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Blocking action of tetrahydrocannabinol upon transmission in the trigeminal system of the cat

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The influence of tetrahydrocannabinol upon polysynaptic reflexes involving the trigeminal system was investigated in cats by recording potentials from either the superior sensory nucleus of the trigeminal nerve or the nerve itself where it enters the pons. Stimulation of the lower eye-lid just sufficient to evoke a mild contraction of the orbicularis muscle was employed. Amplitude of the postsynaptic potentials began to decrease 5 to 10 min after injection of 0·8 or 1·0 mg/kg in most experiments. The presynaptic potential also underwent a striking depression whereas the tibialis nerve potentials, used as control, were practically unaffected. It seems that impairment of the impulse conduction along the presynaptic fibres instead of a central synaptic blockade was the dominant effect of THC. However, a blockade of synaptic transmission is likely to occur in other centres accounting for other neural effects of THC.

THE assumption that the trigeminal system is involved in the central action of cannabis goes back to the original observation by Gayer (1928) that the drug abolishes the rabbit blink reflex (Valle, Souza & Hyppolito, 1966). Sampaio, Lapa & Valle (1967) have demonstrated that cannabis, tetrahydrocannabinol and pyrahexyl induce the disappearance in dogs of the mandibular jerk following electrical stimulation of the central end of the lingual nerve. Thus, the influence of cannabis upon the polysynaptic reflexes which encompass trigeminal nuclei, needs a detailed analysis of the site of action of tetrahydrocannabinol (THC), one of the active principles of *Cannabis sativa* L.

Experimental

MATERIAL AND METHODS

Nine adult cats weighing 2·5–3·5 kg were anaesthetized with sodium pentobarbitone intraperitoneally. Anaesthesia was kept light throughout the experiments.

Stimulation of the trigeminal afferents was through hook electrodes implanted in the conjunctiva of the lower eye-lid. Rectangular pulses of 0·01 msec duration, and intensity just sufficient to evoke a mild contraction of the orbicularis muscle, were delivered to the conjunctiva every 2 sec through an isolation unit. The potentials were recorded from either the superior sensory nucleus of the trigeminal nerve or the nerve itself where it enters the pons, by means of a stainless electrode thoroughly isolated except for the tip. The stereotaxic technique for angle implantation was used to place the active electrode; the reference electrode was attached to the skull. Recording was made through a conventional RC coupled amplifier and the potentials were photographed directly from the oscilloscope display for further analysis.

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When the results of the first experiments appeared to be consistent, the dorsal root potential evoked by single pulse stimulation of the tibialis posterior nerve was also recorded from two animals, so that conduction along the afferent trigeminal nerve could be compared with conduction in a peripheral pathway afferent to the spinal cord.

An ethanolic solution of THC (10 mg/ml) was diluted with polysorbate 80 and saline and the fine suspension slowly injected intravenously in doses of 0·4, 0·8 or 1·0 mg/kg. Higher doses of 1·6 mg/kg were sometimes given, and in control experiments the vehicle alone was given.

At the end of the experiment the animal was killed by an overdose of the anaesthetic and the head perfused with 10% formaldehyde. The electrode position was then checked by histology.

Results

The records from the sensory nucleus of the trigeminal nerve showed a postsynaptic focal potential after a latency ranging from 1·2 to 4 msec. The presynaptic potentials, as recorded from the fibres afferent to the nucleus, appeared 0·8 to 1 msec after stimulation. In some experiments both potentials could be simultaneously recorded (Fig. 1A) from within the nucleus.

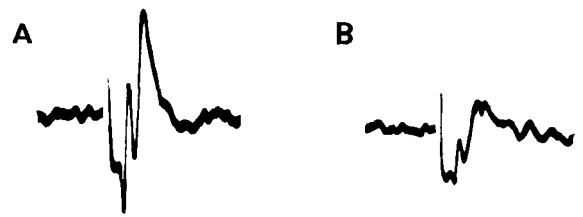

FIG. 1. Potentials recorded from the sensory nucleus of the trigeminal nerve. (A) Control, (B) Depression of the presynaptic and postsynaptic potentials 5 min after 0·8 mg/kg of THC being injected.

The amplitude of the postsynaptic potentials began to decrease 5 to 10 min after the injections of 0·8 or 1·0 mg/kg of THC in most experiments. Their latency did not change even under the influence of 1·6 mg/kg of the drug.

In preparations in which a second dose of THC greater than the first was administered, the depression of the potential provoked by the first dose was only slightly enhanced.

Fig. 1B shows the effect of 0·8 mg/kg of the THC on the amplitude of the pre- and postsynaptic potentials 5 min after the injection. The amplitude was strongly reduced whereas the latency remained unchanged. In Fig. 2 the changes of both pre- and postsynaptic potentials from another experiment are plotted as a function of time. Once again the time course of the depression of both potentials was identical, but the tibialis nerve action potentials were only slightly affected by the drug although the trigeminal potentials were reduced to a mere 5% 30 min after THC was administered.

In two experiments in which the potentials were recorded directly from the trigeminal nerve their reduction was comparable to the one observed in presynaptic intranuclear fibres.

Discussion

Although studies using microelectrodes should be done to establish if synaptic transmission is also impaired, our results indicate that failure to activate the trigeminal sensory nucleus, after administration of THC, may be attributed especially, if not exclusively, to a blocking action of the drug upon the impulse conduction along the presynaptic fibres. Such a depression was evident in all experiments in which afferent potentials were picked up. It might be thought that both nerve conduction and synaptic transmission were blocked. However, records showed increased latency of the postsynaptic focal potential, an effect which would certainly occur were a synaptic block also involved. Studying the effects of phenytoin on the spinal trigeminal nucleus, Fromm & Landgren (1963) found that this drug prevents transmission without interfering with the presynaptic conduction. A constant finding in their experiments was an increase in latency of discharge of the trigeminal neurons, as revealed by microelectrode recording.

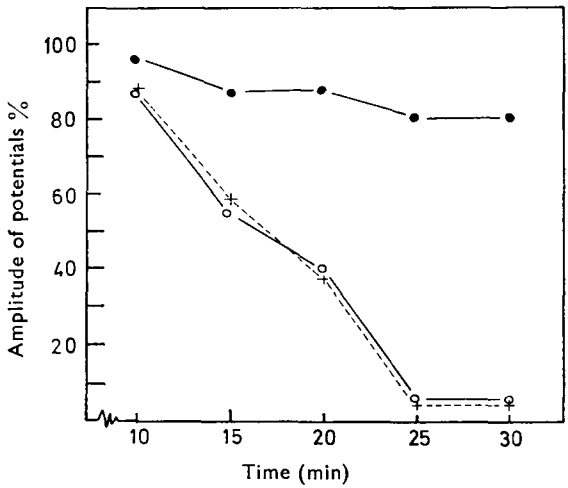

FIG. 2. Changes of the trigeminal nucleus potentials provoked by 1·0 mg/kg of THC. +, presynaptic potential. ○, postsynaptic potential.
The uppermost curve (●) represents the changes undergone by the dorsal root potential. Amplitude of the control potentials was considered as 100%.

In all cases THC provoked strong effects on the conduction by the trigeminal afferent fibres of the nerve impulse; whereas the tibialis nerve potentials were only mildly affected in the two preparations tested. This fact points to a selective action of THC. Such specificity seems to be usually overlooked when considering an explanation for the effects of psychotropic

drugs. Yet, a given drug may block conduction in one neural system and impair synaptic transmission in another. This might be so for certain central effects of THC itself. Xavier & Timo-Iaria (1963) observed that chlorpromazine transforms the polyphasic effects of stimulation of the midbrain reticular formation upon monosynaptic spinal reflexes into pure facilitation; whereas it depresses the reflexes when injected intravenously.

According with the findings of Boyd & Meritt (1965) with a THC derivative, several levels of the nervous system can be influenced by the drug. This point of view may explain other neural effects of the THC such as analgesia and respiratory depression (Valle, 1966).

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