Alterations in local protein synthesis are associated with cognitive impairment in chronically stressed rats

P. Brivio[1], F. Calabrese[1], M. Papp[2] and M. A. Riva[1]
[1]Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy
[2]Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland

Depression is a complex and heterogeneous disorder that represents a major cause of disability in the world.
With this respect, cognitive deterioration is a major problem that can interfere with all areas of a person's life, including work, school and their relationships.
On these bases, it is important to characterize cognitive dysfunctions within the context of a depressive phenotype in order to identify the underlying systems, which may represent an important target for drug intervention. To this aim, adult male Wistar rats were exposed to chronic mild stress (CMS), a well-established model of depression, for 7 weeks before being tested in the novel object recognition (NOR). The animals were then sacrificed immediately after the end of the test session for the molecular analyses.
The behavioral analysis shown that both the anhedonic and the resilient animals developed impairments in the cognitive performance as indicated by the reduction of the discrimination index in the NOR test.
At molecular level, we first investigated the activity-regulated genes (Arc) and the neural PAS domain 4 (Npas4) in the dorsal hippocampus and we found that their expression was markedly increased after the NOR, in control as well as in CMS rats. Among the mechanisms involved in the stress response but also in memory and cognitive functions, we decided to focus on the *de-novo* protein synthesis at synaptic levels.
We investigated the role of NMDA/mTOR activation as fundamental regulators of the initiation as well as of the elongation step.
We found that in the crude membrane fraction, the phosphorylation of the NMDA subunit GluN2B at the serine 1303 was significantly increased in control rats exposed to NOR, but not in CMS rats. Accordingly, pmTOR (Ser2448), a downstream target of the NMDA receptor, was similarly upregulated after the test in normal animals, but not in those exposed to the chronic stress.
Next, we measured one of the element involved in the protein synthesis, namely eukaryotic elongation factor 2 (eEF2) and we found an increase in the ratio of the peEF2/eEF2 after the NOR in control animals but not in those exposed to the CMS paradigm, suggesting a shift from the general translation to the translation of specific mRNA containing the upstream open reading frame (uORF).
We believe that the different modulation of these molecular players may contribute to the cognitive impairment observed in CMS rats. On these bases, pharmacological intervention able to correct these alterations might ameliorate functions that are deteriorated in patients with major depression and stress-related disorders.