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Cannabinoids and Cytochrome P450 Interactions.

Zendulka O[1], Dovrtělová G, Nosková K, Turjap M, Šulcová A, Hanuš L, Juřica J.

Author information

Abstract

OBJECTIVE: This review consists of three parts, representing three different possibilities of interactions between cannabinoid receptor ligands of both exogenous and endogenous origin and cytochrome P450 enzymes (CYPs). The first part deals with cannabinoids as CYP substrates, the second summarizes current knowledge on the influence of various cannabinoids on the metabolic activity of CYP, and the third outline a possible involvement of the endocannabinoid system and cannabinoid ligands in the regulation of CYP liver activity.

METHODS: We performed a structured search of bibliographic and drug databases for peer-reviewed literature using focused review questions.

RESULTS: Biotransformation via a hydrolytic pathway is the major route of endocannabinoid metabolism and the deactivation of substrates is characteristic, in contrast to the minor oxidative pathway via CYP involved in the bioactivation reactions. Phytocannabinoids are extensively metabolized by CYPs. The enzymes CYP2C9, CYP2C19, and CYP3A4 catalyze most of their hydroxylations. Similarly, CYP represents a major metabolic pathway for both synthetic cannabinoids used therapeutically and drugs that are abused. In vitro experiments document the mostly CYP inhibitory activity of the major phytocannabinoids, with cannabidiol as the most potent inhibitor of many CYPs. The drug-drug interactions between cannabinoids and various drugs at the CYP level are reported, but their clinical relevance remains unclear. The direct activation/inhibition of nuclear receptors in the liver cells by cannabinoids may result in a change of CYP expression and activity. Finally, we hypothesize the interplay of central cannabinoid receptors with numerous nervous systems, resulting in a hormone-mediated signal towards nuclear receptors in hepatocytes.

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