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Commentary

Early preservation of mitochondrial bioenergetics supports both structural and functional recovery after neurotrauma

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ABSTRACT

N-acetylcysteine, a precursor to the potent antioxidant glutathione, has been investigated as a potential therapeutic agent for several decades; however, inconsistent efficacy has been reported for diseases of the central nervous system, postulated to result from restricted passage of this molecule across the blood–brain/spinal cord barriers and cellular membranes, resulting in low bioavailability. The amide form of *N*-acetylcysteine (NACA) overcomes these limitations while maintaining a high antioxidant potential, and shows promise for combating secondary pathogenesis attributed to oxidative stress. Neurotrauma precipitates a rapid and prolonged disruption of mitochondrial bioenergetics, whereby the production of reactive oxygen species overwhelms the endogenous antioxidant capacity of the cells. Two noteworthy papers from collaborative teams have recently been published in *Experimental Neurology*, in which NACA was applied to rodent models of traumatic brain and spinal cord injury, respectively. Using sensitive methods to measure respiratory rates in isolated mitochondrial populations, treatment with NACA was shown to maintain mitochondrial function and boost antioxidant reserves, which corresponded with improvements in structural and functional outcomes in both studies. This commentary aims to highlight key findings from this research in a broader context, with an emphasis on methodological advances, future research possibilities, and potential applicability to brain and/or spinal cord injured patients.
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Introduction

Free radicals are highly reactive molecules generated during normal cellular respiration and metabolism, and under physiological conditions, endogenous antioxidant systems maintain redox homeostasis within mitochondria. However, stressors arising from traumatic brain and spinal cord injuries generate an imbalance between free radical production and the cells' antioxidant capacity, resulting in a state of oxidative stress (Gilgun-Sherki et al., 2002). Oxidative stress, an important contributor to the pathophysiology of acute central nervous system (CNS) injury, occurs within minutes of the primary mechanical impact (Bains and Hall, 2012). Excessive calcium uptake during excitotoxicity after injury reduces the membrane potential of mitochondria, enhancing the production of reactive oxygen species (ROS) from membrane enzyme complexes I and III, and subsequently decreasing ATP production (Adam-Vizi and Chinopoulos, 2006; Hagberg et al., 2014) (see Fig. 1). ROS both initiate and perpetuate tissue damage by contributing to metabolic failure, breakdown of macromolecules, and oxidization of proteins, lipids and nucleic acids. Uncontrolled ROS production can also feedback and enhance other secondary injury processes including excitotoxicity, inflammation and mitochondrial dysfunction, ultimately compounding irreversible cell damage and death (Bains and Hall, 2012).

Mitochondrial dysfunction is a key feature of neurotrauma, spanning a spectrum of injury severities from severe traumatic brain injury (TBI) (Aygok et al., 2008) to mild concussive insults (Vagnozzi et al., 2008) and spinal cord injuries (SCI), even in the chronic phase months-to-years post-injury (Huang et al., 2012). Thus, targeting of mitochondrial dysfunction and/or oxidative stress may present a means of providing broad protection across varying types of neurotrauma. This hypothesis was tested in two recently published papers in *Experimental Neurology*, which investigated the mechanisms by which *N*-acetylcysteine amide (NACA) replenishes the antioxidant capacity and restores mitochondrial bioenergetics in two distinct models of CNS injury (Pandya et al., 2014; Patel et al., 2014).

N-acetylcysteine (NAC) is an FDA-approved, thiol-containing compound, which acts as an acetylated cysteine precursor of glutathione (GSH). Considered to be one of the most important endogenous antioxidants, GSH is synthesized by most cells within the body, and is largely responsible for maintaining a balanced redox state. Mitochondrial levels of GSH have been associated with the degree of tissue damage after CNS insult (Sims et al., 2004), suggesting that maintaining or enhancing GSH

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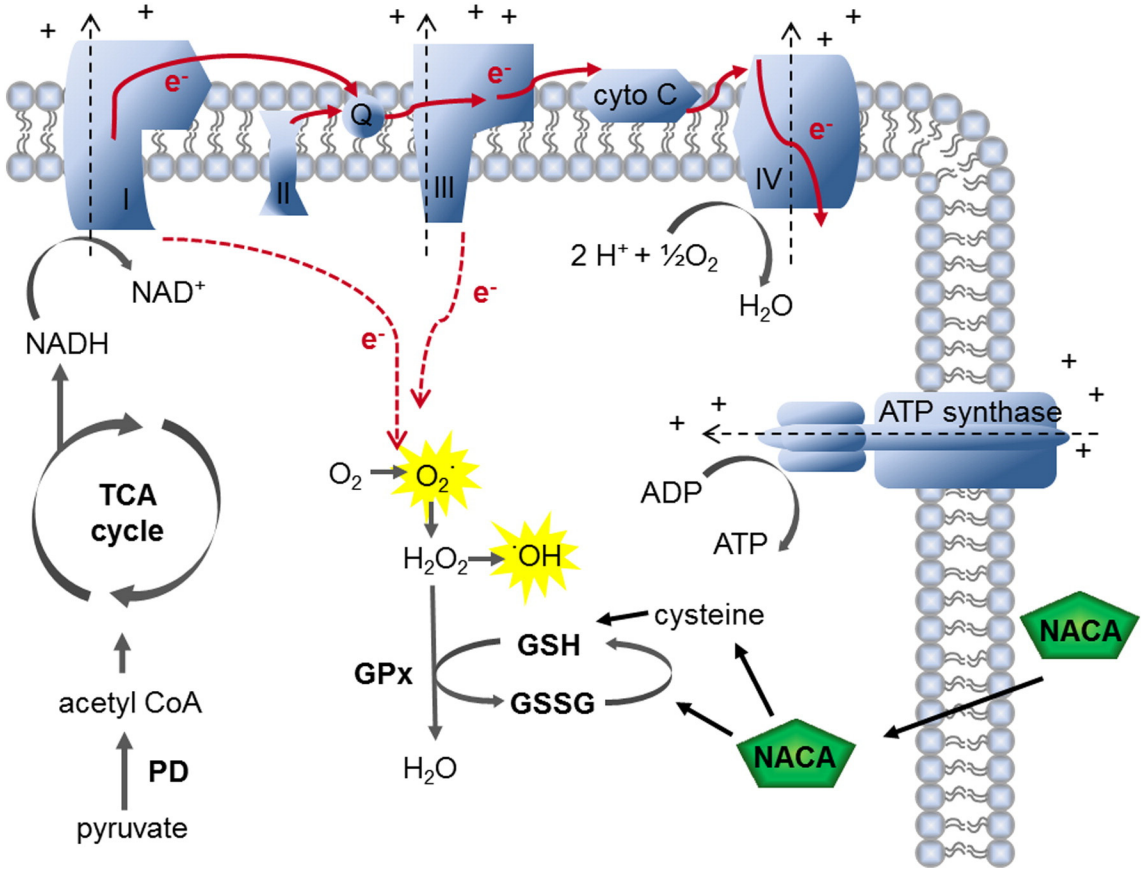

Fig. 1. Schematic illustrating the enzymes comprising the electron transport chain embedded in the inner mitochondrial membrane, and the proposed mechanism of action of N-acetylcysteine amide (NACA). The tricarboxylic acid (TCA) cycle generates the reducing agent nicotinamide adenine dinucleotide (NADH), which donates electrons (red arrows; e-) that flow sequentially through complex I, the ubiquinone cycle (Q), complex III, cytochrome c (cyto c) and complex IV, ultimately reducing $½O_2$ to H_2O. This electron flow results in the pumping of protons (+) to the outer surface of the inner membrane, establishing a membrane potential that is used by the ATP synthase complex to drive the phosphorylation of adenosine diphosphate (ADP) into the energy-carrying adenosine triphosphate (ATP). Some electrons (red dotted line) are misplaced within the mitochondrial matrix, which can interact with O_2 to form reactive oxygen species including $O_2^{\cdot}$ and OH. Under physiological conditions, these free radicals are scavenged by the antioxidant glutathione (GSH), which is converted to glutathione disulfide (GSSG) by glutathione peroxidase (GPx). However, under conditions of cell stress or injury, cellular respiration is disrupted and the production of reactive oxygen species overwhelms the innate antioxidant capacity. NACA (green) readily crosses mitochondrial membranes and replenishes GSH by supplying cysteine, the rate-limiting substrate for GSH synthesis. NACA also assists in converting GSSG back into GSH. Evidence from Pandey et al. and Patel et al. suggests that NACA treatment after traumatic brain or spinal cord injury preserves mitochondrial bioenergetics. Specifically, administration of NACA maintained the enzymatic activity and respiration rate of complexes I and IV, maintained ATP synthase-mediated phosphorylation of ADP to ATP, and preserved the activity of pyruvate dehydrogenase (PD), the main entry point into the TCA cycle. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

activity may be a reasonable therapeutic option in neurotrauma. Composed of glutamate, glycine, and cysteine, the latter amino acid has the lowest intracellular concentration, and thus availability of cysteine is the rate-limiting factor for GSH production under conditions of oxidative stress (Arakawa and Ito, 2007; Shahripour et al., 2013). Upon cell entry, NAC is rapidly hydrolyzed to cysteine and thereby supplies this critical precursor for GSH production.

A number of studies have highlighted the potential benefit of enhancing GSH production by NAC supplementation after experimental TBI (Table 1). An early study by Xiong et al. demonstrated the restoration of mitochondrial function and GSH levels by NAC administration, but only when provided prior to or up to 1 h post-injury, with no efficacy if treatment was delayed to 2 h (Xiong et al., 1999). Studies over the past decade have included acute NAC treatment in an experimental model of closed head injury, which resulted in a reduction in malondialdehyde (MDA), a biomarker of lipid peroxidation, and preservation of neuronal morphology (Hicdonmez et al., 2006). Conversely, another study published in the same year reported no effect on edema or contusion volumes by NAC administration after controlled cortical impact (Thomale et al., 2006). Most recently, evidence of reduced ROS production and apoptosis were demonstrated after repeated doses of NAC, in a weight drop model of TBI (Nazıroğlu et al., 2014). Further, Eakin et al. validated the amelioration of cognitive deficits by NAC treatment across two distinct models of TBI resulting from either a fluid percussion insult or weight drop injury (Eakin et al., 2014).

The literature on experimental SCI presents a more conflicting story. In a clip compression model, similar NAC treatment paradigms have been reported to reduce MDA levels (Hanci et al., 2010) or, contrarily, have no effect on lipid peroxidation (Kaynar et al., 1998). A recent study using continuous intrathecal infusion of NAC beginning after SCI in rats demonstrated neuroprotection as reduced motoneuron loss (Karalija et al., 2012). However, this efficacy did not translate into a larger vertebrate model, as NAC infusion failed to improve neurologic outcomes or urinary markers of lipid peroxidation, in a placebo-controlled trial in dogs that sustained SCIs resulting from the spontaneous rupture of an intra-vertebral disc (Baltzer et al., 2008).

The inconsistencies of NAC after neurotrauma are likely due to a number of variables including type and severity of the injury, choice of outcome parameters, as well as dosing and therapeutic window (Table 1). Reports of NAC efficacy across a range of outcome measures suggest that at least some of the administered dose is reaching the injured CNS; however, it has been well documented that NAC has restricted bioavailability, due to its low lipid solubility combined with the negatively charged carboxyl group at physiological pH, which limits its ability to cross cell membranes (Cotgreave, 1997; McLellan et al., 1995) (see Fig. 2). As such, inconsistent efficacy by NAC may stem

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