Biologia Serbica, 2021, 43(1): 12-15 DOI 10.5281/zenodo.5512203

Minireview

Molecular mechanisms of behavioral manifestations of neurotoxicity induced by platinum-based chemotherapeutics: a beneficial role for antioxidant supplementation

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Accepted: 11 August 2021 / Published online: 20 September 2021

Summary. For decades, platinum-based chemotherapeutics have been widely used in clinical protocols for numerous malignancies. However, despite their undisputed therapeutic potential, there clinical usage is limited by serious adverse effects. Neurotoxicity is one of the most frequent side effects of platinum-based compounds, and is associated with oxidative damage and pro-apoptotic activity. Thus, antioxidant supplementation may play a potential role in the treatment of platinum-based drug-induced neurotoxicity. In support of this, encouraging results were achieved using a variety of antioxidant-rich compounds. Our results suggest that synthetic and natural products with high antioxidant content may attenuate cisplatin-induced neurotoxicity by preventing oxidative damage and apoptosis in the brain. The beneficial role of antioxidant supplementation is further supported by their observed ability to reverse cisplatin-induced behavioral deterioration.

Keywords: antioxidants, apoptosis, cisplatin, oxidative stress.

Although platinum-based chemotherapeutics were initially met with great expectations over half a century ago, they have since failed to live up to their promise as breakthrough treatment for cancer. The antitumor effects of cisplatin, once known as "the drug of the century", were initially observed *in vitro* (Rosenberg et al. 1965) and *in vivo* studies (Kondo et al. 1994), as well as extensive testing in clinical trials (Kehoe et al. 1992).

Along with carboplatin (cis-diammine-1,1-cyclobutanedicarboxylateplatinum) and oxaliplatin (trans-R,R-cyclohexane-1,2-diamineoxalato-platinum II), cisplatin (cis-diamminedichloridoplatinum II), is the most frequently used metal-based chemotherapeutic, with a broad spectrum of therapeutic indications. Cisplatin alone, or more often along with other antineoplastic drugs, is considered to be the first line treatment for numerous cancers, including cancers of the reproductive system (Bergamini et al. 2017; Bucher-Johannessen et al. 2019), lung cancer (Kosmidis et al. 2019), breast cancer (Baek et al. 2020), brain cancer (Angeli et al. 2020), sarcomas (Brown et al. 2018), and lymphomas (Zhang et al. 2016).

The most recent platinum-based chemotherapeutic to be registered worldwide, oxaliplatin, is used to treat late phase malignancies, such as metastatic colorectal cancer (Martín-Aragón et al. 2018), as well as advanced gastric (Zhang et al. 2019) and ovarian cancer (Bogliolo et al. 2015). At the same time, carboplatin has become clinically important for the treatment of advanced ovarian carcinoma (Nguyen et al. 2016), head and neck cancer (Xiang et al. 2019), and lung cancer (Akamatsu et al. 2019).

However, the undisputed therapeutic potential of cisplatin and other platinum-based compounds in chemo-

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therapy protocols have gradually become overshadowed by the severe therapeutic limitations of these drugs. Resistance toward using platinum-based agents is usually divided into two principal categories: inherited resistance to treatment with the currently approved platinum agents and the numerous clinically confirmed adverse effects of various grades of severity. The side effects associated with platinum-based compounds may be classified from minor to dose-limiting, and include: hepatotoxicity, nephrotoxicity, ototoxicity, myelosuppression, gastrointestinal toxicity, neurotoxicity, and cardiotoxicity (Vukovic et al. 2019).

Although evidence suggests that platinum-based chemotherapeutics display poor penetration through the blood-brain barrier (McKeage et al. 2001); both clinical and experimental evidence show that cisplatin is found in high concentrations in patients' brains (Nakagawa et al. 1996), as well as in mice hippocampus (Köppen et al. 2015). Along with cisplatin accumulation in the brain, there is evidence for numerous neurotoxic events accompanied by structural alterations in the human brain (Simo et al. 2013, 2015) and animal experimental models (Zhou et al. 2016).

Although most studies designed to evaluate cisplatin-induced neurotoxicity have focused on peripheral nervous system effects (Lin et al. 2015), numerous reports also confirmed the impact of cisplatin treatment on animal behavioral patterns (Lomeli et al. 2016). It has been reported that chronic cisplatin therapy affects locomotion by decreasing total locomotor and exploratory activity in rats (Shabani et al. 2012; Golchin et al. 2015). The same reports presented evidence showing that rats treated with cisplatin display signs of cognitive impairment. Literature data shows that systemic administration of cisplatin administration in mice is associated with increased cell death and decreased cell division in the CNS: especially in the subventricular zone, the dentate gyrus and other parts of the hippocampus, as well as the prefrontal cortex and corpus callosum (Dietrich et al. 2006; McWhinney et al. 2009; Sioka and Kyritsis 2009). At the same time, clinical trials have shown that cisplatin therapy is accompanied by numerous behavioral alterations (Schagen et al. 2008; Gan et al. 2011). Clinical manifestations of cisplatin-induced toxicity include acute encephalopathy, stroke-like episodes, acute blindness and seizures (Gulec et al. 2013). Although rarely observed, it should be noted that cisplatin therapy has been linked to toxic leukoencephalopathy and destruction of CNS white matter, accompanied by cognitive impairment and emotional dysfunction (Filley et al. 1999).

Although manifested through various clinical symptoms, the majority of platinum-based compound-induced toxicities have in common similar underlying pathophysiological mechanisms, including: DNA damage, increased production of pro-inflammatory cytokines, mitochondrial dysfunction, apoptosis and oxidative stress (Jangra et al. 2016). Cisplatin exerts its cytotoxic properties by reacting with DNA, eventually leading to irreversible apoptosis (Tanida et al. 2012) by a mechanism that includes binding to the N7 reactive center on purine residues, and the formation of interstrand and intrastrand DNA crosslinks. These intrastrand adducts seem to inhibit DNA replication and transcription, resulting in the cytotoxic effects associated with cisplatin. Consequently, there is up-regulation of some proteins that transmit DNA damage signals to downstream signaling cascades. Finally, the increase in p53, MAPK, and p73 levels results in pro-apoptotic action. In addition, it has been reported that cisplatin simultaneously inhibits the proliferation of stem cells and neurogenesis in the subventricular and subgranular hippocampal zone by reducing the expression of anti-apoptotic genes (Manohar et al. 2014).

Furthermore, cisplatin irreversibly affects mitochondrial DNA, with subsequent inhibition of replication and transcription that finally results in mitochondrial dysfunction and cell death (Yang et al. 2006). Concomitantly, since the mitochondrion is a major source for production of reactive oxygen species, this series of events also leads to oxidative damage (Rosic et al. 2018). A similar algorithm was confirmed in the rat CNS (Manohar et al. 2014).

One mechanism of cisplatin-induced neurotoxicity is the disturbance of oxidative stress homeostasis. Cisplatin triggers lipid peroxidation and weakens the capacity of antioxidant defense systems in the brain tissue of rats (Kamisli et al. 2015). We have previously shown that a single dose of cisplatin (7.5 mg/kg i.p.) induced anxiety level imbalance in a clear anxiogenic manner. This was accompanied by oxidative damage in the rat hippocampus, and potentiation of apoptotic mechanisms. The latter was due to both increased expression of Bax and caspase-3 genes, and a decline in Bcl-2 relative gene expression. These events provide a framework for cisplatin-induced neurotoxicity (Kumburovic et al. 2019; Vukovic et al. 2019). Furthermore, the relationship between increased oxidative stress, apoptosis and behavioral outcomes may be due to the fact that patophysiological mechanisms lead to diminished BDNF (*brain-derived neurotrophic factor*) and GABA-A receptor levels in brain regions that are involved in mood regulation. This results in anxiogenic and pro-depressant effect, which is accompanied by cognitive decline (Arsenijevic et al. 2021).

As we become more aware of the causal relationship between oxidative damage and cisplatin-induced neurotoxicity, various studies have been designed to estimate the protective role of antioxidants in the treatment of neurotoxicity. These studies have shown that many different compounds with antioxidant activities have had beneficial effects against cis-

platin-induced neurotoxicity (Stankovic et al. 2020). We have also studied the protective roles of antioxidant supplementation using various compounds in combination with cisplatin treatment, and have observed an attenuation of behavioral dysfunctions in these cases.

Pretreatment with N-acetylcysteine (NAC), which is usually considered to be a safe drug for various clinical indications, was sufficient to ameliorate cisplatin-induced oxidative damage in the rat hippocampus (Vukovic et al. 2019). The decline in lipid peroxidation levels and enhanced antioxidant defense capacity associated with NAC administration was accompanied by prevention of the pro-apoptotic actions of cisplatin. Finally, antioxidant supplementation with NAC was sufficient to diminish the anxiogenic response to cisplatin (Vukovic et al. 2019). A similar neuroprotective effect was reported for taurine, a sulfur-containing amino acid following cisplatin-induced brain injury and behavioral alterations (Owoeye et al. 2018). We have also investigated supplementation protocols that involve natural products with high antioxidant content and have reported their beneficial effects. Namely, *Satureja hortensis* L. extract was found to attenuate the neurotoxic events associated with cisplatin administration (Kumburovic et al. 2019). The extract was obtained from summer savory, and is dominated by polyphenols and flavonoids, among others, that are responsible for its antioxidant properties (Fierascu et al. 2018). Pretreatment with *S. hortensis* extract significantly reduced cisplatin-induced oxidative damage and apoptotic action in the rat brain. Again, the beneficial role of antioxidant supplementation in the treatment of cisplatin-induced neurotoxicity was also supported by its ability to prevent emotional disturbances, as manifested by anxiety-like behavior. Our results are in accordance with an independent study by other authors, who confirmed the neuroprotective effects of nebivolol against cisplatin-associated depressive-like behavior in rats (Abdelkader et al. 2017).

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