ScienceDirect

Chemico-Biological Interactions

Volume 333, 5 January 2021, 109328

The emerging potential of SIRT-3 in oxidative stress-inflammatory axis associated increased neuroinflammatory component for metabolically impaired neural cell

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https://doi.org/10.1016/j.cbi.2020.109328

Highlights

- SIRT3 suppressing the mitochondrial oxidative stress was demonstrated in study.
- Evaluate the relationship of SIRT3-PINCH expression.
- Maintaining the axis to physiological levels for improvement in bioenergetic disruptions.

Abstract

People suffering from conditions like epilepsy, where there is an excess of neuron excitement, stroke, and cardiac arrest, where there are oxygen and glucose deprivation, Alzheimer, Parkinson, and Huntington's disease that causes metabolic and also oxidative stress-inflammatory axis; are known to be more vulnerable to disturbances in the metabolism, and there is a lot of inadequacy in defining the inflammation's mechanistic connections, as well as neurodegeneration and the bioenergetic deficiencies in the CNS. We retrieved relevant studies from PubMed/ScienceDirect/Medline/Public library of science/Mendeley/Springer link as well as Google Scholar. We used various keywords both individually and in combination with the literature search. ‘Epidemiology of neurodegenerative disorders’, ‘neurodegenerative diseases associated hyper inflammation’, ‘Mechanism of inflammation in neuronal cell’, ‘Involvement of SIRTin inflammation’, ‘Pathogenesis of mitochondrial associated metabolic impairment in neurons’, ‘Reactive oxygen species-mediated mitochondrial dysfunction’ were a few of the keywords used for the search. PINCH, which is a chronic neuro-inflammatory component that cannot be detected in matured neurons which are healthy, though expressed in oxidative stress inflammatory axis related tauopathy and diseases that cause neurodegeneration. We attempted to study the regulatory mechanisms that cause changes in the bioenergetics and its neuronal defects and mitochondrial subcellular localization that are PINCH protein-mediated on the other handSIRT1, the most intensively studied sirtuin, in oxidative stress-mediated inflammatory consequence for many diseases but very few research data explore the role of SIRT-3 for correction of the chronic neuroinflammatory component. Thus, in this review, we investigate the very recently identified molecules involving in the pathogenesis during stimulated oxidative stress-inflammatory axis in the excitatory neuronal cell which changes brain metabolism. Simultaneously, in CNS neurons of diseases with a component of chronic neuroinflammation which exhibit neuroprotective response, the consequences (mechanistic and biological) of SIRT-3, could be emerging future targets for neurodegenerative disorder treatment with impaired metabolisms.

Introduction

In the mammalian nervous system, Glutamate is the main excitatory NT and its immoderate release triggers membrane depolarization through receptor-mediated Na^+ and Ca^{2+}influx and elevated production of mitochondrial oxidative phosphorylation and superoxide in the neurons. On the other hand, initiation of non-receptor mediated toxicity occurs by a high concentration of glutamate (extracellular) aids the prevention of uptake of cystine inside the cells through cystine/glutamate antiporter system, which led to reduction of intracellular cysteine and glutathione [1]. The depletion of Glutathione leads to excessive ROS accumulation which results in oxidative stress. The mitochondrial structure and function are affected due to the depletion of antioxidants or excessive accumulation of ROS. Rapid recovery from excitation is obtained by neurons by the restoration of transmembrane ion gradients, replenishment of energy substrates, and removal of ROS. The recovery is dependent upon the optimal mitochondria functioning that leads to the generation of ATP and buffer Ca^{2+} transients. Furthermore, the molecular explanation of glutamate-induced termination of progressive respiratory stimulation via mechanisms that involve activation of PARP-1, usage

of NAD^+ (cystolic), a reduced matrix ATP and substrate supply that is restricted [2].

Though in conditions like epilepsy (excessive neuron excitement), stroke and cardiac arrest (deprivation of oxygen and glucose) or AD, PD, HD (more insidious metabolic along with oxidative stress-inflammatory axis), the mitochondria are unable to act against the stress and neurons and hence, that leads to degeneration which leads to death [3].

On transient exposure to a limited threshold the oxidative, metabolic as well as excitatory stress levels, neurons reciprocated in an adaptively favorable manner through uniting signaling pathways which boost their antioxidant defense, bioenergetics as well as the ability for prevention and reparation of the damage to the cells [4]. For instance, exposing the neurons to glutamate (low level), acts as its protective shield against getting killed by higher glutamate levels and intermittent exercise and fasting could counteract the process of neurodegeneration in the AD, PD, HD, epilepsy, and stroke experimental models [[5], [6], [7]]. However, SIRT1, the most intensively studied sirtuin, in oxidative stress-mediated inflammatory consequence for many diseases but very few research data explore the role of SIRT-3 for correction of the chronic neuroinflammatory component. Thus, in this review, our aim to investigate the very recently identified molecules involving in the pathogenesis during stimulated oxidative stress-inflammatory axis in the excitatory neuronal cell which changes brain metabolism. Simultaneously, the biological and mechanistic result of SIRT-3 neuronal expression of the CNS in conditions having component of long-term inflammation which exhibit neuroprotective response could be an emerging future treatment target for disorders involving neurodegeneration with metabolism impairments.

Section snippets

Literature review

We selected relevant studies that we retrieved from the Google Scholar and Medline/ScienceDirect/PubMed/Public library of science/Mendeley/Springer link. We used several keywords for the literature search both individually as well as in combination that included, ‘Epidemiology of neurodegenerative disorders’, ‘neurodegenerative diseases associated hyper inflammation’, ‘Mechanism of inflammation in neuronal cell’, ‘Involvement of SIRT in inflammation’, ‘Pathogenesis of mitochondrial associated…

Pathogenesis of neurodegenerative disorder

Neurodegenerative conditions including glutamate transport decreases [8], which allows surplus glutamate for it to stay in the synapse that leads to and dysregulated Ca-homeostasis which is NMDAR-mediated excitotoxicity [9] as well as prolongation of the brain's excitotoxic environment [10]. Taking into account,

the multifactorial complex nature of diseases that causes neurodegeneration consists of a condition wherein, the brain and spine's nerve cells are lost which leads to either ataxia or…

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Lysine acetyltransferases (KATs) as well as KDACs, designated as HATs and HDACs, respectively for histone in the mammalian cell [54]. Gene transcription and Histone acetylation strongly correlate with each other, whereas, KDAC non-histone targets, mainly transcription factors, cannot be generalized that elevated acetylation stimulates transcription.

Furthermore, the KDAC superfamily has eighteen members currently. Four classes as per another division have been established based on phylogenetic…

Conclusion

There is a lack of a mechanistic link between PINCH, neurodegeneration, neuroinflammation, and dysfunctional mitochondria. Our study attempted to uncover a vital regulatory mechanism for PINCH expression as well as many of the neuropathological results of an increase in neuronal PINCH. We identified that the transcription factor that is responsible for the induction of PINCH in the tumor necrosis factor-alpha-mediated neuroinflammatory conditions as well as the biological results of an elevated …

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.…

Acknowledgment

We are thankful to the Deanship of Scientific Research at Umm Al-Qura University Makkah, Saudi Arabia for the financial support of our project (Project code 19-med-1-01-0046).…

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...Numerous recent studies hinted the role of SIRT3, a prime modulator of mitochondrial acetylome, are routinely expressed in preclinical and clinical HD brain. Enhanced levels of SIRT3 are a marker of stress against disrupted HD oxidative metabolism (Naia et al., 2021), additionally SIRT-3 involves in modulation of oxidative stress-inflammatory axis which induces metabolically altered brain and outcomes hinted that it may be emerge as potential therapeutic target for various NDs with impaired metabolisms (Almalki et al., 2021). In a very recent study in Striatal synaptosomes of R6/2 mice also revealed lowering of mitochondrial mass with enhanced ROS levels suggesting chronic oxidative stress in HD pathogenesis (Petersen et al., 2022)....

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