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Mitochondria, monoamine oxidase B and Parkinson's disease

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ABSTRACT

The cause of cell death in Parkinson's disease (PD) remains unclear but it is multifactorial with a complex interaction between a range of pathogenic mechanisms. However, alterations in mitochondrial function have been clearly linked to nigral dopaminergic loss in sporadic PD and to the effects of gene mutations in familial forms of the illness. These may underlie the onset of oxidative and nitrative stress, a failure of protein degradation and apoptotic degeneration of dopaminergic cells in PD. Perhaps importantly, monoamine oxidase B (MAO-B) is located in the mitochondrial wall and plays a significant role in dopamine degradation in PD. This can explain the symptomatic actions of MAO-B inhibitors, such as selegiline and rasagiline on motor symptoms of PD. However, both selegiline and rasagiline also are associated with neuroprotective and/or disease modifying activities. The second generation MAO-B inhibitor, rasagiline can prevent multiple pathways that lead to apoptotic cell death and it is effective in *in vitro* and *in vivo* models of neuronal degeneration. However, there may be contributions from its major metabolite, aminoindan and non-MAO-B mediated actions on mitochondria may also contribute to these effects. It is important to determine whether these actions contribute to the possible disease modifying effect of MAO-B inhibitors in PD in man.

Introduction

The motor symptoms of Parkinson's disease (PD) are commonly associated with the loss of dopaminergic neurones in substantia nigra accompanied by the presence of Lewy bodies. The pattern of cell death is in reality, much wider involving a range of brain nuclei and multiple neurotransmitters accompanied by inclusion formation and these contribute to both motor and non-motor symptomatology of PD [1,2]. The underlying cause of cell death remains unknown but it is frequently associated with toxic effects initiated by altered or abnormal handling of α-synuclein and the general classification of PD as a synucleinopathy [3]. Multiple pathogenic mechanisms have been implicated in neuronal loss in PD and these include oxidative stress, nitrative stress, excitotoxicity, altered mitochondrial function, changes in protein degradation at the level of both the proteasome and lysosome, inflammatory processes initiated by glial cell activation and apoptosis [4,5].

It has proved difficult to disentangle these processes to determine which form primary causes of neuronal loss as compared to those that are parts of a secondary cascade of events inevitably initiated once cell death starts. This has important consequences for attempts to affect the pathogenic process occurring in man and many attempts to achieve neuroprotection or disease modification in PD have failed since they focussed on single components of the cascade and not on primary mechanisms [6]. In this brief review, the role played by mitochondria is examined and in turn, how monoamine oxidase B (MAO-B) located in the inner mitochondrial wall might be a target for modifying cell death in PD through the use of selective MAO-B inhibitors.

Toxins, mitochondrial function and PD

A stimulus for examining the role of mitochondria as a causative factor in the loss of dopaminergic neurones in PD came from the discovery of the selective nigral toxicity of MPTP in non-human primates and man [7]. MPTP metabolism by MAO-B located in glial cells led to the formation of MPP+ which was in turn accumulated by dopaminergic neurones through the dopamine transporter. MAO-B, but not MAO-A inhibitors, were shown to prevent MPTP toxicity to dopaminergic neurones both *in vitro* and *in vivo*. Critically, MPP+ was found to be a selective inhibitor of complex I of the mitochondrial respiratory chain and this was taken to explain the toxic actions of MPTP, although this is not entirely correct [8]. Other toxins acting through complex I inhibition are also known, including rotenone and annonacin [9,10], and these too have been used to study cell death in PD. The discovery of MPP+'s effect led to an examination of events occurring in post-mortem nigral tissue in PD. From these investigations came the key discovery of complex I inhibition in substantia nigra that appeared selective to PD and was not present in other brain regions examined or in related neurodegenerative illnesses [11–13]. The same defect was reported, however, in platelets and muscle biopsies from PD. A mitochon-

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drial electron chain defect would lead to oxidative stress which is known to contribute to pathogenesis in PD but perhaps more importantly, it would deprive other intracellular organelles, such as the proteasome or lysosome, of ATP necessary for their normal functioning and can initiate apoptotic cell death cascades. However, the discovery of an approximate on average 30% decrease in complex I activity in PD may not be as straight forward as it first seems.

The complex I defect was not present in all nigral samples from PD and it was more than two SD's away from the mean for control tissue in only 30% of cases. This suggests that mitochondrial defects may be limited to a subpopulation of PD patients. Whether a 30% decrease in complex I activity is of functional significance to the electron transport chain is also unresolved but there are additional deficits in the activity of α-ketoglutarate dehydrogenase [14] and this may amplify the effects of complex I dysregulation. But the biggest mystery is in identifying where these changes take place. Dopaminergic neurones only comprise 2–3% of all cells in the nigral tissue analysed for complex I activity and it is almost impossible to have an overall 30% loss confined to these cells. The biggest contributor may therefore be in glial cells rather than neurones and these may play an important role in pathogenic events.

The cause of the complex I deficiency is also mysterious. No MPP+ like substances have been identified in the substantia nigra in PD [15]. The construction of cybrids using mtDNA from PD patients with low platelet complex I activity has consistently suggested that the deficit is encoded [16]. However, no consistent deletions or other abnormalities in mtDNA have been detected in PD. There is, however, evidence of oxidative damage of functional significance to the electron transport chain occurs in both ageing and PD and imaging studies show mitochondrial dysfunction in both early and advanced PD [17]. There is, however, no evidence for maternal inheritance of mitochondrial defects in PD.

It is from studies of gene defects in familial PD that the best support for a key role of mitochondria in the pathogenesis of PD has come in recent years. Mutations in PINK1, DJ-1, LRRK2 and parkin have all been associated with altered mitochondrial function or mitochondrial mediated cell death [18]. This may be highly important and it is emerging that the mitochondrial forms of PD may not be associated with the formation of Lewy bodies and they may represent a subset of PD distinct from other forms in causation and appearance. Importantly, genome wide association studies (GWAS) have identified that the control of cellular bioenergetics by PGC-1α may be altered in PD [19]. PGC-1α acts through an interaction with PARIS to increase the expression of nuclear encoded subunits of the respiratory chain and can affect dopaminergic cell survival [20].

MAO-B, MAO-B inhibitors and PD

MAO exists as two isoforms with different substrate selectivities and different distributions in brain and between species [21]. In man, dopamine is largely metabolised by MAO-B although it can also be a substrate for MAO-A. However, dopaminergic neurones in the striatum contain relatively little MAO-B but the A-isoform is present. Rather MAO-B is found extensively in glial cells and localised to the outer mitochondrial wall. Under normal physiological conditions, dopamine released into the synapse by impulse flow is rapidly 'inactivated' by the high affinity reuptake process that constitutes the dopamine transporter. In PD, the number of presynaptic terminals in the striatum is extensively depleted and now MAO-B in surrounding glial cells becomes a major focus for dopamine metabolism. This provides a targeted and disease specific mechanism through which dopamine degradation can be inhibited by the use of selective MAO-B inhibitors [22].

Selegiline and rasagiline are selective MAO-B inhibitors that irreversible inhibit the enzyme by the covalent binding of the propargylamine moiety to the active site in the mitochondrial membrane [23] (Fig. 1). The long lasting inhibition of MAO-B is held responsible for the symptomatic improvement in motor symptoms occurring in monotherapy in early PD and as adjunct therapy to L-dopa and/or dopamine agonist treatment in mid- and late-stage illness. However, it has been implied that both drugs may also alter the rate of progression of PD through the DATATOP study and subsequent investigations of selegiline and the TEMPO and ADAGIO studies of rasagiline [24–26]. This raises the question of how such effects might be mediated. Initially, the inhibition of the metabolism of dopamine by MAO-B was thought to lower oxidative stress by preventing the formation of toxic oxygen free radical species [23–27]. But subsequently the emphasis has evolved to support an action of both selegiline and rasagiline in preventing apoptotic processes leading to cell death through effects at the level of mitochondria. Recent interest has centred on rasagiline's actions based on the finding of improved clinical scores with early

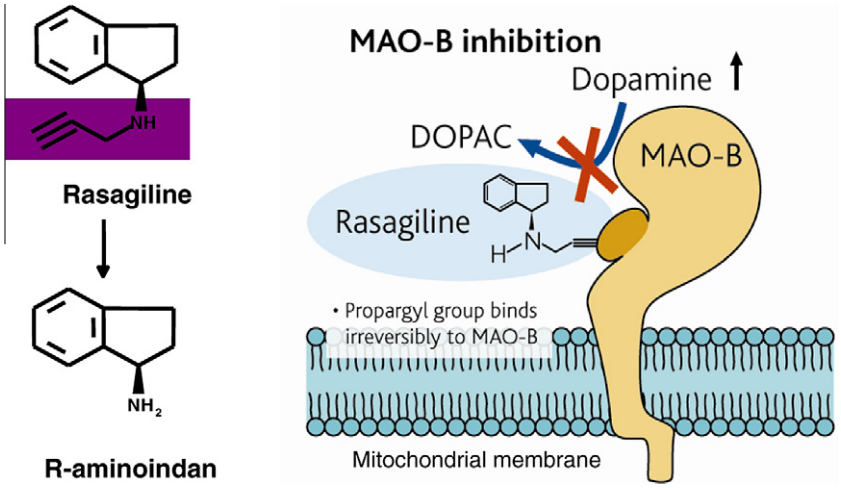

Fig. 1. Structure, mechanism of action and metabolism of rasagiline. Attaching via its propargyl domain, rasagiline irreversibly inhibits MAO-B by covalently binding to the flavin adenine dinucleotide (FAD) moiety of the MAO-B enzyme positioned in the outer membrane of the mitochondria within neuronal cells. As the FAD moiety is required for MAO-B to metabolise dopamine to dihydroxphenlyacetic acid (DOPAC), by blocking this site, rasagiline is able to inhibit the metabolism of dopamine by MAO-B, raising the level of dopamine at the synapse. Rasagiline is metabolised to aminoindan, its major metabolite, which possesses weak MAO inhibitory activity but exerts neuroprotective actions.