

Neuronal activity enhances aryl hydrocarbon receptor-mediated gene expression and dioxin neurotoxicity in cortical neurons

周志銘

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摘要.

Abstract

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor activated by dioxin and polyaromatic hydrocarbons. Recent studies have revealed that AhR activity in central neurons depends on the NMDA receptor. In this study, we investigated how the neuronal activity influence AhR-mediated dioxin-responsive gene expression and neurotoxicity. Our results show that activation of AhR by the selective agonist 2,3,7,8-tetrachlorodibenzo-p-dioxin induced dioxin-responsive gene expression and calcium entry, which were attenuated by AhR small interfering RNA, the NMDA receptor channel blocker MK801, and the action potential blocker tetrodotoxin (TTX). In addition, AhR-mediated gene expression was enhanced in neurons during synaptogenesis (10 days in vitro) compared with younger neurons (4 days in vitro), as was sensitivity to TTX and MK801. Furthermore, TTX and MK801 differentially affected the association of AhR and its transcriptional co-activator cAMP-responsive-element binding protein with the cytochrome P450 1A1 (cyp1A1) gene enhancer. Calcium/calmodulin-dependent protein kinase IV, the cAMP-responsive-element binding protein activating enzyme, was also activated by 2,3,7,8-tetrachlorodibenzo-p-dioxin in an activity-dependent manner. Finally, we found that neuronal susceptibility to dioxin insult was also maturation and activity-dependent. Together, the results suggest that neuronal activity may facilitate AhR-mediated calcium signaling, which in turn enhances AhR-mediated gene regulation and mediated maturation-dependent dioxin neurotoxicity.