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Prostaglandins and cannabis—XI
Inhibition of Δ^1-tetrahydrocannabinol-induced hypotension by aspirin

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Previous reports from our laboratory have indicated that Δ^1-tetrahydrocannabinol (Δ^1-THC), the psychoactive principle of marihuana, can exert a biphasic effect on prostaglandin synthesis in a variety of *in vitro* systems [1–3]. This has led to the hypothesis that at least some of the pharmacological actions of Δ^1-THC could be explained by a mechanism involving prostaglandins as important mediators [4]. Until recently there was little *in vivo* data to support this suggestion; however, we now have obtained evidence which implicates these substances as mediators in the hypotensive action of Δ^1-THC.

The dramatic lowering of mean arterial blood pressure in anesthetized dogs by Δ^1-THC has been described by a number of authors [5–8]. Several metabolites of arachidonic acid, in particular prostacyclin (PGI_2), have recently been discovered to be potent endogenous hypotensive agents. It seems likely, therefore, that the stimulation of PGI_2 production at the relevant tissue sites by a drug such as Δ^1-THC would result in a lowering of blood pressure following drug exposure. A widely accepted test for the involvement of prostaglandins in a particular response has been the inhibition of the effect by prior treatment with aspirin [9]. This apparently is due to the interaction of aspirin with cyclooxygenase, a key enzyme in the biosynthesis of all of the known prostaglandins. On this basis we carried out a set of experiments to determine whether the pretreatment of dogs with aspirin would reduce the hypotensive effect of Δ^1-THC.

Adult mongrel dogs (7–12 kg) were anesthetized with 30 mg/kg of sodium pentobarbital given intravenously and were maintained with small supplemental doses as needed. After tracheal intubation to provide a clear airway, polyethylene catheters were placed in the left jugular vein for the intravenous administration of drugs, in the abdominal aorta via the right femoral artery for the recording of arterial pressure, in the abdominal vena cava via the right femoral vein for the measurement of central venous pressure, and in a carotoid artery for collecting arterial blood samples for measurement of hematocrit. Arterial and venous pressures, lead II electrocardiogram and airway pressure (measured via a side-arm in the endotracheal cannula) were recorded simultaneously on an ink-writing oscillograph (Grass Instrument Co., Quincy, MA, model 7 Polygraph). In addition, rectal temperature was monitored, and body temperature was maintained at about 37.5°. The Δ^1-THC was obtained from the National Institute on Drug Abuse, and intravenous doses of 0.45 mg/kg were administered using 1% solutions in 95% ethanol. Aspirin (Aldrich Chemical Co., Milwaukee, WI) was given intravenously at a dose of 50 mg/kg in a 10% aqueous solution in which the pH was adjusted to 7.3 with sodium carbonate. Prior injection of the vehicle (0.045 ml/kg) had no measurable effect on the dogs.

All parameters were monitored for 40 min prior to the administration of Δ^1-THC and for at least 40 min following drug injection. The aspirin-treated dogs were monitored for 10 min prior to aspirin injection and for a 30-min interval before the Δ^1-THC was given; the aspirin had no significant effect on either heart rate or blood pressure. Hematocrit values remained within normal ranges in all cases.

The decrease in mean arterial blood pressure at various time intervals following the injection of Δ^1-THC is shown in Table 1. The second column contains the control values observed with a group of four dogs and compares well with the literature values obtained under similar conditions [5–8]. The third column shows the blood pressure decrements in a second group of four dogs who received aspirin 30 min prior to the Δ^1-THC. As can be seen from the data, aspirin exerted a pronounced inhibition of the hypotensive action of Δ^1-THC. The inhibitory effect was greatest initially and decreased as the subjects began to recover from the drug effect. Table 2 shows a similar pattern for the effects on heart rate.

The mechanism whereby aspirin is able to block the hypotensive action of Δ^1-THC can be speculated upon in the context of what is already known about the effects of Δ^1-THC on arachidonate metabolism [4]. Some years ago we reported that Δ^1-THC inhibited the synthesis of PGE_2 in a microsomal preparation [1, 2]. Subsequently, using whole cell models, we have observed a stimulation of prostaglandin synthesis [3] which we have determined to be due to an effect of the drug on phospholipase A_2, the enzyme responsible for releasing precursor arachidonic acid [10]. It seems reasonable, therefore, that at least part of the hypotensive response to Δ^1-THC is due to the release of arachidonic acid and its conversion to vasoactive metabolites. The aspirin inhibition is then explained by a reduction in the activity of the cyclooxygenase responsible for the synthesis of the vasoactive prostaglandins. It is interesting to note that a similar interaction between Δ^1-THC and aspirin (as well as other cyclooxygenase inhibitors) has been reported in a totally different model [11]. These authors found that the cataleptic effect of Δ^1-THC in mice could be reduced by prior injection of aspirin and that catalepsy could be restored by further injection of PGE_2.

In summary, we have demonstrated that the hypotensive effect of Δ^1-THC in pentobarbital-anesthetized dogs can be reduced significantly by prior injection of aspirin. A possible interpretation of these results is that Δ^1-THC is stimulating the production of a vasoactive substance such as prostacyclin and that the aspirin is blocking this stimulation by inhibiting its synthesis. These observations are in agreement with a sizeable body of *in vitro* data which we have reported on the effects of cannabinoids on prostaglandin synthesis.

Table 1. Inhibition of THC-induced hypotension by aspirin

Time* (min)	Decrease in mean arterial blood pressure ± S.D. (mm Hg) Δ^1-THC†	Aspirin‡-Δ^1-THC	% I§	P
5	38.5 ± 23	7.25 ± 4.6	81	< 0.0005
10	62.3 ± 22	17.5 ± 12	72	< 0.0005
15	71.8 + 23	27.8 ± 17	61	< 0.005
20	75.0 ± 18	38.5 ± 15	49	< 0.005
30	67.0 ± 13	42.5 ± 19	37	< 0.05
40	60.5 ± 14	39.3 ± 19	35	>0.05

* Post THC injection times.

† Intravenous dose of 0.45 mg/kg in 0.45 ml EtOH; N = 4.

‡ Intravenous dose of 50 mg/kg in 5 ml H_2O at pH 7.3, 30 min prior to THC; N = 4.

§ Percent inhibition of the hypotensive effect by aspirin.

Table 2. Inhibition of THC-induced bradycardia by aspirin

Time* (min)	Decrease in heart rate (beats/min)			
	Δ^1-THC†	Aspirin‡-Δ^1-THC	% I§	P
5	35 ± 23	16 ± 20	54	> 0.05
10	50 ± 26	26 ± 13	48	< 0.01
15	52 ± 24	39 ± 18	25	> 0.05
20	52 ± 24	34 ± 15	35	< 0.05
30	50 ± 21	25 ± 23 (N = 3)	50	> 0.05
40	48 ± 20	27 ± 29	44	> 0.05

* Post THC injection times.
† Intravenous dose of 0.45 mg/kg in 0.45 ml EtOH; N = 4.
‡ Intravenous dose of 50 mg/kg in 5 ml H_2O at pH 7.3, 30 min prior to THC; N = 4.
§ Percent inhibition of the bradycardia by aspirin.

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