Glutamate and its PDZ-interaction: a role in experience-dependent behavioral plasticity in the forced swim test

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BACKGROUND

Although current pharmacological treatment for depression mainly targets the monoaminergic system, recent studies indicate that glutamatergic neurotransmission is also principally involved in the neuropathology of depression [1]. Importantly, pharmacological blockade of NMDA receptors (NMDARs) and mGluR5 (mGluR5) antagonists display antidepressant effects with rapid onset [2]. The antidepressant properties of ketamine require activation and synaptic incorporation of GluA1-containing AMPA receptors [3]. Moreover, hippocampal samples from clinically depressed patients display reduced mRNA levels for GluA1 [4]. These findings argue that GluA1-dependent synaptic plasticity might be critically involved in the development of depression [1,2].

This study aimed to test how GluA1-dependent plasticity contributes to the experience-dependent expression of depression-related behaviors by examining the use of GluA1 transgenic mice and targeted deletion of GluA1 in hippocampus.

METHODS

Transgenic expression of GluA1: In A11 mice a native GFG-GluA1 was expressed in the GluA1-knockout (GluA1−/−) background, while in TGR.1 the most C-terminal lesion of GFG-GluA1 was lacking, thereby blocking PDZ-interaction.

Virus-mediated deletion of GluA1: A Cre-recombinase expressing recombinant adeno-associated virus (rAAV) was stereotactically injected into the dorsal or ventral hippocampus of mice with flxed GluA1-alleles (GluA1−/−), thereby deleting GluA1 from all infected cells.

Forced swim test (FST): Mice were exposed to two sessions of forced swimming, 24-hours apart (FST1 [15 min] and FST2 [30 min] respectively). All behavioral assessment was fully computerized by custom-written software running in MATLAB. Latency to immobility and cumulative immobility were used as measures of behavioral despair.

RESULTS

Expression of GluA1 across the genotypes studied

DAPI immuno-stainings against GluA1 (top) or GFP (bottom) across various brain areas of adult mice showing that the GFP-GluA1 transgene in A11 and TGR.1 mice is strongly expressed in most forebrain areas including striatum (St), hippocampus (Hpc) and Cerebellum (Ct). Inserts illustrate β-galactosidase-activity (X-gal staining).

Hippocampal expression of GluA1 in virus injected mice

Representative images of GluA1-stained sections from dorsal (top) and ventral (bottom) hippocampus

Staining intensity was quantified relative to Cre-injected wild-type mice (WT-Cre). Quantification showed similair removal of GluA1, with significantly more GluA1 lacking in targeted areas (p<0.05).

Behavioral despair in GluA1 transgenic mice

Mice globally lacking GluA1 (GluA1−/−) and mice with blocked PDZ-interaction of GluA1 (GluA1−/− mice, N=9) are impaired in the experience dependent expression of behavioral despair in the forced swim test (FST), as shown by comparable latency to (left) and cumulative immobility (right) across sessions (FST vs FST2). Transgenic GFG-GluA1 expression in A11 mice (N=7) rescues this effect, as latency to immobility and cumulative immobility is reversed in these mice, as it is in wild type (WT, N=10) controls (p<0.05).

Behavioral despair in mice lacking hippocampal GluA1

Mice with selective deletion of GluA1 in dorsal (ΔHpc, N=6) or ventral (ΔHpc, N=13) are strongly impaired in the experience-dependent expression of behavioral despair, as shown by comparable levels of latency to immobility (left) and cumulative immobility (right) across sessions (FST vs FST2). In contrast, wild type mice injected with a Cre-expressing virus (WT-Cre, N=7) show normal reduction in latency to immobility and increased overall immobility (p<0.05).

CONCLUSIONS & OUTLOOK

Emerging drugs targeted at the glutamatergic system in the treatment of depression. Inhibition of NMDA-Rs and mGluR5 and activation of AMPA-Rs has antidepressive-like effects. Similarly, blocking the PDZ-interaction of proteins (e.g. GluA1, mNOS) in the glutamatergic postsynaptic density might exert comparable antidepressive-like effects.

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