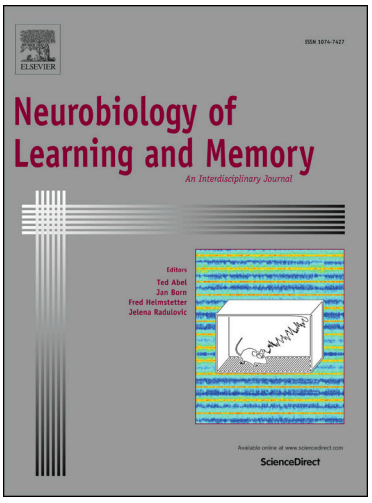

Metaplasticity at the addicted tetrapartite synapse: A common denominator of drug induced adaptations and potential treatment target for addiction

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Metaplasticity at the addicted tetrapartite synapse: A common denominator of drug induced adaptations and potential treatment target for addiction

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Abstract:
In light of the current worldwide addiction epidemic, the need for successful therapies is more urgent than ever. Although we made substantial progress in our basic understanding of addiction, reliable therapies are lacking. Since 40-60% of patients treated for substance use disorder return to active substance use within a year following treatment discharge, alleviating the vulnerability to relapse is regarded as the most promising avenue for addiction therapy. Preclinical addiction research often focuses on maladaptive synaptic plasticity within the reward pathway. However, drug induced neuroadaptations do not only lead to a strengthening of distinct drug associated cues and operant behaviors, but also seem to increase plasticity thresholds for environmental stimuli that are not associated with the drug. This form of higher order plasticity, or synaptic metaplasticity, is not expressed as a change in the efficacy of synaptic transmission but as a change in the direction or degree of plasticity induced by a distinct stimulation pattern. Experimental addiction research has demonstrated metaplasticity after exposure to multiple classes of addictive drugs. In this review we will focus on the concept of synaptic metaplasticity in the context of preclinical addiction research. We will take a closer look at the tetrapartite glutamatergic synapse and outline forms of metaplasticity that have been described at the addicted synapse. Finally we will discuss the different potential avenues for pharmacotherapies that target glutamatergic synaptic plasticity and metaplasticity. Here we will argue that aberrant metaplasticity renders the reward seeking circuitry more rigid and hence less able to adapt to changing environmental contingencies. An understanding of the molecular mechanisms that underlie this metaplasticity is crucial for the development of new strategies for addiction therapy. The correction of drug-induced metaplasticity could be used to support behavioral and pharmacotherapies for the treatment of addiction.

Key Words: Addiction, Nucleus Accumbens, Glutamate, tetrapartite synapse, synaptic plasticity, metaplasticity