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Graphical Review

Oxidative stress and nerve damage: Role in chemotherapy induced peripheral neuropathy ☆

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ABSTRACT

Peripheral neuropathy is a severe dose limiting toxicity associated with cancer chemotherapy. Ever since it was identified, the clear pathological mechanisms underlying chemotherapy induced peripheral neuropathy (CIPN) remain sparse and considerable involvement of oxidative stress and neuroinflammation has been realized recently. Despite the empirical use of antioxidants in the therapy of CIPN, the oxidative stress mediated neuronal damage in peripheral neuropathy is still debatable. The current review focuses on nerve damage due to oxidative stress and mitochondrial dysfunction as key pathogenic mechanisms involved in CIPN. Oxidative stress as a central mediator of apoptosis, neuroinflammation, metabolic disturbances and bioenergetic failure in neurons has been highlighted in this review along with a summary of research on dietary antioxidants and other nutraceuticals which have undergone prospective controlled clinical trials in patients undergoing chemotherapy.

Contents

Introduction

Chemotherapy induced peripheral neuropathy (CIPN) remains one of the major limitations in oncology clinics due to increasing number of cancer patients, lack of effective treatment strategy, relapse of disease [1]. Around 30–40% of patients undergoing chemotherapy develop peripheral neuropathy and experience symptoms of pain and sensory disturbances [2]. According to National Cancer Institute (NCI), CIPN is one of the major reasons responsible for cessation of treatment, and hence is responsible for decreased chemotherapeutic efficacy and higher relapses [3]. Symptoms of peripheral nerve damage range from sensorimotor deficits (tingling sensation, burning pain in the arms, allodynia and hyperalgesia) to various functional deficits (impaired axonal transmission and reduced nutritive blood flow to nerves [4]). The most frequent agents causing CIPN are platinum compounds, taxane derivatives, vinca alkaloids, epothilones, thalidomide and bortezomib, which adversely affect the peripheral nervous system through dissimilar mechanisms summarized in Fig. 1 [5]. Although, the molecular pathomechanism and severity may vary with the inducing agent, physical damage to the neurons by chemotherapeutic agent is a common mechanism underlying

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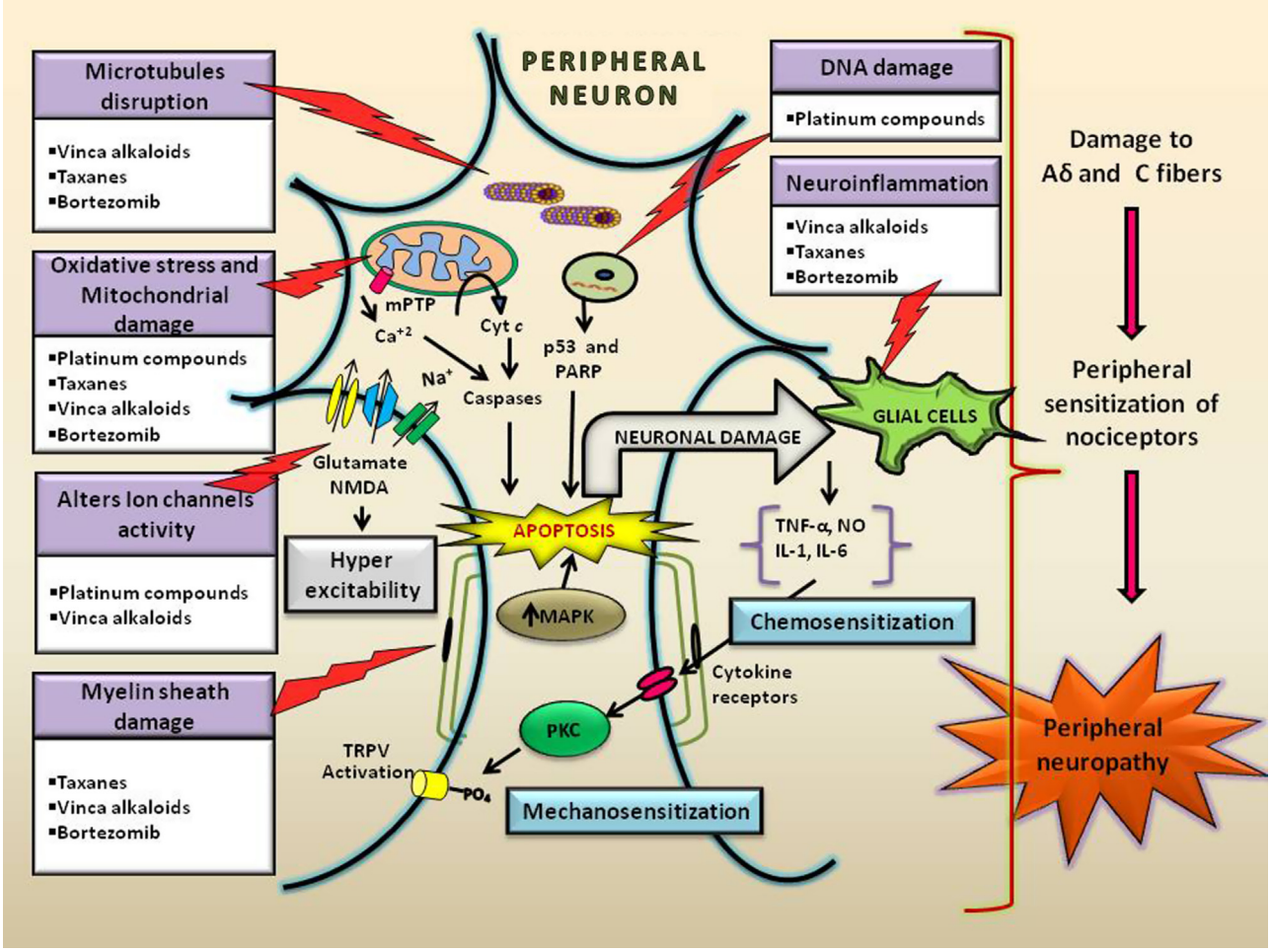

Fig. 1. Pathobiology of peripheral neuropathy induced by several chemotherapeutic agents: peripheral nerve damage associated with taxanes, vinca alkaloids and bortezomib is characterized by various mechanisms like microtubular damage, mitochondrial dysfunction, neuronal apoptosis etc. [24]. Damage to the microtubules causes impairment in axonal transmission and mitochondrial dysfunction. The mitochondrial dysfunction is due to opening of mitochondrial permeability transition pore (mPTP), swollen and vacuolated mitochondria which brings Ca^{2+} deregulation and activation of caspases thus driving the neuronal cell towards apoptosis [34]. These changes consequently stimulate microglia cells which releases the proinflammatory mediators and growth factors to the damaged areas leading to peripheral sensitization thus causing spontaneous discharge and hyper excitability [3]. Further proinflammatory mediators are also capable of damaging myelin sheath [35]. Platinum compounds like cisplatin and oxaliplatin can affect mitochondrial DNA, leading to mitochondrial dysfunction and also induces neuronal apoptosis through activation of mitogen activated protein kinase (MAPK) pathway. These chemotherapeutic agents are also reported to cause peripheral sensitization by the up regulation of N-methyl D-aspartate (NMDA) receptors, transient receptor potential vanilloid (TRPV) channels, and protein kinase C (PKC) [34].Oxaliplatin also alters the Na^+ channel conductance through chelation of Ca^{2+} [36]. All these effects can damage the sensory neurons such as Aδ and C fibers, which leads to neuropathic pain characterized by hyperalgesia and allodynia.

the disease pathology [4]. The physical damage by chemotherapeutic drugs leads to functional impairment in neurons through oxidative stress, inflammation, apoptosis and electrophysiological disturbances. The scope of the present review is to present a basic idea on the possible role of oxidative stress and related pathomechanisms in CIPN based upon the existing experimental evidences.

Susceptibility of peripheral nervous system (PNS) to oxidative stress

It is a recognized fact that antineoplastic agents produce reactive oxygen species (ROS) to induce apoptosis in cancer cells [6]. However, ROS generated during chemotherapy may interfere with the normal cells and tissues and may be associated with the various toxic events like cardio toxicity, nephrotoxicity, neurotoxicity, etc. Certain structural and functional attributes of peripheral nervous system (PNS) make it more susceptible for accumulation of chemotherapeutics and some neurotoxins (Fig. 2) [5]. Lack of an efficient vascular barrier and absence of lymph drainage make the PNS more prone to toxic chemical insults. In addition mammalian nerves are known to be more susceptible to oxidative stress because of their high content of phospholipids, mitochondria rich axoplasm and also due to weak cellular antioxidant defences [7]. It has also been recently observed that structural and functional impairment caused by anti-cancer drugs enhances mitochondrial free radical production. Oxidative stress generated in this regard causes physical damage to neurons by demyelination, mitochondrial dysfunction, microtubular damage and apoptosis [8].

Role of oxidative stress in the neuronal damage and incidence of neuropathic pain

Although neurotoxicity caused by different classes of chemotherapeutic drugs differs to a significant extent, peripheral neuronal degeneration or small fiber neuropathy remains the end result of all CIPNs. It is been suspected that this might occur by a common mechanism i.e. increased neuronal oxidative stress as presented in Fig. 3. In fact, oxidative stress is identified to be responsible for the neuronal damage in different models of neuropathies such as diabetic neuropathy, acrylamide induced neuropathy and Charcot–Marie neuropathy [9–12]. These observations laid the foundation for investigating possible involvement of oxidative stress in CIPN. Chemotherapy induced mitochondrial