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Mini Review

Neuroprotective Effects of Thiazolidine-4-Carboxylic Acid Derivatives on Memory Impairment and Neurodegeneration

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Abstract

Some studies have shown numerous biological activities of thiazolidine derivatives, including neuroprotection. The production of inflammatory markers and reactive oxygen species (ROS) plays a major role in nerve damage that leads to memory impairment. Several studies have shown that alcohol consumption impairs memory in adults. However, the underlying mechanism is still unclear. Ethanol treatment also leads to memory impairment in mice. Exposure to ambient pollutants such as air pollutants also can be adversely impacted the central nervous system (CNS) by the activation of proinflammatory pathways and reactive oxygen species. Thus, targeting neuroinflammation and oxidative distress can be a useful strategy to eliminate the obvious symptoms of neurodegeneration. In addition, treatment with thiazolidine-4-carboxylic acid derivatives reduces oxidative stress, neuroinflammation, and ethanol-induced memory impairment. In general, thiazolidine derivatives may be useful in reducing neuroinflammation by acting on different stages of inflammation. In the current mini-review, we examined the neuroprotective potential of these compounds in a model of ethanol-induced neuritis.

Keywords: Air pollutants; Neuroprotective; Neuroinflammation; Oxidative stress; Thiazolidine; Ethanol

Introduction

It is estimated that 20 - 70 % of urban air pollutants are resulting from traffic combustion [1,2] and 85% of particulate matter (PM) in urban areas is related to traffic [3]. New evidence suggests that air pollution exposure has been known as one of the main sources of neuroinflammation and oxidative stress, causing CNS and neuropathology disease [4-6]. Activation of ROS and pro-inflammatory pathways by PM is thought to elicit maladaptive responses that can in turn adversely impact organ function and the CNS also isn't immune to air pollution impact [4,7,8]. There are several pathways via which can be transmitted inflammatory signals from environment to brain [5], so in people exposed to urban air pollutants, activation of the peripheral immune system may lead to neuroinflammation [9]. Neuroinflammatory reactions are triggered by oxidative stress, cytokines, and chemokines and can lead to impaired neurotransmitter and neurotrophin signaling disorders, abnormal protein accumulation, neurodegeneration, and neuronal remodeling [10]. Prolonged exposure to these pollutants may lead to an increase in the inflammatory markers

upregulation and exacerbate previous neurodegenerative disorders [11-14]. In addition, new findings support the involvement of neuroinflammation in the pathogenesis of emotional and cognitive disorders [15,16]. Neurodegenerative diseases (NDs) pose a greater risk to humans, more precisely to the elderly population [17], and according to the WHO, it will overtake cancer in the next 20 years [18]. These diseases include a number of neurological disorders characterized by a diverse array of pathophysiology and are associated with cognitive impairment and/or mobility impairment [19]. It includes a wide range of disorders, the two most common of which are Parkinson's disease (PD) and Alzheimer's disease (AD) [20]. Neurodegenerative diseases are common to many of the major processes associated with dysfunction and neuronal death, including oxidative stress and the formation of free radicals, neuroinflammation, protein folding and malformation, bioenergy disorders, and mitochondrial dysfunction [21]. Many thiazolidines are available as potential clinical drugs against many diseases; such as rosiglitazone (antidiabetic), pioglitazone (antidiabetic), etozoline (loop diuretic), teneligliptin (antidiabetic), benzylpenicillin (antibiotic), and ralitoline (anticonvulsant) [22]. Despite the high prevalence, limited or no disease-modifying therapy (DMT) is available to manage these disorders, thus emphasizing the significant translation gap from drug development to in vivo experimentation and to clinical trials [23]. Several heterocyclic components such as thiazolidines, exhibit favorable biological activity due to the inherent structural diversity that provides structure modulation to a greater extent [24]. Considering the antioxidant, anti-inflammatory, and neuroprotective properties of thiazolidine derivatives, here in this brief review, we evaluate the effect of thiazolidine-4-carboxylic acid on oxidative stress and neuroinflammation.

Neuroprotective Effects of Thiazolidine-4-Carboxylic Acid Derivatives

Many thiazolidines are screened for potential anti-inflammatory, anti-cancer, anti-viral, anti-microbial, neuroprotective, acetyl / butyrylcholinesterase inhibitory, analgesic, hepatic protective, and immunostimulatory properties [22,25]. Several reports have shown that these compounds are likely to have strong free radical scavenging properties [26,27] which can be attributed to neuroprotection in Parkinson's [28] Alzheimer's [29] and other models of memory impairment [30]. In this regard, the beneficial effects of thiazolidines against various Alzheimer's targets have been recently reviewed [31,32]. Previously reported mechanistic studies showed that thiazolidines mediate anti-inflammatory effects by inhibition of NF-κB [33]. Neuroinflammation is a common feature of all neurological disorders caused by oxidative stress and excites altered neuronal function [34,35]. Increased inflammatory mediators and cytokines cause macrophages to penetrate the brain, which intensifies the underlying pathogenesis [36]. Similarly, other research studies have suggested the role of inflammatory cascades in the pathophysiology of various neurodegenerative models not only in laboratory animals but also in postmortem brain samples [37,38]. In addition, inflammatory cytokines cause behavioral and cognitive impairments [39] disrupts the metabolism of neurotransmitters and reduces nerve flexibility [40,41]. Behavioral and cognitive alteration by ethanol consumption in humans is replicated in animal rodent models [42]. In addition, alcohol consumption can exacerbate the underlying pathology of many neurological disorders such as Alzheimer's disease, memory loss, and depression [43] both by expediting cytokines release and also compromises the endogenous antioxidant defense system [44] and therefore can cause neuronal death with either apoptosis or necrosis (or even both) [45]. As mentioned in most scientific texts, the ethanol-induced nerve damage model is widely used because it covers most aspects of memory impairment and neuroinflammation [46,47]. Inflammation of NLRP3 plays an important role in innate immunity and is, therefore, the inflammasome has been investigated [48]. Mitochondrial dysfunction has been suggested to accelerate neurodegeneration due to increased production of reactive oxygen species (ROS) and inflammatory activation of NLRP3 in neurodegenerative and other inflammatory diseases [49]. Activation of NLRP3 inflammation involves a two-step process. First, activation of the nuclear factor-kappa B (NF-κB) pathway is required to upregulates the expression of pro-interleukin-1β (pro-IL-1β), NLRP3, and caspase-1, which is accomplished by stimulation of TLRs (toll-like receptors) [50,51]. After priming, the NLRP3 complex can be activated by several stimuli, including extracellular ATP, lysosomal rupture, ROS, and ionic flux [52].

The Effect of Thiazolidine-4-Carboxylic Acid on Oxidative Stress and Neuroinflammation

Thiazolidine core has been reported in recent years due to their high pharmacological activity in many pharmaceutical formulations [22]. More interestingly, these molecules have a variety of uses and are marketed as potential candidate drugs against various disorders. Due to their pharmacological significance, including immune history and permeability of the blood-brain barrier (BBB), some thiazolidine-4-carboxylic acid derivatives can target several stages of the inflammatory cascade. The reason for significant antioxidant activity is the presence of phenolic moiety in the structure of thiazolidine-4-carboxylic acid derivatives. Phenolic compounds have strong antioxidant properties, and many natural compounds with a phenolic moiety consistently exhibit favorable biological activity. In addition, the use of compounds containing the structural part of phenol has been extensively studied in the treatment of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease [53,54].

The neuroprotective role of thiazolidine-4-carboxylic acid derivatives in an ethanol-induced neurodegenerative model has been demonstrated. These complex cascades reduce the inflammation caused by oxidative stress. Most neurodegenerative disorders are characterized by complex pathophysiology due to the complex nature of the brain, and for this reason, several drugs have been tested in animal experimental models, but no drugs are eligible for clinical trials [55]. Consistent human data reiterated the generation of free radicals with ethanol consumption [44], and such amassing precipitated cognitive impairment due to narrow anti-oxidants in the brain [56]. Ethanol has a high propensity for ROS generation and this is further validated by an elevated

level of LPO along with a reduced glutathione level and which is consistent with previous findings [35]. Many published reports are evident of showing the relationship between oxidative stress and stimulation of inflammatory cascades [57,58]. Increased oxidative stress and lower levels of antioxidant enzymes may have critical effects on brain tissues [59]. The thiazolidine derivatives have been tremendous potential to attenuate memory impairment and neuroinflammation [28].

Therefore, successful treatment approaches should aim to control neuroinflammation as well as reduce oxidative stress by stimulating antioxidant enzymes. Several studies have reported the antioxidant and anti-inflammatory activity of thiazolidine derivatives [25-27]. GSH, GST and catalase play a tremendous role in suppressing free radicals [60]. Numerous thiazolidine derivatives have been reported as antioxidants through GSH activation and LPO inhibition [61]. Neuroinflammation causes the release of ROS, which is responsible for oxidative stress and which aids to intensify the pathogenesis of neurological diseases such as memory impairment, cognitive deficits and other behavioral disorders [62]. Activation of NLRP3 inflammation is associated with the development of several inflammatory diseases and disorders, especially those related to age, such as Alzheimer's disease and type II diabetes (T2D) [63,64]. The release of ROS and proinflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1β) leads to cellular damage and lipid peroxidation [65]. In a neurodegenerative brain, TNF-α-induced NF-κB plays a central role in regulating inflammation following different transcription and transmission pathways [66]. According to the research reports, the activation of NF-κB inflammatory pathways is directly related to the attachment of TNF-α to its respective receptor [67]. Inhibition of TNF-α helps to alleviate not only inflammation but also cognitive deficits. In addition, molecular binding studies against several targets involved in neuroinflammation such as NF-κB, NLRP3, TLR4, and COX-2 also show neuroprotective effects of synthesized compounds [68]. Findings advise that thiazolidine derivatives can reduce neuronal damage through down regulating the overexpression of proinflammatory cytokines and further by modulating the p-NF-κB and NLRP3 pathways.

Conclusion

Neuronal damage exposed to ambient pollutants and or ethanol consumption activates several proinflammatory cytokines, including TNF-α, NF-κB, NLRP3, and COX-2, and is predominantly associated with oxidative stress. Thiazolidine-4-carboxylic acid derivatives reverse oxidative stress and the inflammatory cascade of ethanol exposure by possibly reducing the ROS/NF-κB/NLRP3/TNF-α/COX-2 cascade, which ultimately leads to their neuroprotective role against neurodegenerative diseases.

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Competing Interests

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Ethical Approval

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Consent To Participate

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