**Influence of cannabis, tetrahydrocannabinol and pyrahexyl on the linguomandibular reflex of the dog**

SIR,—Reflex jaw opening to faradic stimulation of oral structures, particularly the tongue, was described by Cardot & Laugier (1922) among others. As the central pathway of this reflex includes the trigeminal system (Harrison & Corbin, 1942) which, in the rabbit, is sensitive to cannabis, tetrahydrocannabinol and pyrahexyl (Valle, Souza & Hyppolito, 1966), the influence of these agents upon the dog jaw jerk reflex was investigated.

Adult mongrel dogs of either sex weighing between 4·5 and 15 kg, were anaesthetized with pentobarbitone sodium (30 mg/kg i.p.). Jaw opening, arterial blood pressure and either respiration or foot movements after stimulation of the peroneus nerve, were registered on smoked kymographic paper. A glass cannula in the carotid or femoral artery was connected to a mercury manometer through rubber tubing filled with an 8% sodium citrate solution. Openings of the mandible and dorsal flexions of the hindpaw were recorded by means of a pneumatic device consisting of a large tambour as receptor and an adjustable tambour provided with a stylus. Respiration was recorded through a rubber pneumograph around the chest and connected to a tambour. The cut, central end of the lingual nerve at the level of the salivary duct was stimulated by monophasic shocks of 0·5 to 5 V, 2 msec duration at a frequency of 12/min. Drying of the nerve was prevented by immersing it in mineral oil. Water insoluble drug preparations were injected through a catheter inserted into a femoral vein as a fine suspension in polysorbate 80 plus saline or, preferably, as an emulsion in homologous blood plasma. The polysorbate control solution, even if slowly injected, produced a decrease of the arterial blood pressure accompanied by a slight improvement of the jaw jerk reflectivity. In practice it was only after tachyphylaxis to this vehicle had developed that the analysis of the drug preparations was made.

Cannabis crude resin (5 mg/kg), a fraction obtained from it by chromatography on alumina column (0·2–0·4 mg/kg), tetrahydrocannabinol (THC, 0·5 mg/kg) or pyrahexyl (1 mg/kg), all induced a prolonged fall of the arterial blood

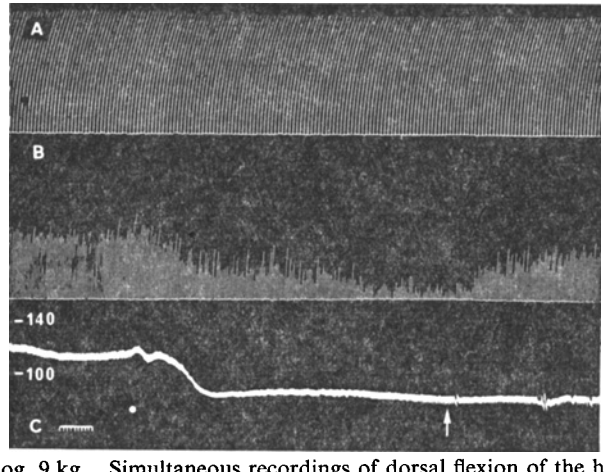


FIG. 1. Dog, 9 kg. Simultaneous recordings of dorsal flexion of the hindpaw (A), of mandibular opening (B), and of carotid blood pressure (C) in mm Hg. The linguomandibular reflex before complete abolition by cannabis crude resin was enhanced by strychnine. At (●) cannabis 5 mg/kg; at (↑) strychnine 50 μg/kg. Time marker: 10 sec.

TABLE 1. CHANGES (MEAN AND LIMITS %) OF DOG JAW-JERK REFLEX AFTER TETRAHYDROCANNABINOL (THC)*

| Agent | Number of animals | Time after intravenous injection (min) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 5 | 10 | 15 | 20 | 25 | 30 |
| Vehicle | 8 | 97·8 (125·7–64·7) | 104·6 (121·7–93·7) | 114·4 (153·2–83·7) | 106·4 (139·9–82·2) | 96·8 (118·5–79·8) | 95·3 (118·7–59·4) |
| 0·1 mg/kg THC | 3 | 92·6 (125·3–64·7) | 107·7 (123·9–91·0) | 104·4 (117·8–58·5) | 83·0 (149·2–80·4) | 70·3 (87·6–50·7) | 75·1 (118·6–38·7) |
| 0·2 ,, ,, | 4 | 82·9 (106·1–52·4) | 57·8 (79·4–32·5) | 38·7 (58·9–18·7) | 29·9 (53·1–5·8) | 24·0 (40·5–2·0) | 19·3 (35·0–0·4) |
| 0·4 ,, ,, | 4 | 61·0 (67·8–51·5) | 35·2 (53·5–25·7) | 19·6 (38·8–6·3) | 9·0 (25·2–0·9) | 5·2 (18·1–0·0) | 4·2 (16·4–0·0) |

* *Mean amplitude in mm of jaw openings, during 20 min before injection, taken as 100%.*

pressure, depressed the respiration, and decreased or abolished the linguomandibular reflex. No impairment of neuromuscular transmission was seen (Fig. 1). These results were observed even after atropine (0·1 mg/kg) or pyrilamine maleate (5 mg/kg). Chlorpromazine in saline, taken as a reference compound, provoked the same effects as THC at a comparable dose level. Mephenesin (20 mg/kg) also decreased the mandibular reflex without influencing the hindpaw flexions. It showed a low potency compared with that of THC.

A transient return of the reflex was seen by increasing the electric stimuli or through intravenous injection of strychnine (0·05–0·1 mg/kg).

The prolonged effect on the blood pressure and the jaw reflectivity precluded, as a rule, repeated injections of the active preparations in the same animal. This inconvenience was surmounted by injecting a single dose of 0·1, 0·2 or 0·4 mg/kg of THC in each dog of a group of at least 3 animals. Our results are in Table 1.

One may argue whether the decrease or disappearance of the mandibular response would really mean a direct action of cannabis derivatives upon the central nervous structures related to the reflex. The similarity of the action to that of chlorpromazine (0·5 mg/kg), with its depression of respiration and a prolonged fall of the blood pressure, the similar muscular relaxation to that induced by mephenesin (20 mg/kg), with increased depth of anaesthesia, and also, the return of the reflex after strychnine may be taken as signs of a central action of cannabis, THC and pyrahexyl. However, since chlorpromazine, besides having a central action, also blocks nerve conduction, as for example, shown with the afferent fibres to the spinal cord of the cat (Xavier & Timo-Iaria, 1964), the possibility must be entertained that those agents could derange the jaw jerk reflexly, either through a blocking action on a presynaptic level or directly via the synaptic transmission.

Eventual interaction of these agents with brain catecholamines was also investigated. No conclusive results upon the reflex were obtained after injecting adrenaline, noradrenaline and isoprenaline (1 $\mu$g/kg). Disappearance of the reflex still occurred, although delayed in some instances, when the animals were treated with reserpine (0·5 mg/kg s.c.) 24 hr previously.

Two synthetic derivatives of THC were studied by Dagirmanjian & Boyd (1962) who found dimethylheptylpyran (DMHP, 0·1 mg/kg) and octylmethylpyran (0·2–0·4 mg/kg) to abolish the cat linguomandibular reflex. We have also made some experiments on cats and noted that under our conditions no major difference between the two species was deduced about the level of doses of THC necessary to extinguish the jaw jerk reflex. If we admit that dogs and cats have comparable sensitivity of the linguomandibular reflex to these agents,

then the relation of potency of THC and DMHP would not differ much from unity. This is interesting because, according to Adams, Harfenist & Loewe (1949), by the approximation method on dogs, DMHP would have 70 times the potency of natural THC. Comparative assays with DMHP and THC in our experimental conditions are needed to check this.

In conclusion, abolition of the dog linguomandibular reflex as well as that of the rabbit corneo-palpebral reflex after cannabis, THC or pyrahexyl seem to indicate a marked depressant action of these agents upon the trigeminal nuclei or related structures, or both, through an unknown mechanism.

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**The influence of 5-hydroxytryptamine on the actions of adrenaline**

SIR,—Intravenous injection of adrenaline produces acute pulmonary oedema in several species of laboratory animals (Visscher, Haddy and Stephens, 1956). It has recently been shown that the simultaneous injection of 5-hydroxytryptamine (5-HT) and adrenaline in the rabbit and in the mouse reduces the intensity of the pulmonary oedema and significantly lowers the mortality rate (Uppal, Sen & Sanyal, 1967). We have now examined the effect of the simultaneous administration of 5-HT and adrenaline on the blood pressure of the rabbit and the dog, on the frog perfused heart, on the rabbit isolated ileum and on the blood sugar level of the rabbit.

The actions of adrenaline and 5-HT were additive except on the blood sugar level of the rabbit. Here the injections of adrenaline (1 mg per animal) caused a rise in the blood sugar level of 88–270 mg/100 ml, over fasting levels. Similar injections of 5-HT caused a rise of 5–25 mg/100 ml, only. When both the substances were administered together, the rise in the blood sugar level was 8–30 mg/100 ml.

The mechanism of the blockade by 5-HT of the hyperglycaemia induced by adrenaline is obscure. It has been suggested that a specific blocking action may be involved in interactions of 5-HT and catecholamines (Gyermek, 1961).

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