Neuroinflammation in chronic kidney disease: effect of indoxyl sulphate on glial cells

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Indoxyl sulphate (IS) is a protein-bound uremic toxin that results from the metabolism of dietary tryptophan and that accumulates in the blood of patients with impaired renal function, as chronic kidney disease (CKD).
High serum levels of IS in patients with CKD suggest its involvement in CKD progression and its presence in plasma is also a powerful predictor of overall and cardiovascular morbidity/mortality. IS is a well known nephrovascular toxin but very few is known regarding its effects on central nervous system (CNS) cells. Considering the growing interest in the field of neurodegenerative complications in CKD, we studied the effect of IS, on CNS cells, focusing our attention on inflammatory and oxidative stress pathway.
The effect of IS (15-60 μM) was evaluated on primary astrocytes and mixed glial cell cultures. Inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expression, tumor necrosis factor (TNF-Î±) and interleukin 6 (IL-6) release and nitrotyrosine formation were evaluated. In these experimental conditions IS significantly increased all pro-inflammatory parameters in primary astrocytes and to a greater extend in mixed glial cell cultures. Moreover, IS increased AhR expression and NF-kB nuclear translocation, both in primary astrocytes and in mixed glial cell cultures. In the same experimental conditions our results indicated also a significant and concentration-dependent increase in ROS production and a reduction of Nrf2 nuclear translocation and HO-1 expression. This effect was more evident in mixed glial cell cultures compared to primary astrocytes alone. It has been also observed that IS can IS also affected cell cycle distribution, increasing the G0/G1 and S phases and decreasing G2 phase in C6 cells and in astrocytes and in mixed glial cells.
NO, TNF-Î±, IL-6 release was also evaluated on serum samples of mice treated with IS (800 mg/kg). Our results shown that IS increased all pro-inflammatory parameters evaluated.
These results lead to the hypothesis of a significant contribution of IS in the clinically observed neurological complications in CKD.