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Review

System-based approaches to decode the molecular links in Parkinson's disease and diabetes

Jose A. Santiago, Judith A. Potashkin *

The Cellular and Molecular Pharmacology Department, The Chicago Medical School, Rosalind Franklin University of Medicine and Science, North Chicago, IL, USA

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ABSTRACT

A growing body of evidence indicates an increased risk for developing Parkinson's disease (PD) among people with type 2 diabetes (T2DM). The relationship between the etiology and development of both chronic diseases is beginning to be uncovered and recent studies show that PD and T2DM share remarkably similar dysregulated pathways. It has been proposed that a cascade of events including mitochondrial dysfunction, impaired insulin signaling, and metabolic inflammation trigger neurodegeneration in T2DM models. Network-based approaches have elucidated a potential molecular framework linking both diseases. Further, transcriptional signatures that modulate the neurodegenerative phenotype in T2DM have been identified. Here we contextualize the current experimental approaches to dissect the mechanisms underlying the association between PD and T2DM and discuss the existing challenges toward the understanding of the coexistence of these devastating aging diseases.

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Introduction

PD and T2DM are a growing public health concern with devastating effects in the elderly population. The International Diabetes Federation has estimated that over 380 million people worldwide are afflicted by diabetes and this number is expected to climb to 590 million by 2035 (www.idf.org). Especially in the elderly population, the increase in T2DM is expected to lead to a concomitant increase in neurodegeneration. In this regard, a substantial amount of epidemiological studies suggests that T2DM is a risk factor for several neurodegenerative diseases including Alzheimer's disease (AD) (Yang and Song, 2013) and PD in some ethnic groups (Cereda et al., 2013; Santiago and Potashkin, 2013b; Sun et al., 2012). Although the exact mechanisms that explain the coexistence of T2DM and PD remain unknown, several studies have revealed potential mechanisms underlying this association. These efforts are in part motivated by recent findings that show that drugs to treat diabetic patients may elicit therapeutic effects in patients with PD (Aviles-Olmos et al., 2013a). In parallel, animal models and network approaches to study the potential links between PD and T2DM are beginning to emerge with the hope of finding an effective treatment. In addition, the molecular framework linking both diseases has begun to be elucidated and common transcriptional signatures may provide further insight into the shared biological mechanisms in PD and T2DM. In this review, we discuss the current experimental

* Corresponding author at: Department of Cellular and Molecular Pharmacology, The Chicago Medical School, Rosalind Franklin University of Medicine and Science, North Chicago, IL, USA.
E-mail address: judy.potashkin@rosalindfranklin.edu (J.A. Potashkin).
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approaches to study the association between PD and T2DM and the potential therapeutic targets these system models have revealed.

Epidemiological and clinical studies in PD and T2DM

Accumulating evidence from epidemiological studies suggest T2DM is a risk factor for PD. Although a potential link between PD and T2DM remains controversial (Palacios et al., 2011; Savica et al., 2012), most of the epidemiological studies indicate a high incidence of T2DM among patients with PD (Santiago and Potashkin, 2013b). Patients with T2DM have a 36% increased risk of developing PD (Hu et al., 2007; Xu et al., 2011). Case–control studies indicate that T2DM is associated with an increased risk of PD in some ethnic groups including Danish, Chinese and Taiwanese (Schernhammer et al., 2011; Sun et al., 2012; Wahlqvist et al., 2012). Similarly, a positive association between PD and T2DM was indicated in large cohort studies and 62% of PD patients with dementia are insulin resistant (Bosco et al., 2012; Hu et al., 2007; Xu et al., 2011).

Notwithstanding the evidence supporting the association between PD and T2DM, there remains uncertainty given the studies that have found inverse associations (D'Amelio et al., 2009; Lu et al., 2014) or no association (Palacios et al., 2011; Savica et al., 2012). One possible factor that may explain the conflictive findings among epidemiological studies is that diagnosis of T2DM is sometimes based on self-report. Another important confounding factor is the impact of drugs used to treat patients with PD and T2DM. For example, PD medications such as levodopa, induces hyperglycemia and hyperinsulinemia (Van Woert and Mueller, 1971). Further, anti-diabetic drugs such as metformin-inclusive sulfonylurea and exenatide may elicit neuroprotection in PD (Aviles-Olmos et al., 2013a; Wahlqvist et al., 2012). Therefore, larger epidemiological studies taking into account these potential confounding factors will be helpful to better understand the association between PD and T2DM.

Interestingly, conditions linked to T2DM appear to be associated with more severe motor symptoms and conditions in PD patients. Not surprisingly, repeated inpatient care and longer duration of hospitalization are observed in PD patients with T2DM (Scheuing et al., 2013). Insulin resistance, a hallmark feature of T2DM, is associated with an increased risk of dementia in PD (Bosco et al., 2012). In addition, T2DM contributes to postural instability and gait difficulty in PD (Kotagal et al., 2013). Given the fact that these symptoms are manifested later in the disease (Hoehn and Yahr, 1967), T2DM is most likely associated with PD progression. Accordingly, patients with T2DM manifest a higher United Parkinson's Disease Rating Scale (UPDRS) and more severe Hoehn and Yahr staging (Cereda et al., 2012). Collectively, these findings highlight the detrimental impact T2DM imposes on PD patients and raise concerns about the potential implications of T2DM in the clinical management of PD patients. The substantial evidence from epidemiological studies heightens the urgency to better understand the molecular mechanisms underlying this association.

Modeling complex disease comorbidity: PD and T2DM

Modeling disease comorbidities is a challenging task in experimental medicine owing to the multiple factors and interrelated conditions associated with complex diseases. Identifying the triggering factors and mechanisms that lead to the development of concomitant diseases with dissimilar phenotypic features and unknown etiology is very difficult. This is the case of PD and T2DM, both complex multifactorial disorders in which a combination of environmental and genetic factors are involved in disease pathogenesis. Genetic risk factors for PD and T2DM account for approximately 5–10% of the cases. Consequently, a wide range of environmental insults is considered important in the development of both diseases.

Several animal models have been proposed to study idiopathic PD. The most common animal models are designed to produce nigrostriatal dopaminergic lesions with environmental toxins including 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), paraquat or rotenone. None of these models exactly recapitulates the clinical symptoms and pathology of PD observed in humans however (Bezard et al., 2013; Potashkin et al., 2010).

In the context of T2DM, animal models include models of insulin resistance and pancreatic beta cell failure, characteristic features of T2DM. Obesity is a risk factor for T2DM; consequently most of the animal models of T2DM are obese (King, 2012). There are both monogenic and polygenic models of obesity used in T2DM research. Monogenic models of obesity include rodent models with severe obesity ($Lep^{ob/ob}$), Zucker diabetic rats (ZDF) and $Lep^{db/db}$ mice with defective leptin signaling and mutations in the leptin receptor, but these models may not accurately reflect T2DM (King, 2012). In contrast, polygenic models of obesity are considered more accurate than monogenic models as they closely mimic the characteristic features of T2DM. Examples of polygenic models of obesity are KK mice that are mildly obese and manifest severe hyperinsulinemia and OLETF rats with mild obesity and late onset hyperglycemia, reviewed in King (2012). In addition to genetic models, high-fat diets are known to induce obesity and insulin resistance in rodents (Winzell and Ahren, 2004).

The models discussed above are designed to mimic PD and T2DM independently but do not recapitulate disease comorbidity. Indeed, understanding the potential link between PD and T2DM has been hampered by the lack of testable models that closely recapitulates existing comorbidity. To address this issue, several studies have studied metabolic abnormalities in rodent models of PD. For example, a 6-OHDA model of PD was used to determine that a high-fat (HF) diet altered insulin signaling, impaired nigrostriatal dopamine function and exacerbated neurodegeneration (Morris et al., 2010, 2011a). Although the impairment of insulin signaling is anticipated with a HF diet, the results from this study provide evidence for the increased vulnerability of DA neurons in response to HF-diet induced insulin resistance. In addition, nutrient excess and mitochondrial dysfunction are implicated in the development of neurodegeneration in diabetes (Chowdhury et al., 2011).

Similarly, another study investigated whether central and peripheral insulin signaling was altered in a 6-OHDA middle-aged rat model of PD (Morris et al., 2011b). In this study, impaired insulin signaling, as demonstrated by increased phosphorylation of the insulin receptor substrate 2 (IRS2) and decreased phosphorylation of v-akt murine thymoma viral oncogene homolog 1 (AKT, protein kinase B), was observed in the striatum but not in skeletal muscle. Despite the differences observed in insulin signaling in the brain and the periphery, lesioned animals exhibited alterations in glucose and insulin levels at later time points.

More recently, a mouse model expressing a mutant form of human α-synuclein (A53T) in neurons was used to investigate metabolic and physiologic abnormalities in response to a high calorie diet (HCD) (Rothman et al., 2013). Strikingly, A53T mutant mice were resistant to HCD-induced obesity and insulin resistance, thus providing evidence for the involvement of α-synuclein in metabolic dysfunction in PD. The authors noted the importance of evaluating whether mutations in other genetic risk factors for PD would display the same phenotype.

Another approach to studying comorbidities is to expose diabetic mice to environmental toxins associated with PD. For example, diabetic mouse models (ob/ob and db/db) treated with MPTP resulted in the accelerated loss of dopaminergic neurons and increased activation of glial cells in the substantia nigra of db/db mice (Wang et al., 2013). Interestingly, neurodegeneration in this model was accompanied by the increased activation of inflammatory molecules including NRLP3, excess production of IL-1β and upregulation of monomeric and aggregated forms of α-synuclein in both pancreas and midbrain of T2DM mice. Moreover, markers of endoplasmic reticulum (ER) stress CHOP

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