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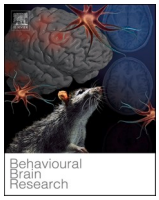

Unveiling new secrets in Parkinson's disease: The glycatome

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ABSTRACT

We are witnessing a considerable increase in the incidence of Parkinson's disease (PD), which may be due to the general ageing of the population. While there is a plethora of therapeutic strategies for this disease, they still fail to arrest disease progression as they do not target and prevent the neurodegenerative process. The identification of disease-causing mutations allowed researchers to better dissect the underlying causes of this disease, highlighting, for example, the pathogenic role of alpha-synuclein. However, most PD cases are sporadic, which is making it hard to unveil the major causative mechanisms of this disease. In the recent years, epidemiological evidence suggest that type-2 diabetes mellitus (T2DM) individuals have higher risk and worst outcomes of PD, allowing to raise the hypothesis that some dysregulated processes in T2DM may contribute or even trigger the neurodegenerative process in PD. One major consequence of T2DM is the unprogrammed reaction between sugars, increased in T2DM, and proteins, a reaction named glycation. Pre-clinical reports show that alpha-synuclein is a target of glycation, and glycation potentiates its pathogenicity which contributes for the neurodegenerative process. Moreover, it triggers, anticipates, or aggravates several PD-like motor and non-motor complications. A given profile of proteins are differently glycated in diseased conditions, altering the brain proteome and leading to brain dysfunction and neurodegeneration. Herein we coin the term Glycatome as the profile of glycated proteins. In this review we report on the mechanisms underlying the association between T2DM and PD, with particular focus on the impact of protein glycation.

1. Introduction

With the growing innovation in research and the development of sophisticated technologies for personalized health care, life expectancy is rapidly increasing each decade worldwide. However, along with an increased life expectancy, the incidence of age-related disorders is increasing at a fast and worrying pace. These disorders are characterized by their progressive disabling nature, accounting for a major impact on the lives and well-being of the patients, their families, and caregivers, and they represent a huge economic burden for societies.

PD is the most common movement disorder and the second most prevalent neurodegenerative disorder, affecting 10 million people worldwide. The neuropathological signature of PD is the presence of intracellular proteinaceous aggregates primarily composed of alpha-synuclein (aSyn), known as Lewy bodies (LBs) and Lewy neurites (LNs) and the loss of neuromelanin pigmentated dopaminergic neurons in the *substantia nigra pars compacta* (SNpc) within the midbrain [1]. The degeneration of dopaminergic neurons in the SNpc leads to the depletion of dopamine in the striatum thus inducing pronounced alterations in dopamine signalling [1–4]. The dopamine deficiency in the striatum and the failure of the basal ganglia underlies the cardinal motor features of parkinsonism seen in PD [1,4–6]. Parkinsonism is the clinical syndrome characterized by resting tremors, bradykinesia, muscular rigidity, postural instability, and gait impairment [6]. Although the dopaminergic neurons are a particularly vulnerable population to aSyn pathology and the most affected neurotransmitter system in PD, other basal ganglia connections, brainstem projections as well as cortical connections and the peripheral nervous system are also affected [7]. Importantly, the imbalance of multiple neurotransmission systems impacts both motor and non-motor features of PD [6,8,9]. PD is also associated with several non-motor features, including cognitive impairment, hyposmia, obstipation, anxiety, depression, and sleep disturbances [6,8,9].

From a clinical point of view, PD is a complex, multifactorial, and

Abbreviations: PD, Parkinson's disease; T2DM, type-2 diabetes mellitus; aSyn, alpha-synuclein; AGE, Advanced Glycation End-products.

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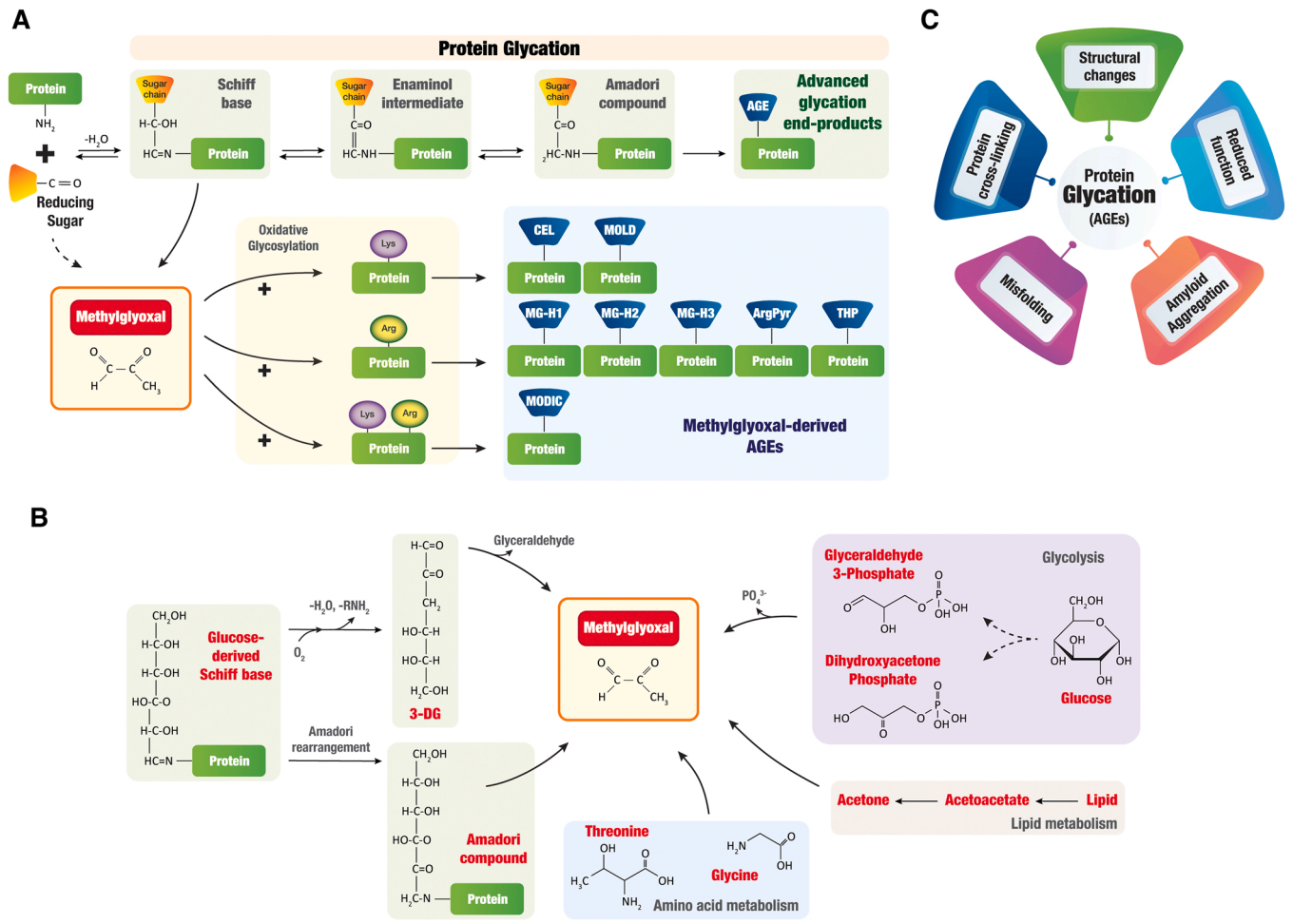

Fig. 1. Schematic representation of protein glycation reaction and its consequences. A) Glycation is a non-enzymatic process that is defined by the reaction between reducing sugars and amino groups from proteins. After the initial formation of a reversible and unstable Schiff base, the reaction can move towards the formation of an Amadori product and culminate into the formation of the irreversible Advanced Glycation End-products (AGEs). MGO is one of the most active glycation compounds, that mainly arises from glucose or amino-acid metabolism. Its reaction with the side-chain of the amino acids Lysine (Lys) and Arginine (Arg) drive to the formation of several AGEs including N(ε)-(carboxyethyl)lysine (CEL), MGO-lysine dimer (MOLD), MGO-derived hydroimidazolones (MG-H1, MG-H2, MG-H3), argpyrimidine [N(Δ)-(5-hydroxy-4,6-dimethylpyrimidin-2-yl)-L-ornithine] and tetrahydropyrimidine, and the MGO-derived cross-link (MODIC). **B)** Schematic of the different formation routes of MGO. C) AGEs in proteins may induce structural changes, either by driving to protein misfolding, or by forming protein cross-links. These alterations may alter protein function or even drive the formation of protein aggregates.

highly heterogenous disease that translates to a large spectrum of clinical presentations and age of onset. Disease progression, prognosis, and therapeutic responsiveness are also highly variable and unpredictable. Currently, the therapeutic options for PD are restricted to the symptomatic management of motor and non-motor features while curative, restorative, preventive, or disease-modifying therapies are still not available. This gap is partially attributed to our poor understanding of the pathogenesis and molecular mechanisms governing the loss of dopaminergic neurons. Moreover, the major obstacles for the development of effective therapeutic strategies include the heterogenous aetiology of PD and the absence of specific biomarkers for the diagnosis, disease progression monitoring, and therapeutic response evaluation.

Epidemiological studies and evidence from pre-clinical research suggest an unequivocal association between Type 2 diabetes *mellitus* (T2DM) and Parkinson's disease (PD). T2DM is a serious long-term condition that has reached pandemic levels, currently affecting more than 463 million people, being among the top 10 causes of death in adults worldwide [10]. T2DM has a major impact on the lives and well-being of individuals, families, and a dramatic economic burden for societies [11]. T2DM accounts for between 90% and 95% of DM. T2DM is initially characterized by the inability of cells to fully respond to insulin, known as "insulin resistance". The state of insulin resistance prompts an increase in the production of insulin from pancreatic β-cells that, over time, can lead to their exhaustion and insufficient insulin production [12]. T2DM besides being considered an ageing-related disorder it has several other risk factors including the dietary pattern, such as increased consumption of highly processed foods and sugar-sweetened beverages, obesity, reduced physical activity, unhealthy lifestyle and behavioural patterns, foetal malnutrition, and increasing foetal exposure to hyperglycaemia during pregnancy. T2DM is most common in older adults, but the incidence in children and younger adults is increasing mainly due to risk factors such as obesity, physical inactivity, and inappropriate diet [13].

In the last 20 years, several studies suggested DM as an important risk factor for the development of neurodegenerative diseases [14–22], being 20% of neurodegenerative diseases associated with DM [23]. In particular, T2DM and metabolic disorders have been shown to increase the risk of developing PD [14,17,24]. Epidemiological studies revealed that 80% of patients with PD have impaired glucose metabolism and T2DM increases the hazard ratio of PD up to 1.4 in the general population [25]. Impressively, this hazard ratio increases up to 3.8 for young diabetic individuals [14,15]. T2DM has also been shown to significantly accelerate the progression of both motor and cognitive deficits [15,18,19,26].

Since the establishment of a strong association between T2DM or metabolic disorders and neurodegenerative diseases, researchers have focused on deciphering and unveiling the molecular mechanisms underlying this association. Both PD and T2DM are ageing-related chronic disorders. In fact, ageing is the most important risk factor for both disorders. Although from a clinical perspective PD and T2DM are very dissimilar, being the first a neurological disorder, and T2DM a systemic metabolic disorder, there is overlap of some clinical features and pathological mechanisms. These include the occurrence of proteinopathy, insulin resistance, increased glycation, oxidative stress, mitochondrial dysfunction, ER stress, impairment of protein degradative pathways and inflammation are further shared dysregulated cellular functions. In this review, we will provide the most recent compelling data enlightening the role of glycation in PD, with particular focus on the glycatome signature in animal models of this neurodegenerative disease.

2. Glycation

Glycation is generally known as the non-enzymatic reaction between a reactive carbonyl group of reducing sugars and the nucleophilic amino group of biomolecules such as proteins (lysine and arginine side chains, protein N-terminus, and thiol group of cysteine residues), phospholipids, or nucleic acids. More specifically, it consists of the nucleophilic attack by the nitrogen atom of the amino group to the electrophilic carbonyl group of an aldehyde or ketone, with the elimination of a water molecule, forming aldimines and ketoimines (Schiff bases). This reaction is the first step of a complex series of reversible and irreversible reactions [27]. This process is non-enzymatic, comprising a complex cascade of reactions usually involving three phases: initiation, propagation, and an advanced phase [28]. The initial reaction between the carbonyl group of reducing sugars or of alpha-dicarbonyl compounds (αDCs) with amino groups of proteins, nucleic acids, and phospholipids, forms an unstable Schiff base [28]. Following structural spontaneous rearrangement, the reaction progresses to relatively more stable and irreversible enol/enamine (enaminol) intermediates and then Amadori products (Amadori rearrangement) [29]. These Amadori products follow a series of multi-step reactions (mostly irreversible) including rearrangements, dehydration, condensation, fragmentation, oxidation (catalysed be free metal cation), and cyclization reactions, leading to the formation of the irreversible advanced glycation end-products (AGEs) [30] (Fig. 1A). In physiological conditions, the process is normally slow since it does not involve an enzyme as catalyst. However, under pathological conditions such as hyperglycaemia and impaired glucose utilization, the process is faster due to the increased availability of reducing sugars and to the accumulation of highly reactive α-oxoaldehydes including methylglyoxal (MGO), glyoxal, and 3-deoxyglucosone. The reactivity of these compounds also determines the rate of glycation. For example, MGO is one of the most powerful glycating agents, being 20,000-fold more reactive than glucose [31]. MGO is mainly a metabolic by-product of carbohydrate, lipid, and amino acid catabolism [32], and mainly derives from the glycolytic triose phosphates: D-glyceraldehyde 3 phosphate and dihydroxyacetone phosphate (Fig. 1C). Protein glycation further depends on temperature, pH, and protein features such as their half-life and exposure of the target sites for this PTM.

It is relevant to distinguish between glycosylation and glycation process. Glycosylation consists of carbohydrates covalent addition to proteins and lipids, forming several glycoconjugates that vary on their glycan composition and complexity. The most common types of glycosylation consist of N- and O-linked glycosylation, and they occur on the amide nitrogen atom of asparagine, or to the hydroxyl group oxygen atom of serine or threonine, respectively [33]. Therefore, the strongest difference between glycosylation and glycation relies on the fact that the glycoconjugates addition in glycosylation depends on a myriad of enzymes and sugar precursors, a highly dynamic and programmed process that is essential for the mediation of several physiological and pathophysiological states [33]. In contrast, and to our knowledge, glycation is considered a non-enzymatic process. Moreover, the PTM addition targets different types of target amino acid residues.

3. Glycation defences

The biological systems are provided with tools to cope with MGO and other carbonyls, preventing their accumulation and consequent glycation. The most important carbonyl-detoxifying pathway is the glyoxalase system that comprises the enzymes glyoxalase (Glo) 1 and 2 and is the major catabolic route for glycating agents [34,35]. The first step for MGO detoxification involves its spontaneous reaction with reduced glutathione (GSH), forming a hemithioacetal. Glo-1 catalyses the conversion of hemithioacetal to S-Lactoylglutathione. This intermediate is a substract for Glo-2 that catalyses its transformation into D-Lactate, recycling GSH in the process. In parallel, MGO detoxification involves the pentose phosphate pathway, required for the formation of NADPH, which provides the recycling of GSH from its oxidized form via the action of glutathione reductase (GR) [36]. The enzymatic detoxification systems also include aldose reductase and aldehyde dehydrogenase, which can clear the glycation agents [35,37]. The aldose reductase catalyses the conversation of MGO or hemithioacetal, formed from the spontaneous reaction of MGO with GSH, to acetol or lactaldehyde, respectively. These products can further be converted into propanediol by aldose reductase [38].

The activity of these enzymes is dependent on the availability of cofactors such as GSH, NADH, and NADPH. Interestingly, these cofactors are shared with the enzymatic defences against oxidative stress, suggesting a strong relationship between carbonyl and oxidative stress [39,40]. Remarkably, in pathological conditions the activity of these enzymatic systems is frequently compromised, leading to increased glycation and to proteostasis imbalances. While these detoxifying pathways are efficient in maintaining proteostasis, they decline with ageing, with a particular decrease in the expression of Glo1 [41,42]. DJ-1 has been reported to present both MGO detoxifying and deglycase activity, acting as a protein repair enzyme [43–45]. However, it is important to mention that Dj-1 deglycase activity is controversial, with some reports considering it as an artifact [46], or rather the result of its methylglyoxalase activity [47,48]. The absence of Dj-1 in neuroblastoma cells, iPSC-derived neurons, primary mouse neurons, and mouse brain does result in a slight increase of the glycation burden (DNA, RNA, and protein glycation) [48]. However, in neurons, Dj-1 methylglyoxalase activity is rather modest (much lower than Glo1 activity), and Dj-1 deficiency does not enhance MGO toxicity, when delivered exogenously [48]. Nevertheless, this putative glycation defence system was linked to PD pathology, since a mutation in the gene coding for this multifunctional protein was linked to early-onset PD, with autosomal recessive inheritance [49]. It is thus relevant to better investigate the role of Dj-1 in a context of brain glycation models, and to understand if its activity in vivo can be modulated by specific PTMs, that could alter its methylglyoxalase activity, or by changes in its levels.

4. Receptor for Advanced glycation end-products (RAGE)

AGEs can bind and interact with several receptors, being the most well characterized the receptor for advanced glycation end-products (RAGE). RAGE is a multi-ligand protein receptor that belongs to the immunoglobulin superfamily, which is present on the surface of several cell types such as neurons, microglia, brain endothelial cells and astrocytes [50–52]. RAGE is a very promiscuous receptor, binding to many ligands such as AGEs, high mobility group box-1 (HMGB1), S100/calgranulins, and amyloidogenic proteins, particularly amyloid-beta peptide and aSyn [51,53–57]. RAGE binding to its ligands triggers the activation of several intracellular signalling cascades that lead to the rapid generation of reactive oxygen species (ROS) and the production of inflammatory cytokines [58]. The RAGE-mediated signalling pathways includes Janus kinase-signal transducer and activator of transcription

(JAK-STAT), Ras-Rac-Cdc42, phosphoinositide 3-kinase-Akt (PI3K/Akt) and mitogen-activated protein kinases (MAPKs), Ras-extracellular signal regulated kinase1/2 (ERK1/2), stress-activated protein kinase/c-jun-NH2-terminal kinase (SAPK/JNK) and p38 mitogen activated protein (MAP) kinase pathways [58–60]. It is important to note that RAGE-mediated signalling pathway is ligand-dependent. Nevertheless, RAGE-ligands interaction and the activation of the forementioned signalling pathways have been shown to activate the downstream effector nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and the signal transducer and activator of transcription 3 (STAT3) in an independent or synergistic manner. NF-κB activates the transduction of a set of inflammatory cytokines and enzymes such as interleukins, TNF-α and cyclooxygenase-2 (COX2), which are crucial for the inflammatory response [61]. Importantly, RAGE itself is an NF-κB regulated target gene and, therefore, NF-κB signalling cascade induces an increased cell surface expression of RAGE, creating a positive feedback loop enhancing the initial signalling and contributing to a state of sustained inflammation [62].

RAGE has been linked to several pathological conditions, such as diabetes complications, chronic inflammation, cancer, and neurodegenerative diseases such as PD [57,63–66]. Increasing evidence suggest RAGE as an important molecular player in the pathogenesis of PD. Increased levels of RAGE and its ligands were reported in the SNpc and frontal cortex of patients with PD and incidental Lewy Body disease, as well as in MPTP mouse model and 6-OHDA rat model of parkinsonism [51,59,67–71]. Additionally, RAGE gene polymorphisms are associated with sporadic PD in the Chinese population [72].

Oxidative stress and neuroinflammatory responses are major players in dopaminergic neurons degeneration in PD, in which microglia and astrocytes activation play important roles [73–77]. Astrocytes have a pivotal role in removing aSyn species, and the distribution pattern of aSyn-positive astrocytes correlates with those of Lewy bodies [78,79]. Activated microglia was reported in the SNpc and putamen in patients with PD [80,81]. RAGE emerges as an important molecular player mediating microglia and astrocytes activation and oxidative stress and neuroinflammation. Specifically, several RAGE ligands were shown to activate both astrocytes and microglia. Increased levels of AGE-albumin, that is the most abundant form of brain AGE and synthesized by activated microglia, were reported in the SNpc in patients with PD and PD-like animal models. In in vitro cultured human dopaminergic neurons, AGE-albumin treatment increased the expression of RAGE and triggered apoptosis [82]. S100B is a member of S100/calgranulin protein and a calcium-binding protein, synthesized in, and constitutively secreted by astrocytes. Increased levels of S100B were described in neurodegenerative diseases, mainly in the SNpc and cerebrospinal fluid (CSF) of patients with PD [83–85]. Exacerbated S100B production triggers abnormal neuronal RAGE stimulation that leads to ROS production, astrocyte and microglia activation, neurotoxicity, and neuronal apoptosis [83,86]. HMGB1 is a histone DNA-binding protein that plays an important role in chromatin remodeling and is released from glial cells in the brain [68,87,88]. The levels of HMGB1 were found to be upregulated in the SNpc, CSF and the serum of patients with PD [68]. In the MPTP mouse model, HMGB1 upregulates tyrosine hydroxylase (TH) expression in a RAGE-dependent manner, leading to dopaminergic neuronal death [89]. MPTP-induced dopaminergic neurodegeneration can be partially rescued by targeting the inhibition of HMGB1 [68].

Although so far underappreciated and underexplored, given the increased evidence of a pivotal role of protein glycation in the pathogenesis of neurodegenerative diseases such as PD, we can speculate about the undeniable role of RAGE and glial cells in the associated pathological mechanisms. Increased protein glycation and mainly aSyn glycation might lead to the activation and increased levels of RAGE, thus exacerbating the oxidative stress state and contributing to sustained inflammation which can drive neuronal cell death via mitochondrial dysfunction. We propose that this should be properly assessed in the future. Remarkably, anti-RAGE therapeutic strategies showed promising results in PD-like animal models. The RAGE ablation in MPTP mice protected nigral dopaminergic neurons from cell death, by blocking of NF-κB signalling cascade, microgliosis and astrogliosis and neuroinflammation [51,90]. Moreover, the RAGE FPS-ZM1, a selective inhibitor of RAGE, blocked 6-OHDA–induced dopaminergic denervation in the SNpc of rats, reduced astrocyte and microglia activation, and attenuated locomotor and exploratory deficits [71].

5. Glycation in Parkinson's disease

AGEs may form during normal metabolism and are a known hallmark of the ageing process [91]. Chronic hyperglycaemia, a hallmark of DM, results in several metabolic and biochemical perturbations including the accumulation of reducing sugars such as MGO and is a causative factor of the accelerated formation of AGEs [92,93]. Glycation and AGEs play a crucial role on the pathogenesis of DM and further contribute to diabetes complications such as neuropathy, cardiomyopathy, nephropathy, and retinopathy [27,34,94]. AGEs are pivotal players in several other disorders such as neurodegenerative diseases, vascular stiffening, atherosclerosis, inflammatory arthritis, and osteoarthritis [28].

Following the evidence that T2DM significantly increases the risk of developing neurodegenerative diseases and being glycation one of the major outcomes of DM, its role on the pathogenesis of these neurological disorders has been explored. Importantly, persistent episodes of hyperglycaemia that often occurs in T2DM, may increase the glucose uptake by brain. The combination between oxidative stress, increased accumulation of reducing sugars, and consequent increased protein glycation in the brain are among the mechanisms of glucose-induced neuronal toxicity [95,96]. In fact, the levels of MGO are increased 2- to 5-fold in patients with DM [97,98], suggesting that the formation of AGEs is potentiated. In agreement, a high glycaemic index diet in mice prompts a 34-fold increase in the formation of AGEs in the brain, primarily in the *substantia nigra* [99].

The formation of AGEs may cause structural modifications in proteins, alter their protein charge and hydrophobicity, and induce protein unfolding, as assessed by different low resolution, but also high resolution biophysical techniques such as NMR [100–102], and may also promote the formation of protein cross-links. These alterations may invariably interfere on protein function, can lead to protein misfolding (which should be properly assessed using high resolution structural techniques), and may promote amyloid aggregation [94,103] (Fig. 1B). Remarkably, several amyloid proteins associated with neurodegenerative diseases are long-lived, increasing their vulnerability to glycation. In fact, aSyn and amyloid-β (Aβ), which are pivotal players in the pathogenesis of PD and AD, respectively, are known targets for glycation. This modification modulates their conformational ensemble and aggregation propensity and increase their cytotoxicity [104]. Insulin, IAPP, albumin, superoxide dismutase 1, lysozyme, and haemoglobin are examples of other proteins that have been reported to undergo MGO-derived modification and form AGEs [105].

For the case of PD, AGEs (pentosidine and pyrraline) were initially detected at the periphery of LBs [106]. Succeeding studies reported increased levels of glycation in the cerebral cortex, amygdala, and *substantia nigra* of patients with PD (polyclonal anti-AGE antiserum against glyoxylic acid-derived AGEs) [69]. Although healthy individuals also present glycated proteins in the cerebral cortex, amygdala, and *substantia nigra*, their levels are higher in patients with PD [67]. Evidence of AGEs in newly formed LBs in cases of incidental Lewy body disease [69] suggest that the formation of AGEs may be a trigger for the formation of these inclusions [107].

As previously mentioned, aSyn is a long-lived protein that by being lysine-rich (15 residues), it is a preferential target for glycation [94]. Interestingly, it is possible to identify AGEs at the periphery of LB deposits, co-localizing with aSyn. These evidence strongly supports a fundamental role of glycation in the molecular pathogenesis of PD, and

it is now known that aSyn glycation influences its nucleation and oligomerization [108].

Pre-clinical observations collected from animal models have contributed to deciphering the potential role of glycation in PD. For example, a mouse model with a deletion of the *SNCA* gene revealed that the absence of aSyn leads to an increase in the levels of glucose, MGO, and Glo1, implicating aSyn in the regulation of brain glucose levels [109]. Although Glo1 should prevent the accumulation of glycation agents, its increase in these mice is not sufficient to detoxify MGO and to prevent an increase in the levels of AGEs [109]. As previously mentioned, Glo1 depends on GSH as a co-factor that is markedly reduced in PD [40,110,111] and with ageing, impairing the functioning of the glyoxalase system and consequent accumulation of glycation agents and AGEs [41]. Glycation has been reported in other experimental models of parkinsonism. The lysine-derived AGEs Nε-carboxyethyl-lysine (CEL) and Nε-carboxymethyl-lysine (CML) were detected in dopaminergic neurons in the MPTP mouse model of parkinsonism (model that induces dopaminergic neurodegeneration) and glycated oligomeric species of aSyn were also reported [70]. *In vitro* studies showed that glycation accelerates aSyn oligomerization by inducing cross-links and induce the formation of aSyn oligomers [112,113]. It is important to note that oligomeric species of aSyn are reported to be more toxic than larger aggregates [67,114–116]. Moreover, glycation of aSyn with MGO may alter aSyn DNA binding properties, inducing super coiled DNA conformation and stabilizing DNA integrity [117], and it may also affect aSyn redox capacity by reducing its ability to bind to Cu^{2+} and of scavenging $Cu2^{+}$-catalyzed ROS [118].

Research conducted by our team gave important contributions to the clarification of the role of glycation in PD, showing that MGO modulates aSyn pathobiology [102,104]. We first detected glycated aSyn in brain preparations from patients with PD [119]. This finding was replicated in several experimental models including yeast cells (Saccharomyces cerevisiae) transformed with human aSyn, H4 neuroglioma cells transfected with human aSyn, as well as in mouse and rat brain (endogenous aSyn) [102]. We observed that MGO-glycation mainly occurs in the N-terminal of aSyn, being the lysine residues 6, 10, 12, 21, 23, 32, 34, 43, and 45 glycated with CEL across the different experimental models, as detected by mass spectrometry (MALDI-TOF) [102]. We further demonstrated that MGO-derived glycation mainly affects the N-terminal region of aSyn, reducing its ability to bind to lipid membranes, an effect which was recently confirmed [120]. In in vitro neuronal-like models of aSyn pathology, we showed that glycation promoted the accumulation and aggregation of aSyn, and the formation of oligomers [102,121]. The enhanced accumulation of aSyn might result from the impairment of both proteasomal and lysosomal clearance systems, and by a defective cellular release of aSyn. The failure of these systems is likely to contribute for the loss of proteostasis and to promote neuronal cell death. In flies overexpressing aSyn, glycation reduced their lifespan and survival, and aggravated their motor impairment. Notably, the observed phenotypes were rescued using the MGO scavengers aminoguanidine and tenilsetam [102]. Using recombinant protein, we observed that MGO-derived glycation increases the propensity of aSyn oligomerization, while preventing its aggregation [102]. These effects were confirmed by another study that suggests that MGO-glycation suppresses aSyn elongation process of fibrils formation, being glycated aSyn unable to incorporate stably into fibrils [122]. The analysis of a homogeneously CEL-glycated aSyn showed that although this variant does not present a higher unfolding degree, it has higher percentage of disordered structure [123]. This study further confirmed significant alterations in the N-terminal residues chemical environment [102,123], suggested an increase of aSyn hydrodynamic radius, and an extension of the N-terminal domain of aSyn [123]. In contrast, this report showed that glycation do not increase the propensity of aSyn to form oligomers. In fact, CEL-glycated aSyn (in all residues) inhibited fibril formation, even in the presence of metal cations, which increase non-glycated aSyn fibrillation [123]. Provided these findings, these authors propose that glycation should occur in already pre-formed Lewy bodies [123]. It is therefore highly relevant to better understand the direct impact of glycation in the intrinsic amyloidogenic properties of aSyn. The use of CEL-aSyn synthetic models has the advantage of allowing to study homogeneous CEL-glycated variant of aSyn. However, the probability of aSyn to become fully CEL-glycated in all lysine residues in vivo is short, since some of these residues are already reported to be target of other PTMs such as ubiquitination, sumoylation and acetylation. The synergistic impact between different PTMs and glycation is currently not known, and therefore it is still not possible to fully understand if MGO-derived aSyn glycation triggers or inhibits its oligomerization/fibrillation.

The effects of glycation were also investigated in a transgenic mouse model of aSyn pathology (Thy1-SNCA). Notably, MGO injection in the *substantia nigra* or in the striatum induced a marked neuronal loss, particularly of dopaminergic neurons [102]. Moreover, this procedure induced aSyn oligomerization and pathology, measured by the phosphorylation of aSyn at serine 129 (pathological hallmark of PD). Ex vivo, glycated aSyn leads to an impairment of synaptic transmission [102]. More recently, we uncovered that upon a single intracerebroventricular injection of MGO, glycation negatively impacts aSyn transgenic (Thy1-SNCA) mice by aggravating or triggering motor, cognitive, olfactory, and colonic dysfunction [124]. Neuropathologically at 5 weeks-post MGO injection, this procedure leads to the accumulation of aSyn in the midbrain, striatum, and prefrontal cortex. Increased levels of AGEs were also detected in the cerebellum and midbrain. The intracerebroventricular MGO-injected Thy1-aSyn mice also show increased phosphorylation and insolubility of aSyn in the midbrain, hallmarks of pathology. This evidence suggest that brain glycation have a pivotal role in aggravating or anticipating the development of PD-like pathology. However, it is relevant to indicate that the same experimental procedure did not induce major alterations in WT mice. Therefore, it will be important to develop and explore other models of brain glycation that allow a sustained MGO insult over-time.

Besides modulating aSyn pathology, it is expectable that being glycation a non-enzymatic reaction, it should target and modulate several other proteins. Therefore MGO-injection should result in several changes in both brain protein levels and in a different profile of glycated proteins, what we define as glycatome. Using a SWATH-MS approach to detect the differently regulated proteins, it is interesting to observe that MGO-glycation in Thy1-aSyn mice mostly affected proteins associated with glutamatergic signalling [124]. In particular, the levels of several pre-synaptic glutamatergic targets, including the glutaminase and the vesicular glutamate transporter (VGLUT), and post-synaptic glutamatergic targets, mainly AMPA (GRIA2 and GRIA3) and NMDA (GRIN1 and GRIN2B) receptors, the astrocytic excitatory amino acid transporter 1 (EAAT1), calcium/calmodulin-dependent protein kinase type II alpha (CAMK2A), and beta (CAMK2B), SH3 and multiple ankyrin repeat domains protein 2 (SHANK2) and protein kinase C beta type (PRKCB), were increased upon MGO injection in Thy1-aSyn mice [124]. These observations not only suggest increased glutamate production and vesicular storage, but also increased glutamate release and neurotransmission, pointing that glycation might elicit an excitotoxic cascade. This excitotoxic phenomenon can further promote the neurodegenerative process, contributing to the exacerbated behavioural deficits [124]. It is interesting to observe that MGO glycation effects are not similar between all brain regions, as MGO-derived glycation in the prefrontal cortex mainly affects the respiratory electron transport chain [124], which is a well described consequence of glycation [104,125–127]. In fact, the increase of MGO is likely to contribute to the exhaustion of the shared cellular defences against oxidative and carbonyl stress, thus contributing to impaired oxidative metabolism and mitochondrial dysfunction. In more detail, MGO-glycation in the prefrontal cortex of Thy1-aSyn mice dysregulated the levels of several components of complexes I, II, III and IV of the respiratory electron transport chain, suggesting that increased levels of MGO in the brain may contribute to mitochondrial dysfunction in the cortical area [124].

Deep analysis of the glycatome in the midbrain of MGO-injected Thy1-aSyn mice indicates that glycated proteins mainly correlate with neurodegeneration-associated pathways including PD, also impacts proteins involved in dopaminergic synapse, and the protein quality control systems [124]. These findings further support that glycation might promote the neurodegenerative process associated to PD.

Evidence from several neurodegenerative diseases and the age-associated accumulation of AGEs support the strong role of glycation in the aetiology, pathogenesis, and progression of these diseases. In fact, glycation might be an important piece of the puzzle linking T2DM and neurodegeneration. Therefore, targeting glycation in a preventive or disease-modifying manner is a promising therapeutic strategy for neurodegenerative diseases such as PD.

6. Is glycation in the brain targetable?

Provided that glycation is a non-enzymatic process, and that it is still not clear if there is a deglycation machinery, it is highly challenging to modulate glycation directly. Therefore, the most promising strategies invariably depend on preventing the increase in glycation agents and consequent formation of AGEs. As previously mentioned, glycation agents may derive from increased levels of glucose or by the failure of the glycation agents detoxifying pathways. Following the accumulated knowledge of T2DM management, the use of antidiabetics is a promising therapeutic avenue. This type of drugs have already been explored in pre-clinical and clinical studies in the context of PD due to their potential in lowering the levels of glucose, and by acting as MGO scavengers and AGEs inhibitors [128].

Metformin is by far the most explored antidiabetic medication mostly because we are experiencing more than 60 years of its medical use for T2DM. Metformin is a pleiotropic molecule, well-recognised for its capacity to lower blood glucose levels, by inhibiting glucose production in the liver and increasing cellular glucose uptake in peripheral tissues [129–132]. Metformin has also been pointed as a glycation suppressor. By lowering blood glucose levels and facilitating glucose uptake and use by cells, metformin can prevent the injurious accumulation of reducing sugars such as MGO, thus decreasing protein glycation. However, this putative effect is likely to go beyond its pivotal action on glucose since metformin is also described to act as an MGO scavenger and an AGEs inhibitor [133–137]. Metformin use in T2DM patients successfully reduces the tissue and systemic levels of MGO and decreases the levels of glycated haemoglobin [134,136,138]. Importantly, metformin can cross the blood-brain barrier [139], making it suitable for the modulation of glycation in the brain. In fact, metformin treatment in T2DM patients has been reported to reduce the risk of mild cognitive impairment, dementia, Alzheimer's disease, and PD [140–150]. In pre-clinical models of neurodegenerative-like diseases, metformin prevented proteinopathy by decreasing amyloid plaque deposition, aSyn aggregation, ameliorating neuropathology, and hampering the neurodegenerative process [151–157].

Glitazones represent another relevant class of antidiabetic medication. This type of compound which includes rosiglitazone, pioglitazone, and mitoglitazone, primarily act as insulin sensitizer that reduces insulin resistance in peripheral tissues such as liver and skeletal muscle, increasing glucose uptake and decreasing its hepatic output. Similar to metformin, glitazones lead to neurological improvement in patients with AD [158–160] and reduce the incidence of PD in patients with T2DM [150,161]. Glitazones has also been demonstrated to suppress glycation-derived effects in in vitro models [162–166]. However, this should be further addressed in pre-clinical models.

Other antidiabetic medications have been explored in the context of PD. The glucagon-like peptide 1 (GLP-1) receptor agonists exenatide, liraglutide, dulaglutide, and lixisenatide, and the dipeptidyl peptidase-4 (DPP-4) inhibitors vildagliptin or sitagliptin have been tested in pre-clinical models of synucleinopathy and in patients with PD and concomitantly T2DM. Most of these studies have shown beneficial effects of these compounds in slowing down PD progression (recently reviewed in [128]).

However, there are some conflicting data, with a few studies showing the absence of effects, or even suggesting that antidiabetics can accelerate neurodegeneration. Several factors can contribute for this discrepancy. The most prominent is related to the heterogenicity of PD and the non-existence of stratification to choose the best course of therapeutic intervention. Furthermore, it is hard to predict the proper dose of antidiabetics to reach a therapeutic concentration in the brain, as well as the time window for drug intervention. We hypothesize that the stratification and sub-classification of patients with PD according to their metabolic profile can overcome some obstacles and successfully identify those individuals who could benefit from antidiabetic medications.

6.1. Are PD-glycatome alterations in the brain targetable?

Following the evidence that MGO-glycation in the brain significantly impacts on glutamatergic signalling dysregulation, we hypothesize that restoring a proper glutamatergic signalling might prevent or delay aSyn-induced neurodegeneration and represent a novel therapeutic target for PD. In support to our hypothesis, altered glutamatergic signalling and firing has been described in patients with PD [167–171]. By using magnetic resonance imaging (MRI), positron emission tomography (PET) and single photon emission computed tomography (SPECT), alterations in glutamate content were described, consistent with increased glutamate neurotransmission [172–174]. The hyperactive glutamatergic neurotransmission pattern is proposed to promote excitotoxic events fostering the neurodegenerative process in PD [175,176]. The excessive glutamatergic firing in patients with PD also contributes to the exacerbation of both motor deficits, including dyskinesias, impaired motor coordination and motor fluctuations [168,177–181], and non-motor features such as depression and cognitive impairment [182–184].

Evidence of an unbalanced glutamatergic response in PD shed light on the potential benefits of anti-glutamatergic drugs, also known as glutamate antagonists, to ameliorate PD pathology. In fact, both experimental and clinical evidence supports beneficial therapeutic outcomes of glutamate antagonist in PD, including the improvement of Parkinsonian motor symptoms, the increase efficiency of dopaminergic agents, as well as modulation of motor complications derived from dopaminergic therapy, and neuroprotective properties with protection of nigral neurons [177,185].

Amantadine is a small, synthetic, tricyclic amine of the adamantanes class and is an established treatment for PD for more than 50 years, both as monotherapy and as an adjunct to levodopa [186–188]. Amantadine has multiple pharmacodynamic actions, acting in several neurotransmitters systems including the dopaminergic and glutamatergic systems, resulting in a unique combination of antiparkinsonian and anti-dyskinetic properties. Amantadine enhances dopamine transmission, by increasing dopamine biosynthesis, turnover, uptake, and synaptic release [189–192]. Furthermore, amantadine is also a low-affinity, non-competitive antagonist of NMDA receptors [193,194]. Nevertheless, due to its pleiotropic effects on neurotransmission, amantadine is associated to acute neuropsychiatric side effects, including visual hallucinations, confusion, blurred vision, leg oedema, dry mouth, and constipation [195].

Memantine is an aminoadamantane compound, an open-channel blocker non-competitive NMDA receptor antagonist with neuroprotective properties [177]. The clinical use of memantine alone or in combination with L-DOPA in patients with PD was demonstrated to not only improve the motor symptoms, decreasing motor fluctuation, and improving drug-induced dyskinesias, but also to ameliorate cognitive performance [196–201]. The most common side effect reported with this non-competitive NMDA receptor antagonist is psychosis [202,203]. A recent study showed that memantine exerts neuroprotective effects by

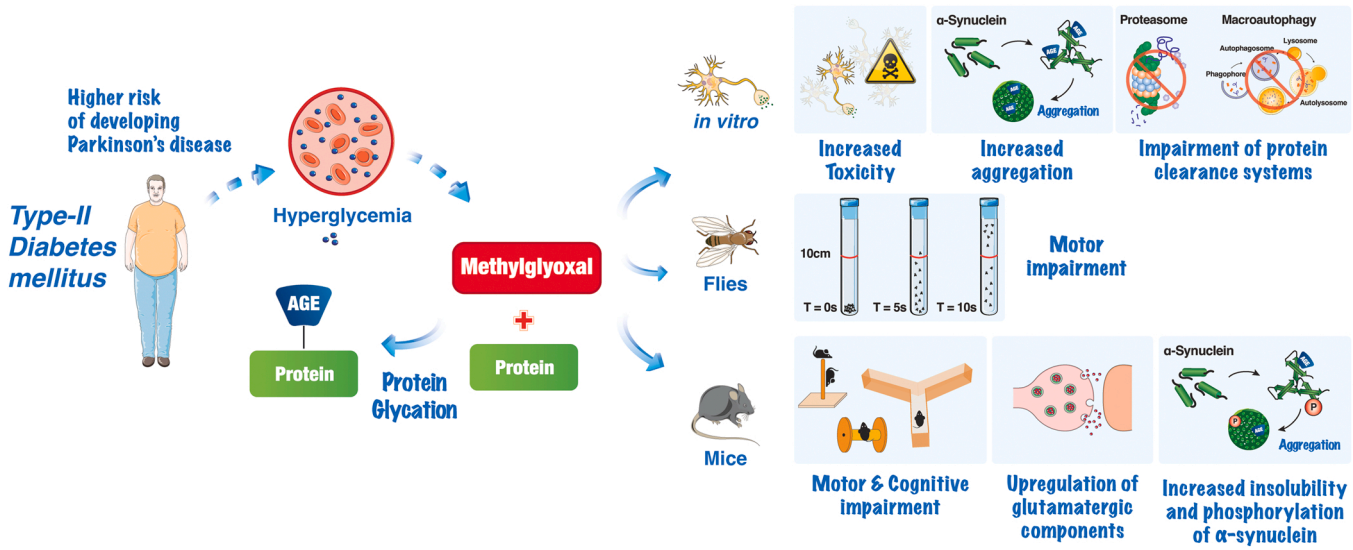

Fig. 2. Schematic representation of protein glycation as the mechanism underlying the association between T2D and PD, and of its major consequences in experimental models of PD. T2D individuals, which may endure hyperglycemic episodes, present higher circulating levels of methylglyoxal. MGO reacts with several proteins, inducing the formation of MGO-derived AGEs (MAGEs). In cellular models of PD, MGO-glycation increases aSyn aggregation and cytotoxicity and impairs several protein clearance mechanisms such as the proteasome and macroautophagy. In flies that express human aSyn, increased brain glycation drives to severe motor impairment, and decreased lifespan. In a mouse model of PD based on the overexpression of human aSyn in the brain, increased brain glycation triggers, anticipates, or aggravates PD-like motor and cognitive dysfunction. This may be due to the potentiation of aSyn pathology, as determined by its accumulation, aggregation, and pathological phosphorylation, or by altering several components of the glutamatergic signalling, that may imbalance calcium homeostasis and induce excitotoxicity.

modulating aSyn propagation, by decreasing aSyn internalization, attenuating cell death. The effects of this glutamate antagonist were mediated by decreased expression of clathrin, EEA1 and the NMDA receptor subunits NR2A. Memantine inhibited the interaction between aSyn and NR2A subunits, decreased the levels of phosphorylated aSyn, overall contributing for nigral dopaminergic neurons survival and a functional improvement of motor deficits in a parkinsonian model [204].

Recently, more competent NMDA receptors antagonists have been developed. NitroSynapsin is an aminoadamantane compound, a selective extrasynaptic NMDA receptor antagonist [205]. Like memantine, it has low affinity, but retain high selectivity for the receptor at micromolar concentrations [206]. However, NitroSynapsin has remarkably higher neuroprotective properties than memantine both in vitro and in vivo [205,207,208]. NitroSynapsin presents a peculiar mechanism of NMDA receptors activity modulation, first because it predominantly targets extrasynaptic NMDA receptors by voltage dependent blockage of excessively open extrasynaptic NMDA receptors. Additionally, nitroSynapsin also exerts non-voltage dependent NMDA receptors modulation by S-nitrosylation of redox sites of the receptor [205,206]. This mechanism of action selectively blocks excessive, tonically activated extrasynaptic NMDA receptors rather than the physiological activity of synaptic NMDA receptors and has a rapid off-rates from the receptor, thus avoiding the common clinical side effects of high-affinity NMDAR antagonists [206–209]. NitroSynapsin has been found to preserve synaptic integrity, by preventing synaptic loss, improving synaptic function, and preventing excessive excitation protecting synaptic integrity [205,207]. Importantly, preliminary research showed that nitroSynapsin protects synapses from oligomeric aSyn-induced damage [210].

Considering the dual roles of NMDA receptors in neurons survival and death, downstream targets that selectively inhibit the pro-death signaling without interfering with pro-survival pathways are being explored in the context of other neurological conditions such as stroke [211]. This approach might also prove suitable to block glutamate excitotoxicity, avoiding the side effects of whole suppression of NMDA receptors.

7. Conclusion

PD is a complex and multifactorial disease for which we still lack curative, restorative, preventive, or disease-modifying therapies. Most research focused on the pathological mechanisms of disease follows the genetic associations with the disease. However, it is important to note that most PD cases are sporadic. In this sense, more recently extensive research has been exploring the impact of risk factors, in particular on the association between T2DM and PD. Several studies have highlighted the pivotal role of glycation in the pathogenesis of aSyn in PD and related synucleinopathies (Fig. 2). The brain glycatome, meaning the signature of glycated proteins in the brain, along with the set of differently regulated proteins upon glycation may be responsible for the pathological alteration of molecular pathways underlying neurodegeneration. Recent evidence suggests that the glycatome signature is likely to be region-specific, and we further hypothesize that it may be cell-type specific, provided the different vulnerability of cells to glycation. By clearly defining the role of the glycatome and consequent protein levels deregulation in disease progression in an aSyn transgenic mouse model, we hypothesize that alterations in brain glycatome prime the development of PD. We therefore anticipate that the monitoring and therapeutic targeting of a pathological brain glycatome could unveil much needed avenues for PD treatment.

Conflicts of interest

We have no conflicts of interest to declare.

Data Availability

No data was used for the research described in the article.

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Author statement

AC and HVM wrote the manuscript and prepared the figures. HVM supervised everything. All authors agreed to its publication.

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