Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

Immediate early gene c-Fos expression as a marker for neural activity in different transgenic mouse models

Autor: Boyi Yang
Institut / Klinik: Zentralinstitut für Seelische Gesundheit (ZI)
Doktorvater: Prof. Dr. P. Gass

It is well established that distinct expression patterns of the immediate early gene c-Fos in specific brain regions can be triggered by specific and unspecific inhibition of NMDA receptors. Here we investigated the pharmacology and activity induced c-Fos expression patterns in mice with genetically altered NMDA receptor and AMPA receptor mediated signalling. We selected (i) an animal model (*Grin2A*$^{S/S}$ mice) for the human mutation of the NMDA receptor subunit 2A, GRIN2A(N615K), which was identified in a young epileptic patient and (ii) a mouse line with gene targeted removal of the AMPA receptor associated protein Ckamp44 (*Ckamp44*$^{-/-}$). The detailed c-Fos expression analysis confirmed that MK-801 induced strong dis-inhibition of excitatory, hippocampal neurons in mice lacking the NMDA receptor subunit GluN2A. In contrast, we found only few c-Fos positive cells in the hippocampus of *Grin2A*$^{S/S}$ mice treated with MK-801 or after induction of audiogenic seizures. In other forebrain regions MK-801 induced c-Fos expression could be observed, and specific c-Fos induction was found in the amygdala and hypothalamus in *Grin2A*$^{S/S}$ mice that suffered from audiogenic seizures. Thus our data show that behavioural impairments and seizure susceptibility of *Grin2A*$^{S/S}$ mice are not due to a loss of function of the GluN2A(N596S) subunit containing NMDA receptors but most likely are mediated by the loss of voltage sensitivity of NMDA receptors of *Grin2A*$^{S/S}$ mice. The attenuated hippocampal c-Fos induction combined with the high efficiency of audiogenic seizures induction in *Grin2A*$^{S/S}$ mice suggest a sensitive, imbalanced excitatory/inhibitory system in *Grin2A*$^{S/S}$ mice that can be shifted to epileptic activity by activation of NMDA receptor mediated signalling. After seizures induction *Grin2A*$^{S/S}$ mice exhibited a very specific c-Fos induction pattern in the amygdala and hypothalamus, but not in the hippocampus. However, hippocampal c-Fos expression could be induced by kainic acid treatment, demonstrating that the c-Fos induction pathway is still operative on *Grin2A*$^{S/S}$ mice. In strong contrast to the *Grin2A*$^{S/S}$ mice, mice lacking the AMPA receptor associated protein Ckamp44 (*Ckamp44*$^{-/-}$ mice) showed a robust MK-801 induced c-Fos expression pattern similar to the pattern observed in *Grin2A*$^{-/-}$ mice. This suggests that in addition to the NMDA receptor, AMPA receptor plasticity can also modulate the inhibition of the central nervous system. A detailed analysis using brain regions and cell type specific manipulations of the NMDA and AMPA receptor signalling is necessary to dissect the molecular and cellular components that lead to the imbalance between the excitatory and inhibitory system in *Grin2A*$^{S/S}$ and *Ckamp44*$^{-/-}$ mice.