Central neopterin production has anti-inflammatory activities

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Neopterin (Neo), an endogenous pteridine, is considered an early and sensitive inflammatory biomarker and it is found at increased levels in cerebrospinal fluid (CSF) and plasma of patients with neurodegenerative diseases. Several studies have suggested that inflammasome activation is a key determinant in the pathogenesis of neuroinflammatory conditions. Inflammasomes are macromolecular protein complexes responsible for the activation of the pro-inflammatory cytokines IL-1β and IL-18 via caspase-1 cleavage, and mitochondrial ROS have been suggested to trigger this process. Considering that CSF neopterin may not correlate with plasma neopterin levels and that our research group recently showed that Neo significantly increases the resistance to oxidative stress in the mouse brain, we evaluated the potential central neopterin production and whether Neo could also exert anti-inflammatory effects *in vitro*. Therefore, we evaluated neopterin and inflammasome markers in LPS-exposed mice plasma and hippocampus by RT-PCR and/or Western Blot. In addition, we pre-conditioned human primary astrocytes to Neo (0-500 nM) followed by a 48h co-exposure to Neo and LPS (5µg/mL). Cell supernatant was collected to quantify IL-1β, TNF-α; and IL-6 secretion by ELISA. Increased neopterin and IL-1β; levels were rapidly observed in plasma and hippocampus (5-30 minutes) from Swiss mice subjected to acute neuroinflammation induced by lipopolysaccharide (LPS) intraperitoneal administration (0,33mg/kg; i.p.). The increased hippocampal neopterin occurred in parallel with inflammasome activation,

evidenced by increased activated caspase-1 content. We observed that neopterin pretreatment (50nM) inhibited the LPS-induced IL-1β; secretion, but did not affected the inflammasome-independent cytokines, TNF-α and IL-6, suggesting that Neo may attenuate inflammasome activation *in vitro*. In conclusion, neopterin appears to be rapidly produced in the brain after a systemic inflammatory stimulus supporting therefore a central production. In addition, Neo conditioning may exert anti-inflammatory effects in vitro. Thus, it could be proposed that Neo released during inflammatory process might represent a protective strategy of non-immune cells.

Keywords: neopterin; inflammasome; central nervous system