Distinct effects of antidepressant treatment on anhedonia and inflammation in stressed rats

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Major depressive disorder is a common disease that represents a leading cause of disability in the world. It is thought to originate from the interaction between vulnerability genes and adverse environmental factors, such as stress to which an individual can be exposed in different moments of life (Caspi et al., 2003). One of themajor problem of depression is the relevant percentage of patients who do not show an adequate response to antidepressant therapy, as well as the high rate of relapse. Indeed, a growing body of evidence described and partially characterized dysfunction of multiple systems, including neurotransmitters, hormones, signaling pathways, neurotrophic and neuroplastic molecules. In addition, it is now well recognized a strong association of depression with alterations of immune/inflammatory system (Anisman, et al., 2008). In fact, elevated blood levels of the pro-inflammatory cytokines including interleukin (IL)-1ß, IL-6 and tumor necrosis factor (TNF)-α are commonly found in depressed patients and high comorbidity exists between depression and diseases characterized by inflammatory alterations (Connor and Leonard, 1998).
On these bases, the purpose of our study was to analyze the expression of several markers of the immune/inflammatory system in an animal model of depression in order to establish its relationship with the depressive phenotype as well as the involvement in the antidepressant response.
To this aim, adult male rats were exposed to a chronic mild stress (CMS) paradigm for 8 weeks and the cerebral mRNA levels of pro-inflammatory cytokines were evaluated. Moreover, a group of animals (sham or CMS) were chronically treated with the antidepressant imipramine (10 mg/kg/day starting from week 2), in order to evaluate the ability of the antidepressant treatment to interfere with potential inflammatory alterations.
We found that the expression of IL-1ß, IL-6, and TNF-α were significantly increased in the hippocampus of CMS rats. These changes were accompanied by a gradual decrease of sucrose consumption over the 8-week period, takes as an index of anhedonia. Moreover, chronic imipramine treatment was able to normalize the anhedonic phenotype caused by CMS, without affect the increased expression of inflammatory markers.
Our findings suggest that exposure to CMS is associated with significant alterations of the inflammatory response. Interestingly, while chronic antidepressant treatment can correct the 'anhedonic' phenotype of CMS rats, it fails to normalize the inflammatory alterations, meaning that anhedonia is not directly associated to inflammatory changes. In a translational prospective, this concept may be relevant for the presence of residual symptoms in humans that are associated with enhanced the risk of relapse or the lack of efficacy of antidepressant therapy.

Anisman, et al. 2008. Prog Neurobiol. 85 (1):1-74.
Caspi et al. 2003. Science. 301 (5631):386-9.
Connor and Leonard. 1998. Life Sci. 62 (7):583-606.