Cannabinoids as Therapeutics
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Cannabinoids and anxiety

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Introduction

As stated in Ethan Russo's chapter the first known reference to the use of *Cannabis for the relief of anxiety was about 1500 bce* in India. In modern times the 1860 *Report of the Ohio State Medical Committee on Cannabis indica* [1] stated:

> "As a calmative and hypnotic, in all forms of nervous inquietude and cerebral excitement, it will be found an invaluable agent, as it produces none of those functional derangement or sequences that render many of the more customary remedies objectionable."

Anxiolytic effects of CB_1 receptor antagonists

Musty [2] found that cannabidiol (CBD) inhibited the development of stress-induced ulcers in rats as compared with diazepam, which produced an equivalent reduction in the number of stress-induced ulcers. Guimaraes et al. [3] tested rats in the elevated-plus maze. In the test, rats are placed in a plus-shaped maze which is elevated above the floor. Two of the maze arms are enclosed with walls and two are not. Time spent in the enclosed arms is taken as a measure of anxiety or fear. Both CBD and diazepam decreased the amount of time spent in the enclosed arms. Since these studies were conducted, Petitet et al. [4] and Thomas et al. [5] have reported CBD is an antagonist of the CB_1 receptor in the micromolar range, suggesting that CBD may have pharmacological effects an antagonist of the CB_1 receptor.

Musty et al. [6] found that CBD increased licking for water in the lick-suppression test, which reliably discriminates between anxiolytic drugs and those that are non-anxiolytic. Equivalent effects were found with the classic anxiolytic drug diazepam. In an effort to find more potent effects, they tested two analogs, 2-pinyl-5-dimethylheptyl resorcinol (PR-DMH) and Mono-methyl cannabidiol (ME-CBD-2). PR-DMH had anxiolytic activity, but was less potent than CBD, while ME-CBD-2 had no anxiolytic properties. CBD also decreased conditioned taste aversion in a dose-related fashion (40 mg/kg gave the peak effect).