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Review

Treatment of traumatic brain injury with anti-inflammatory drugs

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ABSTRACT

Traumatic brain injury rapidly induces inflammation. This inflammation is produced both by endogenous brain cells and circulating inflammatory cells that enter from the brain. Together they drive the inflammatory response through a wide variety of bioactive lipids, cytokines and chemokines. A large number of drugs with anti-inflammatory action have been tested in both preclinical studies and in clinical trials. These drugs either have known anti-inflammatory action or inhibit the inflammatory response through unknown mechanisms. The results of these preclinical studies and clinical trials are reviewed. Recommendations are suggested on how to improve preclinical testing of drugs to make them more relevant to evaluate for clinical trials.

Contents

1. Introduction

There are approximately 1.7 million cases of traumatic brain injury (TBI) in the United States annually (Faul et al., 2010). The causes of

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these TBIs are heterogeneous. Most TBIs are induced by blunt impacts; the remaining result from penetrating or blast injury (Faul et al., 2010). Regardless of how it is induced, TBI ranges in severity that ranges from severe to mild injury. Mild TBI constitutes the vast majority of all TBIs (Faul et al., 2010; Johnson et al., 2015). Regardless of the injury severity, inflammation is an integral part of the pathophysiology of TBI (Finnie, 2013; Johnson et al., 2015). More severe brain injury induces a larger and more prolonged inflammatory response (Kumar and Loane, 2012; Lozano et al., 2015; White et al., 2013; Woodcock and Morganti-Kossmann, 2013). Traumatic injury initiates from a mechanical injury to endothelial cells, neurons, and glia in both clinical TBI and experimental TBI models (Finnie, 2013; Johnson et al., 2015; Kou and VandeVord, 2014; Kumar and Loane, 2012; Woodcock and Morganti-Kossmann, 2013). Damage and death to cells induce extracellular release of a variety of ions, molecules and proteins termed damage-associated molecular patterns (DAMPs) (de Rivero Vaccari et al., 2014). These DAMPs include ATP and K^+, double stranded DNA, and the high mobility group 1 (NMG1) chromatin protein. ATP binds and activates P2X7 receptors and elevated K^+ activates pannexin receptors (Adamczak et al., 2014; de Rivero Vaccari et al., 2014; Kelso and Gendelman, 2014). DAMPs bind extracellular receptors that activate intracellular inflammasomes (Adamczak et al., 2014; de Rivero Vaccari et al., 2014; Kelso and Gendelman, 2014). Activated inflammasomes in neurons and astrocytes that process pro-IL-1β and pro-IL-18 into its biologically active forms (Adamczak et al., 2014). Extracellular IL-1β and IL-18 levels rise soon after injury and are key activators of microglia and other early inflammatory events (de Rivero Vaccari et al., 2014; Kelso and Gendelman, 2014). Inflammasomes are also activated following binding of double stranded DNA or HMG1 to cell surface Toll-like receptors (Kelso and Gendelman, 2014; Laird et al., 2014). The release of TNFα, IL-6, IL-12 and interferon γ is an additional early event in inflammatory response (Kelso and Gendelman, 2014). In addition to releasing DAMPs, mechanical injury damages the mitochondria and produces reactive oxygen species and oxidative stress (Cornelius et al., 2013; Rodriguez-Rodriguez et al., 2014). iNOS and NADPH oxidase are additional sources of reaction oxygen species while iNOS produces reactive nitrogen species (Cornelius et al., 2013; Rodriguez-Rodriguez et al., 2014). Pro-inflammatory cytokines, reactive oxygen and reactive nitrogen species interact to increase vascular permeability and damage (Finnie, 2013; Laird et al., 2014; Rodriguez-Rodriguez et al., 2014). Injury results in vasogenic edema and deposition of platelets and polymorphonuclear leukocytes into the brain parenchyma. Vascular changes, infiltration of peripheral inflammatory cells and activation of resident microglia and astrocytes produce more sustained and widespread release of a wide range of cytokines, chemokines, and bioactive lipids (Finnie, 2013; Kou and VandeVord, 2014; Lozano et al., 2015; Woodcock and Morganti-Kossmann, 2013; Ziebell and Morganti-Kossmann, 2010). These early events enhance brain damage, yet they provide the framework for later inflammatory events that enhance tissue repair and remodeling (Kou and VandeVord, 2014; Lourbopoulos et al., 2015; Lozano et al., 2015).

Altering patterns of microglia activation are key events in switching from inflammation with early and largely deleterious effects to a later phase of tissue repair and remodeling (Lourbopoulos et al., 2015; Lozano et al., 2015). This can occur since microglia can differentiate into either pro-inflammatory M1 or an anti-inflammatory M2 phenotypes (Cherry et al., 2014; Hanisch, 2013; Lourbopoulos et al., 2015). M1 microglia enhance inflammation, increase the number of pro-inflammatory cells, and remove apoptotic cells. They produce pro-inflammatory cytokines IL-1β, TNFα. IL-6, and chemokines that recruit additional inflammatory cells to the injury site. M1 microglia enhance oxidative stress through increased NADPH oxidase and iNOS expression (Rodriguez-Rodriguez et al., 2014).

Microglia also differentiate into one of the M2 microglia broadly termed M2a, M2b, and M2c (Cherry et al., 2014; Gensel and Zhang, 2015). All three subtypes of M2 microglia have anti-inflammatory action (Cherry et al., 2014; Gensel and Zhang, 2015). M2a microglia elevate expression of arginase-1, found in inflammatory zone-1 (FIZZ-1), triggering receptor expressed on myeloid cells-2 (TREM2) and IL-1 receptor antagonist and the CD206 mannose receptor (Gensel and Zhang, 2015). M2a microglia suppress inflammation, induce cell proliferation and migration and mediate tissue repair. M2b microglia express toll-like receptors, high levels of arginase-1, IL-1, TNFα, IL-6, and CD86 (Gensel and Zhang, 2015). The role of M2b is not well understood, but they appear to have both pro-and anti-inflammatory activity. M2c microglia also have anti-inflammatory activity that may differ from M2a microglia. M2c microglia express high levels of TGFβ, CD206, CD163, sphingosine kinase 1 (Gensel and Zhang, 2015). These microglial subsets have been largely defined in vitro (Gensel and Zhang, 2015; Hanisch, 2013). The diversity of in vivo microglial phenotypes is likely to be more complex than in vitro (Cherry et al., 2014; Hanisch, 2013; Lourbopoulos et al., 2015).

The efficacy of anti-inflammatory drugs is directly assessed through changes in the levels of pro- and anti-inflammatory mediators as well as reducing the number and activation state of inflammatory cells. Measurements of inflammatory mediators are difficult since they work at low concentrations and often only act locally in a juxtacrine, paracrine or autocrine manner (Hein and O'Banion, 2009; Kelso and Gendelman, 2014; Lourbopoulos et al., 2015; Woodcock and Morganti-Kossmann, 2013). As a result, preclinical and clinical tests of anti-inflammatory drugs provide only a partial description of the inflammatory mediators produced by brain trauma (Loane et al., 2015; Woodcock and Morganti-Kossmann, 2013; Ziebell and Morganti-Kossmann, 2010) (Tables 2 and 3). Thus it remains poorly understood which inflammatory mediators need to be targeted to get the best therapeutic effect. Examination of the cellular consequences of inflammatory mediators is an alternative to their direct measurement. Microglial or astrocyte activation, immune cell infiltration, BBB breakdown and edema are valuable surrogate markers of early actions of inflammatory mediator after traumatic injury (Finnie, 2013; Loane et al., 2015; Lourbopoulos et al., 2015; Woodcock and Morganti-Kossmann, 2013).

Anti-inflammatory drug action after injury is also assessed indirectly using histological or functional assays (Tables 2 and 3). Mild TBI selectively damages white matter, while more severe TBI damages both gray and white matter (Kou and VandeVord, 2014; Xiong et al., 2013). Histological damage occurs rapidly after TBI and can evolve for days to weeks after injury (Xiong et al., 2013).

Anti-inflammatory drugs have been tested in a variety of experimental TBI models. TBI animal models can be divided into closed head injury models in which the skull remains intact before, and open head injury models in which brain injury occurs through a craniotomy (Johnson et al., 2015; Xiong et al., 2013). The most common closed head model injury drops a weight on the skull. Weight drop produces a focal injury that damages the cortex and underlying hippocampus. A midline impact produces a focal TBI while a lateral impact produces a TBI that is more diffuse. Marmarou's weight drop differs from other weight drop models by affixing a metal helmet to the head of the rodent prior to dropping the weight. Marmarou's weight drop model produces a diffuse TBI.

The two common open head injury models are fluid percussion and controlled cortical impact (Johnson et al., 2015; Petraglia et al., 2014). Controlled cortical impact produces a focal injury in the cortex at the site of impact. More severe impacts may damage the underlying hippocampus as well. White matter injury following controlled cortical impact is more diffuse than gray matter injury (Johnson et al., 2015). Fluid percussion produces a more diffuse gray and white matter injury than controlled cortical impact (Johnson et al., 2015; Petraglia et al., 2014). Fluid percussion and controlled cortical impact produces a more uniform injury than closed head models (Johnson et al., 2015). A few studies cited in this review use a cryogenic lesion model that produces a highly focal injury. Cryogenic models produce a lesion that differs more from clinical TBI than other animal TBI models (Xiong et al., 2013).