Role of Anti-inflammatory agents in Cerebral Ischemia-reperfusion Injury

Cerebral ischemia-reperfusion injury is associated with the production of more ROS and inflammatory response. ROS and inflammation together involved to exaggerate the tissue apoptosis. Alterations of the expression and release of inflammatory mediators in the brain is being investigated as a therapeutic approach to reduce reperfusion induced brain damage. In principle, anti-inflammatory therapy should be considered as an adjuvant therapy to thrombolytics. Several therapeutic strategies that directly or indirectly target post-ischemic brain inflammation have been developed and tested in animal and human studies. The two most important approaches are: i) reducing the overall immune response with non-selective immunosuppressants and ii) targeting a single inflammatory mediator (Jin et al. 2010; Stanimirovic and Satoh 2000).

5.1 Non-selective immunosuppressants

Non-selective immuno modulation consists of using drugs such as glucocorticoids, cyclosporine A or non-steroidal anti-inflammatory drugs (NSAIDs). Animal studies have shown that cyclosporine A and NSAIDs ameliorate brain damage after global and focal ischemia (Akdemir et al 2005; Khansari and Halliwell 2009).

5.1.1 NSAIDs (Non steroidal anti-inflammatory drugs)

In cerebral ischemia-reperfusion, pro-inflammatory stimuli induces metabolism of arachidonic acid through cyclooxygenase enzymes and mediate production of prostanoids (Font-Nieves et al 2012). Mainly cyclooxygenase (COX)-2 plays a pivotal role in the progression of ischemic brain damage. Recent
studies also demonstrated that celecoxib (a selective cyclooxygenase-2 inhibitor), nimesulide (a preferential COX-2 inhibitor) and ibuprofen (a nonselective COX-2 inhibitor) are showing neuroprotection against global ischemia and focal ischemia (Gaur and Kumar 2012; Wang et al. 2012; Cole et al. 1993). Flurbiprofen also protects the brain from ischemia/reperfusion injury by reducing apoptosis and this neuroprotective effect may be partly due to the activation of Akt/GSK-3β signaling pathway (Sun et al. 2011).

5.1.2 Glucocorticoids

Dexametasone and triamcinolone acetonide are anti inflammatory glucocorticoids. They have showed protective effect of brain from ischemia and reperfusion injury by reducing inflammation. (Goericke et al. 2010; Jingmin et al. 2012).

5.2 Drugs targeting a single inflammatory mediator

5.2.1 Theaflavin

Theaflavin is an anti inflammatory drug. In animal studies theaflavin showed cerebroprotection against cerebral ischemia-reperfusion injury by limiting leukocyte infiltration and expression of ICAM-1 and suppressing up regulation of inflammatory-related pro-oxidative enzymes and in ischemic brain (Cai et al. 2006).

5.2.2 Adiponectin

Adiponectin (APN) is a circulating adipose-derived hormone regulating inflammation and energy metabolism. It has beneficial actions in cardiovascular and cerebrovascular disorders. Hypoadiponectinemia is associated with ischemic cerebrovascular disease, however little is known about the cerebroprotective actions of APN as well as its molecular mechanisms. APN exerts potent anti-
inflammatory actions. Furthermore, nuclear factor NF-κB (p65) is a critical transcription factor, involved in inflammatory reactions (Chen et al. 2009). It was predominantly located in the nucleus after I/R injury, whereas APN can obviously inhibit its translocation from cytoplasm into the nucleus. APN exerts a potent cerebroprotective function through its anti-inflammatory action (Chen et al. 2009).

5.2.3 Telmisartan

Telmisartan is an anti-inflammatory drug. Animal studies have shown that Telmisartan exerts beneficial effect in ischemia-reperfusion injury through blockage of AT1 receptor and in addition due to a positive effect via its specific anti-inflammatory PPAR-γ agonist activity (Kasahara et al. 2010; Cianchetti et al. 2008).

5.2.4 Flavonoids

A number of flavonoids are reported to possess anti-inflammatory activity. Hesperidin, a citrus flavonoid possess significant anti-inflammatory and analgesic effects. Recently pigenin, luteolin and quercetin have been reported to exhibit anti-inflammatory activity (Rezai-Zadeh et al. 2008). Quercetin, rutin and resveratrol are flavonoid derivatives, reported with potent anti oxidant and anti-inflammatory effects (Lin et al. 2012; Lanzilli et al. 2012). Recent studies also demonstrated that their anti oxidant and anti inflammatory mechanism may be beneficial in cerebral ischemia-reperfusion (Wang et al. 2012; Takasago et al. 1997; Celik et al. 2010).
References


8. Gaur V, Kumar A. Effect of nonselective and selective COX-2 inhibitors on memory dysfunction, glutathione system, and tumor necrosis factor alpha


