Effect of the antidepressant agomelatine on the IL6 pathway in rats exposed to chronic mild stress: role of suppressor of cytokine signaling 3 SOCS3

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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. 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).

We have recently demonstrated that a seven weeks lasting 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. In this scenario, the pharmacological treatment with the antidepressant agomelatine during the last 5 weeks of stress (daily i.p., 40mg/kg) was able to normalize not only the pathologic phenotype but also the inflammatory state (Rossetti et al 2015). With these premises, the aim of the present work was to further investigate the mechanisms 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. 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 SOCS3 on 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 induce SOCS3 transcription and translation under basal conditions. To better understand how agomelatine modulates IL-6 pathway, we deepened our analyses measuring the nuclear phosphorylation of STAT3 at Ser727, the activation of MAP-kinases, and STAT3-mediated gene expression of molecules involved in the control of apoptosis (i.e. Bcl-XL, Casp1, Casp3).

The results show that in both non-stressed and stressed animals agomelatine is inducing SOCS3 expression by different mechanisms, but with a common potential neuroprotective effect. Furthermore, given the potentiality of IL-6 signaling as target of antidepressant treatment and the key protective activity of agomelatine on this system, probably through SOCS3, this data suggest that SOCS3 modulation might be a valuable target for new drug development.

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