

## Review

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# Glycation in Huntington's Disease: A Possible Modifier and Target for Intervention

Inês Caldeira Brás<sup>a,1</sup>, Annetrin König<sup>a,1</sup> and Tiago Fleming Outeiro<sup>a,b,c</sup>

<sup>a</sup>*Department of Experimental Neurodegeneration, Center for Biostructural Imaging of Neurodegeneration, University Medical Center Göttingen, Göttingen, Germany*

<sup>b</sup>*Max Planck Institute for Experimental Medicine, Göttingen, Germany*

<sup>c</sup>*Institute of Neuroscience, The Medical School, Newcastle University, Newcastle upon Tyne, United Kingdom*

**Abstract.** Glycation is the non-enzymatic reaction between reactive dicarbonyls and amino groups, and gives rise to a variety of different reaction products known as advanced glycation end products (AGEs). Accumulation of AGEs on proteins is inevitable, and is associated with the aging process. Importantly, glycation is highly relevant in diabetic patients that experience periods of hyperglycemia. AGEs also play an important role in neurodegenerative diseases including Alzheimer's (AD) and Parkinson's disease (PD). Huntington's disease (HD) is a hereditary neurodegenerative disease caused by an expansion of a CAG repeat in the huntingtin gene. The resulting expanded polyglutamine stretch in the huntingtin (HTT) protein induces its misfolding and aggregation, leading to neuronal dysfunction and death. HD patients exhibit chorea and psychiatric disturbances, along with abnormalities in glucose and energy homeostasis. Interestingly, an increased prevalence of diabetes mellitus has been reported in HD and in other CAG triplet repeat disorders. However, the mechanisms underlying the connection between glycation and HD progression remain unclear. In this review, we explore the possible connection between glycation and proteostasis imbalances in HD, and posit that it may contribute to disease progression, possibly by accelerating protein aggregation and deposition. Finally, we review therapeutic interventions that might be able to alleviate the negative impact of glycation in HD.

**Keywords:** Huntington's disease, huntingtin, glycation, advanced glycation end products, diabetes mellitus

## INTRODUCTION

The progressive age-associated accumulation of advanced glycation end products (AGEs) results in structural and functional alterations in proteins, possibly increasing the risk of impairments in proteostasis and, thereby, increased risk for the devel-

opment of age-associated disorders [1]. However, whether AGEs are a cause or consequence of aging and age-related diseases is still a matter of debate. The controversy is strengthened by the growing number of known AGE targets and their gradual accumulation during life. The study of glycation has been impaired due to limitations in models and in tools and sensitive techniques to quantify and to detect AGEs in biological samples.

The formation of AGEs is elevated in individuals with altered carbohydrate metabolism [2]. Sporadic or hereditary neurodegenerative diseases, such as

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<sup>1</sup>These authors contributed equally to this work.

\*Correspondence to: Prof. Dr. Tiago Fleming Outeiro, Department of Experimental Neurodegeneration, University Medical Center Göttingen, 37073 Göttingen, Germany. Tel.: +49 551391 3544; Fax: +49 5513922693; E-mail: [touteir@gwdg.de](mailto:touteir@gwdg.de).

Alzheimer's disease (AD), Parkinson's disease (PD), or Friedreich's ataxia (FRDA), are often associated with impairments in carbohydrate metabolism, such as those caused by diabetes mellitus [3]. In particular, increased prevalence of diabetes mellitus has been reported in Huntington's disease (HD) patients and in patients affected by other CAG-triplet repeat disorders [4–6]. The patients often display increased carbohydrate intake [7], hyperinsulinemia and insulin resistance [8, 9]. However, the impact of AGE formation in disease progression remains largely unknown.

In this review, we explore the putative mechanistic links between AGE formation and progression of HD. Furthermore, we discuss several drugs known for targeting different aspects of the glycation process, and posit they may prove useful for mitigating detrimental effects of AGEs in HD.

## HUNTINGTON'S DISEASE: GENETICS AND PATHOBIOLOGY

HD is a progressive neurodegenerative disorder normally manifesting during adulthood [10]. Psychiatric manifestations, such as personality and behavioural changes, often precede the onset of motor dysfunction by several years [11–13]. The motor disturbances include chorea and dystonia, and are followed by cognitive decline. Furthermore, degeneration of the striatum (caudate nucleus and putamen), and a general shrinkage of the brain are observed in *post mortem* studies [14]. Loss of cortical mass is another early event in the pathology progression [15]. Patients recurrently show progressive weight loss and muscle deterioration [16–18], features that are also characteristic in several transgenic mouse models of the disease [19–22].

The disease is caused by an abnormal expansion of a CAG repeat sequence in exon 1 of the huntingtin gene (*HTT*) [23–25]. This is translated into an elongated polyglutamine (polyQ) tract in the N-terminal region of the huntingtin (HTT) protein [24, 26]. The CAG repeat length correlates with both age of onset and severity of the disease. In non-affected individuals, the CAG repeat length is between 9–35. More than 35 repeats causes disease, although incomplete penetrance has been reported for CAG repeats between 36–39. Tracts above 60 result in juvenile onset HD [24]. Importantly, and in contrast to the vast majority of AD and PD cases, genetic testing enables the identification of individuals that will develop HD decades prior to the onset of motor symptoms.

Long polyglutamine tracts lead to the accumulation of intranuclear and cytoplasmic mutant HTT aggregates [27–29], sequestration of glutamine-rich proteins [28, 30], and cell damage in the striatum and cerebral cortex [31–33]. However, hypothalamic atrophy and cell death can also occur [34–37]. Since the discovery of the *HTT* gene, strong efforts have been undertaken to decipher the function of wild-type HTT. The protein expressed in most tissues, but its physiological function is still unclear. Intracellularly, HTT is associated with various organelles as Golgi complex, endoplasmic reticulum (ER) and nucleus [38–41]. Previous studies suggest that HTT interacts with clathrin-coated vesicles, endosomal compartments and microtubules in the neurites and at synapses [42]. Furthermore, wild-type HTT interacts with several partners [24, 43] and it may be involved in transcriptional regulation, and in mitochondrial function [24, 25, 44, 45].

The molecular underpinnings of disease are also still unclear, but it is likely that both a loss of protein function and a toxic gain of function are involved [25, 46, 47]. The age of HD onset correlates inversely with the CAG repeats length. However, repeat length only accounts for approximately 50% of variation in age of onset [48]. Both genetic modifiers and life-style play a role in the observed variability of the initial clinical symptoms, strengthening the need for identifying additional modifiers of pathology [49–51].

Several studies showed a high prevalence of glucose intolerance and diabetes mellitus in patients with neurodegenerative disorders, such as AD, PD, FRDA, and also in HD [3, 6, 52]. Peripheral abnormalities in glucose metabolism might considerably affect the quality of life of HD patients and the neurodegenerative process [53, 54], possibly due to hypothalamic dysfunction and peripheral defects in glucose and fat metabolism [16, 52, 54]. In addition, an altered glucose metabolism might accelerate glycation reactions, a relevant non-enzymatic process that interferes with protein folding and proteostasis (Fig. 1).

## DIABETES MELLITUS: A CULPRIT IN NEURODEGENERATION

Increased levels of AGEs and reactive dicarbonyls are a hallmark of diabetic patients. Due to the association between HD and diabetes, it is important to understand the relevance of AGEs in the context of HD [2, 55]. Diabetes mellitus is a metabolic disorder characterized by elevated glucose levels

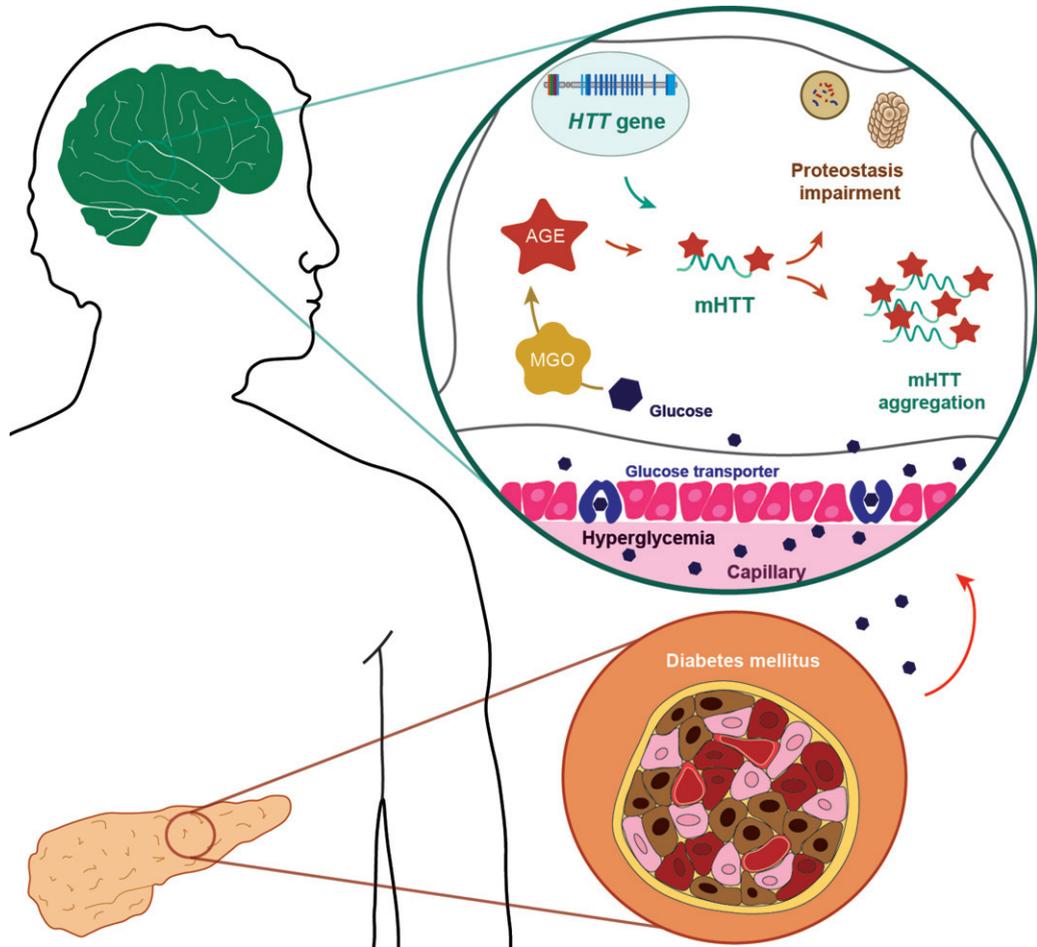


Fig. 1. Glycation in Huntington's disease. The metabolic disease diabetes mellitus results from either the inability of the pancreas to produce sufficient insulin or from cell failure to respond to insulin. Abnormalities in glucose homeostasis and higher prevalence of diabetes mellitus, have been reported in HD patients. During hyperglycemic conditions, glucose transporters increase intracerebral glucose levels, leading to increased glycation. AGEs (advanced glycation end products) can be produced intracellularly by multiple pathways: Methylglyoxal (MGO)-generated AGEs are particularly relevant in neuronal cells. In HD, an abnormal elongation of CAG repeats in the huntingtin gene (*HTT*) results in the production of mutant huntingtin protein with an extended polyglutamine tract (mHTT), causing its aggregation. The cytoplasmic mHTT aggregates impair autophagic and proteasomal pathways. Additionally, glycation can further contribute to the aggregation of mHTT, potentiating deficits in proteostasis pathways and, ultimately, leading to cell death.

in the blood (hyperglycemia). It is caused either by the inability of the pancreas to produce enough insulin (type I) or due to the body cells being insensitive to circulating insulin (type II). Diabetes mellitus also causes several complications in the central nervous system (CNS): both hyperglycemia and insulin-deficiency contribute to neuronal dysfunction. Increased sugar levels lead to a number of metabolic changes including oxidative stress, antioxidant depletion, neuro-inflammation, electrophysiological deficits and hormonal responses [56]. Importantly, the levels of methylglyoxal (MGO), a potent glycation agent, are elevated in diabetic

patients, most likely due to hyperglycemia [57]. Consistently, higher AGE levels were detected in diabetic patients and in animal models of diabetes [58, 59].

Glucose is the preferred energy source of the brain and, since neurons can barely store glucose intracellularly, a continuous glucose supply from the blood is critical for normal brain function [60]. The glucose transporters GLUT1 and GLUT3 that are mainly expressed in blood-brain barrier and neurons, respectively, are insulin-independent. Thus, although the insulin dependent glucose transporter GLUT4 is expressed in some brain areas, it is thought that most glucose uptake in the brain is insulin-independent

[60]. In line with this, several studies suggest that the intracerebral glucose solely depends on plasma glucose levels in murine models [61–63]. Diabetic animal models have brain glucose levels that are approximately 4-fold higher than those in plasma. Even those diabetes patients that are stabilised on proper medication frequently experience hypo- and hyperglycemic episodes [64]. Magnetic resonance spectroscopy in diabetic patients revealed that the glucose levels in the brain's interstitial fluid follow those in the blood plasma, albeit in a dampened and delayed manner [65]. Furthermore, diabetic and non-diseased individuals display altered brain glucose responses to changes in the blood plasma glucose [65]. Whether the transport capacities of the blood-brain barrier adapt to acute or chronic hyperglycemia to prevent high glucose levels in the brain is still debated [66]. In summary, chronic or temporary hyper- and hypoglycemia in the central nervous system are important feature in diabetes, and their impact should be carefully analysed in the context of neurodegenerative disorders.

### THE MAILLARD REACTION: INITIATORS, MECHANISM AND PROPAGATORS

Glycation, also referred to as non-enzymatic glycosylation, is the non-enzymatic reaction of sugars or other reducing carbohydrates with amino acids or nucleotides. In contrast, enzymatic glycosylation is a post translational modification (PTM) that involves the active attachment of sugar molecules at defined sites and, usually, takes place in the ER and Golgi. Glycation reactions were first described in 1912 in the context of food processing by Louis Camille Maillard [67]. The reaction starts with the condensation of a carbonyl group with the amino or thiol group of amino acids, nucleic acids or amino lipids, leading to the formation of early glycation products including Schiff Base and Amadori products. Initiators of the reactions include glucose, fructose and other sugars, as well as reactive dicarbonyls – such as glyoxal and MGO [68]. MGO is a byproduct of glycolysis and, due to its strong glycation ability, is often used to model glycation reactions [69]. In the second step, intermediate compounds are rearranged and break in one of various chemical pathways to form AGEs [68, 70]. It is important to emphasize that glycation is not a single reaction but, instead, a complex network of related reactions that may begin with different initiators and can result in diverse prod-

ucts [71]. Abundant AGEs include the MGO-derived carboxyethyl lysine (CEL), MGO hydroimidazolone, and glyoxal-derived carboxymethyl lysine (CML). Altogether, AGEs are a heterogenous group of compounds: they can occur bound to proteins or exist in a free state. Many AGEs are intrinsically fluorescent and cause cross links between proteins [70, 72, 73]. Furthermore, AGEs are stable compounds that accumulate during aging [1]. Thus, it is not surprising that cells developed mechanisms to detoxify reactive carbonyls. Glyoxalases are evolutionary conserved enzymes that catabolize dicarbonyls to non-toxic metabolites in glutathione-dependent reactions [74]. Single nucleotide polymorphisms (SNPs) in glyoxalases increase the incidence for the diabetic complications nephropathy and retinopathy [75]. Furthermore, dicarbonyls can be catabolized via nicotinamide adenine dinucleotide phosphate (NAPDH)-dependent aldo-keto reductases [76].

A number of studies reported age-associated accumulation of AGEs on crystallins, collagens and other long-lived proteins [1, 2, 77–79]. Whether increased AGE levels are a cause or a consequence the aging process remains a matter of debate [80]. Interestingly, higher levels of CML, a highly abundant AGE, in adults older than 65, were found to be associated with a higher risk of all-cause or cardiovascular disease mortality [81]. In addition, studies in *Drosophilla melanogaster* and *Caenorhabditis elegans* showed that overexpression of glyoxalases increase lifespan, suggesting that glycation reactions contribute to the aging process [82–84].

The receptor for advanced glycation end products (RAGE), is a major pro-inflammatory AGEs receptor and is involved in several neurodegenerative diseases [85, 86]. RAGE ligands in the CNS include CML, beta-amyloid (A $\beta$ ), S100 calcium-binding protein B (S100B) and High Mobility Group Box 1 [87–90]. Upon ligand binding, RAGE signals via the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B), phosphatidylinositol-3 kinase (PI3K) and mitogen-activated protein kinases (MAPKs) [91, 92].

In addition, AGEs are known to play a role in the context of several neurodegenerative diseases including AD, PD and diabetic complications [2, 93–95]. The mechanisms connecting AGE formation and these disorders include inflammation, dopamine glycation, and decreased degradation of the aggregated and cross-linked proteins.

The loss of dopaminergic cells in the *substantia nigra* of PD patients is a hallmark of the disease. Interestingly, the catecholamine dopamine itself can

undergo several chemical transformations that produce toxic molecules. MGO-mediated modification of dopamine leads to the formation of 1-acetyl-6, 7- dihydroxyl-1, 2, 3, 4-tetrahydroisoquinoline (ADTIQ), a toxin that is also present in the brains of PD patients [96]. Enzymatic oxidation of dopamine by monoamine oxidase produces 3,4-dihydrox-yphenylacetaldehyde (DOPAL), a highly reactive molecule that leads to the oligomerization of alpha-synuclein (aSyn), a central player in the pathology of PD and other neurodegenerative disorders known as synucleinopathies [97]. Furthermore, glycation increases aSyn oligomerization *in vitro* and glycated aSyn is present in *postmortem* tissue from individuals with PD and Lewy body disease [84, 98, 99].

Interestingly, several studies suggested that deregulation of glucose metabolism, as in diabetes mellitus, is associated with an increased risk for PD, and with more severe PD features [93]. In AD, AGEs promote aggregation and cross-linking of tau and A $\beta$ . These patients also show higher levels of AGEs in amyloid plaques [100–103]. In addition, levels of amyloid precursor protein (APP) are upregulated through glycation, which ultimately also increases A $\beta$  levels [104]. In summary, intensified research on glycation reaction is highlighting its importance in the pathology of several neurodegenerative diseases.

### GLYCATION AS A POTENTIAL PROMOTER OF HD PATHOLOGY

In contrast to AD or PD, HD is dominantly inherited. Thus, the question is not whether altered carbohydrate metabolism and increased AGE formation increase the risk to develop HD. Instead, one may hypothesize that factors that potentiate glycation, such as alterations in carbohydrate metabolism and increased AGE formation, might modify the age of onset and progression of HD (Fig. 1). Despite many advances on the investigation of the roles of AGEs in neurodegenerative diseases, the contribution of AGE formation to HD pathogenesis remain elusive. However, although several studies suggest that altered glucose metabolism may be an important feature of HD, others found no correlation, and this controversy dates back to the 1970 s.

Interestingly, epidemiologic studies reported an increased incidence of diabetes in HD patients [5, 105]. A study on a Chinese family over five gener-

ations reported a drastically increased incidence of diabetes mellitus among family members affected by HD [106]. In addition, decreased insulin sensitivity and increased insulin levels were found in non-diabetic HD patients [107].

In a proteomic analysis of HD versus control brains, three proteins involved in glycolysis were found to be differentially expressed [108]. However, other studies found no altered carbohydrate metabolism or increased diabetes mellitus incidence among HD patients [109–115]. Therefore, additional epidemiologic studies, preferably longitudinal, on well-characterized cohorts are needed in order to further establish a connection between HD and altered glucose metabolism or diabetes mellitus.

Studies in animal models suggest that HD affects the pancreatic function. The R6/2 mouse model of HD, which expresses exon 1 of the *HTT* gene containing 150 CAG repeats, develops insulin-responsive diabetes [116]. In addition, increased glucose plasma levels have also been observed in different models expressing *HTT* with shorter polyQ repeats (82Q and 89Q) [117, 118]. *HTT* inclusions were found in the Langerhans islets in R6/2 mice [19, 119]. The pathological mechanisms causing diabetes in these mice include decreased beta-cell replication and insulin secretion, and reduced insulin messenger RNA (mRNA) and protein levels [7, 19]. In contrast, pancreatic tissue from HD patients revealed that insulin mRNA and protein distribution and beta-cell area are identical in control and diseased brains [120].

As mentioned above, RAGE is involved in a variety of cellular processes including homeostasis, inflammation, neurodegeneration, development and neurite outgrowth. Interestingly, RAGE levels are elevated both in brains of HD patients and in mouse models [121, 122]. RAGE is expressed in medium spiny neurons and astrocytes in the caudate nucleus and subependymal layer of HD brains [122]. RAGE colocalizes with CML and S100B, mainly in astrocytes and, interestingly, its levels increase with disease severity [123].

DJ-1, the product of the Parkinson-associated *PARK7* gene, was shown to act as a deglycase on early glycation products of cysteines, lysines and arginines [124, 125]. Interestingly, DJ-1 levels are elevated in the frontal cortex of HD brain tissue, R6/2 mice, and in cell models, and overexpression of DJ-1 protects yeast and fly HD models against *HTT*-induced pathology. In contrast, in other cell models, DJ-1 overexpression leads to increased *HTT* aggregation and toxicity [126].

Atrophy of skeletal muscle is observed in HD patients and in the R6/2 mouse model [119, 127]. The mechanisms underlying muscle wasting in HD are unknown but may be the consequence of inclusion body formation in muscle cells of HD patients and mouse models [119, 128, 129]. Furthermore, skeletal muscle gene expression changes were observed both in mouse models and human HD [130, 131]. Interestingly, the muscle expression in HD shares some features with those induced by diabetes or fasting [130].

In a recent study from our group, we found a correlation between glycation and pathogenesis in models of HD. Using yeast and mammalian cell models, we found that increasing glycation increases HTT aggregation and toxicity, and impairs HTT clearance. Furthermore, increasing glycation causes neurotoxicity and impairs lifespan and development in a fly model of HD, confirming *in vivo* effects [132]. In summary, even though additional research is needed to ultimately demonstrate the contribution of AGE formation towards HD age of onset and progression, several lines of evidence point to a critical role of glycation.

### TARGETING GLYCATION AS A THERAPEUTIC APPROACH IN HD

Although no disease-modifying therapies are available for HD [25, 133], patients often receive standard drug treatments to alleviate some of the symptoms of the disease [134, 135].

The association between HD and glucose metabolism alterations has been explored as a possible target for strategies using different hypoglycemic agents [112, 136, 137]. Compounds such as exendin-4, resveratrol, glibenclamide, rosiglitazone, insulin and the fusion of the glucagon-like peptide 1 with a non-glycosylated form of human transferrin (GLP-1Tf) were previously tested in patients and animal models [136, 138–141]. The administration of glibenclamide, exendin-4, GLP-1Tf and resveratrol in animal models resulted in a decrease of the glucose levels in the blood. Interestingly, mice respond to glibenclamide (which induces insulin exocytosis) but not to rosiglitazone (which induces sensitization to insulin) [142]. This supports the hypothesis that diabetes mellitus in the HD mouse model may be caused by an impairment in insulin release rather than by insulin insensitivity. Exendin-4 was the only treatment able to increase the insulin sensitivity [20, 143,

144]. Furthermore, insulin and GLP-1Tf increase plasma insulin levels, in contrast to exendin-4 [145]. Interestingly, both exendin-4 and GLP-1Tf improve motor coordination and life span in HD animal models. Despite the improvement in diabetes mellitus symptoms, chronic treatment with these hypoglycaemic agents has no effect on either the course of diabetes or the progression of HD in mice. More recently, administration of metformin resulted in reduced translation of mutant HTT protein and, therefore, decreased the protein load *in vitro* and in animal models [146]. This drug is regularly used in patients with diabetes mellitus, and was previously tested in another study where it increased the lifespan of mice [147]. However, the effects on glycation pathways or AGEs were not analysed in this study, and remain to be investigated.

Given the evidence implicating AGEs in diabetes, drugs capable of detoxifying the reactive compounds might constitute an important approach in the treatment of diabetes and also of age-associated neurodegenerative disorders [148–151]. Aminoguanidine, also known as Pimagedine, inhibits AGE formation in animal models [152–154], but was discontinued from the clinical trial in humans due to side effects [155]. The rationale behind this clinical trial is a proof of concept that inhibiting AGE formation may be important for attenuating the serious complications of diabetes mellitus [156]. In this context, strategies aimed at lowering MGO levels are an additional possibility [157–159]. D-penicillamine, aminoguanidine and metformin trap dicarbonyl compounds (e.g. glyoxal and MGO) to form substituted triazines [160]. Another strategy to lower MGO levels is to stimulate the anaerobic pentose phosphate pathway of glycolysis [158, 161]. Tenilsetam, another dicarbonyl compound, inhibits protein cross-linking and cell death [100, 162, 163].

Oxidative stress and neuroinflammation are additional factors known to play an important role in the progression of the neurodegenerative process. Interestingly, AGE production is significantly augmented under oxidative stress [148, 164, 165]. Therefore, therapies combining the use of antioxidants and protein glycation inhibitors may be a more effective approach in neurodegenerative diseases [166–168].

Several synthetic compounds inhibit AGE formation [169]. However, these compounds were withdrawn from the clinical trials because of their low efficacy, unsatisfactory safety, and poor pharmacokinetics [170, 171]. Alternatively, natural products have been proven to be safe for human consumption

and many plant extracts have been tested for their anti-glycation activity [172]. Furthermore, previous studies hypothesise that enrichment of diet in natural anti-glycating agents, as polyphenols and other natural antioxidants, may halt the aging process and neurological problems [173].

Finally, as described above, RAGE is as an important subject of research [174], and *in vitro* and *in vivo* studies have demonstrated the potential of RAGE as a therapeutic target in neurodegeneration [150, 151, 175–177]. Additional studies will be important to confirm this.

In summary, future clinical trials aimed at lowering AGE formation and the downstream effect of such species will unveil whether the promising results in animal models translate into clinical application.

## CONCLUSIONS

Currently, there is a limited understanding of the causal effects of both diet and AGEs on aging and age-related diseases. More importantly, aspects of AGE formation, accumulation and detoxification in several neurodegenerative diseases remain poorly understood. A relative low number of studies explored the connection between diabetes mellitus and HD, suggesting this is a field that deserves additional studies. We have recently shown that glycation potentiates mutant HTT aggregation and toxicity in cell and animal models, highlighting the importance of this modification in HD pathology. Investigating common molecular mechanisms underlying these pathways might reveal novel targets for the development of disease-modifying therapies. Interestingly, metformin, a drug commonly used for type II diabetes, recently showed positive effects in HD models. The studies showed a reduction in mutant HTT levels and a reversion of other pathological features characteristic of HD. In conclusion, we hypothesize that the development of therapeutic strategies targeting glycation may serve as an orthogonal approach to treat both diabetic complications as well as neurodegenerative diseases, such as HD.

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## CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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