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Some actions of Δ^1 tetrahydrocannabinol and cannabidiol at cholinergic junctions

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The effects of Δ^1-tetrahydrocannabinol (THC) and cannabidiol (CBD), two pharmacologically active constituents of cannabis resin, have been studied at several cholinergic sites.

THC reduced the twitch response of the transmurally stimulated ileum of the guinea-pig. At a concentration of THC of $1{\cdot}59\times10^{-7}$M, a 50% reduction in response was observed after 25 min exposure to the drug, whilst at a concentration of $3{\cdot}18\times10^{-6}$M the onset of inhibition occurred within 45 s and was complete in 5 minutes. In some of the experiments the THC inhibition could be partially overcome by repeated tetani, otherwise complete inhibition persisted for several hours after the THC was removed. This inhibition of the transmurally stimulated ileum by THC was not affected by pretreatment of the tissue with phentolamine and propranolol. In contrast to THC, CBD was without effect on the transmurally stimulated ileum at concentrations as high as $3{\cdot}18\times10^{-6}$ M.

In some experiments both THC and CBD reduced the response of the guinea-pig ileum to acetylcholine, both compounds being effective at a concentration of $3{\cdot}18\times10^{-7}$ M. These observations differ from the results reported by Gill, Paton & Pertwee (1970) who found that THC was either without effect, or potentiated the action of acetylcholine on the guinea-pig ileum. However this inhibitory action of both THC and CBD may be a general depressant one, as the response of the tissue to histamine was also reduced.

The effects of THC and CBD on the spontaneous release of acetylcholine from the guinea-pig ileum was also investigated. Both compounds reduced the output of acetylcholine; on this preparation CBD was more active than THC, a 15% reduction in acetylcholine output was produced by a concentration of CBD at 4×10^{-7}M compared with THC at $1{\cdot}75\times10^{-6}$M, and a 35% reduction by CBD at $1{\cdot}27\times10^{-6}$M, or THC at $1{\cdot}59\times10^{-5}$ M.

Neither THC nor CBD in concentrations up to $1{\cdot}59\times10^{-5}$M had any effect on the rat phrenic nerve diaphragm preparation, or on acetylcholine induced contractions of the frog rectus abdominis muscle. THC ($1{\cdot}59\times10^{-5}$ mol/kg) was given intraperitoneally to the anaesthetized cat and had no effect on the pre- or post-ganglionically stimulated nictitating membrane.

THC and CBD would therefore appear to be inactive at the cholinergic sites investigated other than at the postganglionic parasympathetic nerve ending.

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REFERENCE

GILL, E. W., PATON, W. D. M. & PERTWEE, R. G. (1970). Preliminary experiments on the chemistry and pharmacology of cannabis. *Nature, Lond.*, **228**, 134–136.

An anticurare effect of hexamethonium at the mammalian neuromuscular junction

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The effect of hexamethonium on blocked or partly blocked neuromuscular transmission has been investigated using the rat diaphragm-phrenic nerve preparation immersed in a saline medium (Liley, 1956) at 36° C.

In preparations in which the contractile responses to nerve stimulation had been reduced to about 20% after the addition of (+)-tubocurarine chloride(8×10^{-7}M) following the addition of hexamethonium ($2{\cdot}8\times10^{-4}$M) the contractions increased to about 40% of the unblocked control within 8 minutes. This partial reversal of the block due to (+)-tubocurarine was maintained until the hexamethonium was washed out.

Endplate potentials (e.p.p.s) were recorded from curarized preparations with an insulated wire electrode placed extracellularly at the endplate region, the indifferent electrode being placed in the bath away from the preparation. Following the addition of hexamethonium, the amplitude of the e.p.p. was increased. The extent of the increase depended on the concentration of hexamethonium; the maximum increase was to 480% of the control size and was obtained with 8×10^{-4}M hexamethonium. When higher concentrations of hexamethonium were applied to the curarized preparation, the increase of the amplitude of the e.p.p. was less. The enhancement of the amplitude of the e.p.p. was seen only after (+)-tubocurarine had been used to produce neuromuscular block; in preparations blocked by gallamine or Mg^{++}, the addition of hexamethonium always resulted in a decreased size of the e.p.p.

In curarized preparations there was no prolongation of the e.p.p. after the addition of hexamethonium, which suggests that this drug had no anticholinesterase action. Hexamethonium had no effect on the velocity of hydrolysis of acetylcholine by erythrocyte acetylcholinesterase.

The mean quantal content of the e.p.p. elicited at 1 Hz was 178 ± 13 (thirty-one cells) in the presence of (+)-tubocurarine, and 149 ± 12 (thirty-four cells) after the addition of hexamethonium at $2{\cdot}8\times10^{-4}$ M.

It is concluded that hexamethonium exhibits an anticurare effect by some postsynaptic action on the muscle cells.