Progress in Neurobiology 145–146 (2016) 98–120

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Review article

Insulin resistance and Parkinson's disease: A new target for disease modification?

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ARTICLE INFO

Article history:
Received 4 November 2015
Received in revised form 28 September 2016
Accepted 2 October 2016
Available online 3 October 2016

Keywords:
Parkinson's disease
Neurodegeneration
Insulin resistance
Disease modification

ABSTRACT

There is growing evidence that patients with Type 2 diabetes have an increased risk of developing Parkinson's disease and share similar dysregulated pathways suggesting common underlying pathological mechanisms. Historically insulin was thought solely to be a peripherally acting hormone responsible for glucose homeostasis and energy metabolism. However accumulating evidence indicates insulin can cross the blood-brain-barrier and influence a multitude of processes in the brain including regulating neuronal survival and growth, dopaminergic transmission, maintenance of synapses and pathways involved in cognition. In conjunction, there is growing evidence that a process analogous to peripheral insulin resistance occurs in the brains of Parkinson's disease patients, even in those without diabetes. This raises the possibility that defective insulin signalling pathways may contribute to the development of the pathological features of Parkinson's disease, and thereby suggests that the insulin signalling pathway may potentially be a novel target for disease modification. Given these growing links between PD and Type 2 diabetes it is perhaps not unsurprising that drugs used the treatment of T2DM are amongst the most promising treatments currently being prioritised for repositioning as possible novel treatments for PD and several clinical trials are under way. In this review, we will examine the underlying cellular links between insulin resistance and the pathogenesis of PD and then we will assess current and future pharmacological strategies being developed to restore neuronal insulin signalling as a potential strategy for slowing neurodegeneration in Parkinson's disease.

Contents

Abbreviations: AB, amyloid beta; AD, Alzheimer's disease; AGE, advanced glycation end products; AKT, protein kinase B; BAD, Bcl 2 antagonist of death; BBB, blood brain barrier; Bcl-2, B-cell lymphoma 2; Bcl-XL, B-cell lymphoma extra large; Bim, Bcl-2 interacting mediator of death; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element-binding protein; CNS, central nervous system; CSF, cerebrospinal fluid; DA, dopamine; DLB, dementia with lewy bodies; DPP-4, dipeptidyl peptidase 4; ERK, extracellular signal regulated kinase; FoxO1, forkhead box O1; GLP-1, glucagon like peptide-1; GLP-1R, glucagon like peptide-1 receptor; GSK-3b, glycogen synthase kinase 3b; 6-OHDA, 6-hydroxydopamine; IDE, insulin degrading enzyme; IGF-1, insulin like growth factor-1; IGF-1R, insulin like growth factor-1 receptor; IRS, insulin receptor substrate; LTP, long term potentiation; MAP-K, mitogen associated protein kinase; MCI, mild cognitive impairment; mTOR, mammalian target of rapamycin; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NF-kB, nuclear factor kappa-light- chain-enhancer of activated B cells; NIRKO, brain/neuron-specific insulin receptor knockout; PD, Parkinson's disease; PDD, Parkinson's disease dementia; PI3-K, phosphoinositide 3-kinase; PGC1α, peroxisome-proliferator activated receptor gamma coactivator-1alpha; PKA, protein kinase A; ROS, reactive oxygen species; SNpc, substantia nigra pars compacta; TH, tyrosine hydroxylase; T2DM, type 2 diabetes; UPDRS, Unified Parkinson's Disease rating Scale.

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http://dx.doi.org/10.1016/j.pneurobio.2016.10.001
0301-0082/

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease and globally affects 1% of people over age 60 (de Lau and Breteler, 2006), with the risk increasing with age. The hallmark of this progressive disorder is loss of nigrostriatal dopaminergic neurons causing characteristic motor signs and symptoms of tremor, rigidity and bradykinesia. Accumulating evidence suggests the onset of PD can begin up to 20 years prior to appearance of the classical motor symptoms while imaging and pathological studies suggest nigrostriatal degeneration can be detected 5–10 years before this clinical milestone (Hilker et al., 2005; Tolosa et al., 2009). During this time, the clinicopathological correlate, or molecular prodrome is thought to pass through a number of stages leading ultimately to neurodegeneration (Schapira et al., 2014). The exact pathophysiological mechanisms underlying neurodegeneration in the PD brain remain uncertain; however significant evidence implicates mitochondrial dysfunction, inflammation, oxidative stress and dysfunction of autophagy systems as being central to PD pathogenesis. Although these pathways have separate divergent routes and multiple points of interconnection leading to cell damage, there are thought to be common points of convergence "upstream" of these deleterious effects, which may be amenable to intervention (Schapira and Tolosa, 2010). Despite the large number of compounds showing neuroprotective properties in vitro or animal models of PD, none so far have convincingly been shown to have any effects on disease progression in clinical trials (Athauda and Foltynie, 2014).

A growing body of epidemiological and clinical data suggest that Parkinson's disease and Type 2 diabetes (T2DM), both age-related diseases, share these similar dysregulated pathways (Aviles-Olmos et al., 2013b; Santiago and Potashkin, 2014), suggesting common underlying pathological mechanisms. In its earliest stage, T2DM develops from insulin resistance (broadly defined as a tissue's reduced responsiveness to insulin), leading to a variety of detrimental effects on metabolism and inflammation. Accumulating evidence suggests that similar dysregulation of glucose and energy metabolism seems also to be an early event in the pathogenesis of sporadic PD (Dunn et al., 2014). While insulin is well recognised for its role in mediating peripheral glucose homeostasis, within the central nervous system (CNS) insulin seems to have neuroprotective effects. Insulin receptors are found in the basal ganglia and substantia nigra and growing evidence is emerging that suggests insulin plays an essential role regulating neuronal survival and growth, dopaminergic transmission and maintenance of synapses (Bassil et al., 2014). In conjunction, there is growing evidence that a process analogous to peripheral insulin resistance occurs in the brains of PD patients, (even in those without diabetes), which suggests loss of insulin signalling may contribute to the development of pathological features of PD.

Alongside the motor deficits associated with PD, one of the most significant non-motor symptoms is the development of cognitive impairment and dementia. The appearance of these symptoms can exacerbate functional impairments caused by motor symptoms (Rosenthal et al., 2010) and confers increased mortality and morbidity (Levy et al., 2002). Although Parkinson's disease dementia (PDD) and Dementia with Lewy bodies (DLB) share similar clinical and pathological features (suggesting these conditions are on the same spectrum of Lewy body diseases), the precise neuropathophysiology underlying the development of cognitive impairment in PD remains unclear. Studies have indicated deposition of Lewy body-related pathology in neocortical and limbic areas to be one of the most significant factors in the development of PDD and DLB (see (Halliday et al., 2014) for review). However the involvement of cerebral amyloid angiopathy, argyrophilic grains and microvascular disease has also been implicated, though their relative contributions remain unclear. Further evidence indicates that 50% of patients with PDD also have evidence of amyloid- β-peptide (AB) plaques and hyperphosphorylated tau-containing neurofibrillary tangles, pathology usually seen in the brains of patients with Alzheimer's disease (AD) (Compta et al., 2014; Irwin et al., 2013). The relative contribution of this AD-type pathology in cognitive decline in PD is still debated but some studies indicate that this co-morbid pathology may act synergistically with Lewy bodies and Lewy Neurites and confer a worse prognosis (Compta et al., 2011; Jellinger et al., 2002; Kotzbauer et al., 2012; Masliah et al., 2001).

The emerging questions thus relate to the extent to which insulin resistance may act as a mediator of both motor and cognitive impairments in PD. In this review, we will therefore focus on the evidence linking insulin resistance and PD, firstly by presenting a brief overview of epidemiological data linking insulin resistance to PD and secondly, by using evidence from experimental models, we will review the data supporting the premise that insulin and insulin resistance play a role in the neurodegenerative processes of PD. Growing evidence suggests that AD-related pathology is undoubtedly relevant for at least a subset of individuals with PDD due to either superimposed AD-type