Ketoconazole potentiates terfenadine-induced apoptosis in human Hep G2 cells through inhibition of cytochrome p450 3A4 activity

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摘要

Abstract

Terfenadine (TF) is a highly potent histamine H1 receptor antagonist that in clinically effective doses is free of significant central nervous system side effects. Ketoconazole (KT) is a worldwide used oral antifungal agent with a broad spectrum of activity against both superficial and systemic mycosis. Simultaneously administration of KT and TF has been reported to induce several potent symptoms including cardiotoxicity, excitotoxicity, inhibition of blood mononuclear cells proliferation, and cardiovascular toxicity. However, the intracellular molecular mechanisms of TF-KT interactions in cells were still uncertain. In this study, we first demonstrated that TF (5-30 microM) induced apoptosis in several types of human cancer cell lines including human hepatoma (Hep G2), colorectal cancer (COLO 205), and fibroblast (CCD 922SK) cells for 24 h. The cellular responses to TF-induced apoptosis were demonstrated to be associated with the p53-signaling pathway, including induction of p53, p21/Cip1, p27/Kip1, bax protein expression and inhibition of bcl-2 protein expression. To realized the role of H1 receptor involved in TF-induced apoptosis, different H1 receptor antagonists including promethazine, mequitazine, and chlorpheniramin (50-100 microM) were administered and demonstrated that these chemicals cannot induced apoptosis through the H1 receptor signaling pathway. Interestingly, we found that the apoptotic effect of TF (2.5 microM) was significantly potentiated by KT (1 microM) treatment in Hep G2 cells through inhibition of the cytochrome p450 3A4 (CYP 3A4) activity. Such results were demonstrated by decreased of the TF activity with recombinant CYP 3A4, which prepared from baculovirus-infected insect cells. Our results provide the molecular basis of TF-KT interaction and this information should allow more rational forecasting of the risk for TF therapy during co-administration of KT. Copyright 2002

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