Redox dysregulation in psychiatric disorders: new biomarkers in animal models and human pathology

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Recent evidence have reported a key role of redox dysregulation, defined as a disequilibrium between oxidant generation and antioxidant response, in the pathogenesis of psychiatric disorders. Signs of redox dysregulation, such as decreased plasmatic levels of antioxidants, impaired function of antioxidant enzymes, increased levels of products of lipid peroxidation in plasma, cerebrospinal fluid and post-mortem brain sections have been found both in early and advanced phases of several mental diseases. Production of reactive oxygen species (ROS) by mitochondria is often thought to be the main cause of oxidative stress, but other sources of ROS are emerging, in particular the NADPH oxidase NOX enzymes, a family of membrane proteins with the sole known function to generate ROS. We have recently demonstrated a crucial role of NOX2 enzyme in the development of neuropathological alterations in rodent models of psychosis. In particular, we observed that, in rats exposed to the social isolation rearing protocol, a well established animal model of psychosis, NOX2-derived oxidative stress was rapidly increased in specific brain regions, such as the nucleus accumbens and the prefrontal cortex. However, the leading cause of NOX2 increase in the brain remained still unclear. To clarify this aspect and to identify early neuropathological alterations occurring in the brain before NOX2 elevations, we exposed rats to a short period of social isolation. Using microarray, immunohistochemistry and molecular biology techniques, we demonstrated that one week of social isolation caused an up-regulation of specific genes mainly involved in blood vessels morphogenesis, in the maintenance of blood brain barrier integrity (BBB) and in neuroinflammation pathways leading to BBB disruption. The expression of specific markers of BBB integrity and permeability was also significantly altered, suggesting that early BBB disruption preceded NOX2 elevations in the brain and might be its leading cause. A translational approach towards human psychiatric pathology was also performed. To this purpose, we investigated if NOX2 expression was increased in post-mortem brain samples of suicidal patients, with a clinical psychiatric anamnesis. We found that NOX2 expression was significantly increased in the cortex of suicidal patients with respect to control subjects. NOX2 elevations was mainly observed in neurons (in particular GABAergic and glutamatergic neurons) and in glial cells. Indirect markers of oxidative stress were also increased in suicidal patients with respect to controls.

These results will improve our understanding of the redox pathophysiology of the psychiatric disorders, entailing important medical impacts. Thus, identification of biomarkers of redox dysregulation might provide innovative diagnostic tools and will open new insights in the treatment concepts for mental diseases.