Role of inflammation in the etiopathogenesis of depression

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It is now well recognized that a disequilibrium in the integrate neuro-endorcrine-immune system may lead to depression. Among others, cytokines are key molecular messengers within this complex system that play an important role in maintaining the homeostasis. Indeed, a role for cytokines in the etiopathogenesis of depression is supported by the observation that pro-inflammatory cytokines appear to be increased in blood or brain of patients suffering from depression. Moreover, psychiatric symptoms may occur during conditions characterized by elevate levels of pro-inflammatory cytokines like during inflammation or in patients suffering from immune diseases. Finally, one of the strongest evidence supporting a causal role for inflammation, and increased levels of pro-inflammatory cytokines, in leading to depression comes from reports indicating that depressive symptoms frequently develop in patients undergoing immunotherapy with cytokines, such as interferon (IFN)-alpha (Hepgul et al., 2010).

It has been suggested that IFN-alpha may induce neuropsychiatric and/or neurodegenerative effects acting on the brain through different mechanisms, that include also unbalancing the tryptophan/kynurenine metabolism that may lead to production of neurotoxic metabolites. The products of the so called kynurenine pathway (KP) may elicit detrimental effects via glutamate neurotoxicity and/or formation of reactive oxygen species (ROS) and oxidative stress. However, even if neurons seem to be an important target in mediating behavioural IFN-alpha-induced changes, so far little is known about the molecular effects induced on these cells by exposure to this cytokine.

This prompted us to investigate the effects of IFN- alpha on the KP by using a *in vitro* model of human neurons (SH-SY5Y cells) extensively used for studying cellular and molecular events involved in neurotoxicity, neurodegeneration, or even neuroprotection. We also evaluated the IFN-alpha-induced effect on cell viability and number in these cells.

Our studies show that IFN-alpha exposure increased the expression of kynurenergic enzymes with an unbalance of the KP toward the synthesis of neurotoxic end-products. We also demonstrated that IFN-alpha exposure induces neurotoxic effects in a time and dose dependent manner by impairing mitochondrial integrity and activity, by recruiting Bcl-2 family members, and through induction of oxidative stress and apoptosis. Finally, we demonstrated that co-treatment with the antioxidant and mithocondrial modulator N-acetyl-cysteine (NAC), prevents IFN-alpha-induced neurotoxic effects (Alboni et al. 2013).

Together our results clearly enlighten the cytotoxic effects of IFN-alpha in this *in vitro* model of human neurons. Moreover, our findings provide further information on the molecular pathways involved in cytokine-induced effects in the brain and help clarify how these factors or pathways may eventually contribute to the pathogenesis of depression.

Hepgul N et al., (2010) Epidemiol Psichiatr Soc. 19:98-102.
Alboni S et al., (2013) Int J Neuropsychopharmacol. 16:1-17.