Non-steroidal anti-inflammatory drugs (NSAIDs) and neuroprotection in the elderly: a view from the mitochondria

The most important risk factor for stroke and neurodegeneration is aging. In fact, survival after stroke diminishes largely with aging. In fact, recovery after brain artery occlusion is dramatically worsened by aging, even normal aging is associated with neuron damage and cognitive decline. Mechanisms involved in aging-related, cognitive decline and susceptibility to neuron damage in stroke and neurodegeneration are largely unknown. One of the most important mechanisms contributing to neural dysfunction and death is excitotoxicity. This process is based on the fact that the excessive glutamate receptor stimulation may lead to neuronal damage. This overstimulation may be due to increased concentration of glutamate, or the prolonged activation of receptors.

Protecting the aging brain against damage remains a big challenge for neurologists and neuroscientists. Interestingly, a large number of basic and clinical studies have provided strong evidence indicating that the prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the incidence of Alzheimer’s disease (AD) (Wang et al., 2015), the most common form of dementia. NSAIDs also decreased glutamate excitotoxicity both in vitro, in rat primary neuronal cultures and hippocampal slices (Grilli et al., 1996), and in vivo, protecting rats against rotenone-induced parkinsonism (Madathil et al., 2013). Recent evidence suggests also that NSAIDs may even protect against the cognitive decline associated to healthy aging in humans (Kern et al., 2012).

NSAIDs present antipyretic, anti-inflammatory and analgesic effects. Therefore, they are mainly used to relieve pain, fever and inflammation. Their best characterized action is inhibition of cyclooxygenase (COX), and thus the synthesis of prostaglandins, which participate in the inflammatory response. NSAIDs can be non-selective COX inhibitors such as aspirin, ibuprofen, indomethacin or sulindac; or selective COX-2 inhibitors, such as rofecoxib and celecoxib. The action mechanism of neuroprotection by NSAIDs is unknown, but reports suggest that it is not related to the classic anti-inflammatory activity of these drugs. It is widely accepted that neuronal excitotoxicity induced by glutamate is mainly caused by one kind of ionotropic glutamate receptor, the N-methyl-D-aspartate receptor (NMDAR), probably because of its high permeability to Ca$^{2+}$. The combination of different subunits constitutes NMDARs: The NR1 subunit, is ubiquitous and essential whereas the NR2 subunit, is a regulatory subunit (NR2A - NR2D). A functional NMDA receptor requires the binding of two NR1 subunits with two other NR2 subunits or with the combination of a NR2 and NR3 subunits. In normal synaptic transmission, the NMDAR, blocked by the Mg$^{2+}$ located in the channel, is activated for short periods of time. However, in pathological conditions, like the prolonged depolarization that takes place in ischemic events, during which Mg$^{2+}$ is fully removed from its binding site at the NMDARs, an overly activation of the receptor causes excessive Ca$^{2+}$ entry through the channel. This Ca$^{2+}$ entry, together with the Ca$^{2+}$ released from the intracellular stores, increases the cytosolic free Ca$^{2+}$ concentration to levels that exceed the capacity of the intracellular Ca$^{2+}$ clearing mechanisms and pumps leading to mitochondrial Ca$^{2+}$ overload. This may cause impaired metabolism and certain processes that trigger cell death such as the one in the neurodegenerative disorders (Pivovarova et al., 2004).

We have reported that oligomers, but not fibrils, of the amyloid β peptide 1–42 (Aβ1–42), the most likely toxin in AD, induce also a sustained entry of Ca$^{2+}$ followed by mitochondrial Ca$^{2+}$ overload leading to cell death in cultures of rat cerebellar granule cells (Sanz-Blasco et al., 2008). The pathway for Ca$^{2+}$ entry remains unknown, but several reports suggest it could be mediated, at least partially, by NMDA receptors. Interestingly, we showed that a series of NSAIDs, including salicylate (the major metabolite of aspirin), ibuprofen, sulindac sulfide, indomethacin and the structural analogue lacking anti-inflammatory activity R-flurbiprofen, are able to depolarize mitochondria. This may cause impaired metabolism and certain processes that trigger cell death such as the one in the neurodegenerative disorders (Pivovarova et al., 2004).

NSAIDs, used at low concentrations, partially depolarize mitochondria and inhibit mitochondrial Ca$^{2+}$ overload, thus preventing the release of cytochrome c and NMDA- or Aβ1–42-induced apoptosis. Aβ1–42 Amyloid β peptide 1–42; NSAIDs: non steroidal anti-inflammatory drugs.
patients might be too severe to be reversed by even the best drugs. In support of this view, it has been shown recently that R-flurbiprofen, a drug that lacks anti-inflammatory activity, prevents and attenuates primary progressive experimental multiple sclerosis in mice, even if the treatment commenced on or after the first signs of the disease (Schmitz et al., 2014). Further research is required to test the use of selected NSAIDs and structural analogues without anti-inflammatory activity in neuron damage associated to aging. This work was supported by grants VA145U13, BIOVAA33/13, BIO103/VAA45/11 from Junta de Castilla y León, Spain and BFUN2012-37146 from Ministerio de Economía y Competitividad, Spain. MCR was supported by a pre-doctoral fellowship from Junta de Castilla y León, Spain and The European Social Fund.

Maria Calvo-Rodríguez, Lucía Núñez, Carlos Villalobos
Instituto de Biología y Genética Molecular (IBGM), Consejo Superior de Investigaciones Científicas (CSIC) and Universidad de Valladolid, c/ Sanz y Fores 3, 47003 Valladolid, Spain

*Correspondence to: Carlos Villalobos, Ph.D., carlosv@ibgm.uva.es.

References
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