PERSPECTIVE

Evidence for using a dual COX 1/2 and 5-LOX inhibitor in neurodegenerative diseases

A complex network of factors contributes to neuroinflammation, such as infections, brain injuries and accumulation of toxic metabolites (Gendelman, 2002). Eicosanoids and several cytokines are the main mediators of inflammatory process; in fact, when an inflammatory condition persists, it can be responsible for the progression of degenerative diseases, such as multiple sclerosis (MS), Parkinson's disease (PD) and Alzheimer's disease (AD) (Lucin and Wyss-Coray, 2009). Toll like receptors (TLRs) activation leads to the recruitment of microglial cells during neuroinflammation, thus contributing to the release of pro-inflammatory cytokines such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, IL-6, and chemokines (Donnelly and Popovich, 2008). Other mediators regulate inflammation, including transcriptional factors as nuclear factor-kappa B (NF-κB), and enzymes, such as 5-lipoxygenase (5-LOX), and cyclooxygenase 2 (COX-2) (Aggarwal, 2004). Both COX-2 and 5-LOX enzymes synthesize eicosanoids, prostaglandins and leukotriens from arachidonic acid. COX-2 seems to be an important brain plasticity regulator, but its increased expression in neurons may contribute to the progression of brain damage, also rising NF-κB expression (D'Acquisto et al., 1997). 5-LOX enzyme plays a key role in producing leukotrienes and it is expressed in different cells, including neurons (Lammers et al., 1996). Leukotrienes production may be detrimental in nerve cells: they have a high affinity with membranes, thus causing lipid peroxidation and neurodegeneration. Most of the non steroidal anti inflammatory drugs (NSAIDs) used in the clinical practice are not selective for COX-1 and COX-2 and may cause side effects, such as gastrointestinal lesions. In particular, the side effects are related to COX-1 inhibition, whereas the anti-inflammatory effects are due to the COX-2 inhibition. Pharmacological inhibition or downregulation of 5-LOX reduces leukotrienes production and may ameliorate neuroinflammatory processes. Based on these evidences, targeting COX 1-2 and 5-LOX enzymes together might be effective for the treatment of the neurodegenerative diseases characterized by inflammation. Flavocoxid is an anti-inflammatory molecule, consisting of the flavonoids baicalin and catechin; its mechanism of action is based on the double inhibition of COX 1-2 and 5-LOX enzyme as well (Bitto et al., 2014). Flavonoids are known as potent antioxidants: they may modulate the oxidative production of arachidonic acid from phospholipids, reducing lipid peroxidation mechanisms and inflammatory pathways activation. Flavocoxid decreases inflammatory processes not only by COX 1-2 and LOX inhibition, but also reducing pro-inflammatory cytokines produced by NF-κB induction. Various papers have been published showing the anti-inflammatory effects of flavocoxid in different experimental models, and last but not least in an Alzheimer transgenic model (Bitto et al., 2017). AD is characterized by the deposit of extracellular β-amyloid (Aβ plaques) and accumulation of hyperphosphorylated tau protein. Furthermore, inflammation in association with oxidative stress promote neurodegenerative process in AD, worsening the prognosis of the disease. It has been demonstrated that eicosanoids, as COX 1-2 and 5-LOX products, may contribute to Aβ plaques deposition, and Aβ triggers NF-κB activation with consequent release of pro-inflammatory cytokines. Aβ plaques act as damage-associated molecular patterns (DAMPs) and activate nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome (Tan et al., 2013). NLRP3 activation leads to increased IL-1β and Caspase-1 release, contributing to inflammation and cell death modulation in AD. Flavocoxid is able to reduce the main molecular AD hallmarks, such as phosphorylated amyloid precursor protein (APP) (Thr668) and Tau (Thr181), decreased inflammatory and apoptotic markers, through both NLRP3 and COX-2 and 5-LOX inhibition. Dual COX/5-LOX inhibition, by using flavocoxid, also prevented glutamate excitotoxicity in a kainic acid-induced excitotoxic brain damage (Minutoli et al., 2015). Kainic acid (KA) is an analog of glutamic acid and when administered is able to cause acute and chronic brain damage. Also in this model, the administration of flavocoxid blunted brain damage following KA injection in rats, decreasing pro-inflammatory cytokines and all the markers related to COX and LOX activation. These results let hypothesize that flavocoxid might be used for the treatment of other neurodegenerative diseases, where inflammation plays a key role and might be detrimental for their progression. Among these, for example, traumatic brain injury (TBI), spinal cord injury (SCI) and PD, are neurodegenerative diseases

characterized by oxidative stress, inflammation, and neuronal loss. Also in these diseases, pro-inflammatory processes are mediated by the activation of TLRs, and, in particular, TLR4 is involved in promoting neuronal death and demyelination. Moreover, previous studies have demonstrated that NF-κB is highly expressed in SCI, TBI and PD, and a correlation between TBI and PD could be possible (Bower et al., 2003). Increased NF-κB activation may be also accompanied by an improvement of COX-2 expression. Augmented COX-2 expression has been found in the substantia nigra pars compacta in post-mortem brains of PD patients (Przedborski, 2007), thus confirming the role of COX iperactivation in neurodisorders. These evidences suggest that blocking eicosanoids overproduction is a rational approach for the management of several neurodegenerative conditions, including TBI, SCI and PD.

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Open peer review report:
Reviewer: Maria E. Figueiredo-Pereira, Hunter College, USA.
Comments to author: This is an important and well written manuscript that summarizes the role played by COX-1/2 and 5-LOX in neurodegenerative diseases associated with neuroinflammation. In addition, it rationalizes the use of the anti-inflammatory drug flavocoxid as an effective therapeutic to prevent/treat these diseases, as it inhibits COX-1/2 and 5-LOX.

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