Published in final edited form as:

Exp Neurol. 2009 July ; 218(1): 9–10. doi:10.1016/j.expneurol.2009.04.001.

Alpha Lipoic Acid and Frataxin: A New Indication for an Old Antioxidant?

James W. Russell

Department of Neurology, University of Maryland School of Medicine & Maryland VA Medical Center, Baltimore, MD 21201, USA

Cisplatin is an effective treatment for breast, ovarian, testicular, and small cell lung malignancies, however its use leads to a dose-limiting and cumulative sensory neuropathy. The effects of cisplatin neurotoxicity can persist for decades (Strumberg et al., 2002). The mechanism of cisplatin toxicity is uncertain, although it has been shown *in vitro* to reduce fast axonal transport, and induces apoptosis in dorsal root ganglion cells (DRG) by forming high affinity adducts between cisplatin and either genomic or mitochondrial DNA (McDonald et al., 2005; Peltier and Russell 2002). Adduct formation is associated with translocation of the proapoptotic protein Bax to the mitochondrion and release of cytochrome c into the cytosol. This series of events leads to a fas receptor-independent form of programmed cell death (McDonald and Windebank 2002). Cisplatin is frequently administered in combination with paclitaxel and the effect of combination therapy has recently been tested in an animal model (Carozzi et al., 2009). Current data are insufficient to conclude if any tested neuroprotective agents, for example amifostine, diethyldithiocarbamate, glutathione, Org 2766, or Vitamin E prevent or reduce the neurotoxicity of platin drugs (Albers et al., 2007).

Dr. Melli and colleagues in “Alpha-lipoic Acid Prevents Mitochondrial Damage and Neurotoxicity in Experimental Chemotherapy Neuropathy” present an intriguing new mechanism for cisplatin neuronal injury. Using an embryonic day (E-15) DRG culture system, neurons exposed to cisplatin showed a significant reduction in frataxin expression (Melli et al., 2008). Human frataxin is a ~17kDa protein whose deficiency has been associated with Friedreich’s ataxia. Friedreich’s ataxia is a progressive neurodegenerative disease that affects both central and peripheral axons. However, like cisplatin neuropathy, Friedreich’s ataxia is associated with significant degeneration of DRG sensory neurons. Frataxin is intimately associated with several aspects of intracellular iron metabolism and detoxification including iron binding/storage and iron chaperone activity (Campanella et al., 2009). Frataxin also interacts with the electron transport chain proteins, activates glutathione peroxidase, and increases the mitochondrial membrane potential. Frataxin deficiency is associated with a severe deficiency in mitochondrial DNA, an event that results in reduced oxidative phosphorylation and altered antioxidant defenses. Furthermore, a major consequence of the severe depletion of mitochondrial DNA would be mitochondrial bioenergetic failure in the peripheral nervous system (Koch and Britton 2008).

Correspondence: James W. Russell, M.D., M.S., Department of Neurology, University of Maryland, School of Medicine, 22 South Greene Street, Box 175, Baltimore, MD 21201-1595, Tel: 410-706-6689; Fax: 410-706-4949, E-mail: JRussell@som.umaryland.edu.

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Another observation in the present study is the formation of autophagosomes in DRG treated with cisplatin. Typical double membrane bound vacuoles containing degenerative mitochondria were observed in DRG neurons. Autophagy is an important process involved in the degradation of cytoplasmic organelles and in particular mitochondria. Recent research shows that autophagosomes form on the surface of the mitochondria and they then peel off from mitochondria. Autophagic programmed cell death (type II) is characterized by the accumulation of autophagic vesicles (autophagosomes and autophagolysosomes) and is often observed when massive cell elimination is demanded or when phagocytes do not have easy access to the dying cells (Shintani and Klionsky 2004). It is unclear if autophagy causes neuronal or axonal pathology or is a result of the injury. However despite this uncertainty, the current observations by Melli and colleagues provide a rational explanation for the pathophysiological changes that occur in cisplatin neuropathy.

In the present study, paclitaxel reduced the number of functioning mitochondria in DRG neurons and Schwann cells, induced apoptosis in both cells, and impaired neurite growth. Paclitaxel is a common adjunctive therapy in women with node positive breast cancer. It is frequently used in combination with cisplatin and other chemotherapeutic drugs and is also used for other solid tumors such as ovarian and non-small cell lung cancer. A length-dependent sensorimotor axonal neuropathy is a common dose-dependent side effect of treatment. It can also rarely cause cranial neuropathies, motor involvement and autonomic dysfunction (Peltier and Russell 2006). Paclitaxel binds to tubulin and hyperstabilizes microtubules thus promoting the assembly and reducing the disassembly of microtubules in unmyelinated and myelinated axons. These changes reduce normal axonal transport. Several potential therapies have been assessed in taxol-induced neuropathy including glutamine and calpain inhibitors (Peltier and Russell 2006). However, these potential neuroprotective therapies have not been tested in large randomized clinical trials.

An important observation in the study by Melli et al is the finding that alpha-lipoic acid (α -lipoic acid) prevented mitochondrial damage and that this was dependent on expression of frataxin. α -lipoic acid had neuroprotective effects with both cisplatin and paclitaxel toxicity in cell culture. In contrast to the data with cisplatin, the effect of α -lipoic acid on paclitaxel induced apoptosis was less significant, which is not surprising as apoptosis is not the main toxic mechanism of paclitaxel. In DRG cultures transfected with anti-frataxin siRNA, there was reduced axonal outgrowth. Cisplatin and paclitaxel showed increased neurotoxicity in frataxin knockdown cultures and α -lipoic acid did not prevent the axonal damage as it did in non-transfected cultures. In contrast, α -lipoic acid increased the expression of frataxin in sensory neurons. A further observation was that whereas cisplatin significantly reduces the expression of frataxin, paclitaxel does not. This is despite an increased neurotoxicity in the anti-frataxin siRNA cultures. The implication of this is not clear. Importantly, the α -lipoic acid had to be administered prior to exposure to cisplatin or paclitaxel in order to prevent neurotoxicity. It should be clearly noted that these are cell culture studies and may not be clinically relevant. However, α -lipoic acid has been shown in a small study to improve neuropathy when used post docetaxel/cisplatin treatment in subjects who had already developed peripheral neuropathy (Gedlicka et al., 2003). Patients were treated with 600 mg intravenous α -lipoic acid once a week for 3–5 weeks followed by 1800 mg orally daily for up to 6 months. These results will need to be confirmed in a larger randomized controlled study.

α -lipoic acid is one of the most extensively studied antioxidants. Oxidative stress has been associated with several types of neuropathy including diabetic and chemotherapy-induced neuropathy (Russell and Kaminsky 2005). In the peripheral nerve, α -lipoic acid reduces oxidative stress and the generation of peroxynitrites, inhibits activation of caspases, and improves peripheral nerve endoneurial blood flow. α -lipoic acid *in vivo* is reduced to active dihydrolipoate and is able to regenerate other antioxidants such as vitamin C, vitamin E, and

reduced glutathione through redox cycling. The antioxidant potential of α -lipoic acid has been used to treat several neurological diseases including multiple sclerosis and stroke. However, it has been used most extensively for the treatment of neuropathy, and in particular in diabetic neuropathy. Most experimental diabetic neuropathy studies have shown variable degrees of improvement with α -lipoic acid treatment. Clinical trials have shown mixed results. However, in one of the larger, multicenter, randomized, double-blind, placebo-controlled studies of diabetic neuropathy, there was a small but significant improvement in the neuropathy symptom score but not in other endpoint measures (Ziegler et al., 1999). In general, short term treatment with α -lipoic acid mildly improves both neuropathic symptoms and deficits and the treatment has relatively few side effects.

The observation that α -lipoic acid prevents neuronal and Schwann cell injury in an experimental cell culture model of cisplatin and paclitaxel-induced toxicity and that this is dependent on levels of frataxin, is a novel finding. It remains to be seen whether these observations will prove to be true in toxic neuropathy in humans and if α -lipoic acid will prevent this neurotoxicity. Further basic science studies to examine alternative mechanism/s of action of α -lipoic acid in chemotherapy-induced neuropathy and more robust clinical trials with α -lipoic acid are needed.

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