STRESS-INDUCED MODULATION OF THE OXIDATIVE BALANCE IN THE RAT BRAIN: EFFECT OF THE ANTIPSYCHOTIC LURASIDONE

Maria Serena Paladini[1], Andrea Carlo Rossetti[1], Vittoria Spero[1], Paola Brivio[1], Mariusz Papp[2], Francesca Calabrese[1], Marco Andrea Riva[1], Raffaella Molteni[1]

[1]Università degli Studi di Milan, Milan - Italy, [2]Institute of Pharmacology, Polish Academy of Sciences, Kracow - Poland

Background and aim: The biological mechanisms underlying the etiology of psychiatric disorders have not yet been elucidated. In this frame, dysfunctions in oxidative balance and energy metabolism have been suggested as major physiological features of these diseases. Indeed, selective neuronal subtypes marked by high-energy demands are particularly vulnerable to environmental risk factors, such as stress exposure. One intriguing aspect for stress vulnerability is represented by the "redox dysregulation," an imbalance between oxidative stress and antioxidant defense systems that may lead to oxidative stress-related neuronal damage. Thus, the aim of our study was to investigate the impact of chronic stress, a well-established preclinical model of psychiatric disorders, on redox homeostasis and to what extent such changes can be modulated by the treatment with the antipsychotic lurasidone.

Methods: In the first part of our study, adult male rats were subjected to the chronic stress paradigm for 7weeks. After 2weeks, both control and stress groups were further divided into matched subgroups to receive chronic administration of vehicle or lurasidone (3mg/kg/d) for the subsequent 5weeks. Moreover, to determine if persistent modifications can still be observed following recovery from chronic stress, in a second experiment after 4weeks of chronic stress and 3weeks of lurasidone (3mg/kg/d) treatment, animals were then left undisturbed for 3weeks. After recovery, the rats were exposed to a single acute episode of immobilization stress, to examine differences in the animal responsiveness to a challenging condition resulting from prior chronic stress exposure and drug treatment. Sucrose intake test was used to monitor the insurgence of stress-induced anhedonic-like phenotype whereas the molecular effects of our paradigm were evaluated using real-time RT-PCR and Western Blot.

Results: We reported that chronic stress was capable of up-regulating the pro-oxidant enzyme NADPH oxidase 2(NOX2) and reducing the nuclear factor-like 2(Nrf-2), a transcription factor that regulates the antioxidant defence. These alterations were normalized after the treatment with lurasidone that was also able to reduce the Kelch-like ECH-associated protein 1(KEAP1) which exerts a repressive control over Nrf-2. Moreover, we investigated the long-lasting impact of chronic stress on the acute-responsiveness: acute stress strongly induced the gene expression of Sulfiredoxin 1(Srxn1), one of the antioxidant genes downstream the transcriptional activity of Nrf-2. This beneficial effect carried out to cope with a sudden challenging situation is impaired by the previous exposure to chronic stress. Chronic lurasidone treatment partially restored the appropriate acute responsiveness.

Conclusions: Our results suggest that chronic stress-induced oxidative damage may represent a key mechanism contributing to the functional and structural impairments that feature psychiatric disorders. Indeed, alongside alterations in the levels of key mediators of the oxidative balance, chronic stress left a long-lasting signature, still present after 3weeks of recovery, and impaired the acute challenge-induced trigger of the antioxidant machinery. Moreover, we provide new insights on the mechanism of action of lurasidone, which can partially restore the redox homeostasis after stress exposure and may ameliorate specific functions that are deteriorated in psychiatric patients.