FUNCTIONAL PROTEOMICS OF NEUROPLASTICITY-RELATED SIGNALING IN A RAT MODEL OF DEPRESSION WITH GENE-ENVIROMENT INTERACTION

Musazzi Laura[1], Roberto Giambelli[1,2], Daniela Tardito[1], Lucia Caffino[1], Aram El Khoury[3], Aleksander Mathé[3], Giorgio Racagni[1], Maurizio Popoli[1]

[1]Center of Neuropharmacology-Department of Pharmacological Sciences, University of Milano, Italy; [2]Department of Experimental and Clinical Pharmacology, School of Medicine, University of Catania, Catania (Italy); [3]Karolinska Institutet, Inst. of Clinical Neuroscience, Karolinska Hospital Huddinge, Stockholm (Sweden).

Depression is a heterogeneous group of brain disorders characterized by a wide range of symptoms that reflect alterations in cognitive, psychomotor and emotional processes. Genetic studies found no evidence of classic Mendelian inheritance for human depression, while an important influence of stress factors, such as early-life adverse events, has been shown to interact with a variable background of genetic vulnerability [1]. Therefore, we employed an innovative experimental design, attempting at reproducing the interaction between environmental adverse events and genetic susceptibility. We used the Flinders Sensitive Line (FSL) rats, a well-validated model of depression carrying genetic vulnerability associated to distinct features of pathology [2]. To reproduce early life stress events the FSL rats and their controls, the Flinders Resistant Line (FRL) rats, were subjected to a standard maternal separation (MS) protoco. Moreover, FSL and FRL rats, with or without early-life stress, were treated with escitalopram (ESC), a proserotonergic antidepressant. In these experimental groups, we studied the impact of MS and ESC treatment on behaviour (the Porsolt swim test was performed) and on the expression and activity of proteins involved in neuroplasticity and in antidepressant action. We studied Extracellular Regulated Kinases (Erk 1/2), αCalcium/CaM dependent Kinase II (αCaMKII), the transcription factor cAMP Response Element Binding protein (CREB) and the neurotrophic factor Brain Derived Neurotrophic Factor (BDNF). To this purpose, animals were sacrificed, prefrontal/frontal cortex (P/FC) and hippocampus (HC) were excised and we evaluated with Western Blot analysis expression and phosphorylation levels of the previous proteins in different subcellular fractions. Our results confirmed the relevance of the interaction between environmental adverse events and genetic susceptibility on both behavioural and molecular patterns. This experimental design superimposing early environmental adverse events on a genetic background of vulnerability allows for molecular studies in an animal model more thoroughly reproducing pathology. Our aim is to better characterize the molecular effectors of plasticity that mediate vulnerability to stress and response to antidepressant action.

This work is funded by EU-FP6 (GENDEP; contract no. LSHB-CT-2003-503428).

[1] Caspi A, Moffitt TE (2006) Nat. Rev. Neurosci., 7:583-590
[2] Overstreet DH, Friedman E, Mathé AA, Yadid G (2005) Neurosci. Biobehav. Rev., 29: 739-59