Dopamine (DA) toxicity in pathogenesis and therapy of Parkinson's disease (PD).

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Parkinson's disease (PD) is the second most common neurodegenerative disorder that affects 1% of the general population over the age of 60 [1]. PD is characterized by progressive dopamine (DA) neuron degeneration in the pars compacta of the substantia nigra (SN) plus Lewy body formation in affected brain areas [2]. The progressive DA neuron degeneration leads to decreased DA content in SN, contributing to onset of PD symptoms. So far PD is still an incurable human disorder and L-DOPA replenishing therapy is the only treatment, which can transiently alleviate PD symptoms, with no therapeutic effects against DA neurons demise in PD patient brains.

Although the pathogenesis of PD is still unclear, increased oxidative stress in DA neurons is commonly recognized to be the pathological factor for DA neuron degeneration in PD [3]. The DA is a neurotransmitter for DA neurons in SN. However DA is unstable and DA can undergo oxidation to generate small molecular reactive oxygen species (ROS) and highly reactive DA quinones (DAQ) [4]. The endogenous DA is supposed to be the culprit for increased oxidative stress in DA neurons [5-7]. The DA toxicity is identified in human mesencephalic neuron-derived cells [8]. The endogenous DA in DA cells can inhibit proteasome activity, leading to DA neurons vulnerability [7]. Achievements from *in vivo* animal model studies also implicate the toxic feature of endogenous DA in DA neurons related to DA neuron degeneration [9-11]. A recent paper demonstrates that DA oxidation mediates mitochondrial and lysosomal dysfunction and DA oxidation represents an important link between mitochondrial and lysosomal dysfunction in PD pathogenesis [12]. The small molecular ROS is supposed to increased oxidative stress in DA neurons via reversible oxidative modifications. However, DAQ is highly reactive and can irreversibly and covalently conjugate with sulfhydryl groups of cysteine residues of proteins, contributing to misfolding, inactivation and aggregation of DA modified proteins [13-16]. The DAQ modified proteins are found to be accumulated in the SN of aged rats and is correlated with DA induced toxicity in human DA neurons [17]. The DAQ can induce mitochondria impairment and inhibit ubiquitin proteasome system (UPS) [13,18,19]. DA can induce irreversible proteasome inhibition via DAQ, rather than through small ROS [20]. The PD associated proteins ubiquitin carboxy-terminal hydrolase L1 and DJ-1 can be covalently modified by DAQ in both brain mitochondrial preparations and SH-SY5Y cells [13]. It is found that a group of rat brain mitochondrial proteins can be covalently modified by DAQ, including chaperonin, ubiquinol-cytochrome c reductase core protein 1, glucose regulated protein 75 / mitochondrial HSP70/mortalin, mitofilin, and mitochondrial creatine kinase [13]. The DAQ induced conjugation can be supported by findings that DAQ can form polydopamine, long-chain molecular building blocks, via covalent reactions, leading to formation of thin, surface-adherent polydopamine films onto a wide range of inorganic and organic materials [21]. Therefore DAQ induced functional protein misfolding, inactivation and aggregation as well as subsequent UPS inhibition and mitochondria impairment significantly account for DA dependent DA neuron degeneration in PD.

The DA induced toxicity can be iron related. Iron accumulation is detected in the SN region of both living and post-mortem PD patient brains [22,23]. Recent findings show that iron species can mediate DA oxidation to produce deleterious ROS and DAQ, leading to DA neuron vulnerability [24]. Free iron ions can form complexes with DA to induce DA oxidation and toxic by-products generation [24]. Deferoxamine (DFO), an iron chelator, can inhibit free iron mediated DA oxidation and subsequent cytotoxicity via abrogation of iron-DA complex formation [24]. Iron chelators with blood brain barrier (BBB) penetrating capacity are supposed to protect against iron related DA neuron degeneration in PD. The DA induced toxicity is also implicated in genetic factors induced DA neuron degeneration. The toxicity of α-syn protein can be DA dependent [25-28]. The auto-oxidation of endogenous DA aggravates non-apoptotic DA cell death induced by overexpression of human mutant A53T α-syn [25]. DAQ can conjugate with α-syn to form unstructured adducts [29]. The conjugation of DAQ with α-syn can slow the conversion of protofibrils to fibrils, leading to accumulation of toxic α-syn protofibrils [30]. Furthermore PINK1 mutations induced DA neuron vulnerability is also DA dependent [31]. The DA dependent toxicity of mutant PINK1 to DA neurons is supported by observations in PINK1 knockout mice [32,33]. It is found that the extra-mitochondrial PINK1 can regulate TH expression and DA content in DA neurons in a PINK1 kinase activity dependent manner [31]. Mutations of PINK1 will significantly increase levels of TH and DA, contributing to DA neurons vulnerability to challenges [31].

The DA related toxicity can be alleviated by ROS scavenges, especially those with DAQ detoxifying capacity. The GSH is an important endogenous ROS scavenger and DAQ detoxifier [4,34]. In the absence of metal ions, GSH can inhibit DA auto-oxidation and tyrosine catalyzed DA oxidation [4]. GSH can

provide its sulfhydryl group to react with and detoxify reactive DAQ [4]. Data from post-mortem studies shows the increased GSH-DA conjugates in PD brains compared to normal controls, suggesting pathological roles of DAQ and protective conjugation of DAQ by GSH in PD brains [35]. Furthermore post-mortem studies also show that the GSH content in SN in early onset PD is significantly decreased by ~50% when compared to aged controls [36]. These findings imply that decreased GSH level in DA neurons can be a pathological factor to DA neuron vulnerability [36]. Future studies searching for new and potent DAQ detoxification agents with BBB penetrating and iron ions chelating capacities should add to our therapies against DA neuron degeneration in PD.

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