

***The stressed brain:
psychopathologic implications and pharmacological intervention***

March 3rd - 4th, 2016

Sala Napoleonica - Università degli Studi di Milano
Via S. Antonio 10 –Milano

ABSTRACT FORM

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| TITLE | Effect of the antidepressant agomelatine on the il-6 pathway in rats exposed to chronic mild stress: role of Suppressor Of Cytokine Signaling 3 (SOCS3) |
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| ABSTRACT (less than 500 words) | <p>Major depression (MD) is a debilitating disorder whose treatment is being challenged by the high rate of failure and relapse of the pathology. Among the molecular systems thought to be involved in the MD etiology and in the mechanism of action of antidepressant drugs, inflammation has emerged as an important actor (Miller and Raison, 2015). In particular, increased levels of pro-inflammatory cytokines have been observed in the plasma and cerebrospinal fluid of depressed patients and, among these inflammatory mediators, interleukin (IL-) 6 has been recently proposed to play a crucial role (Fonseka et al., 2015). IL-6 triggers a peculiar pathway comprising the JAK/STAT signaling proteins and characterized by a specific negative feedback loop exerted by the cytoplasmic protein, SOCS3 (Suppressor Of Cytokine Signalling-3).</p> <p>We have recently demonstrated that a chronic mild stress (CMS) paradigm able to induce a depressive-like phenotype, up-regulates the expression of different pro-inflammatory cytokines in the rat brain and that pharmacological treatment with the antidepressant agomelatine was able to normalize not only the pathologic phenotype but also the inflammatory state (Rossetti et al., 2015). In this context, the aim of the present work was to further investigate the mechanism underpinning the anti-inflammatory activity of agomelatine by evaluating the impact of the drug on IL-6 pathway in the prefrontal cortex of rats exposed to CMS.</p> <p>As expected, stress was able to activate the IL-6 cascade, including SOCS3 gene and protein expression and JAK1/STAT3 phosphorylation, without any suppressive effect of the feedback-loop inhibition. On the contrary, chronic treatment with agomelatine was able not only to normalize the stress-induced activation of IL-6 signaling, but also to modulate SOCS3 translation and transduction under basal conditions. Given the potentiality of IL-6 signaling as target of antidepressant treatment, we suggest that SOCS3 modulation might be a valuable goal for new drug development.</p> |

REFERENCES:

Miller AH, Raison CL - The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol.* 2015 Dec 29;16(1):22-34. doi: 10.1038/nri.2015.5.

Fonseka TM, McIntyre RS, Soczynska JK, Kennedy SH. - Novel investigational drugs targeting IL-6 signaling for the treatment of depression. *Expert Opin Investig Drugs.* 2015 Apr;24(4):459-75. doi: 10.1517/13543784.2014.998334. Epub 2015 Jan 14.

Rossetti AC, Papp M, Gruca P, Paladini MS, Racagni G, Riva MA, Molteni R. - Stress-induced anhedonia is associated with the activation of the inflammatory system in the rat brain: Restorative effect of pharmacological intervention. *Pharmacol Res.* 2015 Nov 1;103:1-12. doi: 10.1016/j.phrs.2015.10.022. [Epub ahead of print]