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INVITED REVIEW

A new look at auranofin, dextromethorphan and rosiglitazone for reduction of glia-mediated inflammation in neurodegenerative diseases

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Abstract

Neurodegenerative disorders including Alzheimer's disease are characterized by chronic inflammation in the central nervous system. The two main glial types involved in inflammatory reactions are microglia and astrocytes. While these cells normally protect neurons by providing nutrients and growth factors, disease specific stimuli can induce glial secretion of neurotoxins. It has been hypothesized that reducing glia-mediated inflammation could diminish neuronal loss. This hypothesis is supported by observations that chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) is linked with lower incidences of neurodegenerative disease. It is possible that the NSAIDs are not potent enough to appreciably reduce chronic neuroinflammation after disease processes are fully established. Gold thiol compounds, including auranofin, comprise another class of medications effective at reducing peripheral inflammation. We have demonstrated that auranofin inhibits human microglia- and astrocyte-mediated neurotoxicity. Other drugs which are currently used to treat peripheral inflammatory conditions could be helpful in neurodegenerative disease. Three different classes of anti-inflammatory compounds, which have a potential to inhibit neuroinflammation are highlighted below.

***Key Words:** auranofin; dextromethorphan; rosiglitazone; Alzheimer's disease; neuroinflammation; neurodegeneration; microglia; astrocytes*

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Introduction

Inflammation in the central nervous system (CNS) contributes to several neurodegenerative diseases (Jonsson et al., 2013). Gene mutations affecting inflammatory pathways have been linked to poorer cognitive functioning in elderly patients and to date no effective treatments for preventing or reducing this inflammation exist (Jonsson et al., 2013). CNS inflammation is driven by two glial cell types: microglia and astrocytes (Gonzalez et al., 2014; Hostenbach et al., 2014); therefore, these cells are the primary targets for novel anti-inflammatory drugs (Lee et al., 2013). Under normal physiological conditions these cells provide trophic support to neurons; however, in neuroinflammation, increased secretion of proinflammatory mediators, glial toxins, excitatory molecules, such as glutamate, as well as decreased release of neurotrophic factors from glia can damage healthy surrounding neurons (Lee et al., 2013). Drugs that counteract these pathological changes without affecting the physiological activity of glia, such as clearing amyloid beta deposits, are excellent candidates for the treatment of neuroinflammatory conditions (Lee et al., 2013).

Several classes of anti-inflammatory drugs have been well studied and are considered safe. They include non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit cyclooxygenase (COX) enzymes; glucocorticoids; and disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate, which have several mechanisms of action (Dinarello, 2010). While most of these drugs have been studied extensively as inhibitors of peripheral inflammation, few have been investigated for their effects on neuroinflammation (Tansey and Goldberg, 2010). This brief highlight will summarize the available evidence of anti-neuroinflammatory activity of three drugs currently approved for use in other disorders.

Auranofin

Gold compounds including 2,3,4,6-tetra-o-acetyl-l-thio-β-D-glucopyrano-sato-S-(triethyl-phosphine) gold, manufactured as auranofin (AF), are used to treat inflammation associated with rheumatoid arthritis (Kean, 1990). While their exact mechanism of action is unclear, it is known that AF inhibits several inflammatory pathways including nuclear

factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation and tumor necrosis factor (TNF)-α production and secretion (Madeira et al., 2012).

Our studies indicate that AF possesses both anti-neuroinflammatory and neuroprotective activities. AF at low micromolar concentrations inhibited human microglia- and astrocyte-mediated neurotoxicity (Madeira et al., 2013, 2014). The anti-neuroinflammatory activity of AF was selective; it inhibited priming of phagocyte respiratory burst and microglial secretion of TNF-α and nitric oxide (NO) (Madeira et al., 2014). AF upregulated hemeoxygenase (HOX)-1, an anti-inflammatory and neuroprotective enzyme in astrocytes (Cuadrado and Rojo, 2008; Madeira et al., 2013). Moreover, AF directly protected neuronal cells from toxicity induced by hydrogen peroxide or stimulated glial supernatants; however, it did not inhibit secretion of interleukin (IL)-6 and IL-8 (Madeira et al., 2013, 2014). After oral administration in rats and mice, AF has been shown to reach CNS concentrations above 0.1 μM required for its protective effects (Madeira et al., 2012, 2013); therefore, AF may be useful in the treatment of neuroinflammation.

Dextromethorphan

Dextromethorphan (DM; d-3-methoxy-17-methylmorphinan) is an anti-tussive agent used in cough medicines (Tortella et al., 1989). DM has been shown to inhibit peripheral production and secretion of several inflammatory mediators including TNF-α, IL-6, NO and superoxide anion ($O_2^{\bullet-}$) (Liu et al., 2003). Several studies have shown that DM reduces glia-mediated neuroinflammation and may have neuroprotective effects (Liu et al., 2003; Keller et al., 2008; Chechneva et al., 2011). DM inhibited microglia-mediated degeneration of dopaminergic neurons *in vitro* and inhibited the production of TNF-α, NO, and $O_2^{\bullet-}$ by stimulated microglia (Liu et al., 2003). Furthermore, DM is a known N-methyl-d-aspartate receptor (NMDAR) antagonist (Tortella et al., 1989). In a mouse model of excitotoxic brain damage, DM reduced lesion size and neuronal cell death, possibly by reducing microglial activation. Low concentrations of DM reduced inflammation-primed NMDAR-mediated excitotoxic brain damage without inducing neuronal apoptosis (Keller et al., 2008). In animal models of multiple sclerosis, DM was shown to reduce the transcription of NOX-2 and $O_2^{\bullet-}$ production in microglia (Chechneva et al., 2011). A phase II clinical trial investigating a combination of DM and quinidine sulfate (a metabolic inhibitor that affects DM concentration in the body) for the treatment of Alzheimer's disease (AD) is currently underway, but results have not yet been released (Misra and Medhi, 2013).

Rosiglitazone

Rosiglitazone (RSG) is currently used in the treatment of type 2 diabetes. RSG is a thiazolidinedione, which activates peroxisome proliferator-activated receptor-γ (PPAR-γ) (Haffner et al., 2002). PPAR-γ agonists are anti-inflammatory by suppressing NF-κB and by directing macrophages towards the anti-inflammatory M2 phenotype (Bouhlel et al., 2007; Gold et al., 2010). RSG may be helpful in the treatment of neuroinflammatory conditions. Hyong et al. (2008) demonstrated that RSG improved neurological status in rats after surgical brain injury. This improvement could be due to decreased IL-1β and TNF-α expression. In a similar study using a stroke model, RSG treatment decreased infarct volume, improved post ischemic neurological function, and reduced neutrophil accumulation in the brain parenchyma of mice. RSG inhibited TNF-α, IL-1β, and IL-6 secretion by cultured cortical microglia (Luo et al., 2006) and has also shown direct neuroprotective activity in the models of traumatic brain injury (Yi et al., 2008). Treatment of mice with RSG enhanced post-traumatic brain expression of neuroprotective heat shock proteins, HOX-1, and anti-oxidant enzymes. Luna-Medina et al. (2005) demonstrated that RSG significantly reduced expression of TNF-α, IL-6, inducible nitric oxide synthase, and COX-2 by stimulated astrocytes through PPAR-γ activation. While complete suppression of COX-2 may cause undesirable CNS effects, such adverse activity has not been reported with RSG treatment (Gold et al., 2010). Studies of the effects of RSG on Alzheimer's disease (AD) progression have yielded mixed results depending on whether or not the patients were carriers of the apolipoprotein E (APOE) allele which is correlated with late-onset AD (Gold et al., 2010).

Conclusion

Neuroinflammation contributes to the pathogenesis of a wide range of neurodegenerative disorders especially during their early stages before irreversible changes, such as plaque formation, have occured (Lucas et al., 2006). Currently no effective treatments directed at reducing this inflammation exist (Klegeris et al., 2007). Development of novel therapeutics is a lengthy process, which can be expedited by developing new applications for drugs that are already approved for use in humans. A number of such approved drugs with known peripheral anti-inflammatory activity have yet to be studied for their effects on neuroinflammation (Dinarello, 2010). By re-purposing old drugs, the time it takes for an effective anti-neuroinflammatory drug to be found and put into clinical trials could be significantly reduced.

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