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Cysteine metabolism and hydrogen sulfide signaling in Huntington's disease☆

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Abstract

The semi-essential amino acid, cysteine, plays important roles in both essential cellular processes as well as in modulation of signaling cascades. Cysteine is obtained both from the diet as well as generated endogenously via the transsulfuration pathway. Cysteine is further utilized in protein synthesis and biosynthesis of various sulfur containing molecules. One of the products of cysteine catabolism, hydrogen sulfide (H_2S), is a gaseous signaling molecule, which regulates a multitude of cellular processes. Cysteine metabolism is dysregulated in several neurodegenerative diseases and during aging. This minireview focuses on aberrant cysteine and H_2S metabolism in Huntington's disease, a neurodegenerative disease caused by expansion of polyglutamine encoding repeats in the gene *huntingtin*, which leads to motor and cognitive deficits.

Keywords

Huntington's disease; Cysteine; Transsulfuration; Golgi stress response; Cystathionine γ-lyase; Hydrogen sulfide

1. Introduction

Huntington's disease (HD) is a neurodegenerative disease triggered by the expansion of polyglutamine (CAG) repeats in the gene *huntingtin* [1]. In HD, the corpus striatum of the brain is profoundly affected and atrophies during disease progression. Symptoms of HD include involuntary movements, muscle wastage, motor and cognitive deficits among others [2-4]. The length of the CAG repeat has been linked to disease progression and pathology in several studies [5-7]. Additionally, genetic modifiers of HD have been identified, that influence the onset or severity of the disease [8,9]. A molecular hallmark of HD is the

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aggregation of mutant huntingtin (mHtt), which disrupts several cellular processes ranging from transcriptional and translational regulation, nuclear cytoplasmic import, amino acid homeostasis and nutrient sensing, antioxidant and stress responses, second messenger signaling, DNA repair and autophagy, to name a few [10-22].

At the molecular level, redox imbalance and oxidative damage are characteristic features of HD [14,23-25]. While reactive oxygen species (ROS) are essential for certain physiological processes, excess production impairs cellular stress responses and elicits neurotoxicity in several neurodegenerative disorders such as HD [17,23]. It has been observed that changes in redox signaling processes, some of which are reversible, often precede neurodegeneration. Production of ROS, reactive nitrogen species (RNS) and reactive nitrogen species (RSS) occur both during normal cellular processes such as mitochondrial function and immune responses, however in pathological conditions, the production of these free radicals and oxidants may exceed the cellular capacity to neutralize them [17]. Accordingly, cells have evolved a diverse array of small molecules and proteins to counteract the damaging effects of these reactive species and free radicals, which are regulated at multiple levels, both during basal conditions and during stress responses.

Central to the maintenance of redox balance in cells, is the reverse transsulfuration pathway, which leads to the biosynthesis of the amino acid cysteine and the antioxidant glutathione (GSH) (Fig. 1A). GSH is one of the most abundant thiols, which functions as a cofactor for several enzymes involved in maintenance of redox homeostasis. Both cysteine and GSH are potent antioxidants and protect cells from a wide variety of damaging stimuli. Besides its essential function as a component of protein synthesis, cysteine serves a precursor of several sulfur containing molecules including GSH, coenzyme A, lanthionine, cysteamine and taurine (Fig. 1B). Cysteine also plays a central role in iron sulfur (Fe–S) cluster protein biogenesis, which sustains several cellular processes [26]. Although cysteine is one of the scarcest amino acids, comprising only 2% of the proteome, it undergoes the largest number of post-translational modifications, which include persulfidation/sulfhydration, nitrosylation, glutathionylation, palmitoylation and sumoylation among others [27,28]. Thus, perturbations in these modifications and/or metabolism of cysteine itself can alter cellular functions. We have shown that disrupted cysteine and H_2S metabolism occurs in several neurodegenerative diseases [14,15,29]. Cysteine metabolism is affected in neurodegenerative diseases in multiple ways as discussed below.

2. Biosynthesis and uptake of cysteine in the brain

Cysteine is a semi-essential amino acid and its availability is the rate limiting step for GSH biosynthesis. Cysteine is obtained both from the diet and also endogenously through the reverse transsulfuration pathway, which refers to the transfer of sulfur from homocysteine to cysteine. Homocysteine, in turn is derived from dietary methionine. In bacteria, the pathway operates in the opposite direction and the biosynthesis of methionine and was referred to as transsulfuration. For the sake of clarity, we will refer to the pathway as transsulfuration. Cystathionine γ-lyase (CSE) is the key enzyme in the pathway and the sole biosynthetic enzyme for *de novo* synthesis of cysteine *in vivo* in mammals, generating the amino acid from cystathionine. Mice lacking CSE die within two weeks on a cysteine-free diet [30,31].

In addition to its essential role as the biosynthetic enzyme for cysteine, CSE utilizes cysteine as a substrate to generate hydrogen sulfide (H_2S), which modulates several physiological processes [32-34].

Cysteine is taken up from the diet through several transporters, which include the system x_c^-, which imports the oxidized form, cystine in a Na^+-independent but chloride-dependent manner. The x_c^- transporter also takes up cystathionine, the precursor for cysteine [28,35]. Other transporters include the excitatory amino acid transporter 3 (EAAT3/EAAC1) and the alanine, serine, cysteine transporters (ASCTs) [28]. Both cysteine and H_2S levels are tightly regulated in cells to avoid toxicity. Excess cysteine may be utilized in the biosynthesis of sulfur containing molecules or degraded by cysteine dioxygenase 1 (CDO1) to form cysteine sulfinic acid, which is further converted to hypotaurine [36,37]. H_2S is catabolized in the mitochondria by the sulfide oxidation unit to thiosulfate and sulfate, with the rate varying in different tissues [33,38,39].

3. Deficiencies in CSE and CBS are linked to disease

Several mutations have been identified in CBS, which alter its folding and/or activity [40]. Mutations in the CBS or CBS deficiency, leads to hyperhomocysteinemia (HHcy) and thromboembolism, which are linked to lifespan and healthspan. CBS deficiency has been linked to hypertension and cardiovascular abnormalities. Elevated homocysteine caused by CBS deficiency has also been linked to ocular defects and lens dislocation and skeletal defects and resembles Marfan syndrome [41-43]. In stark contrast, elevation of CBS, which resides on chromosome 21, is linked to excess H_2S and associated symptoms in Down syndrome [44-46]. Mutations in *Cth*, the gene encoding CSE, although not as frequent as those in *Cbs*, has been linked to cystathionuria and homocystinuria, which may cause vascular abnormalities [47,48]. Abnormalities in the transsulfuration pathway have also been linked to Alzheimer's disease and Parkinson's disease, along with decreased persulfidation [49-51].

4. Dysregulation of cysteine and H_2S metabolism in HD

Disruption of cysteine metabolism results in altered GSH levels and H_2S signaling, which impacts almost all cellular processes. We and others have shown that both cysteine uptake and biosynthesis is compromised in HD. Studies conducted earlier identified CBS as a huntingtin interacting protein, which may affect H_2S production by CBS [52]. We identified a profound depletion of CSE in cell culture and mouse models of HD as well as human postmortem striatal tissue [14]. The dysregulation stems from the influence of mHtt on transcription factors regulating expression of CSE [53]. The diminished expression of CSE in HD was also confirmed by other studies, where expression of CSE was linked to CAG repeats [54]. Furthermore, elevated cystathionine, the precursor of cysteine, has been reported in the R6/2 mouse model, which may arise from depletion of CSE [55]. Under basal conditions, CSE is regulated by specificity protein 1 (SP1) and by the activating transcription factor 4 (ATF4) in response to stress stimuli [56]. SP1 is sequestered by mHtt, leading to decreased transcription of CSE. As a result, the striatal progenitor cell line ST*Hdh*$^{Q111/Q111}$ (Q111), which harbors 111 polyglutamine repeats cannot grow in

cysteine free medium or produce sufficient H_2S in response to stress [14,15]. Transfecting SP1 and its coactivator, TAF4, in Q111 cells elevated CSE expression and restored growth during cysteine deprivation. In addition to the biosynthetic deficit, the cysteine and cystine transporters are also suboptimally expressed at the cell surface, leading to an overall cysteine deficit [57, 58](Fig. 2). The cysteine homeostatic machinery in response to stress is also derailed in HD, exhibiting altered ATF4 dynamics. While the striatal ST*Hdh*$^{Q7/Q7}$ (Q7) express ATF4 in response to cysteine deprivation, the Q111 cells fail to do so. Intriguingly, the Q7 cells upregulated ATF4 and CSE in response to endoplasmic reticulum (ER) stress and deprivation of other amino acids. The inability to induce ATF4 in response to cysteine deprivation occurs due to the elevated oxidative stress associated with HD, which prevents the optimal stress-induced expression of ATF4. This disruption culminates in a vicious cycle that leads to cell death. As a proof of concept, inducing oxidative stress in Q7 cells prevented induction and decreasing oxidative stress in Q111 cells promoted induction of ATF4 in response to cysteine deprivation [15].

One of the modes by which the transsulfuration pathway plays a role in regulation of signaling events is through sulfhydration/persulfidation. Sulfhydration is a posttranslational modification mediated by H_2S and occurs on reactive cysteine residues on target proteins [34,59,60]. Sulfhydration modulates several aspects of mammalian physiology, which includes regulation of vascular functions and neuroprotection [49,50,61]. The diminished levels of CSE also translated to a decrease in overall levels of sulfhydration in the Q111 cells [62]. Additionally, this study also reported that levels of sulfhydration decline during aging, the biggest risk factor for several neurodegenerative diseases.

Another benefit resulting from upregulation of the transsulfuration pathway is inhibition of ferroptosis. Ferroptosis is a form of cell death involving oxidative damage by iron and elevated lipid peroxidation [63]. Numerous studies have shown that depletion of cysteine leads to ferroptosis [64,65]. Interestingly, depletion of cysteinyl-tRNA synthetase (CARS) induces the transsulfuration pathway and inhibits ferroptosis induced by erastin, an inhibitor of the XcT/SLC7A11 transporter, which imports cystine into cells [66]. It is likely that in HD, ferroptosis may play a role in disease progression. Indeed, the tumor suppressor, p53 has been reported to inhibit the cystine transporter and induce ferroptosis [67]. Dysregulation of p53 has been observed in HD and deletion of p53 has proved beneficial in mouse models of HD [68]. Thus, the transsulfuration pathway intersects with several cell death and cell survival pathways.

5. Upregulation of the transsulfuration pathway, stress responses and neuroprotection

As the sulfur metabolites generated via the transsulfuration pathway are beneficial, supplementing these metabolites or augmenting the flux through this pathway was tested in several studies. Supplementing cysteine in the diet and *N*-acetylcysteine in the drinking water of the R6/2 model of HD delayed striatal shrinkage, improved motor deficits and survival [57]. At the molecular level, restoring the induction of ATF4 by the reduction of oxidative stress, also improved survival of the Q111 cells [15]. ATF4 is induced by several

stress response pathways, which constitute the integrated stress response. For instance, the amino acid and ER stress induce ATF4 [15,69]. More recently, we demonstrated that ATF4 is also induced in response to Golgi stress, which leads to increased expression of CSE and H_2S protection in the Q7 and Q111 cell lines. The Golgi apparatus is vital for glycosylation of proteins and its resident glycosyltransferases, glycosidases, and nucleotide sugar transporters regulate addition of various sugars that result in a mature glycan [70]. When the capacity of the Golgi is crossed, Golgi stress ensues in a manner analogous to ER stress. In order to mitigate this stress, cells mount signaling cascades which constitute the Golgi stress response [71]. The Golgi stress response has several different arms and is not as well studied as the ER stress response [72].

Similar to ER stress response, the Golgi stress response also acts via the PKR-like ER kinase (PERK) to induce ATF4 and CSE (Fig. 3). Both ATF4 and CSE were not induced in PERK $^{-/-}$ cells. However, the ER stress response protein, binding Ig protein (BiP/GRP78) is not induced in response to monensin, a Golgi stressor, indicating differences in the two stress responses [29,72]. Golgi stress induced by monensin and nigericin upregulated both ATF4 and CSE and supported growth of Q111 cells in cysteine-free media. Thus, it appears that the CSE/H_2S pathway is induced in response to various stressors. The induction of ATF4 is responsible for induction of CSE and xCT, a subunit of the cystine transporter [15,29,69]. Together, cysteine levels are boosted, leading to upregulation of H_2S production [29]. Although low concentrations of Golgi stressors were protective in cell models of HD, effects in mouse models of HD and the minimal effective dose required to mitigate symptoms remain to be determined.

These findings show that enhancement of the transsulfuration pathway as a whole may be therapeutic in HD. Accordingly, stimulation of the ATF4/CSE axis may be harnessed to upregulate cellular antioxidant defense mechanisms to combat neurodegeneration. Hence molecules that stimulate the transsulfuration pathway may confer adaptive benefits in HD as well as other conditions involving redox imbalance. These findings may be relevant to other neurodegenerative states associated with deficits in cysteine metabolism.

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List of Abbreviations

3-MP	3-mercapto pyruvate
3-MST	3-mercapto pyruvate sulfur transferase
ASCT	alanine, serine, cysteine transporter
ATF4	activating transcription factor 4
BiP	binding Ig protein

CARS	cysteinyl-tRNA synthetase
CAT	cysteine amino transferase
CBS	cystathionine β-synthase
CDO1	cysteine dioxygenase 1
CSAD	cysteine sulfinic acid decarboxylase
CSE	cystathionine γ-lyase
eIF2α	eukaryotic translation initiation factor 2 subunit-α
EAAT3/EAAC1	excitatory amino acid transporter 3
ER	endoplasmic reticulum
GSH	glutathione
HD	Huntington's Disease
HHcy	hyperhomocysteinemia
mHtt	mutant huntingtin
PERK	protein kinase R protein kinase R (PKR)-like ER kinase
SP1	specificity protein 1
xCT/SLC7A11	cystine/glutamate antiporter

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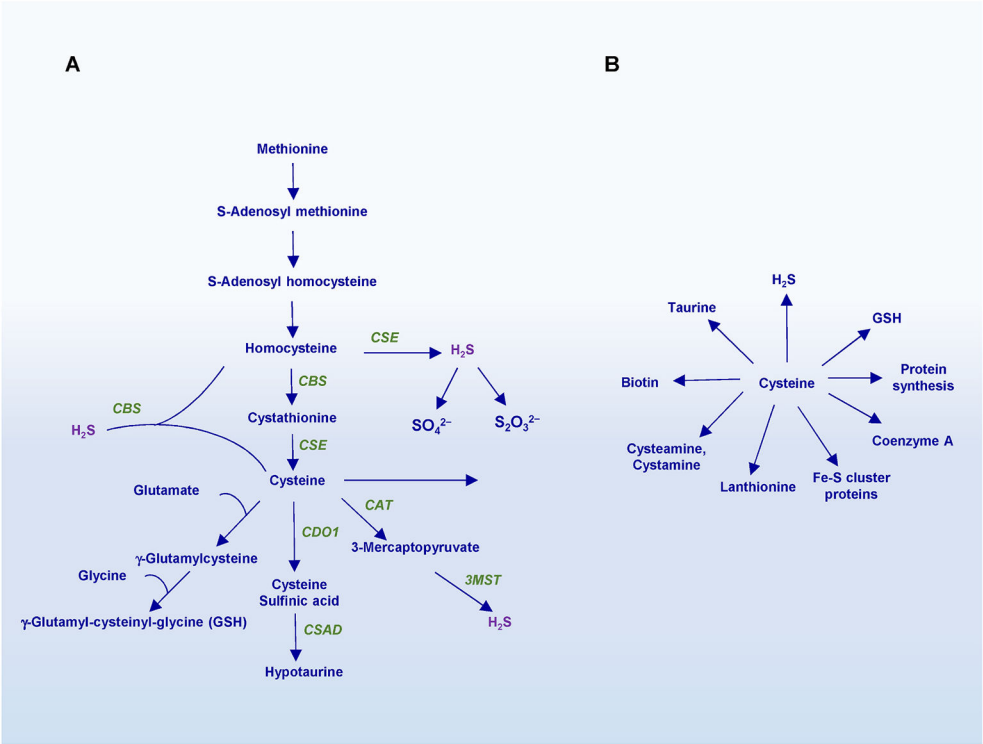

Fig. 1. Biosynthesis of cysteine and its downstream products.

A) The transsulfuration pathway. Dietary methionine is utilized through a series of reactions to generate homocysteine, which is condensed with serine to generate cystathionine by cystathionine β-synthase (CBS). Cystathionine γ-lyase (CSE) then utilizes cystathionine as a substrate to produce cysteine. Excess cysteine may be degraded by cysteine dioxygenase 1 (CDO1) to generate cysteine sulfinic acid, which is further acted on by cysteine sulfinic acid decarboxylase (CSAD) to produce hypotaurine. Cysteine may be used to generate glutathione via γ-glutamylcysteine. Cysteine is also utilized to produce other sulfur containing molecules and Fe–S cluster proteins or used as a substrate to generate hydrogen sulfide (H_2S). Both homocysteine and cysteine serve as substrates for the generation of H_2S. While CSE may synthesize H_2S from either cysteine or homocysteine, CBS generates H_2S using a combination of cysteine and homocysteine. A third enzyme, 3-mercaptopyruvate sulfur transferase (3-MST), in conjunction with cysteine amino transferase (CAT), also produces H_2S using 3- mercaptopyruvate (3-MP) as a substrate. H_2S is also subject to degradation by the sulfide oxidation unit (SOU) in the mitochondria to produce sulfate and thiosulfate. **B) Products and derivatives of cysteine.** In addition to its essential role in protein synthesis, cysteine is the precursor of sulfur containing molecules such as glutathione, taurine, lanthionine, coenzyme A, biotin and the gasotransmitter hydrogen sulfide (H_2S).

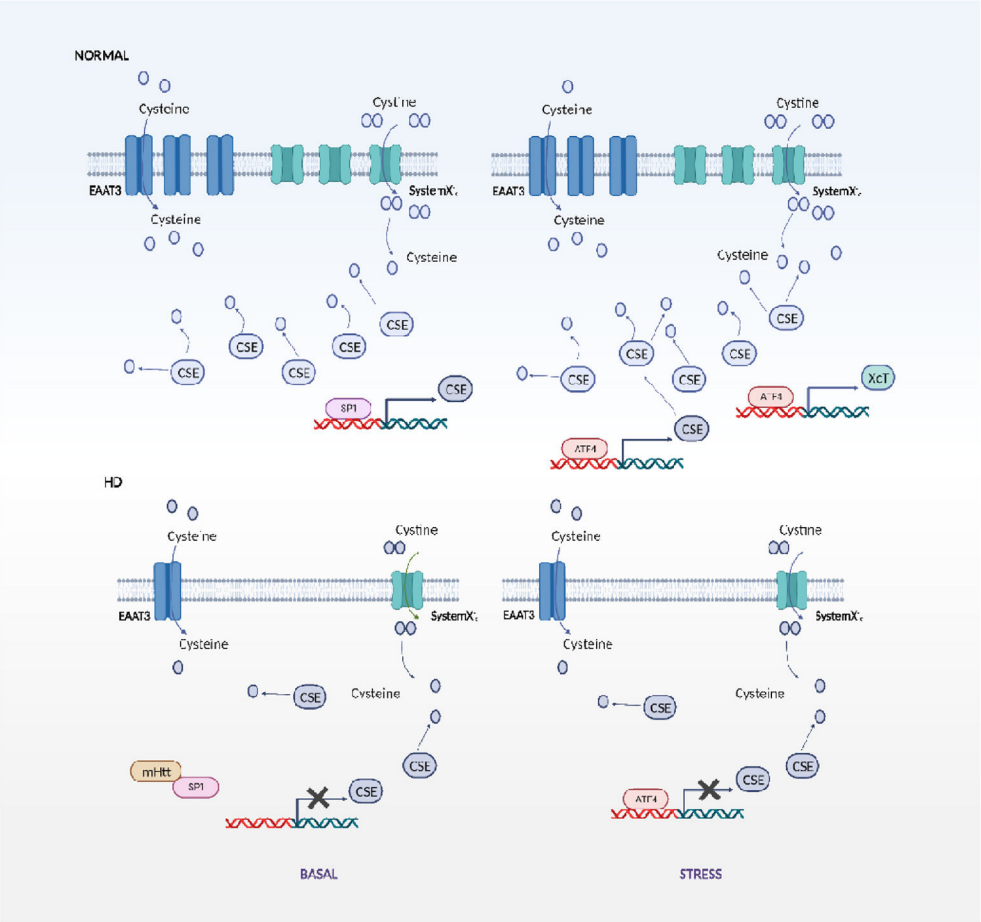

Fig. 2. Disrupted cysteine and H_2S metabolism in Huntington's disease.

The biosynthetic enzyme for cysteine and H_2S, cystathionine γ-lyase (CSE) is regulated by specificity protein 1 (SP1) under basal conditions and by activating transcription factor 4 (ATF4) during response to stress in normal cells. In striatal HD cell lines, SP1 is sequestered by mutant huntingtin (mHtt) leading to decreased transcription of CSE, which leads to decreased cysteine and H_2S production. Additionally the neuronal cysteine transporter, excitatory amino acid transporter 3 (EAAT3/EAAC1) and system Xc^- are dysregulated in HD under basal conditions, leading to an overall cysteine deficit. During stress, in normal cells, ATF4 is upregulated, which stimulates expression of CSE. In HD cells, this induction is blunted, further contributing to the derailment of cysteine metabolism.

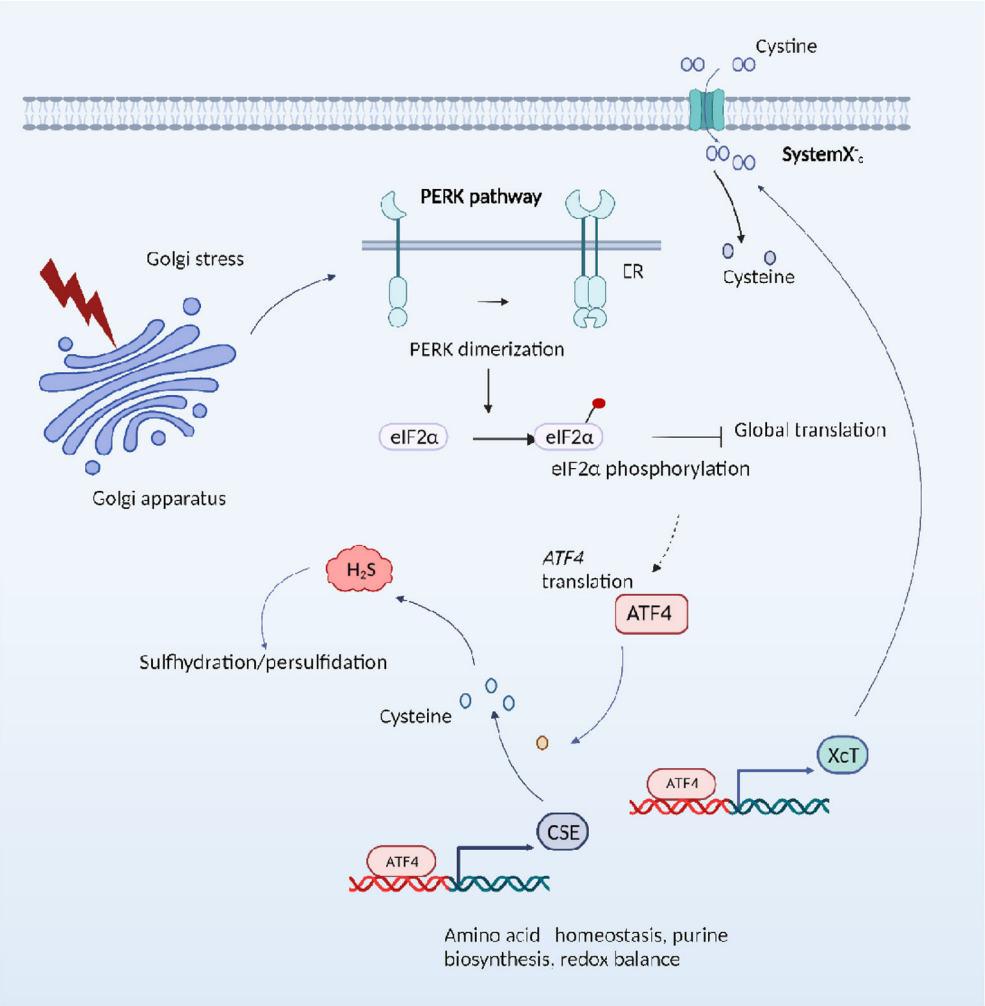

Fig. 3. Mild Golgi stress confers cytoprotection in Huntington's disease.

Treatment of striatal HD cells with Golgi stressors upregulates ATF4 via the protein kinase R (PKR)-like ER kinase (PERK) pathway and stimulates expression of CSE and cysteine biosynthesis via the reverse transsulfuration pathway. Additionally, the cystine transporters (xCT) may also be upregulated by ATF4, in addition to other targets, leading to enhanced cysteine and H_2S levels, and growth in cysteine-deprived conditions.