Cytoskeleton interruption in human hepatoma HepG2 cells induced by ketamine occurs possibly through suppression of calcium mobilization and mitochondrial function

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摘要

Abstract

Ketamine is an intravenous anesthetic agent often used for inducing and maintaining anesthesia. Cytoskeletons contribute to the regulation of hepatocyte activity of drug biotransformation. In this study, we attempted to evaluate the effects of ketamine on F-actin and microtubular cytoskeletons in human hepatoma HepG2 cells and its possible molecular mechanisms. Exposure of HepG2 cells to ketamine at <or=100 microM, which corresponds to clinically relevant concentrations for 1, 6, and 24 h, did not affect cell viability. Meanwhile, administration of therapeutic concentrations of ketamine obviously interrupted F-actin and microtubular cytoskeletons. In parallel, levels of intracellular calcium concentration- and time-dependently decreased after ketamine administration. Analysis by confocal microscopy further revealed that ketamine suppressed calcium mobilization from an extracellular buffer into HepG2 cells. Exposure to ketamine decreased cellular ATP levels. The mitochondrial membrane potential and complex I NADH dehydrogenase activity were both reduced after ketamine administration. Ketamine did not change the production of actin or microtubulin mRNA in HepG2 cells. Consequently, ketamine-caused cytoskeletal interruption led to suppression of CYP3A4 expression and its metabolizing activity. Therefore, this study shows that therapeutic concentrations of ketamine can disrupt F-actin and microtubular cytoskeletons possibly through suppression of intracellular calcium mobilization and cellular ATP synthesis due to down-regulation of the mitochondrial membrane potential and complex I enzyme activity. Such disruption of the cytoskeleton may lead to reductions in CYP3A4 activity in HepG2 cells.