The Possible Relationship and Drug Targets of Ischemic Stroke and Dementia in Oxidative Stress

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Abstract: There are multiple mechanisms of pathogenic factors in dementia and ischemic-reperfusion injury, such as oxidative stress (OS) and the reactive oxygen species (ROS). NADPH oxidases (NOXs) have a broad distribution in brain and participate in the oxidative stress and inflammatory responses. It may be efficient to treat this specific target of NOX to establish a balance between reactive oxygen species and antioxidants. This review will elaborate the possible relationship and mechanism between the occurrence of stroke and its complications and focus on NOXs, ROS and inflammatory responses to figure out the possible signaling pathway in the perspective of oxidative stress. And NOX_2 will be focused to demonstrate the relationship between ischemia-reperfusion and pathogenic factors of dementia via the NOX_2/ROS signaling pathway. And considering the upstream and downstream elements and the end results of this signaling pathway, inhibiting NOX_2 activity can reduce oxidative damage and inflammatory responses, NOX_2 can be considered as a drug target to treat stroke development to reduce the risk of severe dementia.

Keywords: Ischemic Stroke; Dementia; The Reactive Oxygen Species

Introduction

As the 3rd leading cause of death, neurodegenerative diseases (NDs) are primarily contributed to cognitive dysfunction[1]. Cognitive dysfunction after stroke has a high morbidity and may influence up to a third of stroke survivors[2][3]. To date, there are some types of drugs that treat cognitive impairment and even dementia, although these have no cure[4][5]. There are several similar pathogenic factors for ischemic stroke and cognitive impairment. Therefore, elucidating the pathogenic mechanism and the interaction between stroke and dementia will help establish effective symptom relief and cognitive impairment prevention strategies. Regard ischemic stroke as a drug target to prevent the occurrence of cognitive impairment, which can reduce the risk and severity of cognitive dysfunction and provide a new thought for drug development to prevent and treat dementia.

Literature Review

1. The possible pathogenic mechanism of NDs

1.1 The source of ROS

As accessory substance of oxidative phosphorylation (OXPHOS), the major formation of ROS occurs in normal oxygen metabolism and the ATP synthesis[6]. One of the source of ROS is active NOXs in cellular mechanism. NOXs are responsible for the phagocytes to fight off infections[6]. The content of mitochondrial ROS increases to cause OS, which imbalances neutralization between the endogenous antioxidant system and strongly oxidizing free radicals [7], and even damages the tissue and neuron.

1.2 Occurrence within ischemic stroke

Within the duration of ischemia, a series of reactions occurred, including depolarizing neurons, increased influx of calcium ions, ATP deficiency and release of the excitatory neurotransmitter[8]. Subsequently receptors activation increases calcium ions inside neurons and NOX signaling pathways so that neuronal death[8]. In fact, some clinical investigations have revealed the relationship between OS and ischemic stroke[9][10] and the part of ROS in inducing neurodegeneration from stroke. A reduction in OS may protect against the complications caused by ischemic stroke[11][12].

1.3 Pathogenic factors in dementia

There are mutiple pathogenic factors about cognitive dysfunction. In the acute stage of ischaemic-reperfusion injury, as blood flow volume to the brain decreases, the concentration of intracellular calcium ions will increase and glutamate release, which is caused by damage to the stability of cellular ions, will lead to excitatory toxicity with inflammation in ischemia[13][14][15][16]. In general, the dangerous factors of cognitive impairment may be similar to those of stroke and cardiovascular diseases[17]. The pathogenic mechanism of dementia is also related to excess ROS(18). And in NDs, immune activation is strongly related to oxidative damage[19][20][21].

2. The role of NOXs in this relationship

In AD and vascular OS, NOXs and mitochondria are thought to be the primary sources of ROS induced by the β-amyloid[17][22]. Some researches show that there is higher expression and activity of the NOX subtypes in the brain in AD mouse than that in wild-type controls[23][24][25]. In neuron cultures treated with β-amyloid, the content of NOX_2 and NOX_4 increase[22][25][26]. There are several NOX subtypes involved in process of OS and neurodegeneration in CNS. And the most relevant NOX isoform with CNS is NOX_2[27][28]. The interactions between pro-inflammatory factors and activated NOXs in microglia drive OS and neuroinflammation[25].

RAGE as receptors contains multiple ligands, are basic pathogenic factors of AD. Indeed, NOX_2 activation is caused by Aβ via RAGE and subsequently leads to dementia. Ischemic stroke and formation of ROS also activate upstream elements of NOX_2. Finally, ROS formation disrupts BBB and causes inflammation to be a possible pathogenic mechanism of dementia. Therefore, NOX_2 deficiency reduces the incidence of oxidative damage and inflammation.

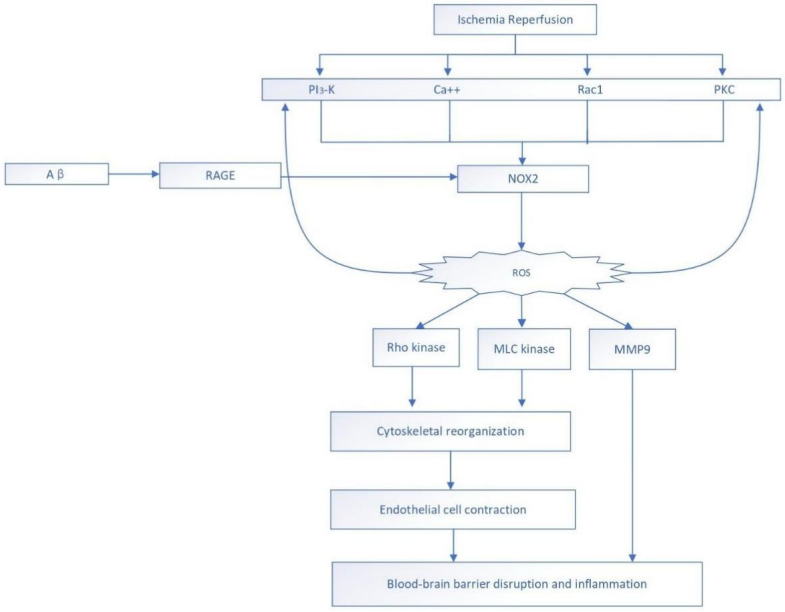

Figure 1. The relationship between ischemic stroke and dementia via NOX_2/ROS signaling pathway.

Conclusion

This review demonstrates the possible relationship between ischemia-reperfusion injury and cognitive dysfunction via the NOX_2/ROS signaling pathway. Subsequently, NOX_2 may be considered as a drug target to treat ischaemia conditions or cognitive impairment via designs of NOX_2 inhibitors. However, NOX_4 and other pathogenic factors also participate in the regulation of ischemic stroke[17]. Therefore, the above factors interact with ROS should also be considered in the relationship between ischemic stroke and dementia to provide a more comprehensive review.

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