Maladaptive plasticity induced by acute/chronic stress and glutamate-based drug treatment approaches

M. Popoli, Dept Pharmacol Biomolecular Sciences University of Milano, Milano Italy

Stressful life events represent a major risk factor for stress-related neuropsychiatric disorders. Neuroimaging studies have shown volumetric reduction and remodeling of neuroarchitecture in brain areas of psychiatric patients, while chronic stress models in rodents have consistently shown reduction of synaptic spines and atrophy/remodeling of dendrites, thus suggesting that stress-induced maladaptive changes have a primary role in psychopathology. Whereas the effects of chronic stress have been investigated at length in animal models, the short- and long-term consequences of acute stressors have been little or not investigated, although it has been shown that in some cases (e.g., PTSD) the first few hours after trauma are crucial for pathophysiological outcome and therapeutic intervention.

In recent studies on acute stress, we have dissected the destabilizing effects of stress in the excitatory Glu system. Acute inescapable stress rapidly enhanced depolarization-evoked Glu release/transmission in the prefrontal cortex (PFC), via a corticosterone (CORT)-mediated rapid (non-genomic) enhancement of trafficking of Glu synaptic vesicles for release, that was sustained for 24 h. Acute stress also dramatically increased the total number of excitatory synapses in PFC. Unexpectedly, significant atrophy of apical dendrites was observed at 24 h, and sustained for at least 14 days. Thus, a single exposure to stress had previously unsuspected long-term functional (Glu release) and structural (dendrite atrophy) consequences. Chronic treatment with traditional antidepressants and single administration of ketamine (10 mg/kg) blocked most of the maladaptive effects of acute stress.

We used the Chronic Mild Stress (CMS) protocol in young adult rats to look at the effects of chronic stress and to the antidepressant mechanism of ketamine. Rats were subjected to CMS for 5 weeks. Sucrose Preference Test (SPT) was used to distinguish stress-resilient (CMS-R) from vulnerable (CMS-V) rats. Ketamine (10 mg/kg) was acutely administered to CMS-V 24 hours before sacrifice. Glu release was measured from hippocampal purified synaptosomes in superfusion. Changes in BDNF mRNA levels were measured by qPCR. Dendritic trafficking of BDNF transcripts was analysed by in-situ hybridization in CA1 and CA3 regions of hippocampus (HPC). Dendritic morphology of CA3 pyramidal neurons was examined in Golgi-Cox stained sections.

SPT allowed to separate CMS-V (sucrose preference <55%) from CMS-R (>55%) rats. Acute ketamine was able to reverse anhedonic behavior in CMS-V. A decrease in basal and depolarization-evoked glutamate release was measured in HPC synaptosomes from CMS-V. Interestingly, ketamine restored basal, but not evoked, glutamate release in CMS-V. A significant reduction in total-BDNF and BDNF-6 splice variant was found in HPC of all CMS rats. Moreover, in situ hybridization studies found reduced dendritic trafficking of total-BDNF and BDNF-6 splice variant mRNAs in CA1 and CA3 of CMS-V. Ketamine treatment, although not reversing changes in BDNF mRNA levels, completely rescued dendritic trafficking in CA3 of CMS-V. Morphological

analysis of CA3 pyramidal neurons showed a reduction in total length and branching of apical (but not basal) dendrites. Ketamine restored these changes to control levels.

Our results from CMS study show that chronic exposure to mild stress induces alterations in Glu release, dendritic trafficking of BDNF transcripts and dendritic morphology in the HPC of vulnerable rats. Interestingly, a single administration of ketamine was able to reverse most of these deficits. Further investigation of the mechanisms underlying individual resilience or vulnerability to stress and fast ketamine antidepressant action could help to clarify the neurobiological underpinnings of depression and to identify new pharmacological targets for faster, more efficient antidepressant drugs.