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INVITED REVIEW

NAD^+ and NADH in Neuronal Death

Weihai Ying

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Abstract Neuronal death is a key pathological event in multiple neurological diseases. Increasing evidence has suggested that NAD^+ and NADH mediate not only energy metabolism and mitochondrial functions, but also calcium homeostasis, aging, and cell death. This article is written to provide an overview about the information suggesting significant roles of NAD^+ and NADH in neuronal death in certain neurological diseases. Our latest studies have suggested that intranasal administration with NAD^+ can profoundly decrease ischemic brain damage. These observations suggest that NAD^+ administration may be a novel therapeutic strategy for some neurological diseases.

Keywords NAD^+ · NADH · neuronal death · brain injury · cerebral ischemia · neurodegenerative diseases

Introduction

β-Nicotinamide adenine dinucleotide (NAD^+) and reduced β-NAD^+ (NADH) are major coenzymes for numerous energy metabolism-associated redox reactions. However, rapidly accumulating evidence has suggested novel paradigms about the metabolism and biological functions of NAD^+ and NADH (Ying 2006; Ying 2007): NAD^+ and NADH appear to be novel mediators of calcium homeostasis, cell death, and aging.

W. Ying (✉)
Department of Neurology (127),
University of California at San Francisco and San Francisco Veterans Affairs Medical Center,
4150 Clement Street, San Francisco, CA 94121, USA
e-mail: Weihai.Ying@ucsf.edu

Multiple families of enzymes catalyze various biochemical reactions by consuming NAD^+. The major NAD^+-consuming enzymes include: (1) poly(ADP-ribose) polymerases (PARPs), which consume NAD^+ to produce poly(ADP-ribose) (PAR) on target proteins (D'Amours et al. 1999; Virag and Szabo 2002; Ying et al. 2005); (2) mono(ADP-ribosyl)transferases, which use NAD^+ as a substrate to produce mono-ADP-ribosylation of proteins (Corda and Di Girolamo 2003; Di Girolamo et al. 2005); (3) bifunctional ADP-ribosyl cyclases/cyclic ADP-ribose hydrolases, which can consume NAD^+ to both generate cyclic ADP-ribose and hydrolyze cyclic ADP-ribose into free ADP-ribose (Ziegler 2000); and (4) NAD^+-dependent histone deacetylases, i.e., the Sir2 family proteins (sirtuins), which deacetylases histones by consuming NAD^+, leading to generation of acetyl-*O*-ADP-ribose and nicotinamide (Blander and Guarente 2004).

Neuronal death is a critical pathological event in multiple neurological diseases, including cerebral ischemia, Parkinson's disease, Alzheimer's disease, and multiple sclerosis (MS). Many studies have suggested that NAD^+ and NADH play significant roles in neuronal death. Generalization of the information regarding the roles of NAD^+ and NADH in neuronal death is warranted not only for understanding the pathogenesis of multiple CNS diseases, but also for suggesting new strategies for treating those illnesses.

Roles of PARP-1 in neuronal injury

Many *in vitro* studies have indicated that PARP-1 activation mediates cell death induced by oxidative stress (Eliasson et al. 1997; Zhang et al. 1994), oxygen-glucose deprivation (Eliasson et al. 1997), and *N*-methyl-D-aspartate (NMDA)-induced excitotoxicity (Zhang et al. 1994). It was long

hypothesized that PARP-1 induces cell death by depleting NAD^+ and ATP (Berger 1985). However, until recently, there was no direct demonstration of this hypothesis. Recent studies by us and other researchers have provided direct evidence demonstrating that NAD^+ depletion mediates PARP-1 cytotoxicity (Ying et al. 2003; Alano et al. 2004; Du et al. 2003). It was also indicated that mitochondrial permeability transition (MPT) and apoptosis-inducing factor (AIF) translocation link NAD^+ depletion to cell death (Alano et al. 2004; Ying 2006). PARP-1 activation may induce MPT by producing glycolytic inhibition (Ying et al. 2003; Ying et al. 2005) or SIRT1 inhibition (Pillai et al. 2005). These studies have collectively suggested a novel paradigm regarding the mechanisms underlying PARP-1-induced cell death (Fig. 1).

Several latest studies have further suggested novel information for understanding PARP-1-induced cell death: first, our recent study has demonstrated that NADH treatment can block PARP-1-induced astrocyte death (Zhu et al. 2005), suggesting that depletion of intracellular NADH might be involved in PARP-1-mediated cell death; second, the ADP-ribose generated by the joint actions of PARP-1 and poly(ADP-ribose) glycohydrolase (PARG) can activate TRPM2 receptors, leading to increased $[Ca^{2+}]_i$ and neuronal death (Fonfria et al. 2004; Fonfria et al. 2005; Yang et al. 2005); and third, extracellular signal-regulated kinases 1/2 could regulate PARP-1 activity by directly phosphorylating the enzyme, suggesting a significant role of extracellular signal-regulated kinases 1/2 in PARP-1-mediated cell death (Kauppinen et al. 2006). Future studies are needed to search for the potential common pathway linking these seemingly diverse mechanisms.

Animal studies using various PARP inhibitors have also indicated that PARP-1 mediates ischemic brain injury of male animals. The studies using PARP-1 knockout mice have further demonstrated a key role of PARP-1 in ischemic brain damage of male mice (Eliasson et al. 1997; Endres et al. 1997). It was also found that PARP inhibition can produce long-term protective effects in experimental stroke (Goto et al. 2002).

Cumulative evidence has indicated that oxidative stress mediates pathogenesis of Parkinson's disease (PD) (Beal 2004; Wolozin and Golts 2002; Ying 1997), raising the possibility that PARP-1 may also mediate the neuronal injury in PD. This possibility was enhanced by the findings that PARP-1 activation plays a key role in the neuronal death induced by 1-methyl-4-phenyl-1, 2,3,6-tetrahydropyridine (MPTP) in both *in vitro* studies (Cosi et al. 1996; Mandir et al. 2002) and *in vivo* studies (Iwashita et al. 2004; Mandir et al. 1999; Przedborski et al. 2000). It was also reported that nicotinamide treatment can decrease MPTP-induced neurotoxicity *in vivo* by inhibiting PARP (Yang et al. 2004).

Oxidative damage was indicated as one of the pathogenic factors in Alzheimer's disease (AD) (Keller et al. 1998; Mhatre et al. 2004; Moreira et al. 2005; Ying 1996; Zhu et al. 2004). Recent studies have also suggested a role of PARP-1 in the neuronal injury in AD: increased nuclear PARP activity was found in the brains and peripheral cells of AD patients (Cecchi et al. 2002; Iwashita et al. 2004); and PARP-1 activation also mediates β-amyloid-induced neuronal death, which is an *in vitro* model of AD (Fonfria et al. 2005; Hensley et al. 1996).

It was reported that 7-ketocholesterol, a lipid breakdown product found in the brain and cerebrospinal fluid (CSF) of MS patients and in experimental autoimmune encephalomyelitis (EAE), contributes to microglial activation-induced neuronal damage by a PARP-1-dependent pathway (Diestel et al. 2003). In a study using a monkey EAE model of MS, excessive PARP-1 activation was also observed in the astrocytes surrounding demyelinated EAE plaques (Kauppinen et al.

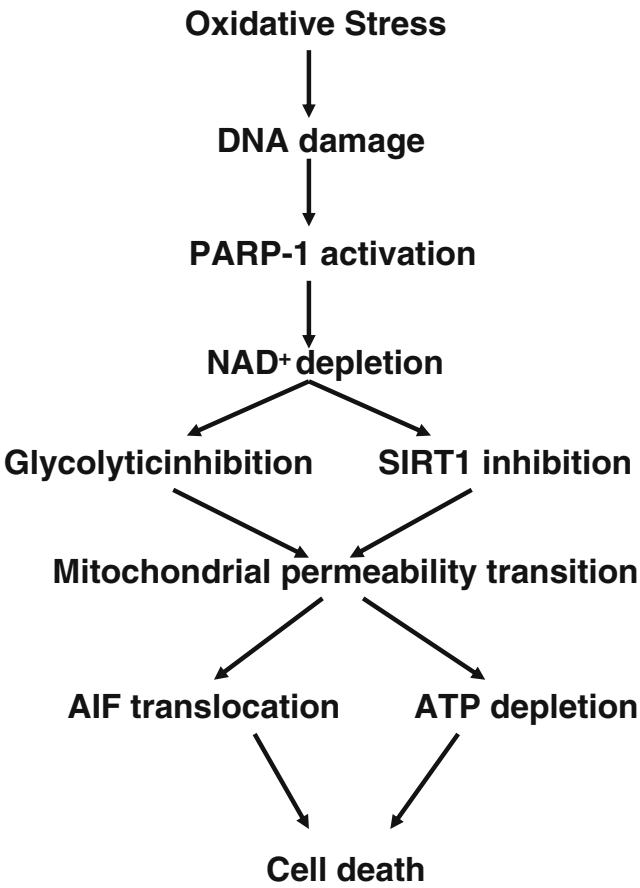

Fig. 1 Diagrammatic presentation of the mechanisms underlying PARP-1-mediated cell death. Oxidative stress generated under numerous pathological conditions such as brain ischemia can produce DNA damage leading to excessive activation of PARP-1. PARP-1 activation can produce NAD^+ depletion, thus, leading to inhibition of glycolysis and SIRT1, resulting in mitochondrial permeability transition (MPT). MPT can lead to AIF translocation from mitochondria to nucleus and ATP depletion, resulting in cell death.

2005). Collectively, these observations have raised the possibility that PARP-1 may contribute to MS pathology.

Roles of PARG in ischemic brain injury

PARG is a key enzyme in PAR catabolism (Davidovic et al. 2001), which is an endo-exoglycosidase present in low abundance in cells. Increasing evidence has suggested that PARG inhibition may prevent PARP-1-mediated cell death by several potential mechanisms (Ying et al. 2001; Ying and Swanson 2000): (1) PARG inhibition could slow the rapid PAR turnover, thus, preventing NAD^+ depletion; (2) PARP-1 can auto-poly(ADP-ribosyl)ate itself, leading to PARP-1 auto-inhibition (D'Amours et al. 1999). Therefore, PARG inhibition could prevent removal of PAR from PARP-1, thus, indirectly inhibiting PARP-1 activation; (3) PARP-1/PARG activities can generate ADP-ribose by hydrolyzing PAR, leading to activation of TRPM2 receptors and increased neuronal death (Fonfria et al. 2004; Fonfria et al. 2005; Yang et al. 2005); and (4) Ca^{2+}–Mg^{2+}-dependent endonuclease (CME) is one of the major endonucleases mediating DNA fragmentation in apoptosis (Boulares et al. 2002). Because CME is a substrate of PARP-1 and poly(ADP-ribosy)lation of CME leads to CME inhibition (Boulares et al. 2002; Yakovlev et al. 2000), PARG inhibition may prevent removal of PAR from CME, thus, leading to persistent CME inhibition.

Many *in vitro* and *in vivo* studies have supported the hypothesis that PARG may be a new target for decreasing oxidative cell death and ischemic tissue damage (Cuzzocrea and Wang 2005): First, our latest study shows that intranasal delivery with the PARG inhibitor gallotannin (GT) decreased infarct formation by 60–70% in a rat model of transient (2 h) focal brain ischemia, when the drug was administered either at 2 or 5 h after ischemic onset (Wei et al. 2006). Second, *in vivo* studies have shown that genetic PARG inhibition and PARG inhibitors can significantly decrease ischemic damage of intestine (Cuzzocrea et al. 2005) and kidney (Patel et al. 2005). Third, cell culture studies have further shown that inhibition of PARG by PARG antisense oligonucleotides (Burns et al. 2004), RNA silencing (Blenn et al. 2006) and PARG inhibitors (Bakondi et al. 2004; Hwang et al. 2002; Kim and Koh 2002; Ying et al. 2001; Ying and Swanson 2000) can decrease the cell death induced by oxidative stress and other PARP activators.

Roles of Sir2 in neuronal injury

Sir2 is a member of NAD^+-dependent sirtuins. It was found that Sir2 activation through treatment with the sirtuin activator resveratrol or through increased *sir-2.1* dosage can reduce neuronal dysfunction induced by mutant polyglutamines in transgenic *elegans* (Parker et al. 2005). Resveratrol can also rescue mutant polyglutamine-specific cell death in neuronal cells derived from HdhQ111 knock-in mice. These results suggest that Sir2 activation may decrease the cytotoxicity of mutant polyglutamines.

Roles of other NAD^+- and NADH-related enzymes in neuronal injury

Many studies have indicated that nuclear translocation of the NAD^+-dependent glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mediates apoptosis induced by various inducers. Recent studies have suggested that the GAPDH translocation may contribute to the pathological changes in PD and Huntington's disease: the widely used PD medicine deprenyl in subnanomolar concentrations prevented nuclear translocation of GAPDH (Hara et al. 2006). In mice treated with MPTP, low doses of deprenyl also block the binding of GAPDH to Siah1 in the dopamine-enriched corpus striatum. A latest study also suggested that a ternary complex of GAPDH–Siah–mHtt mediates the nuclear translocation of mutant Huntingtin, which is required for the cytotoxicity of mutant Huntingtin (Hara et al. 2006).

Axon degeneration often occurs in neurodegenerative diseases. The studies on Wallerian degeneration slow (Wlds) mice have suggested important mechanisms underlying axon degeneration (Coleman 2005): the mutation of Wlds mice leads to overexpression of a chimeric protein (Wlds) consisting of nicotinamide mononucleotide adenylyltransferase 1 (NMNAT1) and the ubiquitin assembly protein Ufd2a. It was found that injury-induced axon degeneration is delayed by the mutation. Recent studies have suggested that the increased NMNAT1 expression, resulting from the mutation, mediates the protective effects of the Wallerian mutation (Araki et al. 2004; Wang et al. 2005). However, the mechanisms underlying the protective effects of increased NMNAT1 expression are unclear. One study suggested that the increased NMNAT1 expression produces its effects by affecting SIRT1—a member of sirtuins (Araki et al. 2004). However, Wang et al. (2005) suggested that NMNAT1 may affect axon degeneration by preventing NAD^+ loss in degenerating axons.

Prevention of neuronal injury by administration with NADH and NAD^+

NADH has been used in clinical trials to treat PD patients. Significant beneficial effects of NADH administration in treating PD patients were found in several studies, which

may partially be accounted for by the capacity of NADH to increase bioavailability of plasma levodopa (Birkmayer et al. 1993; Kuhn et al. 1996). Treatment with NADH was also reported to improve the cognitive functions of AD patients (Demarin et al. 2004), suggesting the potential of NADH for treating AD patients.

We conducted intranasal delivery of NAD^+ into the brains to test our hypothesis that NAD^+ may decrease ischemic brain damage (Ying et al. 2007): in a rat model of 2-h transient focal ischemia, intranasal administration with 10 mg/kg NAD^+ at 2 h after ischemic onset can profoundly decrease infarct formation and neurological deficits. These results suggest that NAD^+ may be a novel therapeutic agent for cerebral ischemia and other PARP-1-mediated diseases.

Summary

A number of recent studies have indicated critical roles of NAD^+ and NADH in the neuronal death in certain neurological diseases. It was also suggested that NAD^+ and NADH may be used to decrease the brain damage under several neurological conditions. Future studies are certainly warranted to further investigate the novel properties of NAD^+ and NADH in cell death and to further investigate the therapeutic potential of these important molecules.

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