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Review

Correlation between the biochemical pathways altered by mutated parkinson-related genes and chronic exposure to manganese

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ABSTRACT

The studies presented in this review attempt to describe the operative properties of the genes involved in generation of early and late onset of Parkinson's disease or Parkinson-like disorders and how mutation in these genes relate to onset of manganism. These include the genes α-synuclein, parkin, PINK1, DJ-1, ATP13A2, and SLC30A10 which are associated with early-onset of Parkinson's as well as those genes linked with late onset of the disorder which include, LRRK2 and VPS35. Since mutations in these genes and excess Mn potentially disrupt similar cellular processes within the basal ganglia, it is reasonable to hypothesize that the expressed symptoms of Parkinson's disease may overlap with that of manganese (Mn) toxicity. There appears to be four common processes linking the two disorders, as mutations in genes associated with Parkinsonism initiate similar adverse biological reactions acknowledged to stimulate Mn-induced dopaminergic cell death including; (1) disruption of mitochondrial function leading to oxidative stress, (2) abnormalities in vesicle processing, (3) altered proteasomal and lysosomal protein degradation, and (4) α-synuclein aggregation The mutual neurotoxic processes provoked by mutations in these genes in concert with the biological disturbances produced by Mn, most likely, act in synchrony to contribute to the severity, characteristics and onset of both disorders.

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1. Introduction

Chronic exposure to Mn can lead to a disorder known as manganism characterized by severe neurological deficits that often resemble the involuntary extrapyramidal symptoms associated with Parkinson's disease. The disorder is most often linked to occupations such as welding, steel and battery manufacturing and Mn mining in which exposure to abnormally high atmosphere levels is a daily occurrence, although, toxicity is also observed in patients with chronic liver disease as hepatic failure precludes the obligatory route required for its elimination (Hauser and Zesiewicz,

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1996; Criswell et al., 2012). Although similar to Parkinsonism, the observed symptoms produced by Mn are somewhat distinct as manganism is characterized by only mild tremors at rest, a masked-like face and a more upright standing position. Most notable is significant loss of balance, limb rigidity, slurred speech, excessive salivation and a distinctive gait often referred to as a cock-like walk. Differences in the neurological deficits expressed between Mn toxicity and Parkinsonism originate with the site of the injury as manganism presumably associates with altered functional behavior of neurons within the globus pallidus as well as dopaminergic neurons in the striatum, whereas, Parkinsonism predominantly correlates with degeneration of dopaminergic neurons in the substantia nigra pars compacta. The distinguishing clinical features resulting from these differences vary considerably even though both conditions significantly alter the signaling output of the basal ganglia.

Although the origins of the lesions between the two disorders are distinct, many of the characteristics of Mn intoxication can coincide or possibly evolve to more Parkinson-like features as there is considerable evidence in the literature suggesting that chronic exposure to Mn may predispose an individual to acquire earlier onset of a Parkinson-like syndrome (Gorell et al., 1999; Hudnell, 1999; Pal et al., 1999; Racette et al., 2001; Kim et al., 2002; Racette et al., 2005). One of the fundamental similarities between the manganism and Parkinsonism results from the fact that Mn is capable of suppressing dopamine release in the striatum generating symptoms which overlap with that observed in Parkinson's disease (Guilarte et al., 2006; Guilarte et al., 2008; Roth et al., 2013). Thus, the classical distinguishing characteristics between the two neurological disorders may, in fact, merge based on the relative magnitude to which Mn inhibits dopamine release. It is important to note that these dopaminergic neurons which originate in the substantia nigra pars compacta remain essentially intact upon chronic exposure to Mn (Olanow et al., 1996). This is particularly significant as Mn has also been reported to accumulate not only in the globus pallidus but also, though to a lesser extent, in both the substantia nigra pars reticulata and pars compacta (Park et al., 2003; Verina et al., 2011; Robison et al., 2012; Zhang et al., 2013) as well as the striatum (Erikson et al., 2005). The fact that these neurons survive and dopamine content within the striatum is essentially unaffected (Guilarte et al., 2006) suggests that the action of Mn on dopamine release is likely to be a local response probably occurring within the presynaptic nerve terminal. The observation that Mn inhibits amphetamine-induced dopamine release implies its actions may be mediated *via* the dopamine transporter (DAT) (Guilarte et al., 2006). In support of this are recent findings demonstrating that Mn promotes internalization of DAT and suppresses dopamine release in DAT transfected HEK cells (Roth et al., 2013). Accordingly, inhibition of dopamine transmission by Mn has the potential to produce a neurological condition resembling that observed in patients with Parkinson's disease which likely contributes to the general pathology seen in manganism.

Similar to other neurological disorders, onset, severity, and individual symptoms expressed in Mn toxicity as well as the progression of the disorder often deviates unpredictably implying underlying genetic variability as a potential origin responsible for the divergence in the pathological lesions and features expressed. This is clearly demonstrated by a study by Sadek et al. (2003) describing a patient who worked as a welder for a total of three years. Within one year after beginning employment, symptoms of Mn toxicity were initially perceived by the individual as a disturbance in his gait which upon continued progression and subsequent neurological testing was diagnosed as manganism. What makes the history for the development of the neurological deficits in this individual so remarkable is the precipitous rate of onset as opposed to the more typical case which requires longer exposure times usually in excess of ten years. The cause for the rapid onset of the neurological deficits in this short a time frame is unknown but, more than likely exposes a genetic predisposition in this individual. Interestingly, within several years of the initial diagnosis of manganism, he developed a unilateral tremor in his right hand more characteristic of Parkinsonism. His family history was only suggestive for older-onset of Parkinson's disease in a maternal great aunt.

The contribution of a genetic component responsible for precipitating the onset of manganism, in some individuals, is further intimated by the reality that not all welders, Mn miners or others exposed to high levels of the metal develop manganism yet exposures are comparable to their fellow workers that acquire the disorder. Clearly, this underscores the potential impact of genetic makeup in contributing to the vulnerability to develop Mn toxicity as well as the specific nature of the symptoms expressed. Assuming susceptibility to develop manganism is, in part, genetically regulated, then the most obvious association linking the two disorders would be the genes linked with early-onset of Parkinson's disease which include parkin (PARK2), DJ-1 (PARK7), PINK1 (PTEN-induced putative kinase 1, PARK6), ATP13A2 (PARK9) and SLC30A10 as well as LRRK2 (leucine-rich repeat kinase 2, PARK8) and VPS35 (vacuolar protein sorting-associated protein 35, PARK17) which associate with late onset of the disorder (Wider and Wszolek, 2007; Lesage and Brice, 2009; Yang et al., 2009; Houlden and Singleton, 2012). By linking mutations of these genes to acquisition of manganism may help clarify why symptoms and features between the two neurological disorders appear to be interrelated and why stress-related events provoked by Mn may accelerate onset of Parkinson-like symptoms.

This review is intended to focus on the function and properties of the most studied genes which have been linked to either early or late onset of Parkinsonism and to illustrate how the proposed mechanism of action for each may possibly relate to onset and severity of Mn toxicity.

2. PARK1 (α-synuclein)

Aggregation of α-synuclein in the brain is a central pathological feature of several neurodegenerative disorders classified as synucleinopathies which include Parkinson's disease (Marques and Outeiro, 2012). α-Synuclein is present in neurons as well as glial cells where it preferentially localizes to presynaptic terminals and is most abundant in the neocortex, hippocampus, striatum, thalamus, and cerebellum. It has been associated with a diverse array of activities including functioning of the ubiquitin–proteasome system (Bennett et al., 1999, Chu et al., 2009), maintenance of synaptic functionality (Watson et al., 2009), dopamine-mediated toxicity (Abeliovich et al., 2000; Tabrizi et al., 2000; Periquet et al., 2007), vesicle trafficking defects (Bonini and Giasson, 2005) and regulation of oxidative stress (Junn and Mouradian, 2002). Selective toxicity for dopamine neurons has been suggested to be caused by the actions of reactive oxidative products of dopamine on α-synuclein function and aggregation (Pham et al., 2009). Aggregated α-synuclein is a major constituent of Lewy bodies associated with Parkinsonism and mutations are linked with familial Parkinson's disease (Spillantini et al., 1997; Baba et al., 1998; Schulz-Schaeffer, 2010). The fact that the other early and late onset genes associated with Parkinson's disease have the potential to influence aggregate formation implies α-synuclein is a central element associated with dopaminergic cell death.

α-Synuclein is a 140 amino acid protein whose primary sequence is divided into three regions: the amphipathic N-terminal region, the hydrophobic central region and the largely acidic C-terminal region (Maroteaux et al., 1988). Native α-synuclein is normally a monomeric random coil protein which assumes various conformations that