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Review

Intrinsic Mechanisms of Poly(ADP-Ribose) Neurotoxicity: Three Hypotheses

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Abstract

Poly(ADP-ribose) (PAR) is a branched and negatively charged polymeric macromolecule formed by poly(ADP-ribose) polymerases. Targeting of PAR onto acceptor proteins affects their functioning and regulates cellular homeostasis. A large body of evidence demonstrates that increased neo-formation of PAR has a crucial role in neurodegeneration. Consistently, strategies aimed at reducing PAR synthesis are of therapeutic relevance to treatment of several experimental neurodegenerative diseases. However, how PAR causes neuronal death is still elusive. This review provides an appraisal of the possible molecular mechanisms underlying PAR neurotoxicity, highlighting the pleiotypic effects of the polymer on neural cells exposed to different stressful conditions.

Keywords: Neurodegeneration; PARP; PARG; Poly(ADP-ribose); Gene expression; Brain ischemia

Contents

INTRODUCTION

Poly(ADP-ribosyl)ation is a post-translational modification of proteins with emerging roles in cellular homeostasis (D'Amours et al., 1999; Herceg and Wang, 2001; Tong et al., 2001; Chiarugi, 2002b). It is operated by poly(ADP-ribose) polymerases (PARPs), a growing family of enzymes transforming NAD into long, branched polymers of poly(ADP-ribose) (PAR) (Smith, 2001; Ame et al., 2004). PAR is then targeted to a large number of acceptor proteins whose functioning is significantly affected because of the negative charge and steric hindrance conferred by the polymers (D'Amours et al., 1999). In contrast with the numerous poly(ADP-ribosyl)ating enzymes, poly(ADP-ribose) glycohydrolase (PARG) is the sole protein capable of degrading PAR so far identified (Davidovich et al., 2001). Under control conditions, ongoing cycles of PAR formation and hydrolysis onto acceptor proteins finely regulates key cellular functions such as DNA duplication, repair, and transcription (D'Amours et al., 1999; Herceg and Wang, 2001; Kraus and Lis, 2003) as well as mitosis (Chang et al., 2004) and protein degradation (Ullrich et al., 2001a). However, excessive activation of PARP-1, the oldest member of the PARP family, turns PAR from a

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homeostatic regulator into a highly cytotoxic molecule (Herceg and Wang, 2001). Neurons are particularly sensitive to deregulation of PAR homeostasis and numerous studies demonstrate that hyper-poly(ADP-ribosyl)ation is a key trigger of neurotoxicity (Ha and Snyder, 2000). The neuropathological significance of massive PAR formation is well exemplified by the remarkable therapeutic efficacy of genetic inactivation or pharmacological inhibition of PARP-1 in experimental models of cerebral ischemia (Szabo and Dawson, 1998), neurotrauma (Whalen et al., 1999), Parkinson disease (Mandir et al., 1999), experimental allergic encephalomyelitis (Scott et al., 2001; Chiarugi, 2002a), neuroinflammation (Ullrich et al., 2001b; Chiarugi and Moskowitz, 2003), excitotoxicity (Mandir et al., 2000), meningitis (Koedel and Pfister, 1999), monocular deprivation (Nucci et al., 2000) and subarachnoid hemorrhage (Satoh et al., 2001). Further corroborating the neurotoxic potential of PAR, it has been reported that cerebral accumulation of PAR prompts spontaneous, progressive neurodegeneration in the brain of *Drosophila* with a loss-of-function mutation of PARG (Hanai et al., 2004). In spite of its relevance to neuropathology however, molecular mechanisms underlying the neurotoxic effects of hyper-poly(ADP-ribosyl)ation and intraneuronal PAR accumulation remain elusive. Nevertheless, thanks to a real explosion of interest among basic researchers and pharmaceutical companies, hints on intrinsic mechanisms of PAR-dependent neurotoxicity have emerged. Here, I will group them into three main pathogenetic hypotheses.

THE SUICIDE HYPOTHESIS

This is the oldest pathogenetic interpretation of PAR-dependent neurotoxicity. It originally stems from the pioneering studies of Berger and colleagues on the role of PARP-1 in radiation-induced cell death (Berger, 1985). In vitro experiments clearly indicates that massive DNA damage causes an excessive activation of PARP-1, which in turn depletes NAD pools within only a few minutes (Gaal et al., 1987; Berger, 1985). This results in an impairment of NAD-dependent metabolic pathways including glycolysis and mitochondrial respiration, with consequent depletion of ATP production and energy shortage. Further depleting ATP pools, NAD shortage activates nicotinamide phosphoribosyl transferase and nicotinamide mononucleotide adenylyl transferase (two enzymes of the NAD salvage pathway) which consume ATP to re-synthesize NAD (Berger et al., 2004). This metabolism contributes to the generation of a lethal, futile cycle which eventually leads to necrotic cell death (Gaal et al., 1987; Ha and Snyder, 1999). This interpretation, originally called the ‘‘suicide hypothesis’’ (Berger, 1985) (Fig. 1), has been validated in numerous in vitro models of genotoxic stress (Szabo and Dawson, 1998), and considered an evolutionary strategy of multicellular organisms to prevent survival of excessively damaged and therefore potentially neoplastic cells (Gaal et al., 1987; Herceg and Wang, 2001).

Relevance of the suicide hypothesis to PAR neurotoxicity is controversial. In light of the remarkable therapeutic efficacy of PARP-1 inhibitors in models of brain ischemia, several researchers consider energy utilization by hyper-poly(ADP-ribosyl)ation as causative in post-ischemic brain damage (Szabo and Dawson, 1998). It has been hypothesized, indeed, that profuse formation of reactive oxygen and nitrogen radicals in the ischemic brain tissue (Lee et al., 2000; Lipton, 1999) triggers massive genotoxic stress which in turn causes PARP-1 hyperactivation and ATP consumption (Fig. 1), thereby worsening energy

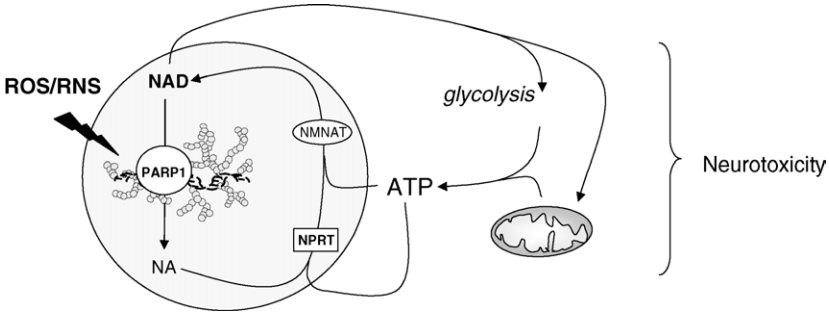

Fig. 1. Schematic representation of the suicide hypothesis. In the injured CNS, formation of reactive oxygen and nitrogen species (ROS and RNS) causes massive DNA damage. The latter is a powerful trigger of PARP-1 activity which, by transforming large amounts of NAD into poly(ADP-ribose) and nicotinamide (NA), depletes intracellular NAD pools. Consequently, the main NAD^+-dependent metabolic pathways such as glycolysis and mitochondrial respiration are impaired. NAD depletion also activates NAD re-synthesis through the concerted actions of nicotinamide phosphoribosyl transferase (NPRT) and mononucleotide adenylyl transferase (NMNAT), two ATP-dependent enzymes. These events cause severe ATP starvation which eventually leads to energy failure and neurotoxicity.