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Tamoxifen and its derivatives bind to and act at cannabinoid receptors CB1 and CB2 with high affinity

Anna Radominska Pandya
University of Arkansas for Medical Sciences, USA

Tamoxifen (Tam) is classified as a selective estrogen receptor modulator and is chemotherapeutic agent for treatment of estrogen receptor (ER)-positive breast cancer, due to its ability to act as an ER antagonist. We have shown that Tam and its cytochrome P450-generated metabolite 4-hydroxy-Tam (4OH-Tam) also exhibit cytotoxic effects in ER-negative breast and pancreatic cancer cells. These observations suggest that Tam and 4OH-Tam can produce cytotoxicity via ER-independent mechanism(s) of action. Cannabinoids compounds have also been shown to exhibit anti-proliferative and apoptotic effects in ER-negative breast cancer cells, and estrogen can regulate expression levels of CBRs. This study investigated whether CBRs might serve as novel molecular targets for Tam and 4OH-Tam and we have shown that they bind to CB1 and CB2 with significant affinity. Furthermore, Tam and 4OH-Tam exhibit inverse activity at CB1 and CB2 in membrane preparations, reducing basal G-protein activity and also act as CB1/CB2R-inverse agonists regulating the downstream intracellular effector adenylyl cyclase in intact cells. These results suggest that CBRs are molecular targets for Tam and 4OH-Tam and may contribute to the ER-independent cytotoxic effects reported for these drugs. Therefore, we hypothesize that the cytotoxicity observed in these cells may be attributed in part to the binding of these drugs to CB1 and/or CB2 causing activation or suppression of downstream genes regulating cell proliferation. If our hypothesis is correct, CBRs could constitute a novel molecular target and structural scaffolds for which effective, non-toxic, natural and synthetic cannabinoids might be developed for treatment of various types of cancer.

Biography

Anna Radominska Pandya serves as a Professor in the Department of Biochemistry and Molecular Biology at UAMS. She is the Editor in Chief for Drug Metabolism Review. She received her PhD from the Institute of Biochemistry and Biophysics, Polish Academy of Sciences in Warsaw, Poland. She has published 175 papers in various peer-reviewed journals, and has received twelve R01 grants from the NIH and DoD. Her research interests include: The regulation and suppression of human UGTs and their role as anti-proliferative agents in cancer models, the interactions between UGTs and cannabinoid receptors, the delivery of *UGT* genes and drugs into cancer cells using nanomaterial, and the roles of UGTs in the biotransformation of drugs including resveratrols and drugs of abuse such as marijuana and synthetic cannabinoids.

radominskaanna@uams.edu

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