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Persistent increase in ventral hippocampal long-term potentiation by juvenile stress: A role for astrocytic glutamine synthetase

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A traumatic childhood is among the most important risk factors for developing stress-related psychopathologies such as posttraumatic stress disorder or depression later in life. In rodents, it can be modeled by juvenile stress, resulting in increased anxiety and impaired coping with stressful challenges in adulthood.
In the current study, we found that juvenile stress led to a reduced synaptic efficacy, as indicated by decreased ratios of field excitatory postsynaptic potential slope to fiber volley amplitude at Schaffer collaterals in the ventral CA1. However, this was associated with increased long-term potentiation (LTP) of synaptic transmission after high-frequency stimulation.
Recent studies suggest that the active neurotransmission at excitatory terminals is maintained by the glutamate-glutamine cycle in astrocytes. We therefore tested whether these processes also guide the lasting changes on plasticity observed after juvenile stress by blocking a key enzyme, the astrocytic glutamate degrading enzyme glutamine synthetase (GS). Indeed, the pharmacological inhibition of GS by methionine sulfoximine in slices from naïve rats mimicked the effect of juvenile stress on vCA1-LTP. Supplying glutamine to overcome the GS deficiency normalized vCA1-LTP in slices from juvenile stressed rats to control levels. This functional GS deficiency was further paralleled by an allostatic reduction of GS mRNA expression levels in the ventral CA1 *Stratum radiatum* in rats with a history of juvenile stress.
Together, our results suggest a critical role for the astrocytic glutamine/glutamate cycle in mediating long-term effects of juvenile stress on plasticity in the ventral CA1, a region associated with anxiety and emotional memory processing.

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ATP, astrocytes and central respiratory control in the lamprey

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The paratrigeminal respiratory group (pTRG) is a brainstem region responsible for the respiratory rhythm generation in the lamprey, a lower vertebrate that has proved to be highly useful to demonstrate that the basic features of rhythmogenic networks have been conserved throughout vertebrate evolution. Experiments were

performed on the isolated brainstem of the adult lamprey to investigate the respiratory role of ATP and astrocytes. The vagal motor output was used to monitor respiratory activity. Bath application and microinjections (30-50 nl) of several drugs were employed. Bilateral microinjections of 1 mM ATP-γ-S, a nonhydrolyzable ATP analog, performed into the pTRG caused marked increases in respiratory frequency. Bath application of the P2 receptor antagonist PPADS (100 μM) did not alter respiratory activity, but prevented the increases in respiratory frequency in response to microinjections of ATP-γ-S into the pTRG. We investigated the possible involvement of astrocytes in the ATP-induced effects. The contribution of astrocytes to the modulation of the respiratory activity was ascertained by using the gliotoxin aminoadipic acid (AAA). Bath application of 1 mM AAA caused increases in the frequency and amplitude of vagal bursts followed by progressive decreases in both these respiratory variables and abolished the responses to ATP-γ-S microinjected into the pTRG, indicating that pTRG astrocytes play a key respiratory role. Consistently with the glial function of providing glutamine to neurons for glutamate synthesis, bath application of 5 mM glutamine (Gln) caused a rapid recovery of baseline respiratory variables. In addition, to ascertain whether ATP and astrocytes contribute to acidification-induced increases in respiratory activity the pH of the perfusing solution was reduced from 7.4 to 7.0. Marked low pH-induced increases in the respiratory motor output were still present after bath application of PPADS, but were completely abolished after AAA application. However, bath application of Gln in the presence of AAA restored the low pH-induced responses. The results show that astrocytes are involved in the modulation of respiratory activity and that their role is highly conserved throughout vertebrate evolution. The results also reveal the existence of a central, ATP-independent, pH sensitivity that requires astrocyte metabolic support.

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Impact of Connexine 30 overexpression on astroglial and neuronal networks

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Glial cells, and more importantly astrocytes play an important role in cognitive functions, behavior states and cerebral pathologies. They are indeed involved in brain information processing via the modulation of neuronal excitability, synaptic activity and plasticity [1]. A typical feature of astrocytes is their prominent interconnection via gap junction channels formed by connexins, i.e. connexin 30 (Cx30) and connexin 43 (Cx43), which provide direct electrical and metabolic coupling. Remarkably, Cx30 is expressed postnatally in the CNS and mostly by astrocytes, and not only controls the functional extent of astroglial networks, but also modulates synaptic transmission [2]. However, the impact of a temporally- and spatially-restricted modulation of astroglial connectivity on astroglial network and neuronal activity is yet unknown.
The aim of our study is to investigate the impact of increased Cx30 levels specifically in astrocytes on hippocampal synaptic efficacy.
For this purpose, we used stereotaxic injections of adeno-associated viruses (AAVs) to increase Cx30 in astrocytes from the CA1 hippocampal area of juvenile wild-type mice (P15). Using this strategy, we investigated the impact of Cx30 overexpression on the size of the astroglial network, cellular properties and on neuronal network compare to wild-type mice injected with AAV-GFAP-GFP as control. In particular, we show that injections with CX30- AAVs lead to : (1) the increase of the levels of Cx30 expression in hippocampus visualized by immunolabeling and western blot; (2) the increase of the size of astroglial networks, highlighted by dye coupling experiments with biocytin locally injected in one astrocyte and diffusing to connected astrocytes by gap junctions, (3) the change of astroglial and neuronal properties of pyramidal cells and parvalbumin (PV)