg^{-1}, i.p.) in rats treated twice daily for 10 days with PVP (40–120 mg kg^{-1}, △) or Δ^9-THC (2–6 mg kg^{-1}, ●). Each point represents the mean ± s.e.m. from 6 rats.

metabolites measured in rats that had been chronically treated for up to 10 days with Δ^9-THC, compared with the values in PVP-treated rats (Table 2). Fifteen min after injection of clomipramine no differences ($P > 0{\cdot}05$) were detected in the levels of brain amines determined in PVP-treated and Δ^9-THC-treated rats, except for an increase in the 5-HIAA level in rats treated for 2 days with Δ^9-THC. However, 30 min after clomipramine, the levels of DA and 5-HIAA were elevated and the level of NA reduced in rats treated for 5 days with Δ^9-THC. After 2 days of Δ^9-THC treatment, 30 min after clomipramine, the level of 5-HT was increased.

DISCUSSION

The results confirm that clomipramine, a drug which inhibits some of the actions of Δ^9-THC acutely, induces characteristic changes in the behaviour of rats that have been chronically treated with Δ^9-THC for up to 10 days. It is suggested that these behavioural changes may be indicative of a withdrawal syndrome and hence may indicate the development of physical dependence on Δ^9-THC. The severity of the behavioural changes induced by clomipramine appears to be dependent on the period of Δ^9-THC administration. This suggests that an interaction between clomipramine and an unidentified system develops in rats chronically treated with Δ^9-THC. Like the development of physical dependence, the degree of manifestation of this interaction is dependent on the period of Δ^9-THC administration.

The development of tolerance with chronic administration to the hypothermia and changes in behaviour induced by acute administration of Δ^9-THC, is similar to that of previous reports (Davis et al 1972; Lomax 1971; Taylor & Fennessy 1978b). The observations that marked tolerance developed to the Δ^9-THC-induced hypothermia and changes in behaviour exemplify that, at the time of clomipramine injection, the rats in the present study were tolerant to some of the effects of Δ^9-THC.

Chronic Δ^9-THC treatment did not produce consistent changes in the whole brain levels of the amines or 5-HIAA. The reduction in the levels of NA and 5-HT induced by chronic Δ^9-THC treatment have been reported previously (Ouellet et al 1973; Palermo Neto et al 1975; Taylor & Fennessy 1978b). The decrease in the level of NA is contrary to most observations in our previous study (Taylor & Fennessy 1978b) and those of Mazurkiewicz-Kwilecki & Filczewski (1973). Since the number of studies that have examined the effect of chronic Δ^9-THC treatment on brain amine levels is limited, and because of differences in dosage schedules, routes and time of administration, it is difficult to critically evaluate the role that these monoamines may play in the effects of chronically administered Δ^9-THC. The observations that chronic Δ^9-THC treatment reduced the level of HVA and that the magnitude of this reduction appeared to be dependent on the period of the Δ^9-THC treatment should be examined further. This

Table 2. Effect of clomipramine HCl (15 mg kg^{-1} i.p.) on the whole brain levels of noradrenaline (NA), dopamine (DA), homovanillic acid (HVA), 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) in rats chronically treated twice daily for up to 10 days with Δ^9-THC.

	Brain level (% control)					
	Number of days of treatment					
	2		5		10	
Amine or metabolite	Time after clomipramine (min) 15	30	15	30	15	30
NA	108·81 ± 6·68	113·54 ± 10·14	90·27 ± 6·81	82·93 ± 5·98*	94·37 ± 3·72	106·48 ± 10·21
DA	109·90 ± 6·78	99·26 ± 11·18	102·21 ± 4·76	123·13 ± 6·00*	101·22 ± 5·78	112·80 ± 9·97
HVA	82·51 ± 15·68	119·52 ± 28·19	83·94 ± 8·63	85·75 ± 6·01	103·38 ± 25·22	64·66 ± 31·11
5-HT	114·93 ± 9·02	131·63 ± 6·44*	97·62 ± 4·93	102·25 ± 5·80	91·94 ± 3·43	99·29 ± 5·55
5-HIAA	140·14 ± 14·08*	118·16 ± 8·96	104·46 ± 10·40	113·34 ± 4·71*	113·92 ± 10·33	116·63 ± 9·53

The levels were determined 15 or 30 min after clomipramine, which was injected when the next dose of Δ^9-THC was due, and are expressed as percentages of the levels determined in PVP-treated animals. Each group was of at least 5 rats. *$P < 0{\cdot}05$ compared with PVP (control), Student's t-test.

may be of importance when considering a possible relationship between some of the actions of Δ^9-THC and dopaminergic mechanisms (Malor et al 1977; Poddar et al 1976).

The behavioural changes induced by clomipramine in rats chronically treated with Δ^9-THC were not associated with consistent changes in the brain levels of the amines or their acid metabolites. It has not been established whether the attenuation of the difference in HVA levels in Δ^9-THC- and PVP-treated groups by clomipramine is associated with the behavioural changes induced by clomipramine. Similarly, the changes in behaviour induced by clomipramine were not associated with a change in body temperature, which is in keeping with our previous report (Taylor & Fennessy 1978a). Previously, body temperature was recorded intermittently (30 min before and 30 min, 4 and 8 h after, clomipramine), a method which may not detect small changes in the animals temperature because of the handling associated with the insertion of the thermistor probe. In the present study however, body temperature was recorded continuously.

The behavioural changes induced by clomipramine appear to be characteristic of animals chronically treated with Δ^9-THC. The total number of writhes and backward kicks are representative of indices of the behavioural changes, both quantified and non-quantified, induced by clomipramine. The observation that the severity of the behavioural changes is dependent on the period of chronic Δ^9-THC treatment suggests that clomipramine interacts with a mechanism that has been altered from that in a naive rat, by a continuous exposure to Δ^9-THC during chronic treatment. The reported changes in the levels of 5-HT following chronic treatment, the involvement of 5-HIAA in the expression of tolerance during chronic Δ^9-THC treatment (Taylor & Fennessy 1978b) and the ability of clomipramine to inhibit 5-HT uptake, are all suggestive of an interaction on tryptaminergic mechanisms. However, the involvement of other neurotransmitter systems, for example, the dopaminergic system, cannot be excluded.

Since, clomipramine has been shown to inhibit some of the acute actions of Δ^9-THC, the induction of behavioural changes by clomipramine in rats chronically treated with Δ^9-THC appears to parallel the precipitation of withdrawal symptoms by naloxone in rats chronically treated with morphine. Therefore, the changes in behaviour induced by clomipramine are suggested as being indicative of an abstinence syndrome and hence physical dependence on Δ^9-THC. The observation that cessation of chronic Δ^9-THC treatment does not result in behavioural changes (Taylor & Fennessy 1978a) is possibly due to the long half-life of Δ^9-THC. Following cessation of chronic treatment, the tissue levels of Δ^9-THC do not fall abruptly below the levels that may have become necessary to maintain the animals 'normal' behaviour. Clomipramine is able to interfere in some way with these effects of Δ^9-THC.

Therefore, it is concluded that, since an antagonist of some of the acute actions of Δ^9-THC can precipitate withdrawal symptoms in rats tolerant to Δ^9-THC, and since the severity of the withdrawal is dependent on the period of Δ^9-THC administration; physical dependence on Δ^9-THC does occur in the rat. However, the neurochemical basis of this withdrawal behaviour has not been established.

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