Amphetamine activates connexin43 gene expression in cultured neonatal rat cardiomyocytes through JNK and AP-1 pathway

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摘要

Abstract

Objective: Amphetamine has been known to induce cardiac dysrhythmia and sudden death. However, the molecular mechanism for the induction of dysrhythmia is not known. Connexin43 (Cx43) plays an important role for arrhythmogenesis. This study was undertaken to test the hypothesis that amphetamine could induce Cx43 expression in cardiac myocytes. Methods: Neonatal Wistar rat cardiac myocytes were cultured under the stimulation of amphetamine. Cx43 mRNA and protein expression were examined by Northern and Western blots, respectively. We used c-Jun N-terminal kinase (JNK) inhibitor, SP600125, and JNK1 dsRNAi to investigate the signal pathway of amphetamine-induced expression of Cx43. Results: The level of Cx43 protein significantly increased from 4 to 24 h after addition of amphetamine (10 μM). The Cx43 mRNA increased maximally to 4.2-fold at 6 h after addition of amphetamine and returned to the baseline level at 48 h. These increases of Cx43 protein at 24 h were completely attenuated ($P<0.001$) by SP600125 (20 μM) and JNK1 dsRNAi. Amphetamine increased and SP600125 decreased the immunohistochemical labeling of Cx43. Amphetamine increased and SP600125 decreased the phosphorylated JNK and c-Jun proteins. Gel-shifting assay showed that DNA-binding activity of AP-1 increased after addition of amphetamine and SP600125 and JNK1 dsRNAi abolished the binding activity induced by amphetamine. Conclusions: These findings indicate that amphetamine activates Cx43 gene expression in cultured rat neonatal cardiac myocytes. Amphetamine mediates the Cx43 gene expression, at least in part, through the JNK pathway. These findings

from our study suggest that Cx43 plays a role for the molecular mechanism of amphetamine-induced cardiac dysrhythmias.