Delta-9-tetrahydrocannabinol (THC) and macromolecular synthesis: mechanisms of action

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We have reported (Nahas, Desoize, Armand & Morishima, 1975) that in 10^{-5} to 10^{-4} M concentration, THC inhibits the incorporation of [^{3}H]-leucine, [^{3}H]-uridine and [^{3}H]-thymidine in cultured human lymphocytes stimulated with phytohemagglutinin (PHA). The present experiments were designed to clarify the mechanism of action of this depressant effect of THC on blastogenesis.

First, the time course of this effect of THC was studied. We observed that within 15 min after its addition, THC inhibited the incorporation of three precursors of protein, RNA and DNA: leucine, uridine and thymidine. This data indicates that THC does not exert its inhibitory effect specifically on the synthesis of a single macromolecule; such a type of specific inhibition is characterized by a lag in the synthesis of the macromolecules that are not primarily affected by the inhibition. In the present experiments, cell synthesis of all three macromolecules was inhibited at the same time.

In a second series of experiments we measured the effect of THC on uptake of leucine, uridine and thymidine into the intracellular pool. This uptake was significantly inhibited by the drug. This inhibition of precursor uptake in the cellular pool can explain the impairment of macromolecular synthesis.

Pool formation of precursors may be inhibited by three mechanisms which were next studied. Inhibition of transport enzymes, increased cellular 'leaking', or inhibition of ATP synthesis. Cellular 'leaking' was tested by incubating for 2 h lymphocytes with [^{14}C]-aminoisobutyric acid (a substance which is transported into the cell, but not incorporated into macromolecules); the cells were then washed, incubated for 30 min with THC and centrifuged; radioactivity was measured in the supernatant; it was not different from that obtained in control preparations. Effect of THC on cellular energy production was tested by: (a) measuring effect of THC on lymphocyte anaerobic glycolysis (glucose consumption and lactate production): it was not affected by the drug; (b) measuring cellular ATP concentration: there was no significant decrease compared with control cultures.

It would therefore appear that THC exerts its inhibitory effect on macromolecular synthesis to a greater extent by interfering with the transport enzymes of the plasma membrane. THC is known to bind on the plasma membrane (Chari-Bitron, 1971). At the level of the plasma membrane THC might act directly by altering its physico-chemical characteristics (Seeman, 1972). THC would therefore exert its inhibitory effect on cell anabolism during every stage of the cell cycle.

References

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Is the gastric antisecretory property of clonidine in rats of central origin?

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It seems now established that even though clonidine is ineffective (Boissier, Giudicelli, Larno & Fichelle, 1970) or even stimulates the gastric secretion of anaesthetized rats as it does in pentagastrin-stimulated Heidenhain pouch dogs (Curwain & Endersby, 1974), it possesses powerful gastric antisecretory properties in conscious rats (Walz & Van Zwieten, 1970) and in man (Kaess & Von Mikulicz-Radecki, 1971). This report describes the effects of clonidine in the 4 h-pylorus ligated rat and in basal or stimulated gastric secretion in chronic fistula rats in order to verify the hypothesis that this action is probably of central origin.

Dose response curves were established in male Sprague–Dawley rats (250–300 g) either by the 4 h-pylorus ligated Shay rat preparation or in 2 × 2 h basal secretion tests in chronic gastric fistula rats (Pascaud, Errard & Blouin, 1974), some of the latter bearing stereotaxically implanted micro-cannula in the lateral ventricle of the brain. On rats with gastric fistulae, the