Modulation of the inflammatory response after antidepressant treatment in rats

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Growing evidence suggests that alteration of the inflammatory/immune system contributes to the pathogenesis of major depression (Dantzer, 2008). For example, depressed patients exhibit increased levels of inflammatory markers in both periphery and brain and high co-morbidity exists between depression and diseases associated with inflammatory alterations. These observations have strong clinical implication. Indeed, although several antidepressant drugs are available on the market more than 30% of depressed patients fails to achieve remission, suggesting the necessity to identify systems/pathways that are useful to reveal novel neurobiological target for antidepressant medications.
Accordingly, aim of this study was to evaluate the ability of antidepressant treatment to modulate specific components of the immune response in the rat brain following a systemic inflammatory challenge with the cytokine-inducer lipopolysaccharide (LPS). It has been demonstrated that the effects of LPS administration in rats follow a precise temporal profile with an earlier 'sickness behaviour', which peaks in the first 2-6 h and a 'depressive-like behaviour', which became manifest 24 h later when sickness behaviour is diminished (Frenois et al., 2007). Therefore in our study rats pre-exposed to chronic antidepressant treatment and challenged with an acute injection of LPS were sacrificed 2, 6, or 24 h after the inflammatory challenge, in order to establish the ability of the antidepressant to interfere with the initial or the later phase of the inflammatory response. Real time PCR was used for gene expression analyses at central levels whereas ELISA was employed for protein analyses at plasma level.
Our results demonstrate that antidepressant treatment attenuates the inflammatory response induced by LPS injection. Specifically, we found a significant reduction of the LPS-induced up-regulation of pro-inflammatory cytokines in the brain as well as in periphery of antidepressant-treated rats. At central level, these effects appear to be associated to inhibition of NF-kB-driven transcription as well as alteration of mechanisms responsible for microglia activation. Specifically, chronic antidepressant treatment limits the LPS-induced up-regulation of CD11b, one of the most used markers for this cellular phenotype, with a parallel increase of CD68, suggesting the induction of active phagocytosis that might contribute to the anti-inflammatory effect. The attenuation of microglia activation involves neuron-glia cross-talk. Indeed, LPS reduced the expression of neuronal CX3CL1 thus leading to increased microglia activation, an effect normalized by the antidepressant. In addition, we found that antidepressant treatment was also able to alter basal and LPS-induced changes of the kynurenine pathway, which represents a point of convergence between inflammatory and neurotransmitter defects associated with depression (Molteni et al., 2013).
In summary, our results provide novel evidence on the ability of the antidepressant treatment to interfere with molecular systems involved in inflammatory response. Since, in a translational perspective, inflammation may contribute to the development of depression in a significant number of patients and may be responsible for residual symptoms that impair or limit clinical remission, the ability of antidepressants to modulate or interfere with immune/inflammatory system may represent an add-on value for their therapeutic activity.

Dantzer R. et al., Nat Rev Neurosci 2008; 9:46-56.

Frenois F. et al., Psychoneuroendocrinology 2007; 32:516-31.

Molteni R. et al., Eur Neuropsychopharmacol. 2013. [Epub ahead of print]