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PENTOSE-PHOSPHATE PATHWAY DISRUPTION IN THE PATHOGENESIS OF PARKINSON'S DISEASE

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Abstract

Oxidative stress is known to be a key factor in the pathogenesis of Parkinson's disease (PD). Neuronal redox status is maintained by glucose metabolism via the pentose-phosphate pathway and it is known that disruption of glucose metabolism is damaging to neurons. Accumulating evidence supports the idea that glucose metabolism is altered in PD and dysregulation of the pentose-phosphate pathway in this disease has recently been shown. In this review, we present an overview of the literature regarding neuronal glucose metabolism and PD, and discuss the implications of these findings for PD pathogenesis and possible future therapeutic avenues.

Keywords

• Glucose metabolism • Oxidative stress • Parkinson's disease • Pentose-phosphate pathway.

Introduction

Parkinson's disease (PD) is a disabling and currently incurable neurodegenerative condition that is thought to affect around 2% of the world population over the age of 65 [1]. It has been shown that the motor and non-motor symptoms that characterise PD are caused by degeneration of dopaminergic neurons in the nigrostriatal pathway (although many different cell types die in PD) [2]. In losing the dopaminergic input to the striatum, output is subsequently dampened and patients experience a number of symptoms such as resting tremor, rigidity, bradykinesia and postural instability [3]. There is considerable evidence to support a pivotal role for excess reactive oxygen species (ROS) and mitochondrial dysfunction in the pathogenesis of PD [4]. Oxidative stress markers are raised in PD post-mortem brain samples and increased levels of markers positive for neuroinflammation have also been shown [5]. The increased levels of ROS are thought to be generated during dopamine metabolism, and exacerbated by low levels of total glutathione (GSH) and high iron and calcium concentration in the substantia nigra pars compacta (SNpc) [6]. It has been shown that neuronal management of excess ROS is achieved through metabolism of glucose via the pentose-phosphate pathway (PPP) [7-9]. Importantly, accumulating evidence, from a number of different experimental models, suggests that glucose metabolism is perturbed in PD. A recent paper by Dunn *et al.* [10] showed evidence of PPP dysregulation in post-mortem sporadic PD brain samples, suggesting that disruption of normal glucose metabolism may be an important mechanism in the pathogenesis of this disease. Similarly, recent papers have also shown a possible link between α-synuclein, the protein found deposited in Lewy bodies and glucose metabolism. In this review, we explore the links between glucose metabolism and neurodegeneration in PD. Tremendous progress has been made in understanding the possible causes of PD and how to treat it. However, current treatments are focused on addressing the symptoms of neurodegeneration, rather than targeting the mechanisms that cause neurons to die. In the light of recent findings, we suggest that manipulation of the PPP could be a valid target for future therapeutic intervention in PD.

The relationship between oxidative stress and the mitochondria in neurons

In PD, as with a large number of neurological conditions, it is neurons that degenerate. As such, it could be suggested that some properties of neuronal homeostasis are intrinsically damaging, or that neurons are more vulnerable to oxidative stress than other cell types. Neuronal regulation of the respiratory chain enzymes occurs in part due to interactions between neurons and astrocytes. Cytochrome c oxidase (CcO) is inhibited by the use of nitric oxide as a signaling molecule from astrocytes. The accumulation and metabolism of nitric oxide in neurons results in high levels of peroxynitrite formation, which is damaging to neurons and is thought to contribute to increased levels of oxidative stress [11]. Neurons are also highly dependent on mitochondrial ATP-production. In most cell types, low levels of

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ATP promote upregulation of glycolysis to make up the ATP deficit, however neurons are non-glycolytic [12] and therefore more vulnerable to changes in mitochondrial output. This may explain why neurons are so heavily dependent on neighbouring astrocytes, which by virtue of the astrocyte-neuronal lactate shuttle (ANLS), provide a critical source (lactate) of neuronal ATP [13,14]. In this case, although the co-dependent relationship between neurons and astrocytes is beneficial to neurons, it also leaves them extremely vulnerable [11].

A number of post-mortem brain analyses have shown increased levels of oxidative stress signals in PD, including markers of lipid peroxidation, protein carbonyl modifications and DNA and RNA oxidation [4]. It has been suggested that the presence of cytosolic dopamine itself renders dopaminergic neurons particularly susceptible to oxidative stress [15], as these redox reactions produce reactive quinones, superoxide species and hydrogen peroxide [16]. Iron has been shown to catalyse oxidation reactions in the presence of dopamine, which produces free radicals and subsequently tissue damage [17]. Increased extracellular iron levels in SNpc tissue of PD sufferers on autopsy [18] support the idea that dopamine may contribute to a higher oxidative stress load in dopaminergic neurons than in those that are non-dopaminergic. Thus, it has been suggested that oxidative stress could play a role in the formation of Lewy body pathology [19].

Another important feature of neuronal degeneration in PD is the dysfunction of mitochondria. The synthetic opioid metabolite 1-methyl-4-phenylpyridinium ion (MPP+) has been shown to selectively target the dopaminergic neurons of substantia nigra when injected intravenously [20]. On a cellular level, MPP+ causes decreased membrane potential and reduces oxidative phosphorylation due to Complex I damage [21], with striking similarity to the Complex I damage which is also seen in PD post-mortem brain tissue [22]. Damage to other components of the respiratory chain, including complex IV (cytochrome c oxidase), i.e. the target for astrocytic nitric oxide [23] has also been shown [24,25]. Importantly, a study comparing glucose and oxygen metabolism in patients carrying mitochondrial DNA mutations, to PD patients, concluded that impaired mitochondrial functioning is not a primary insult in the pathogenesis of PD and that damage to the mitochondria may occur instead as a result of intracellular changes taking place [26].

Neuronal glucose metabolism and the pentose phosphate pathway

In many cell types, glucose is metabolised primarily via the glycolytic pathway to generate pyruvate. Comparison of neurons and astrocytes has shown that neurons have a lower glycolytic rate than astrocytes. Astrocytes respond to nitric oxide by upregulating glycolysis [23,27,28], whereas neurons are unable to respond to stress in this way as they have low Pfkfb3 (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3) activity [28]. Studies in rat specimens have shown that the rate-limiting enzyme Pfkfb3, is present in astrocytes, but undetectable in neurons due to its constant ubiquitylation and proteasomal degradation [12]. Thus, neurons actively metabolise glucose via PPP. Glycolysis and the pentose-phosphate pathways are metabolically linked by the common intermediate, glucose-6-phosphate (G6P) [29]. The PPP regenerates NADPH, which can be utilised to maintain neuronal redox status and combat oxidative stress via regeneration of reduced glutathione (GSH) by the action of glutathione reductase [7,12]. Figure 1 shows these pathways diagrammatically. It has been shown that the level of GSH in cells in culture is directly related to the production of NADPH by the PPP [8] and the PPP is the primary source of NADPH in cells [9]. Importantly, forcing neurons to metabolise glucose via glycolysis causes a decrease in NADPH levels and high levels of neuronal oxidative stress, increased formation of reactive oxygen species (ROS) and cell death.

Glucose enters neurons via GLUT3 transporters on the plasma membrane of neurons. Phosphorylation of glucose by hexokinase provides the pentose-phosphate pathway with G6P, which is the substrate for glucose-6-phosphate dehydrogenase. 1 mole of NADPH is generated for every mole of G6P that is dehydrogenated. Further along the pathway, another mole of NADPH is generated when 6PG undergoes dehydrogenation. One molecule of glucose catalyses the net production of 2 molecules of NADPH. Ribose-5-phosphate is the end product of the pentose phosphate pathway. NADPH is used in the redox cycling of glutathione to reduce oxidative species.

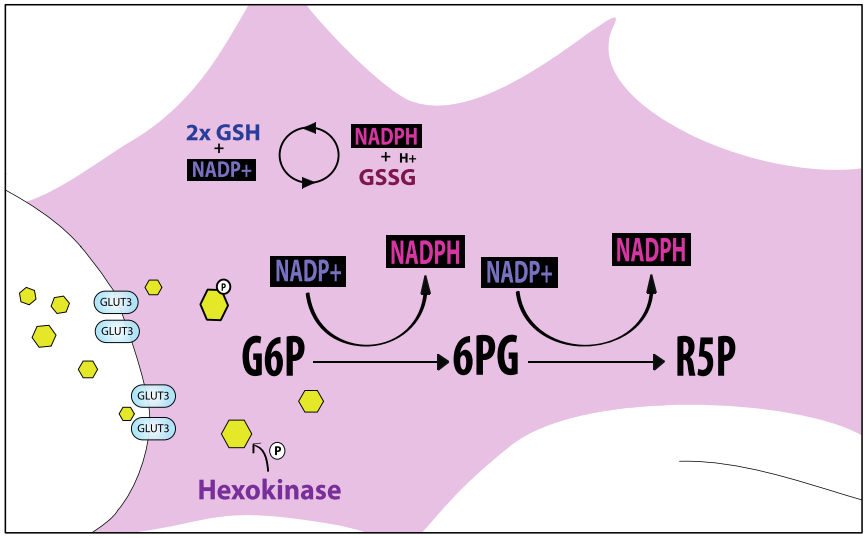

Figure 1. Simplified diagram of neuronal glucose metabolism via the pentose phosphate pathway. GLUT3: glucose-transporter 3, G6P: glucose-6-phosphate, 6PG: 6-phosphogluconate, R5P: ribose-5-phosphate, NADP+: nicotinamide adenine dinucleotide phosphate, NADPH: reduced nicotinamide adenine dinucleotide phosphate, GSH: reduced glutathione, GSSG: oxidised glutathione (glutathione disulphide).

Oxidised GSSG is recycled back to its reduced form by glutathione reductase.

As discussed, neurons are normally exposed to high levels of ROS, possibly because their relatively high rate of oxidative phosphorylation and nitric oxide signaling from neighbor astrocytes [11]. As such, maintenance of neuronal redox status via the PPP generating NADPH is vital to protect against oxidative damage and allow neurons to function normally. The importance of this and the extent to which neurons rely on the PPP for survival is highlighted by findings that inhibiting or decreasing glucose metabolism by the PPP is deleterious to neurons [9,30].

Links between faulty glucose metabolism and PD

There is accumulating evidence to suggest that dysregulation of glucose metabolism in Parkinson's disease is an important mechanism in disease pathogenesis. An increasing number of ^{18}F deoxy-glucose PET (2-FDG) in vivo studies have shown glucose hypometabolism in various brain regions, in both sporadic [31] and familial PD patients [32]. Similarly, it has also been shown that deep brain stimulation of the subthalamic nucleus in patients with advanced PD affects glucose metabolism [33], supporting the idea that glucose homeostasis is tightly linked to the degenerative changes taking place in this disease. Measurement of glucose metabolites in the brains of PD patients has been shown increased levels of lactate [34], and measurement of pyruvate in PD CSF has shown an increase in levels of the metabolite, accompanied by decreased levels of citrate, acetate, succinate and malate [35]. Together, these findings support the idea that overall alteration in glucose metabolism may be a feature of PD. On a cellular level, genetic microarray studies of the substantia nigra in PD show a strong association with the transcriptional regulator PGC-1α, which is involved in the control of glucose usage [36]. Investigating possible links between glucose metabolism and PD has led to a number of reports that increasing glucose availability using glucagon-like-peptide (GLP) analogues is able to attenuate PD phenotypes on both a molecular and clinical level [37]. This has led to ongoing phase II clinical trials using the GLP-1 agonist exendin-4 (EXENATIDE-PD trial, NCT01971242), which are a positive step towards establishing a class of disease-modifying drugs for PD.

The pentose-phosphate pathway in Parkinson's disease pathogenesis

Targeting the PPP in neuronal cell models has been shown to recapitulate many of the cellular phenotypes associated with PD, such as increased oxidative stress, mitochondrial damage, decreased GSH levels, and neuronal death [12]. Using L-buthionine sulfoximine to decrease total glutathione levels in rats, has shown that the increased oxidative stress that result from decreasing total GSH leads to damage of the respiratory chain complexes I and IV [38]. An important rodent study using pharmacological inhibition of the PPP to decrease NADPH levels globally produced a selective degenerative effect on dopaminergic neurons leading to motor deficits that resemble PD, such as bradykinesia [39]. This supports the idea that dopaminergic neurons are more sensitive than other neuronal subtypes to increases in ROS, but also highlights a possible mechanistic link between the PD and the PPP.

Given that neuronal glucose serves to produce NADPH for glutathione cycling, it is unsurprising that studies have shown decreased levels of GSH in the SN of PD patients. This decrease is thought to be up to 40% [40]. Similarly, reduced levels of GSH are also seen in brain tissue from individuals with incidental Lewy bodies, which is commonly thought to represent pre-symptomatic PD [41]. In Alzheimer's disease brains, GSH levels are shown to be unchanged [42]. Importantly, it has been documented that protein levels of the PPP rate-limiting enzyme G6PD are increased in AD [43], neuromuscular diseases [44], myocardial infarction [45], and in hepatocyte cell models [46]. Studies in post-mortem PD samples has shown that in early PD, NADPH production is not increased in the putamen and cortex, and that G6PD and 6PGD protein levels are conversely decreased in the putamen [10]. This suggests that PPP dysregulation could be an important mechanism in PD neurodegeneration. Interestingly, olfactory neurons, which have the highest PPP activity of all neuronal cell types in the brain [47] are among the first neurons to be involved in PD neurodegeneration [48]. Whether this is due to their dependence on the PPP, thus leaving them more vulnerable to changes in glucose flux through the PPP, remains to be elucidated. In addition, studies examining the role of the PPP in other neurological disorders such as ALS and ataxia telangiectasia, suggest that down-regulation of the PPP could be key factors in the neurodegenerative processes [49,50].

Taken together, these studies strongly support the idea that mitochondrial damage in PD is a knock on effect of a reduction in anti-oxidant reserve, and that impaired glucose metabolism is likely to be a key event in PD pathogenesis.

A role for α-synuclein in glucose regulation?

The role of α-synuclein (AS) in PD pathogenesis is an important, yet little understood mechanism. Many functions of α-synuclein have been suggested, including functioning as a ferrireductase [51] or in neurotransmitter release [52]; however, there is currently little consensus on an exact role for this protein. Glucose deprivation in primary dopaminergic neurons and differentiated SH-SY5Y cells has been shown to cause AS aggregation and cell death [53]. Interestingly, AS-knockout mice show an upregulation of glucose metabolism and are protected against the mitochondrial damage caused by complex I inhibitor MPTP [54]. A recent study has suggested that glucose uptake may be controlled by α-syn signalling via the LPAR2/Gab1/PI3K/Akt pathway [55]. Importantly, MPTP toxicity is mediated through nitric oxide from inducible nitric oxide synthase [56] and knockout of the human SNCA gene in neuronal cultures confers protection against nitric oxide-mediated toxicity [57]. It has been shown that AS is able to activate nitric oxide synthase in rats [58,59]. Inhibition of mitochondrial cytochrome c oxidase by nitric oxide causes upregulation of glycolysis [23,28] and the PPP [60], and nitric oxide has been shown to control the balance

of glucose metabolism between these two pathways [61]. As such, these studies suggest that there may be either a direct or an indirect functional link between AS and nitric oxide, and that AS may exert some control over glucose metabolism in the brain. If this is the case, further investigation into these links may lead to the opening of important therapeutic avenues for PD in the future.

Conclusions

In conclusion, there are clear links between PD and neuronal glucose metabolism, PPP activity, and oxidative stress. Increased oxidative stress is implicated in the pathogenesis of PD. We propose that that PPP dysfunction and perturbed glucose metabolism are early events in the etiology of PD and hypothesise that dysregulation of the PPP in PD is a key event in neurodeneration (Fig. 2).

In a study in which G6PD was over-expressed in dopaminergic neurons in mice in vivo, it has been shown that mice are protected against MPTP toxicity [62]. Thus, the PPP may be an important potential target for PD disease modifying therapies. As the studies on GLP-1 agonist use as a neuroprotective agent have shown, glucose metabolism is already proving to be a druggable target for other disorders [63] and could also prove crucial for the pharmacological management of PD. The increasing healthcare burden of PD and inefficacy of current treatments needs further investigation into agents targeting the PPP for PD treatment that may take us a step closer to finding a cure for this devastating disease.

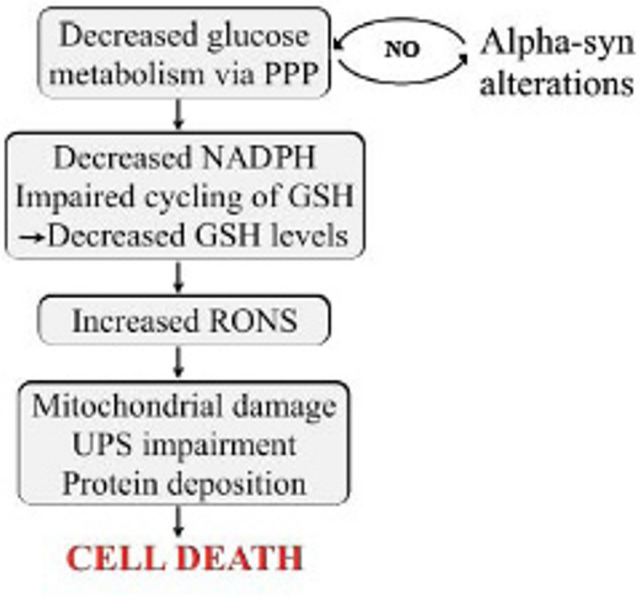

Figure 2. Proposed mechanism of Parkinson's disease pathogenesis. RONS: reactive oxygen and nitrogen species. In familial forms of PD, alterations to α-synuclein such as genetic mutations or increases in gene dosage, are proposed to affect regulation of pentose-phosphate pathway (PPP) in neurons, via nitric oxide signaling. This results in decreased flux of glucose through the pentose-phosphate pathway. In sporadic PD, age related decline of metabolic enzymes, exacerbated by individual differences, is predicted to cause decreased flux of glucose through the PPP.

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