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Adiponectin: a pivotal role in the protection against cerebral ischemic injury

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Adiponectin (APN), an adipokine which weights 30 kDa, is first identified in 1995 and almost exclusively secreted by adipocytes[1]. Its physiological and clinical significance has been extensively explored in these years. A comprehensive review of adiponectin and its relating significance is beyond the scope of this article. Although its relationship with cerebral ischemia and ischemic stroke has been reviewed previously[2,3], I try to briefly address the pivotal role of adiponectin in the protection against cerebral ischemic injury in the current article.

STRUCTURE AND BIOSYNTHESIS

There are 3 major oliogmeric multimers of APN: the low-molecular-weight trimer, the middle-molecular-weight hexamer, and the high-molecular-weight (HMW) 12-18 multimers[4,5]. HMW adiponectin has been proposed to be the most potent form and drives the physiological role of adiponectin, as evidenced by some *in vitro* and human studies[1,6]. Also, a globular fragment of adiponectin (gAd) exists. It is generated as the full-length adiponectin is cleaved by leukocyte elastase which are secreted from activated monocytes and/or neutrophils. As compared with other isoforms, it remains at low circulating levels, only accounting for about 1% of total adiponectin[7]. The expression of adiponectin are under the regulation of several transcriptional factors, including CCAAT-enhancer-binding proteins, peroxisome proliferator-activated receptor γ, and sterol regulatory element binding protein 1c[6].

PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL ROLES IN HUMAN DISEASES

The physiological role of adiponectin is mainly involved in insulin sensitivity and regulation of metabolism of glucose and lipids[8]. Furthermore, it has pleiotropic effects including anti-inflammation, anti-

atherosclerosis, anti-thrombosis, and promotion of endothelial repair and angiogenesis which are protective in endothelial injury, atherosclerosis, and cardiovascular diseases[9-11].

Adiponectin is abundant in peripheral circulation, representing about 0.01% total plasma proteins[12], and has a rapid turnover rate[10]. Decreased circulating adiponectin level is noted in obesity for increased oxidative stress in accumulated fat[13,14]. Clinically, hypoadiponectinemia has been noted in various diseases, such as ischemic stroke[15,16], coronary artery disease, insulin resistance and diabetes, hypertension, dyslipidemia, metabolic syndrome, hepatic steatosis and fibrosis, and cancer[17]. On the contrary, hyperadiponectinemia has been noted in congestive heart failure and chronic kidney disease[18,19].

ADIPONECTIN IS PROTECTIVE AGAINST CEREBRAL ISCHEMIC INJURY

Exogenous accumulation from the circulation but not endogenous production in damaged brain tissues after cerebral ischemic injury

In many pre-clinical studies, adiponectin has been consistently shown to be protective against cerebral ischemic injury. However, the expression of adiponectin after cerebral ischemic injury is not endogenous in ischemic cerebral tissues but exogenous from the peripheral circulation.

There are studies exploring the expression profiles of adiponectin after middle cerebral artery occlusion (MCAO) in mice and rats. The study by Yatomi *et al.*[20] showed that, plasma adiponectin levels peaked soon at 1-3 h, decreased later, reached the nadir in 48 h, and then returned to baseline gradually in the rat after MCAO. However, the expression pattern of adiponectin in ischemic cerebral hemisphere differed. Adiponectin showed higher levels in ischemic cerebral hemisphere than non-ischemic one during 72 h to 7 days after ischemia/reperfusion injury. Moreover, its expression was evident in endothelium only, not in neurons, glia, or macrophages. Finally, its expression in the endothelium of ischemic hemisphere seemed to be exogenous from the circulation but not endogenous from damaged cerebral hemispheres since there was no mRNA expression of adiponectin detected by reverse transcription polymerase chain reaction in these area. Another study by Shen *et al.*[21] showed similar findings. They found that adiponectin started to rise 1 h in ischemic hemisphere after cerebral ischemia/reperfusion injury in mice, peaked in 3 days and lasted till 7 days. They found the expression of adiponectin occurred only in vascular endothelial cells but not in neurons or glial cells. Furthermore, they could not find the mRNA expression of adiponectin in ischemic cerebral hemisphere. Taken together, adiponectin accumulates in vascular endothelial cells instead of *de novo* generation in ischemic brain after cerebral ischemic injury.

Adiponectin alleviates cerebral ischemic injury through multi-mechanisms

Adiponectin is protective against cerebral ischemic injury and the mechanisms accounting for this are diverse. The study by Nishimura *et al.*[22] reported that adiponectin exerted a cerebroprotective action through an endothelial nitric oxide synthase (eNOS)-dependent mechanism in cerebral ischemic injury. They showed that adenovirus-mediated delivery of adiponectin augmented the status of phosphorylation of endothelial nitric oxide synthase and reduced the infarction volume in adiponectin knockout (APN-KO) mice.

Another important mechanism of adipoenctin being protective against cerebral ischemic injury is anti-inflammation. The study by Chen *et al.*[23] showed that exogenous supplement of gAd via jugular vein reduced cerebral infarct size, neurological deficits, and expression of endogenous matrix metalloproteinase 9, interleukin (IL)-1β, tumor necrosis factor-α and IL-8, and inhibited the translocation of nuclear factor (NF)-κB from cytoplasm into the nucleus in the rat after MCAO. The indirect evidence of its anti-inflammatory mechanism comes from another study by Jung *et al.*[24]. They found more rolling leukocyte and leukocyte adhesion were observed in the APN-KO mice than in the wide type mice after cerebral ischemia/reperfusion injury. They proposed that adiponectin inhibits the interaction between the endothelium and leukocytes and hence alleviates the inflammatory insult in cerebral ischemic injury.

Adiponectin exerts anti-oxidation against cerebral ischemic injury as well[25,26]. The study by Song *et al.*[25] showed that intracerebral injection of gAd attenuated infarct size and neurological deficits aggravated by NADPH oxidase activator in mice after MCAO along with increased activities of superoxide dismutase (SOD) and catalase, and reduced content of malondialdehyde (MDA). The study by Li *et al.*[26] reported similar findings. They showed intraperitoneal supplement of adiponectin improved neurological deficits, decreased infarct size, and attenuated neuronal injury along with decreased MDA levels and increased SOD activity levels in mice after MCAO. The study by Wang *et al.*[27] reported adiponectin attenuated oxygen and glucose deprivation-induced neuronal injury and mitochondrial oxidative stress in hippocampal neuronal HT22 cells as evidenced by attenuated reactive oxygen species and malondialdehyde, and increased superoxide dismutase and glutathione peroxidase activity.

Also, adiponectin has been related to PKA, CREB, and BDNF in the protection against cerebral ischemic injury. The study by Bai *et al.*[28] reported activation of cAMP/PKA-CREB-BDNF signaling pathway by adiponectin was protective against ischemia/reperfusion injury with reduced infarct volume, neurological deficits and brain water content.

Finally, anti-apoptosis after cerebral ischemic injury by adiponectin has been found in *in vivo* and *in vitro* studies[25-27,29], including that by our group[30].

APN-gene modified cell therapy alleviates cerebral ischemic injury

The pre-clinical studies of APN-gene modified cell therapies in the treatment of cerebral ischemic injury are growing recently. The study by Nishimura *et al.*[22] showed that adenovirus-mediated expression of adiponectin reduced brain infarction volume, increased cerebral blood flow, and improved neurological deficits, through an eNOS-dependent mechanism in cerebral ischemic injury. The study by Shen *et al.*[31] reported that adiponectin could promote focal angiogenesis in cerebral ischemic injury. They showed that after MCAO mice receiving intracerebral injection of adeno-associated viral vector carrying the APN gene had reduced ischemia-induced brain atrophy, improved neurological function and increased number of microvessels along with increased AMPK phosphorylation and vascular endothelial growth factor expression. Furthermore, the study by Miao *et al.*[32] showed this angiogenetic effect was more significant in aged mice than young mice.

Our group[30] showed that pre-treatment of baculovirus-mediated expression of APN through intra-cerebral injection was protective against cerebral ischemic injury in both normal weight and obese rats through reducing brain infarct and edema, neurologic deficits, and p38-mediated neuronal apoptosis.

Recently, it has been shown that genetically-transplanted endothelial progenitor cells with adiponectin by lentivirus could reduce cerebral infarction volume, improve behavior outcome, increase microvessel density, and reduce cell apoptosis[33].

gAd alleviates cerebral ischemic injury

Among adiponectin isoforms, the globular adiponectin has been mostly studied and consistently shown to be protective against cerebral ischemic injury[23,25,29]. The data regarding whether other isoforms of adiponectin could exert protection against cerebral ischemic injury are currently lacking and warrant further studies.

In summary, adiponectin, an adipokine secreted by adipocytes, exists in a relatively large amount in the peripheral circulation. During the cerebral ischemic injury, it accumulates in the damaged cerebral vasculature instead of *de novo* generation by damaged cerebral tissues. It exerts multiple protective mechanisms against cerebral ischemic injury including eNOS-dependent mechanism, anti-inflammation, anti-oxidation, anti-apoptosis, and promotion of angiogenesis. Since adiponectin is an adipokine naturally

secreted by human adipose tissues, and has multi-mechanisms protective against cerebral ischemic injury, it is of great potential in the application of clinical treatment of ischemic stroke in the future.

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Authors' contributions

Wu MH is responsible for design and conceptualization of the study, drafting and revising the manuscript, and obtaining funding.

Availability of data and materials

Not applicable.

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Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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