Antidepressant treatment restores stress-induced anhedonia and the associated activation of the inflammatory system in the rat brain

A.C. Rossetti[1], M.S. Paladini[1], G. Racagni[1], M. Papp[2], M.A. Riva[1] and R. Molteni[1]

[1] Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan (Italy);
[2] Institute of Pharmacology, Polish Academy of Sciences, Krakow (Poland).

It is well known that stress represents a crucial risk factor for the development or the exacerbation of major depression, however even if this disease occurs in a significant percentage of stress-exposed subjects, most of them are able to successfully cope with the adverse situation and avoid such psychopathology. Over the past decade, there has been increasing attention on the involvement of the immune/inflammatory system in the aetiology of depression (Dantzer, R. et al., 2008), however whether this system plays a pathogenic role in the insurgence of the disease or it represents a merely epiphenomena is still elusive. On these bases, the purpose of our study was to establish to what extent brain inflammation may contribute to the development and/or the maintenance of a pathological anhedonic phenotype and to evaluate the ability of pharmacological intervention in modulating such molecular changes.

To this aim, adult rats were exposed to a chronic mild stress (CMS) paradigm, a procedure known to induce an anhedonic phenotype (Papp, M. et al., 2012), for 2 and 7 weeks and the cerebral expression of several mediators of the immune/inflammatory system was assessed by real-time PCR in different brain regions in parallel with the evaluation of anhedonia. In addition, a separate cohort of rats were exposed to CMS for 7 weeks and chronically treated with the antidepressant drugs imipramine (10 mg/kg daily i.p.) or agomelatine (40 mg/kg daily i.p.).

We found major changes in the dorsal hippocampus, where the levels of the pro-inflammatory cytokines IL-1β and IL-6 were increased after 2 weeks of stress only in rats become anhedonic (+51% $p<0.01$ and % +27 $p<0.05$ vs CTRL) without changes in animals resilient to the stress procedure. A similar profile was observed for the mRNA levels of the marker of microglia activation CD11b (+50%, $p<0.05$ vs CTRL), conversely, the expression of the anti-inflammatory cytokine TGF-β was not affected by CMS. Interestingly, we also found that the modulation of the enzymes KMO and KATII, two key components of the kynurenine pathway, was different in stress-induced anhedonic animals in comparison to resilient rats. After longer exposure to CMS, both antidepressants were able to normalize not only the pathological phenotype but also to ameliorate the overall inflammatory changes observed at the molecular level.

These data suggest that the immune/inflammatory system may have a key role in the pathological consequence of stress exposure, thus contributing to the subject's vulnerability for depression, and support that this system may be used as therapeutic target for more effective antidepressant drugs.

References

1. DANTZER, R., O'CONNOR, J.C., FREUND, G.G., JOHNSON, R.W., KELLEY, K.W., 2008. *From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 9, 46-56.*

2. PAPP, M., 2012. *Models of affective illness: chronic mild stress in the rat. Curr Protoc Pharmacol Chapter 5, Unit 5 9*.

Word count: 414