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Biochemistry and Molecular Pharmacology

The Mechanism of Action of the Cannabinoids

Therapeutically Useful Cannabinoids

Interest in the cannabinoid acid metabolites of THC was revived recently by data we obtained showing that they exhibit some of the properties that are associated with nonsteroidal antiinflammatory agents (NSAIDs). The acids being non-psychoactive, were long thought to be without any biological actions of their own. In fact, our findings support the possibility that several effects believed to be due to THC may actually be mediated by the acid metabolites. In addition to helping explain the pharmacology of THC, our findings have suggested a route to the discovery of novel NSAIDs with minimal adverse side-effects, a much sought after goal of pharmaceutical research. Using THC-7-oic acid as a template molecule, we have designed and studied several dimethylheptyl side-chain analogs that show similar antiinflammatory properties, but at doses as low as 10 to 100 μ g/kg p.o. The most promising candidate has been named ajulemic acid which, in addition to its antiinflammatory actions, shows analgesic properties comparable to morphine in potency but devoid of the undesirable side effects. Ajulemic acid has recently been subjected by initial trials in humans based on its generally low toxicity in a variety of in vitro and animal models, and a Phase I trial where it showed no psychotropic activity. We have also found evidence for the existence of an endogenous cannabinoid acid, NAGly, that arises from the metabolism of anandamide, the endogenous THC. Like the THC acids, NAGly shows analgesic and anti-inflammatory activity.

AJULEMIC ACID

(1',1'-DIMETHYLHEPTYL-THC-7-OIC ACID)

