The web of depression: heliacal rising of hippocampal dark matter

Sabine Spijker

Department of Molecular and Cellular Neuroscience, Center for Neurogenomics and Cognitive Research, Neuroscience Campus Amsterdam; s.spijker@vu.nl

Major depressive disorder (MDD) is a complex neuropsychiatric disorder that is characterized by persistent negative mood, a multifaceted anhedonic state, and impaired cognitive function. Here, we modeled sustained depression-associated memory deficits using the social defeat-induced persistent stress (SDPS) paradigm in rats. Importantly, these hippocampus-dependent cognitive deficits persist up to three months following a 5-day social defeat in rats. This depressed state is characterized by increased levels of extracellular matrix (ECM) proteins, which resides in perisynaptic places, number of perineuronal nets (PNNs), reduced maintenance of hippocampus CA1 long-term potentiation (LTP), and reduced inhibitory input to CA1 pyramidal cells. We show that only during the 7–9 weeks after the social defeat sessions, both the cognitive deficits and the increase in PNN and synaptic ECM occur. Both late treatment with the tricyclic antidepressant imipramine and with enriched housing as behavioral therapy normalized expression of ECM/PNN proteins, and rescued the hippocampal LTP deficit and cognitive impairments. Yet, although pair-housing from social defeat onwards was able to rescue the affective problems, the cognitive deficits remained, indicative of independency of these specific traits. Furthermore, we found that ECM proteins crucially limit synaptic plasticity and are the cause of cognitive impairments in our model as *in vivo* breakdown of CSPG-rich PNN proteins in the CA1 region three months after social defeat restored the impairments in PNN levels, LTP, inhibitory input and memory function. We propose a novel mechanism by which PNN-mediated hippocampal cognitive deficits develop during a state of enduring depression, and identify a new therapeutic entry point to overcome these.