Stress-induced synaptic changes: modulation by lurasidone treatment

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Psychiatric diseases may often represent the consequence of exposure to stressful events at different stages of life. The psychopathological phenotype is characterized by structural and functional changes in different brain regions, which are associated with impaired synaptic function and reduced neuronal plasticity. With this respect, it is important to identify the changes brought about by stress exposure in order to establish to what extent treatment with psychotropic drugs may be able to normalize such alterations.

In our studies, we investigated neuroplastic and synaptic changes in two animal models of vulnerability to depression based on prolonged stress exposure during gestation (prenatal stress, PNS) or at adulthood (chronic mild stress, CMS). Moreover, we examined the ability of the novel multi-receptor antipsychotic drug lurasidone to normalize the alterations induced by stress exposure.

In the first paradigm, we investigated the postnatal developmental profile of Brain-Derived Neurotrophic Factor (BDNF) in the pups born from dams exposed to stress during the last week of gestation. PNS exposure reduced the levels of BDNF transcripts with the long 3'-UTR, which are specifically targeted to dendrites (An et al., 2008). These alterations became fully manifest at the transition between adolescence and early adulthood, and they were prevented by sub-chronic treatment for two weeks with lurasidone during adolescence (Luoni et al., 2014).

In the second paradigm, adult male rats were exposed to CMS for 2 weeks and sucrose consumption test was used to distinguish between susceptible and non-susceptible animals. After this period, control and CMS-susceptible rats were randomized to receive vehicle or lurasidone (3 mg/kg/day) for 5 more weeks, while continuing the stress procedure. We found that the pool of BDNF transcripts characterized by dendritic localization was persistently down-regulated after 7 weeks of stress, and that chronic lurasidone treatment was able to revert stress-induced anhedonia and to normalize BDNF mRNA levels in the prefrontal cortex of CMS rats. We also found that prolonged exposure to CMS produced synaptic deficits within the prefrontal cortex, as shown by reduced expression of PSD95, and alterations in two mechanisms that are important for synaptic homeostasis and protein translation, namely mTOR and eEF2 (Hoeffer and Klann, 2010). These alterations, which reproduce changes observed in depressed subjects, were also normalized by chronic treatment with lurasidone (Luoni et al., 2015).

Our results demonstrate that lurasidone shows antidepressant properties in the PNS model and in the CMS model and this may occur through the modulation of synaptic and neuroplastic proteins. The adaptive changes set in motion by chronic treatment with lurasidone may ameliorate functional capacities, closely associated with neuronal plasticity, which are deteriorated in patients with major depression and stress-related disorders.