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Convergent Molecular Pathways in Type 2 Diabetes Mellitus and Parkinson's Disease: Insights into Mechanisms and Pathological Consequences

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Abstract

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemic conditions. A higher risk of developing Parkinson's disease (PD) in patients with T2DM has become evident in recent years. However, the molecular mechanisms underlying the interplay between T2DM and PD pathogenesis remain unknown. Nevertheless, emerging epidemiological studies have demonstrated many common molecular pathways that play an essential role in regulating normal cellular functioning are independently implicated in the progression and etiopathogenesis of T2DM and PD. This review summarizes some common shared pathophysiological mechanisms, including insulin resistance, inflammation, mitochondrial dysfunction, endoplasmic reticulum stress (ER stress), autophagy, and the ubiquitin–proteasome system (UPS) that independently mediate the onset and etiopathogenesis of T2DM and PD. In this review, we summarize the studies that have reported the relationship between T2DM and PD. This review will provide insights into the common involvement of molecular pathways that may provide alternative treatment strategies for both T2DM and PD.

Keywords Diabetes mellitus · Parkinson's disease · ER stress · Mitochondrial dysfunction · Autophagy · Ubiquitin–proteasome system

Abbreviations

6-OHDA	6 Hydroxy dopamine
ABA	Abscisic acid
AIM2 inflammasome	Absent in melanoma 2 inflammasome
AKT	Protein kinase B
AMP	Adenosine monophosphate
AMPK	Adenosine monophosphate-activated protein kinase
ATF4	Activating transcription factor 4
ATF6	Activating transcription factor 6
Atg	Autophagy related
BBB	Blood-brain barrier
Bcl-2	B cell lymphoma 2
BDNF	Brain-derived neurotrophic factor
BiP	Immunoglobulin heavy chain binding protein
cAMP	Cyclic AMP
CAT	Catalase
CHOP	C/EBP homologous protein
CMA	Chaperone-mediated autophagy
COX-2	Cyclooxygenase-2
CREB	CAMP response element binding protein
CSF	Cerebrospinal fluid
DA	Dopamine
DA-ergic	Dopaminergic
DAMP	Damaged-associated molecular pattern
DJ-1	DnaJ-1
DM	Diabetes mellitus
Drp1	Dynamin-related protein-1
EIF2AK3	Eukaryotic translation initiation factor 2 alpha kinase 3
eIF2α	Eukaryotic initiation factor 2 alpha
ER	Endoplasmic reticulum

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ERK	Extracellular signal-regulated kinases ERK1
ETC	Electron transport chain
Fis1	Fission 1
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide–l
GLP-1R	GLP-1 receptor
GLUT4	Glucose transporters type 4
GPCR	G protein-coupled receptor
Grp78 protein	Glucose-regulated protein 78
GSK3-β	Glycogen synthase kinase-3beta
hA	Human amylin
HFD	High-fat diet
h-IAPP	Human islet amyloid polypeptide
Hrd1	HMG–CoA reductase degradation protein-1
IAPP	Islet amyloid polypeptide
Iba-1	Ionized calcium binding adaptor molecule 1
IFN-γ	Interferon gamma
IkBα	NF-kappa-B inhibitor alpha (I-kappa-B-alpha) (IkB-alpha)
IKK-β	Inhibitor of nuclear factor-kappaB (IkappaB) kinase beta
IL	Interleukin
IL-18R α/β	IL-18 receptor α/β
iNOS	Inducible nitric oxide synthase
IPD	Idiopathic PD
IPL	Inferior parietal lobule
IRE1α	Inositol requiring enzyme 1 α
IRN	Isorhynchophylline
IRS	Insulin receptor substrate
LAMP1	Lysosomal-associated membrane protein type 1
LB	Lewy body
LC3	Microtubule-associated protein 1A/1B-light chain 3
LC	Locus coeruleus
L-DOPA	Levodopa
LRRK2	Leucine-rich repeat kinase 2
MafA	Musculoaponeurotic fibrosarcoma oncogene family A
MAPK	Mitogen-activated protein kinase
MFG	Middle frontal gyrus
MFN	Mitochondrial mitofusin
MHC	Major histocompatibility complex
Miro 1	Mitochondrial rho GTPase 1
MMP	Mitochondrial membrane potential
MPP^+	1-Methyl-4-phenylpyridinium
MPTP	1-Methyl-4-phenyl-1, 2, 3, 6-tetrahydrodropyridine
MSK1	Mitogen and stress-activated kinase-1
mTOR	Mechanistic target of rapamycin
NADH	Nicotinamide adenine dinucleotide (NAD) + hydrogen (H)
NADPH-oxidase	Nicotinamide adenine nucleotide phosphate oxidase
NF-KB	Nuclear factor-κB
NLRP3 inflammasome	NOD-, LRR-, and pyrin domain-containing 3 inflammasome
Nrf2	Nuclear factor erythroid 2–related factor 2
P2X4R	P2X purinoceptor 4
P2X7R	P2X purinoceptor 7
Pael-R	Parkin-associated endothelin receptor-like receptor
Park2	Ub ligase Parkin
PARP	Poly ADP-ribose polymerase
PD	Parkinson's disease
PERK	Pancreatic ER kinase (PKR)–like ER kinase
PGC1-α	Peroxisome proliferator-activated receptor gamma coactivator 1
PI3K	Phosphatidylinositol 3-phosphate kinase
PINK1	PTEN-induced putative phosphatase 1
PKA	Protein kinase A
PKB	Protein kinase B
PPARs	Peroxisome proliferator-activated receptors
PQ	Paraquat
PTEN	Phosphatase and tensin homolog
Rab10	Ras-related protein Rab 10
ROS	Reactive oxygen species
SNCA	Synuclein alpha
SNpc	Substantia nigra pars compacta
SOCE	Store-operated calcium entry (SOCE)
SOCS	Suppressor of cytokine signaling
SOD	Superoxide dismutase
STZ	Streptozotocin
SUMO-1	Substrate for ubiquitin-like modifier-1
T2DM	Type 2 diabetes mellitus
TFB1M	Transcription factor B1 mitochondrial
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor-α

TOM20	Translocase of the outer membrane 20
TRPC1	Transient receptor potential channel 1
UCH-L1	Ubiquitin carboxy-terminal hydrolase L1
UCP2	Uncoupling protein 2
UPDRS	Unified Parkinson Disease Rating Scale
UPR	Unfolded protein response
UPS	Ubiquitin proteasome system
VDAC	Voltage-dependent anion-selective channel
WFS1	Wolfram syndrome gene 1
XBP1	X-box-binding protein 1

Introduction

Studies have observed that individuals with diabetes mellitus (T2DM) are at a greater risk of developing Parkinson's disease (PD) [1]. T2DM is a metabolic disease characterized by the aggregation of amylin protein in the β-cells of pancreatic islets, insulin resistance, and chronic hyperglycemia [2]. PD is a neurodegenerative disorder characterized by the loss of dopaminergic (DA-ergic) neurons in the basal ganglia, substantia nigra pars compacta (SNpc) regions of the brain [3]. Previous clinical studies have reported an increased prevalence of T2DM in patients with PD [4]. These studies reported higher insulin resistance in PD patients compared to healthy individuals, suggesting a potential link may exist between T2DM and PD [1]. Preclinical studies have also demonstrated the crucial role of insulin in regulating brain DA-ergic activity and its dysregulation in developing PD-like symptoms [1]. Previous reports suggest that mitochondrial dysfunction, endoplasmic reticulum (ER) stress, dysfunction in the UPS, and alterations in autophagy may be common underlying mechanisms in the course of T2DM and PD [5]. Another commonality is the formation of amylin protein-mediated amyloids fiber which plays a central role in the pathogenesis of T2DM and PD [6]. This suggests that the most potent drugs for T2DM could be used as a potential therapeutic approach against amyloidogenic neurodegenerative disorders [7]. For example, exenatide, glucagon-like peptide–l (GLP-1) agonists, and antidiabetic agents have been shown to exhibit neuroprotective and neurotrophic effects in the treatment of PD [8]. These observations raise the intriguing question of how T2DM could contribute to the pathogenesis of PD and whether, from a therapeutic perspective, the development of strategies targeting T2DM becomes a valuable approach to prevent PD. In this review article, we have focused on the common signaling pathways between T2DM and PD and the molecular mechanisms. Targeting these common signaling pathways could provide alternative and efficient treatment strategies for T2DM and PD.

T2DM and PD Comorbidity

An association between T2DM and PD was reported a few decades ago and ever since, many epidemiological and molecular studies have investigated a correlation between T2DM and PD development, summarized in Table 1 [9]. Most of these epidemiological studies suggest that T2DM is associated with an increased risk of PD in diverse populations. Reports indicate that T2DM may predispose to PD-like symptoms and may even exhibit a more aggressive phenotype when showing comorbidity with PD [10]. T2DM and PD share some common pathophysiological mechanisms mediated by similar detrimental genetic and environmental factors. Recent studies have reported that patients with T2DM have a 30–36% increased risk of developing PD and often display parkinsonian-like symptoms [11]. Reports also suggest that patients with idiopathic PD (IPD) have a genetic susceptibility that puts these individuals at risk for developing both diseases [12]. For example, a single nucleotide polymorphism in Akt gene, encoding Akt kinase that regulates cell growth and survival, has been implicated in the pathogenesis of both T2DM and PD [13]. Also, decreased expressions of (DnaJ-1) DJ-1, encoded by the PD-related park7 gene, were reported in pancreatic islets of patients with T2DM [14]. Recent studies have also reported that exposure to environmental toxins like maneb, paraquat (PQ), and rotenone, including heavy metals like iron, magnesium, and copper, increases the risk of developing T2DM and PD onset [15]. Exposure to pesticides and heavy metals results in loss of β-cell function in T2DM and may put individuals at higher risk of developing PD onset/progression [6].

A previous meta-analysis study based on four prospective studies indicated T2DM as a potential risk factor for the development of PD [5]. Another comprehensive updated meta-analysis on 7 observational cohort studies reported that patients with T2DM were associated with a 38% increase in the risk of developing PD compared to non-diabetic individuals [16]. In yet another meta-analysis that involved case–control studies with a much larger sample size also reported individuals with T2DM may have an increased incidence of PD compared to normal healthy individuals [16]. A longitudinal study reported that hypertension and T2DM as the most frequent comorbidities in patients with PD compared to control subjects [17]. A large prospective cohort study in Finland found an increased risk of 80% of developing PD-like symptoms in patients with T2DM and a similar study in the USA found that patients with T2DM were 40% more likely to develop PD-like symptoms [18]. Observational studies implying different strategies also reported that

Table 1 Studies investigating the association between diabetes and PD progression

Study design	Sample size	Results	Diabetes and PD association	References
Retrospective study	200 IPD patients and 200 controls	The cumulative incidence of ischemic stroke, myocardial infarction, and diabetes mellitus was higher in control than in PD patients	22 controls and 13 cases with diabetes	[147]
Retro prospective, case control study	119 presumptive etiology of IPD and 238 controls	The cumulative incidence of ischemic stroke, hypertension, and diabetes mellitus (DM) was not significantly different between control and PD patients	Diabetes more prevalent among controls	[148]
Cohort study	791 PD patients out of total 24,831 patients reported Parkinsonism whereas remaining 24,040 patients did not report any symptoms	Rates of diabetes among the population with Parkinsonism were higher than expected	29.7% of PD patients and 21.5% of controls had DM	[149]
Cohort study	15,306 PD patients; 30,612 controls	The occurrence of diabetes, ischemic heart disease, and myocardial infarction was more common in persons with Parkinsonism compared to those without Parkinsonism	PD patients and controls showed similar admission rates for diabetes	[150]
Case control study	352 IPD patients; 484 individuals without PD	Risk of PD was reduced in case of female and male smokers with and without diabetes	Diabetes prevalence in 7.4% of PD patients and 12.6% in controls	[151]
Population-based cross-sectional study	197 PD patients and 197 controls	PD cases did not differ significantly from referent subjects with respect to proportion with diagnosis of diabetes, ischemic heart disease, and myocardial infarction	PD patients did not show significant comorbidities	[152]
Hospital series case control study	178 PD patients and 533 individuals with other neurological diseases	Diabetes, high blood pressure, high blood glucose, high blood cholesterol, and triglycerides were significantly less frequent in IPD than in controls	3.4% of PD patients and 10.9% of controls had DM	[153]
Prospective, cohort study	51,552 individuals with 633 PD diagnosis	T2DM is linked to a higher risk for the development of PD	T2DM is associated with increased PD	[154]
Longitudinal, cohort study	1,030 PD patients	Diabetes was associated with parkinsonian signs, especially gait disturbance, postural reflex impairment, and vascular factors, that play a key role in this association	Diabetes is associated with more severe PD	[155]
Meta-analysis	NA	A significant upregulation of substantia nigra genes in PD, which have biological association with diabetes, cancer, and inflammation	Shared dysregulated pathways between T2DM and PD	[156]
Prospective, cohort study	556 patients with PD	Men with diabetes have a higher risk of developing PD than non-diabetic men	T2DM is associated with an increased risk of PD in men	[157]
Case control study	318 PD patients and controls	Preceding a diabetic condition increases the risk for the onset of PD	Diabetes preceding PD onset	[158]

Table 1 (continued)

Study design	Sample size	Results	Diabetes and PD association	References
Meta-analysis	NA	Diabetes is an important risk factor for PD	Diabetes could be risk factor for future PD	[5]
Genome-wide association studies	NA	Type 1 and 2 diabetic patients have deficits in cognitive functions	Shared molecular pathways between PD and T1DM	[159]
Cohort study	656 PD patients	No evidence of a relationship between DM and risk of developing PD	No association between PD and DM	[160]
Case control	1931 PD patients and 9651 controls	High risk of developing PD with T2DM	T2DM is associated with an increased risk of PD, especially early onset of PD	[161]
Prospective, cohort study	21611 diabetic patients and 267 051 controls	Diabetes could be a risk factor for future PD progression	T2DM is associated with an increased risk of PD	[11]
Case control	53 PD patients with dementia and 57 patients with PD	The prevalence of insulin resistance is significantly higher in PD-associated dementia as compared to those nondemented PD	Insulin resistance is associated with an increased risk of dementia in PD	[26]
Case–control	89 patients with diabetes and 89 controls	Onset of diabetes before the onset of PD is a high-risk factor for more severe PD symptoms	T2DM is associated with increased PD severity	[19]
Case–control	603,413 PD patients and 472 718 Controls	Diabetic patients showed a significantly increased risk of PD compared to the control subjects	Diabetes is associated with increased risk of PD	[162]
Case–control	64,166 diabetic patients and 698 587 controls	Increased incidence of PD risk in T2DM by 2.2-fold	T2DM is associated with increased risk of PD	[163]
Integrative network analysis	NA	Mitogen-activated protein kinase (MAPK) cascade, serine-threonine kinase activity, activation of the immune response, insulin receptor, and lipid signaling are convergent pathways between TDM and PD	Convergent molecular pathways between T2DM and PD	[164]
System-based approach	NA	T2DM and PD pathophysiology are strongly linked to each other	A positive association between T2DM and PD	[165]
Case–control	NA	The association between diabetes and postural instability and gait difficulty persisted after controlling for comorbid hypertension and body mass index	Diabetes is associated with severe postural instability and gait difficulty in PD	[166]
Meta-analysis	1,761,632 individuals	Individuals with diabetes had higher incidence of PD compared to non-diabetic individuals	Diabetes is associated with a 38% increased risk of PD	[16]
Retro prospective, case–control	36,294 diabetic patients and 108,882 healthy controls	Increased risk of PD with patients having DM compared to non-DM patients	DM increased the risk of PD by 23%	[4]
A record-linkage cohort study	2,017,115 T2DM patients and 6,173,208 reference cohort	There were significantly increased rates of PD following T2DM	T2DM was relatively higher in patients with PD	[167]

Table 1 (continued)

Study design	Sample size	Results	Diabetes and PD association	References
Population-based case study	25 patients with PD and DM 25 PD patients without diabetes	DM was associated with higher tau (cerebrospinal fluid) CSF level, lower striatal dopamine (DA) transporter binding, and higher motor score in patients with PD	PD with DM was associated with severe motor progression or cognitive decline	[10]
Retrospective observational cohort study	NA	Antidiabetic drug thiazolidinediones reduced risk of developing PD in the diabetic patients	Treatment of diabetes decreased PD progression by 30%	[168]
Cohort study	33,443 individuals with PD	DM and being underweight were associated with increased incidence of PD	Significant interaction between diabetes and PD development	[169]

patients with T2DM had 32% more chances of developing PD in the UK and 23% in Taiwan and 36% in Denmark [4]. Reports also suggest that T2DM may predispose to a PD-like pathology and induce a more aggressive phenotype when coexisting with PD. For example, patients with T2DM had higher Unified Parkinson Disease Rating Scale (UPDRS) motor scores and more severe Hoehn and Yahr staging [19]. Other than the progression, T2DM has also been implicated in posture instability, difficulty in gait strides during the development of PD [20]. Previous studies suggest that these associations between T2DM and PD progression are likely due to more than one mechanism involved. The precise mechanism by which T2DM is related to PD onset and progression is mostly unknown; however, some strikingly common dysregulated pathways like impaired insulin signaling, inflammation, mitochondrial dysfunction, ER stress, autophagy, and dysfunctions in UPS are among some of the shared mechanisms between both chronic diseases [6].

Insulin Resistance in T2DM and PD

Insulin regulates cell growth, gene expression, protein synthesis, mitochondrial function, and autophagy [21]. Insulin acts as a ligand and binds to its receptor resulting in enhanced tyrosine kinase activity that phosphorylates insulin receptor substrate (IRS)-1&-2 that binds to p85-phosphatidylinositol 3-phosphate kinase (PI3K) phosphorylating Akt and glycogen synthase kinase-3beta (GSK3-β), thereby regulating glucose metabolism [21]. Any link between T2DM and PD may relate to dysregulations in the common pathways due to chronic hyperglycemia conditions. People with T2DM suffer from insulin resistance which results in the progressive loss of insulin secretion from pancreatic β-cells, ultimately leading to hyperglycemic conditions in T2DM [22]. PI3K/Akt signaling is inactivated, which inhibits the transport of plasma glucose into cytoplasm resulting in dysregulated blood glucose homeostasis and insulin resistance in T2DM. Chronic hyperglycemia results in the generations of reactive oxygen species (ROS) that have been implicated in the loss of β-cell mass in T2DM [23]. Furthermore, studies have also shown that GLP-1 suppresses glucagon secretion from α-cells and regulates glucose-dependent insulin secretion from pancreatic β-cells in T2DM [24]. This loss in function and mass of β-cell in T2DM may be attributed to the consequence of glucolipotoxicity, accumulation of cholesterol, and inflammation in islets [25].

Insulin also regulates the activation of neural stem cells, cognition, synaptic formation, and neuronal apoptosis [26]. Implications of neuronal insulin resistance are commonly seen in various neurodegenerative diseases [27, 28]. Studies have suggested the role of insulin in regulating DA-ergic activity and a reciprocal insulin regulation by DA-ergic

neurons. Recent evidence showed the prevalence of insulin resistance exhibiting impaired glucose tolerance in patients with PD [29]. Interestingly, some drugs used to treat PD, such as levodopa (L-DOPA), induce hyperglycemia conditions indicating insulin resistance may increase the risk of developing PD [29].

Dysregulation of PI3K/Akt signaling pathway may alter the expression of α-synuclein, leading to DA-ergic cell death [30]. Studies have also highlighted the role of leucine-rich repeat kinase 2 (LRRK2) in insulin-dependent intracellular signaling. Reports suggest that phosphorylation of Ras-related protein (Rab10), an endocytic sorting protein, by LRRK2 is crucial for glucose transporters type 4 (GLUT4) translocation to the neuronal plasma membrane is inhibited in PD patients with the LRRK2 (G2019S) mutation [31]. These studies show that insulin resistance can be a potential risk factor for T2DM and the pathologic driver of neurodegeneration in PD.

Inflammation in T2DM and PD Etiopathogenesis

Inflammation is a highly regulated process that protects against tissue damage that has been implicated in the pathogenesis of T2DM and PD [32]. Studies have reported elevated inflammatory response mediated by immune cells, cytokines, and chemokines in the islets of patients with T2DM [33]. Inflammatory response likely causes insulin resistance by activating cytokines which is reciprocally mediated by hyperglycemia conditions thereby promoting severity in T2DM [34]. Insulin resistance causes activation of microglia and inflammation mediated by nuclear factor-κB (NF-κB) and the PI3K/Akt pathway [35, 36]. Inflammatory cytokines like tumor necrosis factor-α (TNF-α) induce the inactivation of insulin receptor substrate-1 (IRS1), which inhibits activation of downstream regulators promoting T2DM conditions [37]. Activated cytokines downregulate anabolic cascades in insulin signaling resulting in insulin sensitivity and dysregulations in glucose metabolism [38]. Several lines of evidence have suggested the role of pro-inflammatory cytokines in regulating insulin resistance and dysregulations in glucose homeostasis in T2DM. Reports suggest that low-grade pancreatic tissue inflammation plays a critical role in the pathophysiology of T2DM [39]. Similarly, studies have shown that a high glucose/cholesterol diet can induce activated microglia mediating pro-inflammatory cytokines—interleukin-6 (IL-6) and TNF-α release in an in vivo model of T2DM [40]. Reports also suggest increased levels of infiltrating macrophages that release IL-1β, which leads to loss of β-cell function and its progressive destruction in T2DM [41]. Studies have also shown that hyperglycemia activates (P2X purinoceptor 7) a P2X7 receptor that induces NOD-, LRR-, and pyrin domain-containing 3 (NLRP3) inflammasome activation to increase IL-1β secretion resulting in pancreatic β-cell dysfunction and death [42]. Treating T2DM rodents with anti-inflammatory drugs like aspirin resulted in the decrease of pro-inflammatory cytokines release, thereby alleviating insulin resistance [43]. Also, these anti-inflammatory drugs have been reported to result in dysregulations in IKK-β signaling pathways that otherwise mediate insulin resistance and T2DM [44]. Similarly, exogenous administration of TNF-α or IL-6 results in insulin resistance and lower levels of cytokines were observed in TNF-α knock-out mice [38]. The newly discovered cytokine IL-37 binds to IL-18 receptor α/β (IL-18Rα) chain and shows anti-inflammatory properties by inhibiting IL-6, IL-18, IL-33, IL-1β, and TNF-α, suggesting a potential therapy for low-grade inflammation in T2DM [39]. Taken together, these observations suggest inflammation as a key feature in the regulation of insulin resistance and the development of T2DM.

Inflammation also plays a very important role in the pathogenesis of PD. Previous studies report that activated microglia and astrocytes promote neuroinflammation as key pathways of PD progression [45]. Activation of microglia and subsequent microgliosis events may be mediated by the aggregation of α-synuclein released by damaged and injured neurons in PD [46]. Aggregation of misfolded α-synuclein acts as damaged-associated molecular patterns (DAMPs), inducing NLRP3 inflammasome in PD, which then interacts with caspase-1 forming activated NLRP3–caspase-1 complex followed by secretion of IL-1β from microglia [47]. Similarly, activation of reactive astrocytes results in sustained neuroinflammation that mediates degenerations in PD [48]. Elevated levels of pro-inflammatory cytokines, including IL-6, IL-1β, TNF-α, and IFN-γ, have been observed in a 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)–induced mouse model of PD [49]. Elevated concentrations of pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α were observed in the brain, CSF, and blood of PD patients [50]. Reports suggest that activated glial cells secrete various pro-inflammatory cytokines resulting in neuroinflammation and neurodegeneration via NF-kB signaling [51]. The β2-adrenoceptor, a G-GPCR, is expressed in microglia, astrocyte, and postsynaptic neuron surface. Treatment with its agonist clenbuterol and formoterol activates cAMP/PKA/CREB/IkBα pathway that results in inhibition of the NF-kβ inflammatory pathway in the intra-nigral LPS induced rat model of PD [52]. Taken together, these observations suggest that inflammation is a key feature in the regulation of insulin resistance in T2DM and neuronal death in PD. The role of insulin resistance and inflammation in promoting T2DM conditions and neurodegeneration in PD is given in Fig. 1

Mitochondrial Dysfunctions in T2DM and PD

Mitochondria is essential for glucose-stimulated insulin secretions from β-cells and its dysfunction has been implicated in T2DM [53]. The prevalence of mitochondrial diabetes constitutes about 0.5–1% of all types of DM mediated by impaired insulin secretions, unlike other T2DM mediated by insulin resistance [54]. Depletions in mtDNA dramatically decrease oxygen consumption and suppress glucose-stimulated insulin secretion in T2DM [54]. Studies on the role of mtDNA in the etiopathogenesis of T2DM are scarce. Yet, a dozen loci in nuclear-encoded mitochondrial genes have been directly related to T2DM by regulating β-cell function [55]. A co-transcription factor peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC1-α) and a transcription factor B1 mitochondrial (TFB1M) are essential for the normal functioning of mitochondria. During mitochondrial dysfunction, PGC1-α and TFB1M have been implicated in the pathogenesis of T2DM by decreasing oxygen consumption, ATP production, and concomitantly insulin secretion [56]. Another such gene UCP2, mitochondrial C4 metabolite exchanger, was found to be highly expressed in islets of different animal and human models of T2DM. Hyperglycemia induces glucose oxidation by elevating NADH and pyruvate in mitochondrial complex I, III resulting in ROS production, thereby impairing β-cell function [57].

Mitochondria perform a plethora of functions by regulating various cellular processes like Ca^{2+} homeostasis, stress response, and apoptotic pathways [58]. Mitochondrial dysfunction has been implicated in the pathogenesis of PD. α-synuclein aggregation in mitochondrial is characterized by the generation of ROS, decrease in the activity of mitochondrial complex I enzyme, decrease in ATP levels, cytochrome-c release, and caspase-3 activation [59]. α-synuclein-mediated mitochondrial dysregulations may be

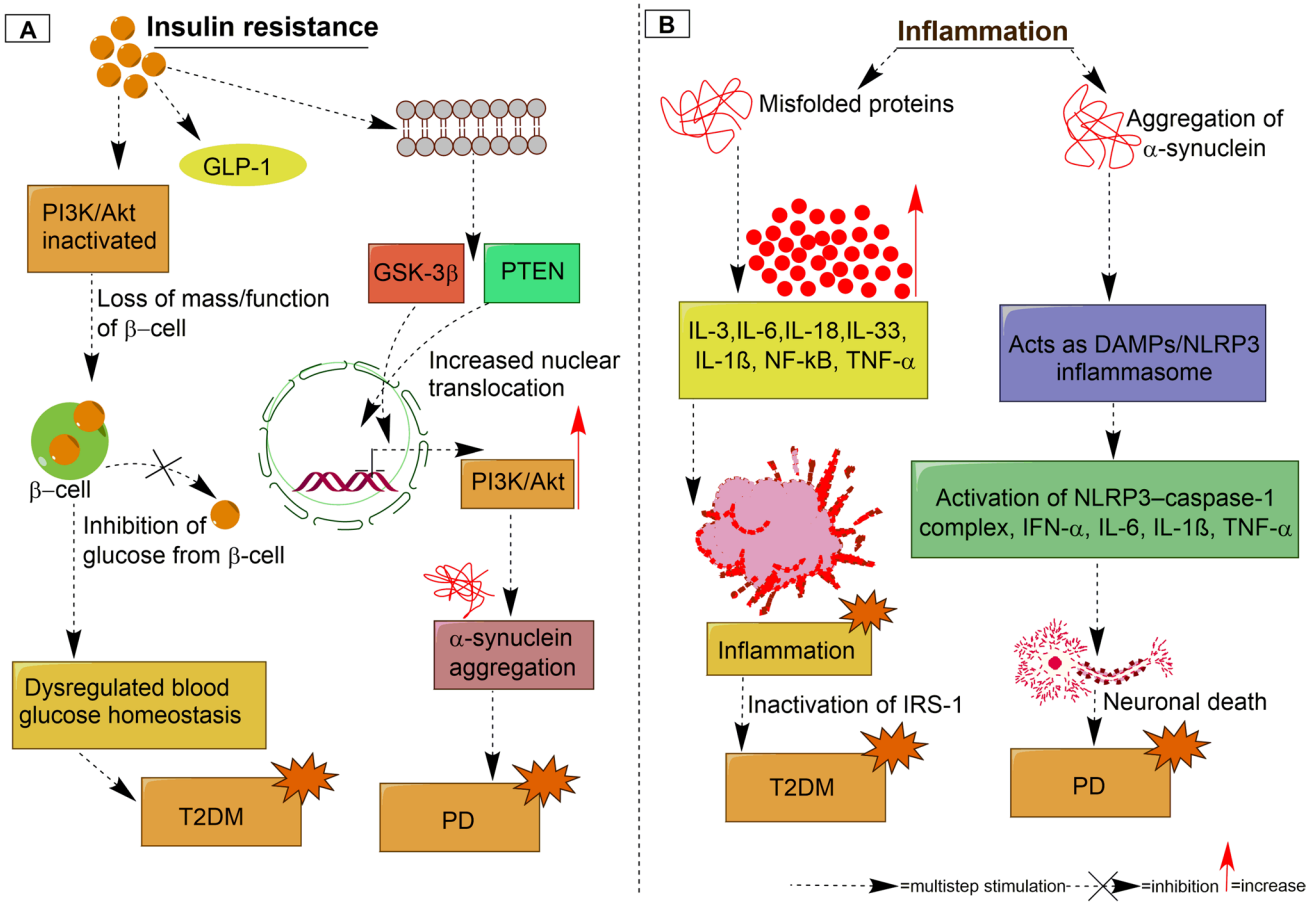

Fig.1 Diagrammatic representation of the possible role of (**A**)insulin resistance and (**B**) inflammation in promoting T2DM conditions and neurodegeneration in PD. Abbreviations: DAMPs, damage-associated molecular patterns; GLP-1, glucagon-like peptide; GSK3β, glycogen synthase kinase 3 beta; IFN-α, interferon alfa; IL-3, interleukin-3; IL-6, interleukin-6; IL-18, interleukin-18; IL-33, interleukin-33; IL-1β, interleukin 1 beta; IRS-1, insulin receptor substrate 1; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NLR family pyrin domain-containing 3; PD, Parkinson's disease; PI3K, phosphoinositide 3-kinase; TNF-α, tumor necrosis factor alfa; T2DM, type 2 diabetes mellitus

due to α-synuclein-induced p38 MAPK activation, which phosphorylates and activates Drp1 (dynamin-related protein-1), causing mitochondrial fission [60]. Neurons have incredibly high metabolic demands making them highly susceptible to mitochondrial dysfunction [61]. The very first report on the role of mitochondrial dysfunction in PD pathogenesis came from the accidental infusion of the MPTP, which selectively inhibited mitochondrial complex I of electron transport chain [58]. Later studies reported environmental toxins MPP^+, rotenone, and paraquat target the mitochondrial respiratory chain resulting in mitochondrial dysfunction in PD (57). Overexpression of mutant A53T or wild-type human SNCA gene in different in vitro and in vivo models of PD resulted in cytochrome c release, increased mitochondrial Ca^{2+} and nitric oxide (NO) levels, and decreased mitochondrial complex I [62]. Parkin and PINK1 genes together regulate mitochondrial function and biogenesis and their mutations have been reported to result in mitochondrial impairments by reducing complex I activity and increasing mitochondrial ROS production in the different PD models [63]. DJ-1 protein fractionally located at the mitochondria acts as a neuroprotective intracellular redox sensor and its mutation/inactivation/knockout resulted in the decrease of mitochondrial complex I activity, decreased mtDNA levels, respiratory control ratio, and ATP levels in the experimental PD models [64]. Similarly, overexpressions of the LRRK2 gene resulted in decreased mitochondrial membrane potential (MMP) and ATP levels, thereby impairing mitochondrial function in PD patients [65]. These observations indicate that mitochondrial function is paramount for the normal functioning of the cellular processes and its dysregulations are implicated in the etiopathogenesis of T2DM and PD.

There is a strong correlation between neuroinflammation and mitochondrial dysfunction in the pathogenesis of T2DM and PD. In the MPTP-induced PD mice model, neuroinflammation involving microglia activation has been reported in the brain's striatum and substantia nigra regions. Activated microglia release IL-1β and IL-6 and induce activation of iNOS and NADPH-oxidase [66]. Activated microglia also release excitotoxins like quinolinic acid and glutamate that overstimulate glutamate receptors expressed in neurons, thereby increasing membrane lipid peroxidation, reactive nitrogen species, and mitochondrial damage [67].

In T2DM, inflammation and mitochondrial dysfunction are correlated with each other. Systemic inflammation is also one of the factors responsible for insulin resistance and pathogenesis of T2DM. Damaged mitochondria releases mitochondrial DAMP molecules, such as cytochrome C, mt.DNA, and ATP. When released in circulation, the mitochondrial DAMPs activate systemic inflammatory responses. It has been reported that there is an elevation in circulating cell-free mt.DNA in the plasma of T2DM patients. The circulating cell-free mt.DNA induces AIM2 inflammasome-dependent activation of caspase-I and secretion of IL-18 and IL-1β from macrophages. It concludes in chronic inflammation in T2DM patients [68].

Excessive microglial activation causes loss of mitochondrial membrane potential along with ROS production leading to neurodegeneration [69]. Increased oxidative stress oxidizes lysine, threonine, proline, and arginine residue of mitochondrial proteins, mitochondrial ETC components, and mt.DNA, resulting in mitochondrial dysfunction [70]. It has been reported that the presence of glia increased neurodegeneration in neuron/glia culture from rat mesencephalon in rotenone-induced toxicity associated with $O_2^{\cdot -}$ release from microglia. Intranigral LPS-injected rats showed increased microglia activation; increased release of pro-inflammatory cytokines and iNOS, COX-2, and SN DA-ergic neurodegeneration; and reduced striatal DA level. LPS also induced significant nigral and striatal mitochondrial complex I and II in LPS-injected rats. Thus, inflammation causes loss of mitochondrial function, ultimately leading to DA-ergic neurodegeneration [71]. When injected into the rat brain ventricles, DA inhibits mitochondrial complex I, leading to increased cellular ROS and α-synuclein aggregation. Metabolism of DA also generates ROS (H_2O_2, DA-quinone, and semiquinone) as a by-product. This oxidative stress contributes to inflammatory response, as seen in PD patients [72].

Endoplasmic Reticulum Stress in the Pathogenesis of T2DM and PD

ER plays a crucial role in correct folding and post-translational modification of cell surface receptors, secretory proteins, and integral membrane proteins [8]. Aggregation of unfolded or misfolded proteins in ER lumen induces ER dysfunction resulting in ER stress [73]. There is an initiation of a complex signaling pathway called unfolded protein response (UPR) during the ER stress conditions. There are three specific sensor proteins of ER stress named as follows: Activating transcription factor 6 (ATF6), inositol requiring enzyme 1 α (IRE1α), and eukaryotic pancreatic ER kinase (PKR)–like ER kinase (PERK) [74]. Various studies have proposed ER stress as an underlying mechanism in the pathogenesis of T2DM and PD [75]. Reports suggest that ER stress–mediated β-cell loss in T2DM is regulated by the key transcription factors and gene networks [76]. ER stress mediates islet amyloid polypeptide (IAPP), inducing pancreatic β-cell apoptosis in T2DM. When ER homeostasis is destroyed, then PERK gets activated, and it subsequently triggers phosphorylation of eIF2α, ultimately leading to ATF4 upregulation. However, when UPR stress cannot restore the ER homeostasis, PERK activates downstream effectors and mediators of apoptosis, including caspase-12, CHOP, and Bcl family genes. Activation of the PERK-CHOP pathway also induces activation of NF-κB,

resulting in inflammation and aggravating β-cell apoptosis in T2DM [77]. Under normal conditions, ATF6 causes upregulation of Grp78 protein. But diabetes-induced ATF6 is associated with dilation of ER cisterns and an increase in ER volume, reflecting ER's increased functional capacity [78]. Another study has reported that ER stress induces phosphorylation of IRE1α that further activates its downstream effector XBP-1 and concludes in a series of events leading to UPR response in T2DM [74]. Mutation in EIF2AK3, encoding human eIF2α-kinase, which regulates transitional control in response to ER stress, has been reported in T2DM, suggesting its role in normal β-cell functioning and survival [79]. Similar studies also demonstrated aberrant expression of ER stress biomarkers including p-PERK, p-eIF2α, p-IRE1α, CHOP, BiP, cleaved caspase-3, and caspase-8 in the individuals with T2DM [73]. More evidence for the role of ER stress in T2DM etiology comes from a study where ER stress–mediated overexpressions of BiP, CHOP, and p58 were observed in β-cells of patients with T2DM compared to the healthy non-diabetic patients [80]. A similar study found a fold increase in ER stress in β-cells of T2DM patients compared to the normal, non-diabetic individuals [81]. Studies have shown that prolonged ER stress induces apoptosis by activating the caspase-3 pathway in rats with T2DM. The caspase-mediated apoptotic pathway involves activating caspase-8 that activates caspase3/caspase6/7/PARP (poly ADP-ribose polymerase) signaling resulting in apoptosis in pancreatic β-cell during T2DM [2]. Studies have also shown that genetic variations in Wolfram syndrome gene 1 (WFS1), encoding ER Ca^{2+} channel, result in selective loss of β-cell in young-onset diabetes and T2DM. This reduction in ER stress–mediated β-cell mass may be due to chronic exposure to gluco- and lipotoxicity [79]. It is very unlikely that loss of β-cell entirely accounts for reduced insulin secretions in T2DM and more detailed studies are required to determine the role of ER stress–mediated reduction in β-cell mass.

Correspondingly in PD, studies have shown that ER stress induces the aggregation of α-synuclein into LB that promotes neurodegeneration [82]. Studies have shown that IRE1α gets activated and induces activation of the caspase-12 mediated apoptotic pathway in the MPP + treated PC12 cells, causing DA-ergic neuronal death. Isorhynchophylline (IRN) treatment inhibits IRE1α-mediated ER stress resulting in the protection of PC-12 cells from caspase-9-dependent apoptosis [83]. Activation of PERK in ER stress conditions phosphorylates eIF2α, activating ATF4. An increased level of ATF4 further elevates transcription of CHOP that downregulates Bcl-2. Studies have shown that β-asarone, a component of Acorus tatarinowii Schott volatile oil, regulates the ER stress–autophagy by inhibiting the PERK/CHOP/Bcl-2/Beclin-1 pathway resulting in neuroprotection in 6-OHDA-induced parkinsonian rats [84]. Activation of the ATF6 pathway in the ER stress causes trafficking and proteolytic processing of ATF6. Activated ATF6 regulates the expression of XBP1 and ER chaperone. A study has shown that aggregation of α-synuclein induces ER stress response that causes activation of PERK and ATF6 pathway in an α-syn-induced rat model of PD. In the absence of re-establishment of ER homeostasis, ATF6 activates proapoptotic CHOP protein in SNpc DA-ergic neurons. However, Grp78 over-expression downregulates ER stress mediators and proapoptotic mediators resulting in DA-ergic neuroprotection [85].

It has also been demonstrated that both HMG–CoA reductase degradation protein-1 (Hrd1) and Parkin-associated endothelin receptor-like receptor (Pael-R) are aberrantly expressed in DA-ergic neurons [75]. Hrd1 is a key enzyme for ER-associated degradation of unfolded or misfolded proteins and Pael-R is a substrate for Parkin, an E3 ubiquitin ligase [86]. Therefore, ER stress caused by the accumulation of Pael-R is relevant to the pathological mechanisms that underlie autosomal recessive PD. However, recent studies have also investigated that Pael-R is ubiquitinated by Hrd1 thereby preventing ER stress–induced neuronal apoptosis in PD [75]. Besides that, an in vivo study has demonstrated that the inhibition of X-box-binding protein 1 (XBP1), a key regulator of the unfolded protein response (UPR), induces chronic ER stress and specific DA-ergic neurodegeneration [87]. Restoring XBP1 levels by gene therapy decreased striatal denervation and neuronal death in the 6-OHDA-induced mice model of PD [88]. In another similar study, activation of XBP1 provided neuroprotection against MPTP-induced DA-ergic loss in in vitro and in vivo models of PD, indicating the crucial role of UPR in the survival of DA-ergic neurons [89]. MPTP-induced ER stress causes dysregulations in ER Ca^{2+} homeostasis by inhibiting store-operated calcium entry (SOCE) and transient receptor potential channel 1 (TRPC1), resulting in DA-ergic neuronal loss [90]. Recent studies have reported that ER stress–mediated apoptosis was implicated in the PD by activating the apoptotic pathways [91]. These observations suggest that ER stress may be a common pathological pathway and its inhibition can be a common therapeutic target in the treatment strategies against T2DM and PD. Figure 2 depicts the role of mitochondrial dysfunction and endoplasmic reticulum stress in the pathogenesis of T2DM and PD.

Impairment of Autophagy in T2DM and PD

Autophagy is a catabolic process that maintains cellular hemostasis by enabling cells to stride past unfavorable stress conditions by regulating the intracellular conditions through cytoplasmic turnover of proteins and organelles [92]. Autophagy, if altered, may be associated with a distinct form of cell death resulting inT2DM and PD onset/progression. Loss of autophagic function by cells results in amyloid aggregation, i.e., amylin protein and α-synuclein in T2DM and PD, respectively [93]. Upregulation of common

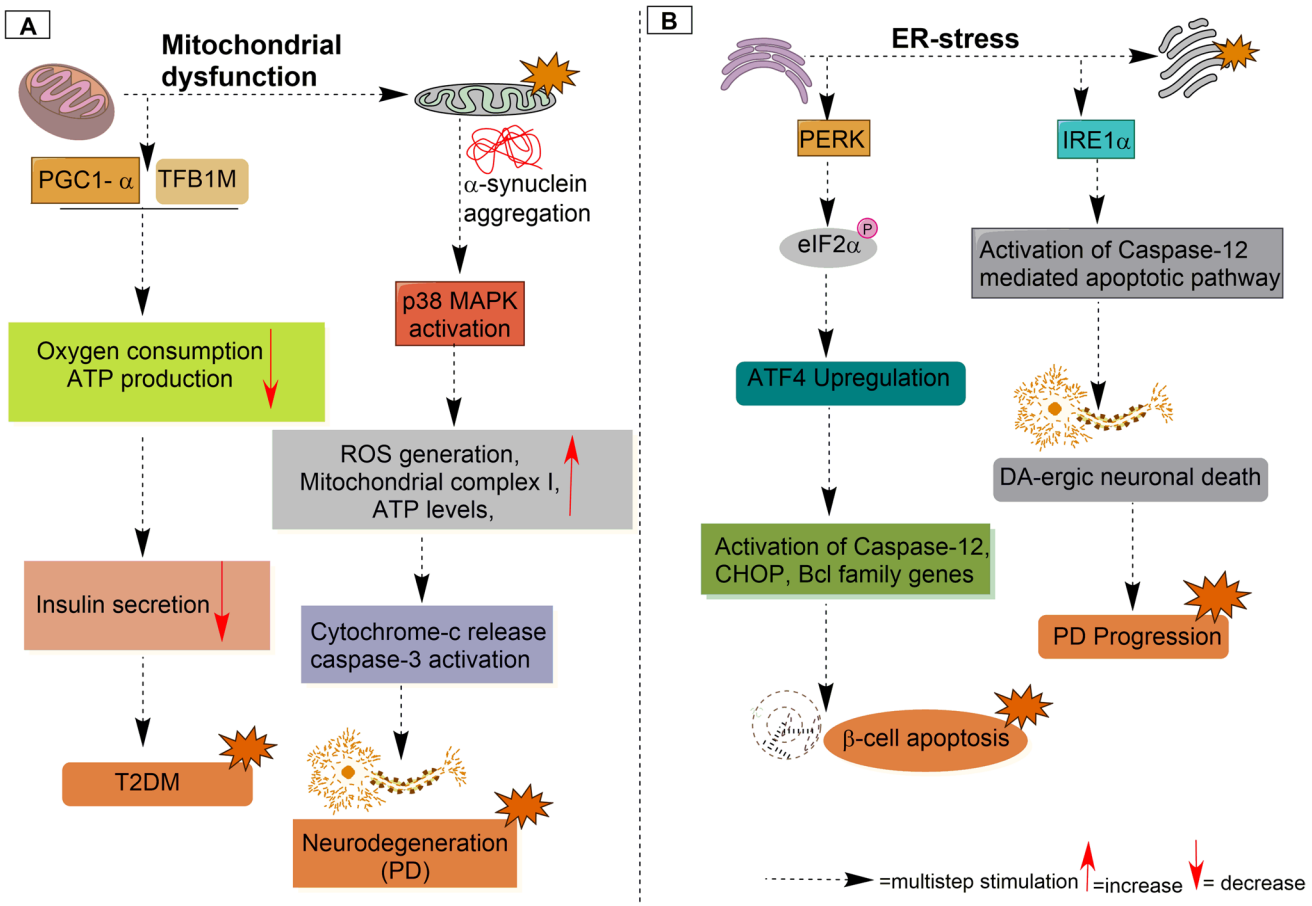

Fig.2 Schematic illustration of the role of (**A**) mitochondrial dysfunction and (**B**) endoplasmic reticulum stress in the pathogenesis of T2DM and PD. Abbreviations: ATF4, activating transcription factor 4; ATP, adenosine triphosphate; CHOP, C/EBP homologous protein; Bcl, B-cell lymphoma; DA-ergic, dopaminergic; eIF2, eukaryotic initiation factor 2; IRE1α, inositol requiring enzyme-1 alpha; Parkinson's disease; PERK, protein kinase R-like endoplasmic reticulum kinase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; MAPK, mitogen-activated protein kinase; PD, Parkinson disease; ROS, reactive oxygen species; T2DM, type 2 diabetes mellitus; TFB1M, transcription factor B1 mitochondrial

autophagic markers like LC3-II, p62, beclin-1, p-mTOR, and p-AMPK has been reported in T2DM and PD [94]. Recent investigations have found the role of autophagy in controlling insulin signaling and lipid metabolism. Under normal conditions, autophagy is essential for the survival and maintenance of β-cell function, but during stressful conditions, it prevents β-cell dysfunctions by serving as an adaptive mechanism [95]. Studies have shown the accumulation of autophagosomes and undigested autophagic vacuoles in the pancreatic β-cells in T2DM [96]. Impaired autophagy resulted in dysregulated vascular function and its stimulation by upregulating autophagy markers LC3-II, Beclin-1, and p62 improved vascular function in the mesenteric arteries of T2DM mice [97]. Atg7 and Atg12-Atg5 play central roles in the biogenesis of autophagosomes and their dysregulations increase sensitivity towards insulin and have been therefore implicated in T2DM pathogenesis [98]. Recent work demonstrated upregulating autophagy genes reduced insulin secretion and the incidence of diabetes in STZ-treated β-cells [99]. In another experiment, metformin, a T2DM drug, was shown to decrease the formation of autophagic vacuoles in T2DM by enhancing AMP kinase activity that inhibits the mTOR pathway resulting in the removal of autophagic vacuoles [96]. Exendin-4, an agonist of the glucagon-like peptide GLP-1 receptor (GLP-1R), promotes insulin secretion and regulates autophagic markers, such as mTOR, LC3-II, LAMP1, parkin, Atg7, and p62, further validating the fact that autophagy plays crucial role in regulating T2DM [92].

Similarly, autophagy has been implicated in the etiopathogenesis of PD. Many genes and protein products of PD-related genes, either causative or risk factors for PD, appear to have an essential role in regulating autophagy pathways. α-synuclein, an insoluble aggregated protein implicated in PD, is usually degraded by chaperone-mediated autophagy (CMA) binding to its pentapeptide sequence motif [100]. α-synuclein enters into lysosome by binding to

lysosomal-associated membrane protein type 2A (LAMP-2A), where it is degraded by proteases [101]. However, during dysregulated autophagy in PD, LAMP-2A does not take up mutant α-synuclein due to its very high binding affinity, which does not allow proper translocation of α-synuclein into the lysosome and its subsequent degradation [102]. Mutations in LRRK2, one of the major causes of PD, disrupt aggresomal formation and autophagic clearance of accumulated protein aggregates [103]. PINK1 regulates parkin translocation to impaired mitochondria driving their elimination via autophagy. In normal conditions, LRRK2 gets degraded by CMA; however, very high concentrations of LRRK2 during PD can block CMA by inhibiting translocation complex at lysosomal membrane, thereby resulting in dysregulations in autophagy function [104]. The autophagic adapter protein p62, a component of the PINK1-parkin pathway, is involved in the proteasomal degradation of misfolded or unfolded proteins. It interacts with the mitochondrial outer membrane proteins like mitochondrial mitofusin (MFN), VDAC, Fis1, and TOM20 that facilitate its recruitment to LC3, which promotes their incorporation into phagophores [104]. Defective p62 function and mutation in PINK1 lead to the accumulation of ubiquitinated protein aggregates resulting in persistently damaged mitochondria and cell death promoting PD pathology [105]. These observations imply that autophagy plays a crucial role in the pathogenesis of PD and T2DM or even the convergence point for the symptoms of T2DM and PD.

Dysregulated Ubiquitin Proteasomal System in T2DM and PD

Accumulation of damaged protein is harmful to normal cellular functioning; therefore, its degradation is essential [106]. UPS is one of the major pathways that degrade various proteins following polyubiquitination [107]. Studies have shown that UPS plays a significant role in insulin secretion by regulating various key proteins in the β-cell secretory cascade [108]. It also regulates various crucial proteins like IRS-2, MafA, or CREB essential for the β-cell survival [109]. Inhibition in UPS function may cause a decline in the level of insulin secretion in the pancreatic β-cell [110]. Recent studies suggest that the formation of toxic human islet amyloid polypeptide aggregates (h-IAPP) results in the loss of β-cell function leading to T2DM progression [111]. The increased expression of h-IAPP in T2DM downregulates ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), causing alteration in UPS causing deleterious consequences on β-cell function and survival [112]. Studies have also shown that toxic human amylin (hA) protein interacts with 20S core and 19S lid subunit of the β-cell proteasomal complex resulting in decreased proteolytic activity in T2DM [113]. Dysregulations in UPS have been reported to decrease insulin signaling by downregulating insulin receptor and insulin substrate (IRS) proteins in T2DM [114]. The downregulation in IRS proteins is mediated by dysregulations in the suppressor of cytokine signaling 1 (SOCS1) and SOCS3, substrate-recognition modules in elongin BC ubiquitin-ligase complex [115]. Additionally, IRS stability is regulated by a negative feedback mechanism in which insulin-dependent activation of mTOR phosphorylates IRS proteins and their subsequent ubiquitination and degradation of ubiquitin ligase subunit Fbw8 [116].

Similarly, dysregulations in UPS have been implicated in the pathogenesis of PD, leading to aggregation of α-synuclein [117]. It has been observed that alterations and dysfunction in UPS due to over-expression of α-synuclein may lead to DA-ergic neurodegeneration in PD. UPS components with PD-related protein parkin and UCH-L1 are implicated in the degradation of the misfolded α-synuclein protein [118]. Aggregates of α-synuclein may, in turn, selectively bind to 6S subunit of 26S proteasome inhibiting UPS function to induce further neuronal toxicity [119]. Therefore, proteasome and α-synuclein aggregation may reciprocally regulate a feed-forward mechanism and exacerbate the onset and progression of PD. Mutations in the catalytic and autoinhibitory domain Ub ligase Parkin (Park2) and phosphatase and tensin homolog (PTEN) PTEN-induced putative phosphatase 1 (PINK1) interrupt proteasome activity and lead to α-synuclein aggregation [120]. Mutation in DJ-1, a substrate for ubiquitin-like modifier-1 (SUMO-1) conjugation, has been implicated in the onset of PD [121]. Moreover, studies have also shown that deficiency of DA activates PKA (protein kinase A) and α-synuclein aggregate activates MAPK and mitogen and stress-activated kinase-1 (MSK1). The resultant activation of these enzymes causes phosphorylation of tyrosine hydroxylase enzyme that gets degraded by UPS, resulting in degradation and loss of DA-ergic neurons [122]. Protein degradation by UPS in T2DM and PD is crucial in cellular functioning, and evidence suggests its disruption as an important risk factor for T2DM and PD pathogenesis. Illustrative representation of the role of dysregulated autophagy and ubiquitin proteasomal system in promoting T2DM conditions and PD is given in Fig. 3.

Memory Impairment in T2DM and PD

The hippocampus region of the brain is susceptible to hyperglycemia associated with diabetes. It also plays a very crucial role in learning and memory. Diabetic animal models have shown that neuronal apoptosis in the hippocampus leads to spatial memory and cognition impairment [123]. Studies have shown that caffeine consumption abrogates memory deficits associated with downregulation of A_1 receptors and upregulation of A_{2A} receptors in the hippocampus in the mice model of T2DM [124]. It has been also shown that a high-fat diet (HFD) induces memory loss through microglia

activation. Activated microglia increased pro-inflammatory markers like TNF-α, and Iba-1 in the hypothalamus and hippocampus region of the brain, causing inflammation. Treatment with abscisic acid (ABA) rescued all these HFD-induced changes in rats and improved cognitive function [125]. Central neuroinflammation and bleeding can interfere with normal blood–brain barrier (BBB) function and lead to memory and learning disabilities. Studies have shown that long-term use of *Mangifera Indica Lin* extract decreased microglia-mediated inflammation, limited hippocampal and cortical atrophy, and lowered tau phosphorylation, resulting in improved memory and learning disabilities [126]. It is reported that purinergic receptors play a crucial role in memory impairment in T2DM. DNA damage mediates downregulation of P2X purinoceptor 4 (P2X4R), resulting in increased levels of activated microglia in the hippocampus. These studies show that memory impairment is implicated in the pathogenesis of T2DM [127].

PD patients have comorbidities like-cognitive dysfunction, depression, and anxiety that significantly burden their quality of life [128]. Several studies have shown that PD is associated with impairment in memory [128–130]. Deltamethrin is most commonly used in controlling pests, and its administration causes hyperactivity and impairment in cognition and DA-ergic degeneration [130]. IPD patients have shown memory impairment, but it has been observed in the recall stage with relatively spare recognition. Aarsland et al. conducted a study with 1346 IPD patients without dementia and found that memory deterioration is the most common cognitive dysfunction in these patients, with the prevalence of mild cognitive impairment in 25.8% of patients [131]. The features associated with cognitive dysfunction in PD are impairment in visuo-perceptual processing and working memory. Kawashima et al. have reported that there is reduced activation of middle frontal gyrus (MFG) and inferior parietal lobule (IPL) regions of the brain in PD patients with cognitive impairment, suggesting that these regions

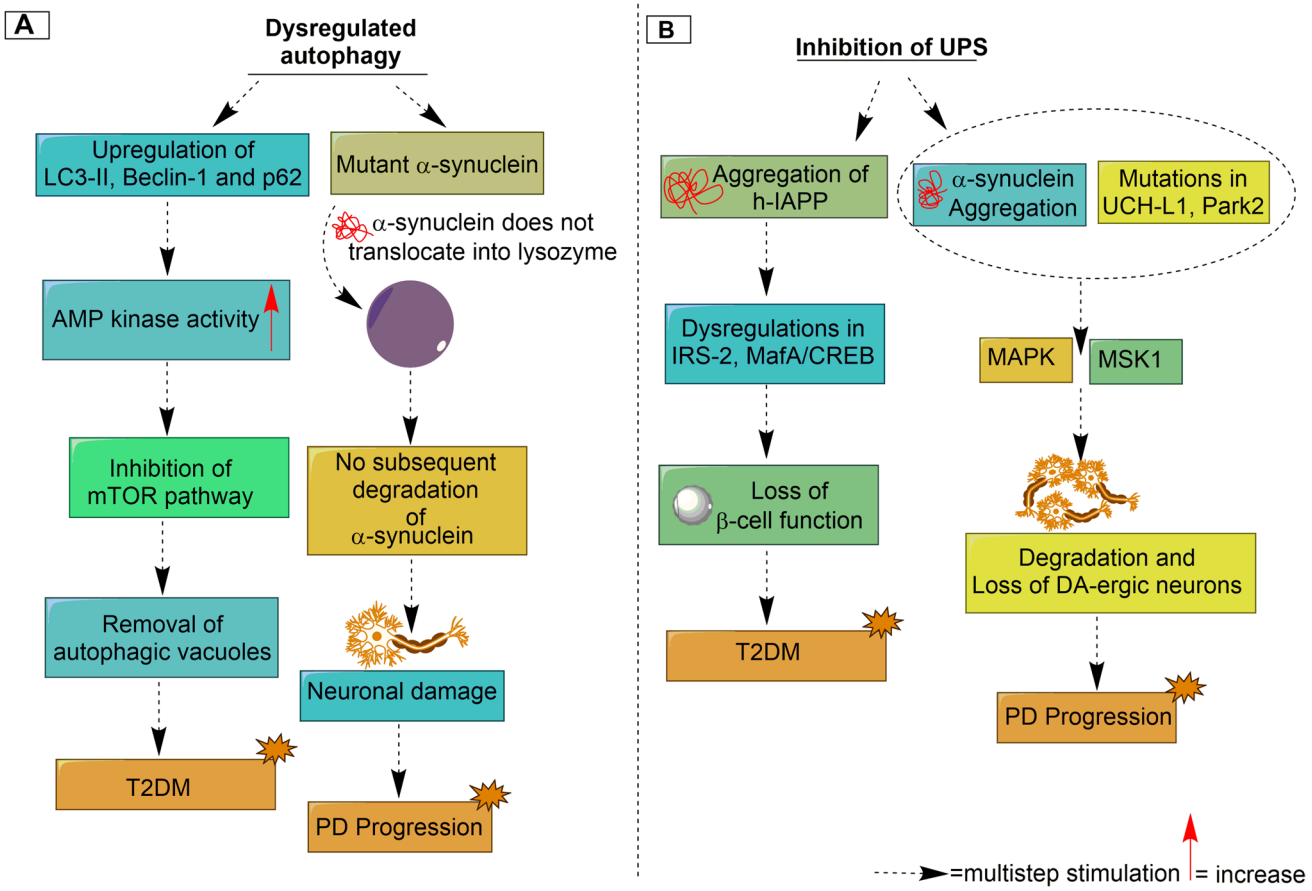

Fig.3 Illustrative representation of the role of dysregulated (**A**) autophagy and (**B**) ubiquitin proteasomal system in promoting T2DM conditions and PD. Abbreviations: AMP, adenosine monophosphate; CREB, cAMP response element-binding protein; DA-ergic, dopaminergic; h-IAPP, human islet amyloid polypeptide; IRS-2, insulin receptor substrate 2; MafA, MAF BZIP transcription factor A; MAPK1, mitogen-activated protein kinase 1; MSK1, mitogen- and stress-activated kinase 1; PD, Parkinson's disease; Park2, Parkin RBR E3 ubiquitin-protein ligase 2; T2DM, type 2 diabetes mellitus; UCH-L1, ubiquitin C-terminal hydrolase L1

may be associated with the pathophysiology of impairment in working memory in PD patients that involves fronto-striatal network dysfunction [129]. PD-induced cognitive dysfunction is associated with alternation in the DA-ergic vs. cholinergic neurotransmission [128].

DA signaling is crucial for normal memory function. In the cortex and medial temporal lobe, mesocorticolimbic DA modulates memory consolidation and retrieval, whereas striatal DA facilitates learning [132]. Studies have shown that etazolate, a pyrazolo pyridine compound, prevents long- and short-term memory deficits in the 6-OHDA-induced rat model of PD by increasing BDNF and antioxidant levels in the hippocampus [128]. The parahippocampal gyrus and salience network are consistently involved during memory retrieval. Other studies have shown that DA-ergic dysfunction in salience network and median temporal lobe leads to memory impairment in PD. It has been reported that rotenone exposure causes neurodegeneration in the cortex and hippocampus, resulting in cognitive dysfunction in the mice model [133]. Studies have shown that microglia-mediated neuroinflammation concluding in neuronal apoptosis is a pathological characteristic in memory impairment associated with PD [133, 134]. It has been reported that microglia-mediated disruption of the blood–brain barrier leads to neurodegeneration, resulting in impairment in memory and learning in rotenone induced mice model of PD [133]. Depletion of norepinephrine (NE) and damage to locus coeruleus (LC) noradrenergic neurons are early events in PD. It exacerbates the DA-ergic neurotoxicity and motor deficits. The studies have shown that damage to LC/NE increased α-synuclein expression, Ser129-phosphorylation, and synaptic loss, causing hippocampal neurodegeneration through microglia-mediated neuroinflammation and ferroptosis, as a result of which learning and memory get impaired in PQ and a maneb-induced mice model of PD [134].

Common Therapeutic Targets Against T2DM and PD

T2DM and PD have shared pathogenesis that leads to the onset and establishment of either disease. It suggests that targeting a common molecular pathway may provide a novel therapeutic target against both diseases. Aggregation of amylin peptide, mitochondrial dysfunction, oxidative stress, inflammation, autophagic dysfunction, and loss of UPS function are some of the etiological factors that play a crucial role in the onset and development of PD. There is a co-existence of insulin receptors and DA-ergic neurons in SNpc in both diseases. Another thing is that reduction in insulin signaling in basal ganglia is associated with depletion of DA in the striatum [135].

Several studies have shown that antidiabetic agents play a neuroprotective role in PD. Metformin has been the most common drug for years for the treatment of T2DM. Studies have shown that metformin has a neuroprotective effect against PD. Alteration in mitochondrial respiration is associated with PD [136]. Metformin can act as an inhibitor of complex I of mitochondria, thereby reducing elevated mitochondrial respiration and maintaining mitochondrial homeostasis [137]. Other studies have shown that it activates AMPK/BDNF and effectively improves motor deficits, and suppresses aging-induced gene activation, reactive astrocytes in a 6-OHDA-induced mice model of PD [138]. It has also been reported that metformin has a role in autophagy. Metformin treatment enhances neuronal autophagy through AMPK activation, increasing expression of LC3-II and decreasing expression of p62 resulting in DA-ergic neuroprotection [139]. It suggests that metformin is an emerging therapeutic drug targeting the shared pathogenesis of both T2DM and PD.

Another emerging therapy is the incretin hormone. It affects insulinotropic secretion and improves insulin resistance. Incretin hormone includes glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. GLP-1R is expressed in different organs like islets, heart, immune cells, kidneys, and intestine. GLP-1 binds to its receptor GLP-1R of islet cells and evokes an antihyperglycemic effect and robust insulin release. It also inhibits apoptosis of β-cell and promotes β-cell proliferation [140]. The synthetic version of GLP1 agonist, exendin-4, is exenatide, which was approved in 2005 for use against T2DM.

Clinical studies have shown that treatment with exenatide improves motor deficits and cognitive dysfunction in PD patients [141]. GLP-1R is also expressed in different regions of the CNS, including the cortex, hypothalamus, striatum, SNpc, hippocampus, brain stem, and in the subventricular zone. The studies have shown that exendin-4 improves motor deficits and protects DA-ergic neurons in the MPTP-induced mice model of PD. Another study involving the LPS and 6-OHDA-induced PD model in SNpc has reported that after 7 days of treatment with exendin-4, amphetamine-induced circling behavior reduced, and DA production increased in basal ganglia [142]. Another GLP-1 analogue, liraglutide, binds to and stimulates GLP-1R, causing an increase in the cAMP. It leads to a cascade of intracellular events mediated by PKB/Akt and MAPK/ERK pathways, such as inhibition of neuronal apoptosis, neuronal cell survival, cell growth, repair, regeneration, and activation of Ca^{2+} channels. Finally, it concludes with neuroprotection, neuronal development, and memory formation [140, 142].

Insulin signaling is also one of the common molecular targets that gets disrupted in both T2DM and PD. Studies have shown that there is decreased level of insulin signaling markers and increased level of its negative regulator PTEN

in the SNpc regions of PD brain compared to control. It suggests that restoring insulin pathway or inhibiting nuclear aggregation of PTEN could be possible therapeutic target against both T2DM and PD [143].

Since there are many shared pathways between T2DM and PD, so, use of anti-parkinsonian therapy for T2DM and antidiabetic therapy for PD or vice versa in which research is going on. For example, DA agonist is most commonly used for the treatment of motor symptoms associated with PD. L-DOPA is the most commonly used DA agonist. Studies have shown that treatment of PD patients with L-DOPA decreased insulin secretion. Bromocriptine is another DA agonist used commonly for treatment of PD. It was the first DA-ergic drug approved for the treatment of T2DM. Studies have shown that its treatment improved glucose tolerance by suppressing growth hormone release from pituitary adenomas in obese T2DM patients as well as in non-diabetic obese

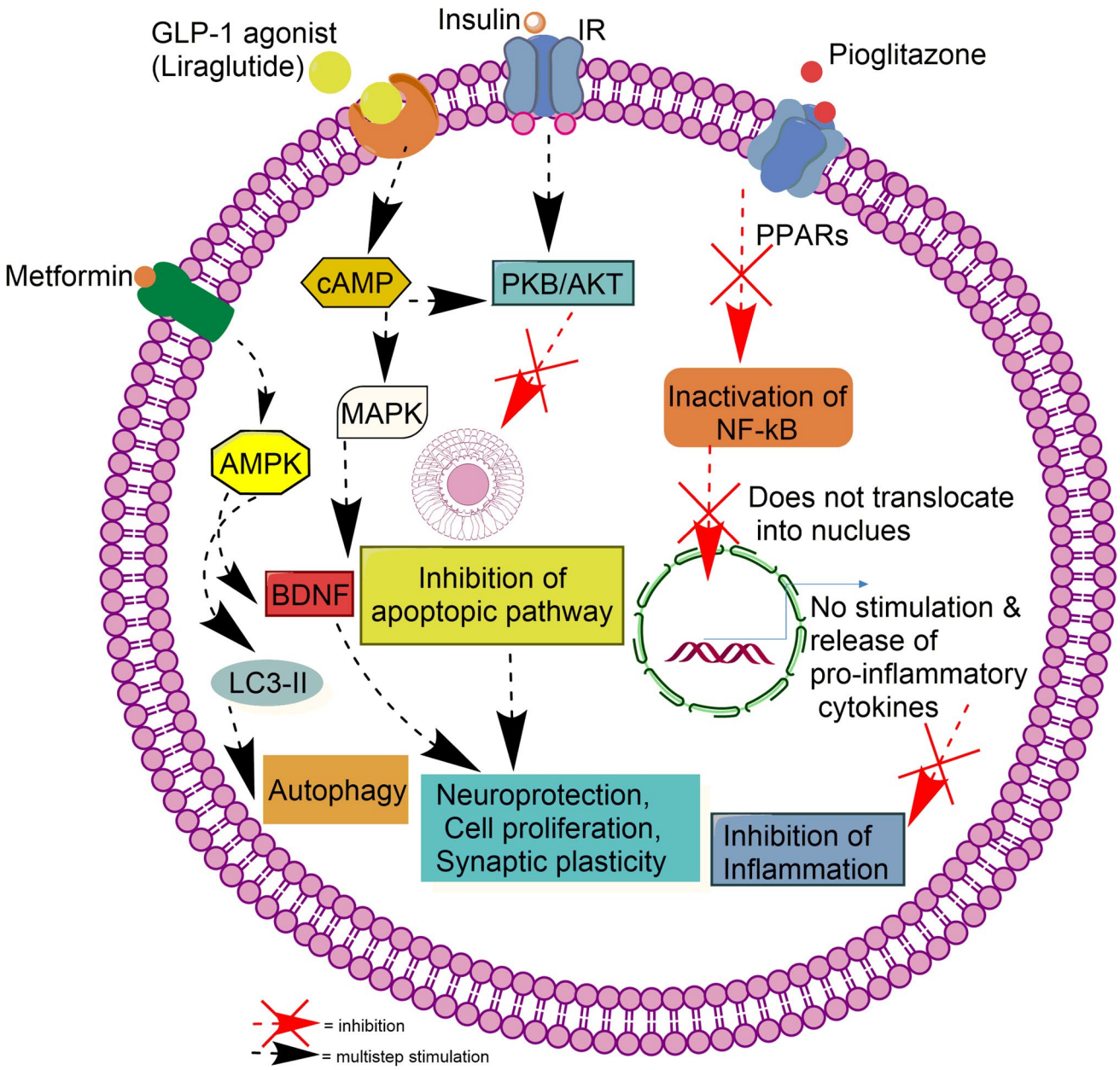

Fig.4 Illustrative representation of therapeutic action of antidiabetic agents against PD pathogenesis. Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; BDNF, brain-derived neurotrophic factor; cAMP, adenosine 3′,5′-cyclic monophosphate; GLP-1, glucagon-like peptide 1; IR, insulin receptor; LC3-II, light chain 3-II; MAPK1, mitogen-activated protein kinase; PKB, protein kinase B; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; PPARs, peroxisome proliferator-activated receptors

human and animals. It resulted in decreasing growth hormone–mediated antagonism action of insulin [144]. Thus, use of DA agonist is also a possible therapeutic strategy against both T2DM and PD.

Pioglitazone, a peroxisome proliferator-activated receptor (PPARs) agonist that improves hyperglycemia and ameliorates insulin resistance, may also be a potential therapeutic agent for PD. It has been reported that a PPAR pathway has a crucial role in the pathogenesis of PD. Studies have shown that pioglitazone rescued DA-ergic neurons through microglia inhibition in a PD model [145, 146]. Other studies have suggested that combinations of pioglitazone and statin modulate several inflammatory pathways (e.g., iNOS expression, cyclooxygenase-2 (COX-2) activity, and inhibition of NF-kB) and offer anti-inflammatory-mediated neuroprotection [146]. Studies have also shown that a combination of pioglitazone and statin lowers the incidence of PD in T2DM patients [145]. This suggests the PPAR pathway as a possible molecular target for therapeutics against both T2DM and PD. Illustrative representation of therapeutic action of antidiabetic agents against PD pathogenesis is given in Fig. 4.

Conclusions

In conclusion, implications in insulin signaling dysregulate blood glucose homeostasis and insulin resistance in T2DM and cause DA-ergic cell death in PD. ER stress results in dysregulations in the β-cell functioning and survival in T2DM and impaired Ca^{2+} hemostasis resulting in DA-ergic neuronal loss in PD. Mitochondrial dysfunction decreases oxygen consumption and suppresses glucose-stimulated insulin secretion in T2DM and decreases mitochondrial complex I activity, MPP, and ATP levels in PD. Dysregulated autophagy results in amyloid aggregation, i.e., amylin protein and α-synuclein in T2DM and PD, respectively. And dysfunctional UPS may decrease insulin secretion in the pancreatic β-cell and neurotoxicity in PD. Thus, T2DM and PD share some common but independent molecular pathways that play a crucial role in their progression and etiopathogenesis and can therefore provide common and alternate therapeutic approaches for treating T2DM and PD.

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Author Contribution ACM conceptualized, framed, and finally edited the manuscript; Sandeep, MHA, and LR wrote the manuscript.

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Data Availability No data is used in this review.

Declarations

Ethics Approval and Consent to Participate Ethical approval is not required.

Consent for Publication The authors have given consent for publication.

Conflict of Interest The authors declare no competing interests.

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