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An Investigation of the Involvement of GABA in Certain Pharmacological Effects of Delta-9-Tetrahydrocannabinol

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PERTWEE, R. G., S. E. BROWNE, T. M. ROSS AND C. D. STRETTON. *An investigation of the involvement of GABA in certain pharmacological effects of delta-9-tetrahydrocannabinol.* PHARMACOL BIOCHEM BEHAV **40**(3) 581–585, 1991.—Experiments were performed with mice to determine whether doses of the benzodiazepine, flurazepam, or the GABA uptake inhibitor, NO-328, known to potentiate catalepsy induced by delta-9-tetrahydrocannabinol (THC), would also interact synergistically with THC in the production of certain other effects. No synergism was detected either in the production of antinociception (tail flick test) or in a test in which the ability of flurazepam to delay onset of clonic convulsions induced by intravenous infusion of pentylenetetrazole was compared in the presence and absence of THC or cannabidiol. The hypothermic effect of THC was unaffected by NO-328 but enhanced by flurazepam, albeit only at doses higher than those needed to potentiate THC-induced catalepsy. In vitro experiments with guinea pig ileum showed that the ability of THC to inhibit electrically evoked contractions was unaffected by delta-amino-n-valeric acid, a $GABA_B$ receptor antagonist, and that preparations rendered tolerant to GABA responded normally to THC. Contractions induced by GABA in unstimulated ileal longitudinal muscle were attenuated by THC. We conclude that there is little evidence from our data that any of the THC effects studied were GABA mediated.

Delta-9-THC Cannabidiol Benzodiazepine Flurazepam Pentylenetetrazole Gamma-aminobutyric acid
Mice Body temperature Hypothermia Antinociception Anticonvulsant effect Guinea pig isolated ileum

RESULTS from previous studies with mice suggest that the cataleptic effect of delta-9-tetrahydrocannabinol (THC) is mediated by the putative inhibitory neurotransmitter, gamma-aminobutyric acid (GABA) (18,19). The present study was directed at investigating the involvement of GABA in other effects of THC. The initial approach was to determine whether doses of certain GABA-mimetics known to potentiate THC-induced catalepsy (18,19) also interact synergistically with THC in the production of hypothermia or antinociception. These responses were selected for study because they can be produced both by THC and by GABA agonists (6, 10, 11, 15, 22). The GABA-mimetics used were flurazepam and R(−)N-[4,4-di(3-methyl-thien-2-yl)-but-3-enyl] nipecotic acid hydrochloride (abbreviated to NO-328). Flurazepam is a benzodiazepine, a group of drugs, the primary mode of action of which is to enhance the response of $GABA_A$ receptors to neuronally released GABA (7). NO-328 is an inhibitor of GABA uptake (2). Another property shared by THC and certain GABA agonists is the capacity to inhibit electrically evoked contractions in guinea pig ileal longitudinal muscle by acting at prejunctional sites (8, 17, 21). Consequently, the possibility that GABA mediates THC-induced inhibition of electrically evoked ileal contractions was also investigated. Finally, since there are reports that THC and cannabidiol (CBD) share the ability of benzodiazepines to prevent convulsions (3, 14, 16), experiments were carried out to determine whether either of these cannabinoids would enhance the ability of flurazepam to prevent convulsions induced in mice by pentylenetetrazole.

METHOD

Drugs

THC was supplied by NIDA and CBD by Sigma. They were mixed with two parts of Tween 80 by weight and dispersed in Krebs solution (in vitro experiments) or 0.9% w/v aqueous NaCl solution (saline). NO-328 was supplied by Novo Industri A/S and was dissolved in water. Flurazepam hydrochloride and pentylenetetrazole were obtained from Sigma and were dissolved in saline. Delta-amino-n-valeric acid and GABA were also obtained from Sigma and were dissolved in Krebs solution. When salts were used, the doses are expressed in terms of these salts.

In Vivo Experiments

Experiments were carried out with adult male albino MF1 mice. The body temperature experiments were performed at an ambient temperature of 22°C. All other in vivo experiments were conducted at 34°C to avoid any large fall in deep body temperature. Control animals received drug vehicle instead of drug. Pentylenetetrazole was infused intravenously. Other drugs were injected subcutaneously (flurazepam) or intraperitoneally (THC

and NO-328) in a volume of 0.25 ml/25g.

Body temperature was recorded using a thermistor probe (YSI 402) which was inserted 3 cm into the rectum at set intervals. Except when held in the hand for the measurement of body temperature, the mice were kept unrestrained, each in a separate cage. Hypothermia has been expressed in terms of the temperature response index. This index is the area in °Chr between the curve for rectal temperature against time and a horizontal line passing through the rectal temperature value measured at the time of THC injection (time zero).

Antinociception was measured by a tail flick test in which the time taken ("latency") for a lightly restrained mouse to flick its tail away from a radiant heat stimulus was noted. Any mouse failing to respond within 10 s was excluded from the study. The method was based on the tail flick test described by D'Amour and Smith (4).

Anticonvulsant activity was measured by infusing pentylenetetrazole through a cannula inserted into a tail vein (1.1 ml/min; 2.5 mg/ml) and noting drug effects on the time taken for clonic seizures to commence (repeated contractions of forelimbs and neck muscles) (14). Each mouse was lightly restrained throughout the infusion.

In Vitro Experiments

Segments of guinea pig whole ileum or of longitudinal muscle-myenteric plexus dissected from whole ileum (20) were suspended under 1 g tension from an isometric transducer. They were immersed in Krebs solution kept at 37°C and bubbled with 95% O_2–5% CO_2. Washing was by overflow. The Krebs solution had the following composition (mM): NaCl 118, KCl 4.75, $NaHCO_3$ 25.0, KH_2PO_4 1.19, $CaCl_2$ 2.54, $MgSO_4$ 1.19 and glucose 11. For the whole ileum experiments, hexamethonium bromide (70 μM), mepyramine maleate (0.125 μM) and choline chloride (20 μM) were also present. The strips of whole ileum were stimulated electrically with supramaximal pulses applied using coaxial electrodes (0.1 Hz; 0.4 ms pulse width). The bath volume was 25 ml, and injection volumes did not exceed 0.1 ml. The longitudinal muscle strips were mounted in a 3-ml bath (maximum injection volume = 40 μl).

Data Analysis

Experimental values have been expressed as means and their limits of error as standard errors. Differences between means have been evaluated by Student's *t*-test for paired or unpaired data, the Mann-Whitney U-test or the Kruskal-Wallis test ($p>$ or <0.05).

RESULTS

Body Temperature and Antinociception Experiments

In the absence of flurazepam or NO-328, THC doses of 5 or 10 mg/kg significantly decreased body temperature and increased tail flick latency (Tables 1 to 3). Pretreatments with flurazepam (3 mg/kg) or NO-328 (5 mg/kg) known to enhance the cataleptic response to THC (19) had no detectable effect on THC-induced hypothermia or antinociception (Tables 1 and 2), even though the doses of THC used were submaximal. Pretreatment with a much higher dose of flurazepam also failed to alter the antinociceptive effect of THC (Table 2). However, doses of flurazepam higher than 3 mg/kg did enhance THC-induced hypothermia (Table 3). In this second series of body temperature experiments, flurazepam was administered immediately before THC. This was to ensure that, at the time of THC administration, the body temperatures of flurazepam- and saline-pretreated animals would be similar, it being known that flurazepam can itself produce hypothermia. A hypothermic dose of NO-328 found in pilot studies to be submaximal (data not shown) did not affect the hypothermic response to THC (Table 3).

TABLE 1

EFFECT OF PRETREATMENT WITH FLURAZEPAM (AT −30 MIN) OR NO-328 (AT −20 MIN) ON THC-INDUCED HYPOTHERMIA

Treatments					
Pretime Zero		Time Zero			
Drug	Dose (mg/kg)	Drug	Dose (mg/kg)	Mean Tro (°C ± s.e.)	Mean Temperature Response Index (°Chr ± s.e.)
FZ	3	THC	10	37.7 ± 0.3	6.4 ± 1.0
VEH	—	THC	10	37.9 ± 0.2	4.8 ± 0.8
NO-328	5	THC	10	36.2 ± 0.1*	4.8 ± 0.8
VEH	—	THC	10	37.8 ± 0.2	5.3 ± 1.7

FZ = flurazepam; VEH = drug vehicle; n = 6. Significance levels for differences between pairs of treatments have been determined by the Mann-Whitney U-test (*$p<0.01$).

Experiments With Pentylenetetrazole

Flurazepam significantly delayed the onset of pentylenetetrazole-induced convulsions when injected at doses of 3 or 10 mg/kg, the higher of these doses having the greater effect (Table 4). In contrast, neither THC nor CBD showed any detectable anticonvulsant activity, nor did either of these cannabinoids enhance the anticonvulsant effect of a submaximal dose of flurazepam (Table 4). The doses of flurazepam and THC used are known to interact synergistically in the production of catalepsy (19) and the dose of CBD used is within the range known to delay the onset of tonic (but not clonic) convulsions induced in mice

TABLE 2

EFFECT OF PRETREATMENT WITH FLURAZEPAM (AT −30 MIN) OR NO-328 (AT −15 MIN) ON THC-INDUCED ANTINOCICEPTION

Treatments					
Pretime Zero		Time Zero			
Drug	Dose (mg/kg)	Drug	Dose (mg/kg)	n	Mean Tail Flick Latency (s ± s.e.)
FZ	3	THC	5	6	3.4 ± 0.5
VEH	—	THC	5	6	3.0 ± 0.3
FZ	30	THC	5	6	2.0 ± 0.2
VEH	—	THC	5	6	2.7 ± 0.4
NO-328	5	THC	5	6	3.3 ± 0.6
VEH	—	THC	5	5	3.2 ± 0.4
—	—	THC	5	6	2.8 ± 0.2*†
—	—	Tween	10	6	2.2 ± 0.2

FZ = flurazepam; VEH = drug vehicle; n = number of mice used. Significance levels for differences between pairs of treatments have been determined by the Mann-Whitney U-test (*$p<0.05$). †Significantly less ($p<0.01$; Mann-Whitney U-test) than the mean tail flick latency following injection of 10 mg/kg THC (4.5 ± 0.5 s; n = 6).

TABLE 3

EFFECT OF PRETREATMENT WITH FLURAZEPAM (AT −10 S) OR NO-328 (AT −10 S) ON THC-INDUCED HYPOTHERMIA

Treatments						
Pretime Zero		Time Zero				
Drug	Dose (mg/kg)	Drug	Dose (mg/kg)	n	Mean Tr at Time Zero (°C ± s.e.)	Mean Temperature Response Index (°Chr ± s.e.)
FZ	3	THC	10	12	37.8 ± 0.1	6.5 ± 0.8
FZ	3	Tween	20	12	37.8 ± 0.1	2.4 ± 0.5
VEH	—	THC	10	12	37.9 ± 0.2	6.3 ± 1.1§
VEH	—	Tween	20	12	37.8 ± 0.1	1.0 ± 0.2
FZ	10	THC	10	12	37.8 ± 0.1	8.9 ± 0.8*
FZ	10	Tween	20	12	37.8 ± 0.1	3.0 ± 0.5
VEH	—	THC	10	12	37.9 ± 0.1	4.1 ± 0.5§
VEH	—	Tween	20	12	38.0 ± 0.1	1.1 ± 0.4
FZ	30	THC	10	12	37.7 ± 0.1	10.0 ± 0.4†
FZ	30	Tween	20	12	37.7 ± 0.2	3.5 ± 0.4§
VEH	—	THC	10	12	37.6 ± 0.2	3.9 ± 0.6§
VEH	—	Tween	20	12	37.9 ± 0.1	0.6 ± 0.2
NO-328	2.5	THC	10	6	37.6 ± 0.2	9.9 ± 0.8
NO-328	2.5	Tween	20	6	37.4 ± 0.2	4.3 ± 0.9‡
VEH	—	THC	10	6	37.5 ± 0.2	5.8 ± 1.0‡
VEH	—	Tween	20	6	37.5 ± 0.2	0.9 ± 0.5

FZ = Flurazepam; VEH = drug vehicle; n = number of mice used. The asterisks and dagger indicate that the interaction between the pretreatment drug and THC was more than additive [*$p<0.05$; †$p<0.01$; Mann-Whitney U-test applied to a procedure for multiway analysis (1)]. Significance levels for differences between VEH/Tween groups and groups receiving VEH/THC, FZ/Tween or NO-328/Tween have been determined by the Kruskal-Wallis test (‡$p<0.05$; §$p<0.01$).

TABLE 4

EFFECT OF THC AND CBD ON THE ANTICONVULSANT EFFECT OF FLURAZEPAM (FZ)

Treatments					
−30 min		Time Zero			
Drug	Dose (mg/kg)	Drug	Dose (mg/kg)	n	Convulsant Dose of PTZ (mg/kg ± s.e.)
VEH	—	—	—	6	45.1 ± 4.3
FZ	1	—	—	6	88.4 ± 17.3
FZ	3	—	—	6	119.8 ± 11.8*
FZ	10	—	—	6	148.9 ± 8.5†
FZ	3	THC	10	6	92.3 ± 13.8
FZ	3	Tween	20	6	105.3 ± 11.3
VEH	—	THC	10	6	46.9 ± 4.9
VEH	—	Tween	20	6	56.7 ± 6.5
FZ	3	CBD	300	6	92.7 ± 12.4
FZ	3	Tween	600	6	119.2 ± 15.5
VEH	—	CBD	300	5	44.8 ± 2.4
VEH	—	Tween	600	6	38.9 ± 2.9

PTZ = pentylenetetrazole; CBD = cannabidiol; VEH = vehicle; n = number of mice used. Convulsant dose of PTZ = 1000 rt/w where r = PTZ infusion rate (mg/s), t = infusion time needed to initiate a clonic seizure (s) and w = body weight (g). Significance levels for differences between pairs of treatments have been determined by the Mann-Whitney U-test. Significance levels for differences between the group receiving VEH only and the groups receiving FZ at doses of 1, 3 or 10 mg/kg have been determined by the Kruskal-Wallis test (*$p<0.05$; †$p<0.01$).

by pentylenetetrazole or electroshock (3).

In Vitro Experiments

As shown in Table 5, both THC and GABA reduced the amplitude of the electrically evoked twitch response in the guinea pig isolated whole ileum preparation. In vitro pretreatment with GABA attenuated its own inhibitory effect but not that of a submaximal dose of THC. It was also found that a concentration of delta-amino-n-valeric acid which significantly decreased the inhibitory effect of GABA did not antagonize the response to THC (Table 6). Contractions induced by GABA in the guinea pig ileum longitudinal muscle preparation were attenuated by THC in a concentration-related manner, the most prominent effect being a reduction in the maximal response to GABA (Fig. 1).

DISCUSSION

The results confirmed previous findings that THC is hypothermic and antinociceptive and that it can attenuate the electrically induced twitch response in guinea pig ileum (11, 15, 17, 21). The results also confirmed that flurazepam can enhance THC-induced hypothermia (12), albeit only at doses higher than those required to augment the cataleptic effect of THC. In contrast, the GABA uptake inhibitor, NO-328, had no effect on THC-induced hypothermia and, similar to flurazepam, failed to alter the degree of antinociception produced by THC. It is unlikely, therefore, that THC produces either of these responses by elevating GABA concentrations in the synapse, be it through

TABLE 5

EFFECT OF PRIOR IN VITRO EXPOSURE TO GABA ON THE ABILITY OF GABA AND THC TO ATTENUATE THE TWITCH RESPONSE EVOKED BY ELECTRICAL STIMULATION OF GUINEA PIG ISOLATED ILEUM

Treatment A		Treatment B			
Drug	Concentration (M)	Drug	Concentration (M)	n	Mean Maximum Attenuation of Twitch Response by Treatment B (% ± s.e.)
GABA	3×10^{-4}	GABA	3×10^{-6}	6	4.1 ± 1.1*
—	—	GABA	3×10^{-6}	6	14.0 ± 2.2
GABA	3×10^{-4}	THC	1×10^{-8}	5	37.0 ± 8.5
—	—	THC	1×10^{-8}	5	35.4 ± 8.5

Preparations were exposed to Treatment A for about 5 min, after which the organ baths were washed out with Krebs solution. Responses to GABA (Treatment B) were recorded twice in the same preparation, once 30 min before and once 50 to 60 min after exposure to Treatment A. The responses to Treatment B recorded before and after Treatment A were then compared. In the cannabinoid experiments, each preparation received only one addition of THC. This was made either to tissue exposed to Treatment A (GABA) 30 min earlier or to unpretreated tissue. The THC concentration used and the lower concentration of GABA were submaximal. Significance levels for differences between pairs of treatments have been determined by Student's *t*-test for unpaired (THC experiments) or paired data (*$p<0.01$). n = number of preparations used.

TABLE 6

EFFECT OF PRIOR IN VITRO EXPOSURE TO DELTA-AMINO-N-VALERIC ACID ON THE ABILITY OF GABA AND THC TO ATTENUATE THE TWITCH RESPONSE EVOKED BY ELECTRICAL STIMULATION OF GUINEA PIG ISOLATED ILEUM

Treatment A		Treatment B			Mean Maximum Attenuation of Twitch Response by Treatment B
Drug	Concentration (M)	Drug	Concentration (M)	n	(% ± s.e.)
DAVA	5×10^{-4}	GABA	3×10^{-6}	6	7.7 ± 1.3*
—	—	GABA	3×10^{-6}	6	16.9 ± 3.7
DAVA	5×10^{-4}	GABA	3×10^{-5}	6	32.5 ± 6.7*
—	—	GABA	3×10^{-5}	6	42.0 ± 5.6
DAVA	5×10^{-4}	THC	1×10^{-8}	7	41.1 ± 8.9
VEH	—	THC	1×10^{-8}	7	28.1 ± 6.3

VEH = vehicle; DAVA = delta-amino-n-valeric acid. n = number of preparations used. Preparations were exposed to THC once only, 5 min after the addition of DAVA or VEH. Responses to GABA were recorded twice in the same preparation, once at least 25 min before the addition of DAVA and once 5 min after. The pre- and post-DAVA responses were then compared. The concentrations of GABA and THC used were submaximal. Significance levels for differences between pairs of treatments have been determined by Student's *t*-test for paired (GABA experiments) or unpaired data (*$p<0.01$).

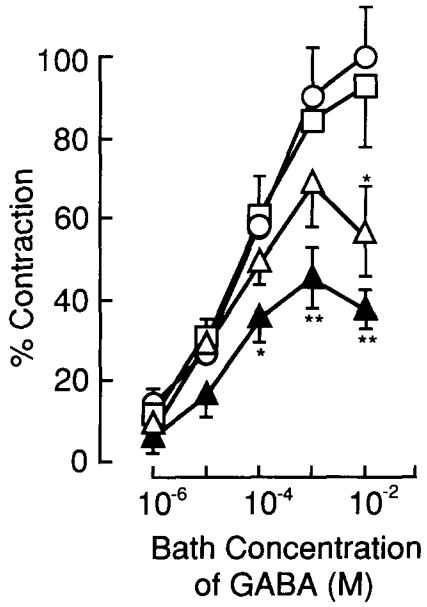

FIG. 1. Effect of THC on the contractile response to GABA of longitudinal muscle strips prepared from guinea pig ileum (mean ± s.e.). At least 20 min was allowed to elapse between each GABA addition. Each strip was used to construct two log concentration-response curves, the first in the absence (○) and the second in the presence of Tween (□) or in the presence of THC at bath concentrations of 1.25 nM (△) or 125 nM (▲). The bath was washed out after each addition of GABA. For the second series of GABA additions, the bath was replenished with THC or Tween after each washout. One dose of GABA was added 30 to 40 min after each addition of THC or Tween. The mean maximum contraction induced by GABA in the absence of THC or Tween has been taken as 100%. For each GABA concentration, reponses in the presence and absence of THC (n = 6) or Tween (n = 4) have been compared by Student's *t*-test for paired data (*$p<0.05$; **$p<0.01$).

effects on GABA release, uptake or metabolism. However, the possibility that THC-induced hypothermia and/or antinociception is mediated by GABA-releasing pathways cannot yet be excluded. Thus it could well be that THC produces these effects by increasing the response of GABA receptors to neuronally released GABA through an effect on the receptors' recognition sites or signal transduction pathways. Consistent with such a mechanism is the finding that THC can interact synergistically with GABA agonists in the production of catalepsy (19) and, against this mechanism, the observation that THC antagonizes GABA in the ileal longitudinal muscle preparation (see below).

It was found that the ability of flurazepam to delay the onset of clonic convulsions induced by pentylenetetrazole was unaffected either by THC or by CBD. These results contrast with those obtained previously by Koe et al. (9), who reported that the antipentylenetetrazole effect of diazepam could be enhanced by THC. The reasons for this difference remain to be elucidated. Nonetheless, it is worth noting that the dose of THC used in the earlier study was much higher than the one used by us. THC and CBD also failed to interact with pentylenetetrazole in the absence of flurazepam, and this finding is consistent with results obtained previously in other laboratories (3,9).

The in vitro experiments described in this paper confirmed that GABA can inhibit the electrically induced twitch response in the guinea pig ileum. This effect of GABA, thought to be mediated by prejunctional $GABA_B$ receptors (5,8), was attenuated by delta-amino-n-valeric acid, a $GABA_B$ receptor antagonist (13). However, the inhibitory effect of THC on the twitch response was affected neither by delta-amino-n-valeric acid nor by a GABA pretreatment known to render the ileum tolerant to GABA's inhibitory effect on the twitch response. Hence there is no evidence from the present study that THC inhibits the twitch response of the guinea pig ileum by acting through GABA receptors. At similar concentrations to those at which it inhibited electrically evoked ileal contractions, THC also attenuated contractions induced in ileal longitudinal muscle strips by GABA, which was presumably acting through prejunctional $GABA_A$ receptors (5). This finding is consistent with the ability of THC to inhibit ileal contractions induced at prejunctional sites by 5-hydroxytryptamine or electroshock (17,21) but conflicts with the cannabinoid's ability to interact synergistically with GABA agonists in the production of catalepsy (19). Clearly, further experiments are required to establish whether THC inhibits the contractile effect of GABA in ileal longitudinal muscle by interacting directly with prejunctional $GABA_A$ receptors or whether the cannabinoid acts elsewhere, for example, at some prejunctional site located "downstream" of these receptors.

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