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Cysteamine: an old drug with new potential

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Cysteamine is an amino thiol with the chemical formula $HSCH_2CH_2NH_2$. Endogenously, cysteamine is derived from coenzyme A degradation, although its plasma concentrations are low. Most experience with cysteamine as a drug originates from the field of the orphan disease cystinosis, in which cysteamine is prescribed to decrease intralysosomal cystine accumulation. However, over the years, the drug has been used for several other applications both *in vitro* and *in vivo*. In this article, we review the different applications of cysteamine, ending with an overview of ongoing clinical trials for new indications, such as neurodegenerative disorders and nonalcoholic fatty liver disease (NAFLD). The recent development of an enteric-coated cysteamine formulation makes cysteamine more patient friendly and will extend its applicability for both old and new indications.

Endogenous cysteamine production

Cysteamine (synonyms: β-mercaptoethylamine, 2-aminoethanethiol, 2-mercaptoethylamine, decarboxycysteine, thioethanolamine and mercaptamine) was initially described as part of the coenzyme A pathway (Fig. 1a), which is highly conserved in mammals. Coenzyme A is synthesized from pantothenate (vitamin B5) and cysteine [1]. Its main functions include the synthesis and oxidation of fatty acids and the oxidation of pyruvate in the citric acid cycle. The endogenous production of cysteamine occurs during the degradation of coenzyme A, when pantetheine is formed (Fig. 1a). The latter is hydrolyzed by pantetheinase (also called vanin) into cysteamine and pantothenic acid. Subsequently, cysteamine is oxidized into hypotaurine by cysteamine dioxygenase [2]. As well as cysteamine, cysteine can also be converted into hypotaurine. It is first oxidized into cysteine sulfinate by cysteine dioxygenase, followed by decarboxylation of cysteine sulfinate into hypotaurine by cysteine sulfinate decarboxylase. After formation of hypotaurine from either cysteamine or cysteine, it is oxidized into taurine by hypotaurine dehydrogenase (Fig. 1b). Taurine is excreted either in urine, or in feces in the form of bile salts [3].

Pharmacokinetic and pharmacodynamic properties of cysteamine

The exact mechanism of action of cysteamine is not completely understood for many indications. The thiol cysteamine can be oxidized into the disulfide cystamine, which in turn can be reduced to cysteamine. This mechanism underlies the biphasic effect of cysteamine. When used at low concentrations, it can promote the transport of cysteine into cells, which can be further used to synthesize glutathione, one of the most potent intracellular antioxidants, which in turn influences cellular redox homeostasis. Accumulating evidence indicates that the oxidative state of a cell regulates numerous signaling pathways involved in cell proliferation and survival and influences gene expression of several redox-sensitive genes [4,5]. As well as its antioxidant properties, the free thiol group of cysteamine can react with free thiol or the disulfide bounds of peptides and proteins, which can interfere

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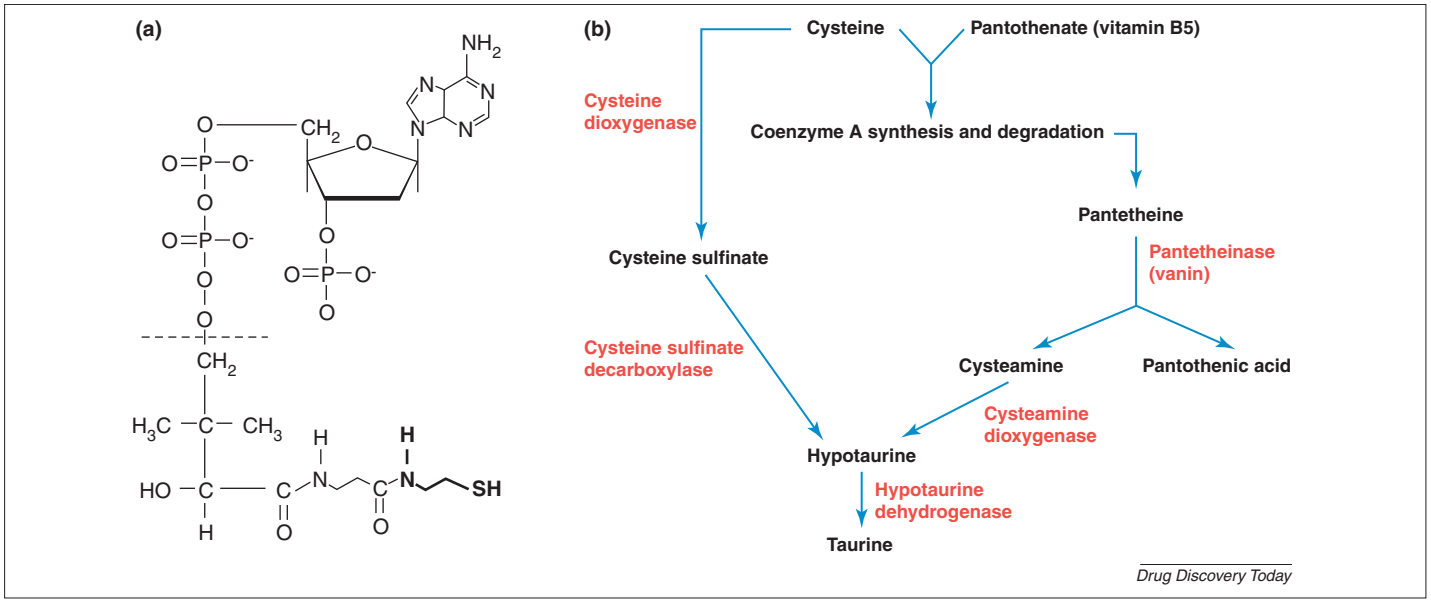

FIGURE 1

The structure of coenzyme A and cysteamine metabolism *in vivo*. **(a)** Structure of coenzyme A. The broken line indicates the point at which pantetheine is cleaved. Cysteamine is indicated in bold. **(b)** Cysteamine metabolism *in vivo*. Cysteamine is formed from pantetheine, which is a degradation product of coenzyme A. Cysteamine, as well as cysteine, can be converted into hypotaurine, which is oxidized into taurine.

with their function. By contrast, when used at higher doses, cysteamine oxidation in the presence of transition metals generates hydrogen peroxide (H_2O_2) molecules, which cause oxidative stress. In addition, high doses of cysteamine diminish the activity of glutathione peroxidase, the enzyme that catalyzes the oxidation of glutathione to its disulfide [6]. Thus, divergent results of studies using cysteamine can frequently be explained by the antioxidant effect of the drug, hence counteracted by its direct toxicity when higher doses are used. Careful dose selection and monitoring are mandatory while designing preclinical or clinical trials.

In humans, basal plasma cysteamine is usually below the limits of detection (<0.1 μM). After ingestion of cysteamine, a peak concentration in plasma is reached after approximately one hour. Doses of cysteamine bitartrate (trade name Cystagon®, Mylan Pharma, USA) of approximately 15 mg/kg lead to peak plasma concentrations of 0.03–0.07 mM [7], whereas ingestion of cysteamine together with food decreases the absorption of the drug by approximately 30% [8]. In patients with cystinosis (OMIM 219800), a maximum decline in white blood cell (WBC) cystine levels is reached after the same time as peak plasma cysteamine concentrations, followed by a decline in cysteamine plasma levels and an increase in WBC cystine levels to original values after six hours [7]. Thus, the drug should be administered four times per day. In 2007, it was demonstrated that cysteamine administration in the small intestine led to higher cysteamine plasma levels with a higher area under the curve, when compared with gastric administration of the drug. This lead to the development of enteric-coated cysteamine bitartrate (called RP103) by Raptor Pharmaceutical Corp. (USA), which can be administered twice daily [9].

Following its discovery as part of the coenzyme A pathway, cysteamine has been studied for various therapeutic strategies (Fig. 2). Over time, different formulas of cysteamine have been used, including cysteamine hydrochloride (HCl) ($C_2H_7NS{\cdot}HCl$, 1 mg = 0.7 mg cysteamine base), phosphocysteamine ($C_2H_7NS{\cdot}PO_3$, PO_3, 1 mg = 0.4 mg cysteamine base) and cysteamine bitartrate ($C_2H_7NS{\cdot}C_4H_6O_6$, 1 mg = 0.3 mg cysteamine base). In this review, all doses are indicated as cysteamine base, unless stated otherwise.

Previous uses of cysteamine

The first reports on the use of cysteamine in animals concerned studies on morbidity and mortality after exposure to radiation. The radioprotective property of the drug was first described in 1954 and relied on its effect against the formation of $OH^{\bullet}$ radicals [10]. Both cysteamine and its oxidized form, cystamine, have been used in clinical trials to treat radiation sickness in patients receiving radiotherapy as part of cancer treatment. Given that neither of the drugs resulted in significant improvement, both ceased to be used for this purpose [10,11].

In 1973, it was discovered that cysteamine showed ulcerogenic properties when administered in high doses (generally >200 mg/kg) to rats [12]. The development of duodenal ulcera is caused by increased gastric acid secretion [13], increased serum gastrin levels and increased gastric and plasma ghrelin levels [14], combined with an increased expression of hypoxia-inducible factor 1α (HIF-1α). This leads to the production of several growth factors as well as antiangiogenic factors. The sum of these reactions is an antiangiogenic effect that predominates the angiogenic effect, thereby enabling ulceration instead of wound healing [13]. Given that the pathological changes found in rats mimic the pathological and functional abnormalities found in human duodenal ulcers, the cysteamine rat model is a useful tool to study the pathophysiology behind duodenal ulcer formation in humans.

It was also found that cysteamine caused a depletion of tissue somatostatin in rats [15]. Subsequent studies in other animal models, including sheep, male broiler chickens, pigs and carp, showed increased growth rates if daily doses of 50–90 mg/kg day were used, whereas doses >140 mg/kg restricted growth and led to the formation of duodenal ulcera. Also, increased mRNA

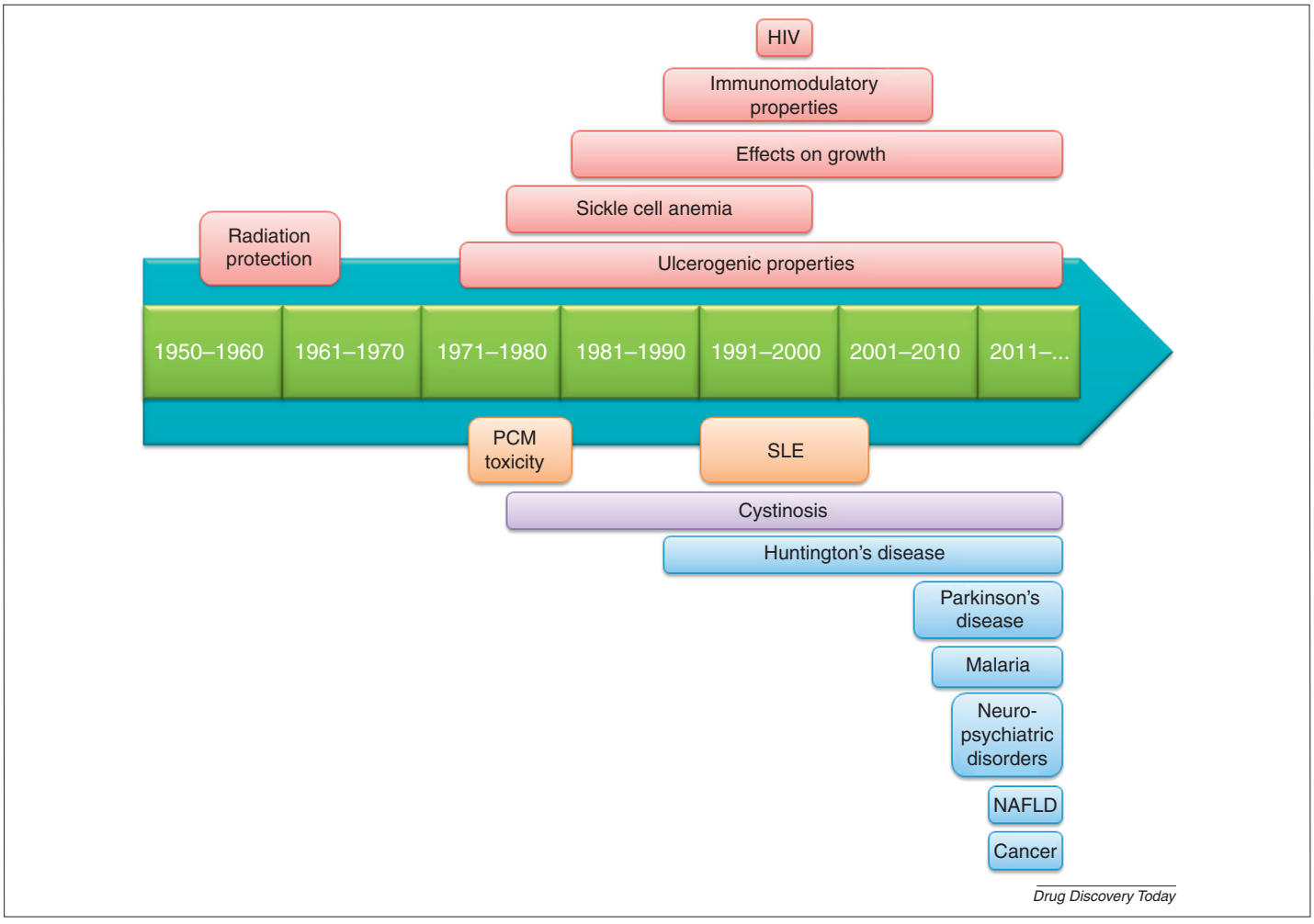

FIGURE 2

Timeline describing the studies using cysteamine or cystamine from 1950 onwards. Previous animal and *in vitro* studies are indicated in red, previous human trials with an unfavorable outcome are indicated in orange, current indications are indicated in purple and possible new indications are indicated in blue. *Abbreviations*: NAFLD, nonalcoholic fatty liver disease; PCM, paracetamol, SLE, systemic lupus erythematosus.

expression of insulin-like growth factor (IGF)-I, IGF-II, IGF-I receptor and IGF-I binding protein 3 was found [16–19].

Additionally, cysteamine was tested as a possible treatment for sickle cell anemia [20], for HIV-I [21] and as a possible immunomodulatory agent [22]. However, these studies showed conflicting results and no clinical trials were performed. Cysteamine was also studied as a possible treatment for systemic lupus erythematosus (SLE). One clinical trial was performed, but no subsequent trials were conducted because of disappointing results [23]. Furthermore, cysteamine has been used with good results for the treatment of paracetamol (acetaminophen) hepatotoxicity. However, *N*-acetylcysteine (NAC) appeared to be more effective and had a better safety profile and, therefore, is now the treatment of choice for paracetamol toxicity [24].

Current use of cysteamine: cystinosis

Cystinosis is a lysosomal storage disorder, caused by mutations in the gene encoding cystinosin, lysosomal cystine transporter (*CTNS*) on chromosome 17p3. The disease is characterized by cystine accumulation in cells throughout the body. Patients present with generalized proximal tubular damage (called renal Fanconi syndrome), resulting in polyuria, polydipsia and failure to thrive within the first year of life. If left untreated, cystinosis causes end-stage renal disease around the age of ten years. As cystine accumulates in all cells throughout the body, extrarenal organs, including the eyes, various endocrine organs, muscles and the central nervous system, are also affected [25].

Cysteamine was introduced as a possible treatment for cystinosis in 1976 [26] and is still the only treatment available. The drug enters the lysosome through an unknown transporter where it breaks the disulfide bond in cystine, leading to the formation of cysteine and cysteine–cysteamine disulfide [25]. Cysteine can leave the lysosome through the cysteine transporter, the cysteine-cysteamine disulfide via an as yet unidentified cationic amino-acid transporter (Fig. 3).

Next to its cystine-depleting effect, cysteamine has been shown to increase intracellular glutathione levels in cystinotic cells, thus restoring the altered redox state of the cells [27]. Also, increased rates of apoptosis in cystinotic cells, which are thought to be the result of increased caspase 3 and protein kinase Cε activity, is counteracted by cysteamine administration [28].

Adequate treatment with cysteamine reduces the rate of progression toward end-stage renal disease and postpones or even

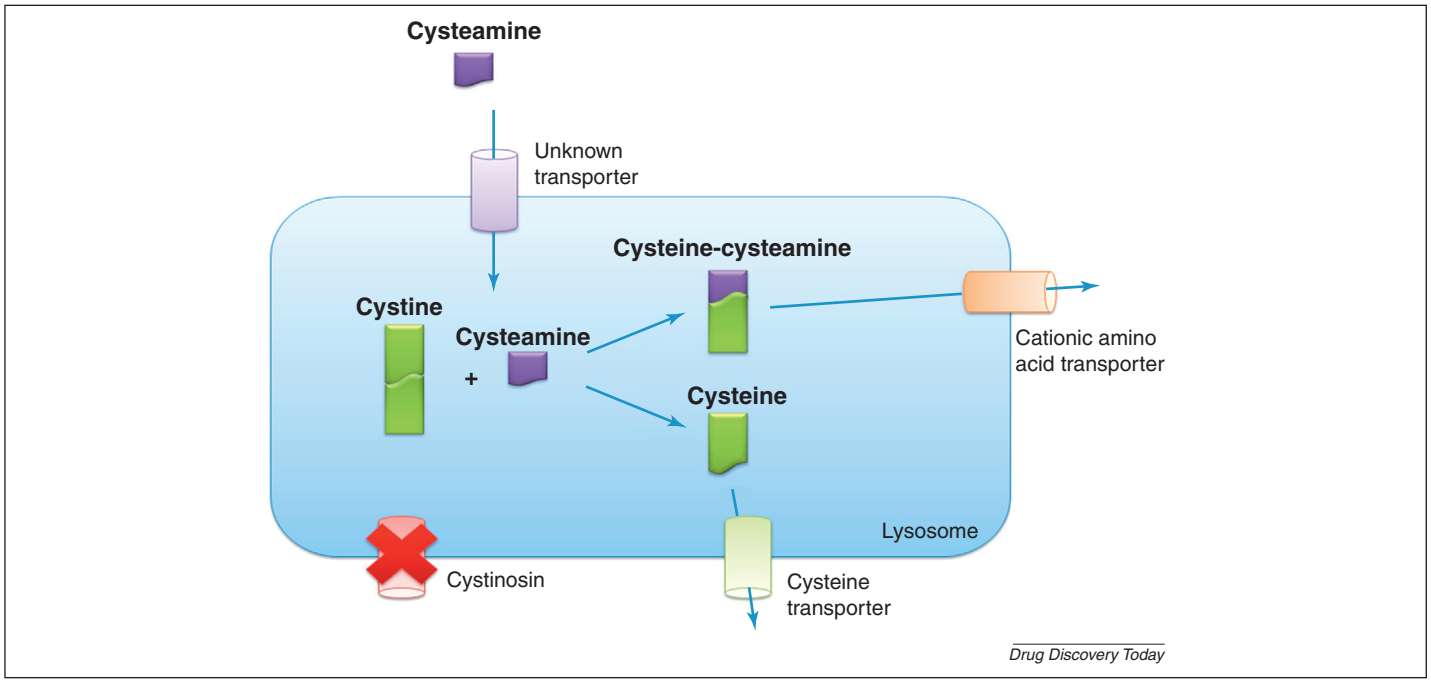

FIGURE 3

Mechanism of action of cysteamine in cystinotic cells. Cysteamine can enter the lysosome through an unknown transporter. Once inside the lysosome, it breaks the disulfide bond in cystine, leading to the formation of cysteine (which can leave the lysosome through the cysteine transporter) and a cysteamine–cysteine disulfide (which can leave the lysosome through an undefined cationic amino acid transporter).

prevents the occurrence of extrarenal complications. Also, growth significantly improves after cysteamine administration [29–33].

Initially, cysteamine therapy was hampered by several adverse effects, including hyperthermia, lethargy and rash, all of which were reversible after cessation of cysteamine administration. None of these adverse effects were noted after it became common practice to introduce cysteamine in a low dose with a subsequent gradual increase over several weeks [34]. Currently, the most common adverse effects of cysteamine include gastrointestinal complaints, for which the concomitant use of proton pump inhibitors is advised [35,36], and disagreeable breath and sweat odor owing to the conversion of a small amount of the ingested cysteamine to methanethiol and dimethyl sulfide [37]. Recently, three patients with cystinosis treated with cysteamine were reported to have developed lupus nephritis [38–40]. In addition, six patients with cystinosis treated with high cysteamine doses were reported with new adverse events, comprising vascular proliferative lesions on their elbows, skin striae and severe bone and muscular pain [41]. Skin and bone lesions caused by cysteamine treatment are likely to be because of its interference with collagen crosslinking in analogy to D-penicillamine [42].

It is unknown whether cysteamine is teratogenic. Rat studies showed an increased risk for intrauterine death, intrauterine growth retardation and fetal malformations (especially cleft palate and kyphosis) in pregnant rats given high doses of 100 and 150 mg/kg [43]. There is no information regarding its possible teratogenicity in humans. Based on the data from animal studies, cysteamine is classified as a category C drug according to the US Food and Drug Administration (FDA) Use-In-Pregnancy categories. It is advised for female patients with cystinosis to stop cysteamine administration before conception until after the baby is born. It is uncertain whether cysteamine is excreted into breast milk, thus breast-feeding is discouraged.

Recently, a phase III clinical trial demonstrated noninferiority of the enteric-coated RP103 cysteamine formulation administered bid compared with Cystagon® administered qid for lowering WBC cell cystine levels. Average daily doses of RP103 were 82% of the incoming dose of Cystagon®. A safety extension study is currently underway [44].

New applications of cysteamine

Huntington's disease

The neurodegenerative Huntington's disease (HD) (OMIM 143100) is caused by the intracerebral accumulation of huntingtin, a large protein that is widely expressed during development and that has a complex and dynamic distribution within cells. It is predicted to have a pleiotropic function regulating axonal trafficking, gene transcription and cell survival [45]. Huntingtin has a polyglutamine sequence (CAG) close to its N terminus. HD occurs when this sequence of the gene encoding huntingtin (*HTT*, 4p16.3) expands beyond 35–40 residues, causing progressive motor dysfunction (chorea, later evolving to bradykinesia and rigidity), cognitive decline and psychiatric disturbances. In developed countries, HD has a prevalence of 4–10 per 100,000, with a mean age of onset of 40 years, with death occurring 15–20 years later [46].

The first report of a possible usefulness of cysteamine in HD originates from 1986, when it was hypothesized that the somatostatin-depleting properties of the drug could normalize the increased somatostatin levels in the basal ganglia. However, in a clinical trial conducted in five patients, neither changes in extrapyramidal signs nor improvement of dementia scores were

observed after administering the highest tolerable dose (4 g/day) over two weeks [47].

Subsequently, it took almost 20 years for interest to be reignited in the use of cysteamine to treat HD. This time, the drug was tested as an inhibitor of transglutaminases, given that transglutaminase 2 activity is increased in the brain cortex, cerebellum and brain nuclei of patients with HD [48]. Transglutaminases are enzymes that catalyze protein crosslinking by forming γ-glutamyl-ε-lysine side-chain peptides, or by incorporation of small amines into proteins. Initially, it was suggested that transglutaminase 2 catalyzes crosslinking of mutated huntingtin, leading to aggregate formation [49]. Later, it was found that transglutaminases cause disease progression in HD regardless of huntingtin aggregation. Instead, transglutaminase induces increased crosslinking of actin–cofilin complexes in the presence of mutant huntingtin, thus causing the formation of aberrant actin–cofilin rods, which make the cell vulnerable to cell stress and death [50].

In 1984, it became evident that cystamine can inhibit transglutaminase activity by binding to the cysteine in its active center [51]. Much later, in 2002, a study was conducted using transgenic mice expressing exon 1 of the human *HTT* with expanded CAG repeats. These mice developed a progressive and fatal neurological condition, resembling HD in humans. The intraperitoneal injection of cystamine into these mice resulted in a significant decrease in transglutaminase activity. Also, even after the onset of tremor, the administration of cystamine significantly improved symptoms, delayed the onset of unusual behavior, ameliorated weight loss and decreased mortality [52].

Intact cells have high free glutathione levels, which catalyze the immediate reduction of cystamine into cysteamine. Therefore, it is probable that the effects of cystamine that were discovered in the above-mentioned experiments were in fact a result of the action of cysteamine. In addition, the transglutaminase-inhibiting effects are caused by the thiol group of cysteamine, which is not present in cystamine. Moreover, cystamine does not cross the blood–brain barrier, whereas cysteamine does [53].

As well as decreasing transglutaminase activity, cysteamine might also be beneficial in the treatment of HD in four other ways. First, cysteamine inhibits the activity of pro-apoptotic caspase 3, which is independent of the decrease in transglutaminase activity [54]. Second, the drug has antioxidant properties as a result of increasing glutathione production [55]. Third, cysteamine increases the production of several heat shock proteins (HSP), including the murine HSP 40 kDa (Hsp40), the gene encoding which is an ortholog of the human DNAJ protein 1 (HDJ1), which can assist in proper folding of mutated huntingtin containing the expanded CAG sequence [52,53]. Finally, cysteamine increases brain levels of brain-derived neurotrophic factor (BDNF), which is a neuronal growth factor that improves the survival of striatal neurons [51]. Increased BDNF levels after cysteamine administration are caused by the increased expression of the heat shock DNAJ-containing protein 1 (HSJ1), which in turn stimulates BDNF release. Furthermore, transglutaminase 2 was shown to inhibit the release of BDNF [56].

Recently, a phase I trial using cysteamine in nine patients with HD was conducted. Treatment was started at a dose of 10 mg/kg/day and was increased by 10 mg/kg/day weekly until the maximum tolerable dose was reached (10–50 mg/kg/day for a total duration of two to five weeks). Dose-limiting adverse effects comprised nausea, weight loss, halitosis (only with doses of 40 mg/kg/day or more) and motoric complaints (difficulty with walking, running and balance), although no differences in the unified HD rating scale (UHDRS) motor scores were observed. Of the eight patients who completed the study (one patient terminated treatment because of projectile vomiting), an investigator global assessment showed improvement in two patients and no change in the remaining six patients [57].

Currently, a randomized, controlled, double-blind multicenter phase II–III trial using RP103 cysteamine formulation versus placebo is in progress. In this study, a total of 96 patients will be enrolled. The initial duration of the follow-up is 18 months, followed by an open-label trial in all patients being treated with RP103 for another 18 months. The primary end-point will be based upon the UHDRS.

Other neurodegenerative and neuropsychiatric disorders

Parkinson's disease (PD) (OMIM 168600) is a progressive neurodegenerative disease caused by the loss of nigral dopaminergic neurons owing to cell dysfunction or cell death by apoptosis or autophagy, resulting in a depletion of dopamine [58]. Given that promising results have been obtained in HD, cystamine and cysteamine were tested in a mouse model of PD treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), inducing the loss of dopaminergic neurons. The effect of cystamine and cysteamine in the treatment of neurodegenerative diseases (HD and PD) in animal and *in vitro* studies were recently reviewed elsewhere [59]. It was shown that cyst(e)amine treatment before, during and several days after MPTP administration significantly decreased dopaminergic neuronal cell death within the substantia nigra and improved dopamine status. This positive effect is probably because of the increased secretion of BDNF in combination with reduced oxidative stress. However, the best effect was observed when administration of cyst(e)amine was started before MPTP [60,61]. In humans, treatment of PD is initiated when symptoms are overt. Therefore, it remains unclear whether cysteamine will improve neurological decay in PD, when brain damage is already present.

The fact that cysteamine increases dopamine concentration in certain regions of the brain, decreases somatostatin levels, enhances BDNF secretion and promotes the production of glutathione, suggested that cysteamine could be of use in the treatment of schizophrenia. Both cystamine and cysteamine (administered at 150 mg/kg/day for seven days) increased BDNF levels in frontal cortex and improved neuronal cell survival in a mouse model of schizophrenia [62].

The BDNF-increasing effect of cysteamine might also be beneficial in the treatment of major depressive disorders. A mouse study showed significantly less depressive behavior after cysteamine administration (measured by the open field test, forced-swimming test and tail suspension test), probably caused by increased hippocampal BDNF levels [63].

As well as schizophrenia and major depression, it was suggested that patients with other neuropsychiatric disorders associated with decreased BDNF levels, such as attention-deficit hyperactivity disorder (ADHD), Alzheimer's disease, neuropathic pain and Rett syndrome, would benefit from cysteamine treatment [64].

However, so far, no studies have been conducted to evaluate the effect of cysteamine in these disorders.

Nonalcoholic fatty liver disease

The term 'NAFLD' is used to describe a range of related liver disorders. It is caused by an imbalance between the acquisition and the removal of triglycerides, which are formed by the coupling of three free fatty acids to a glycerol backbone. The earliest stage is hepatic steatosis, characterized by the intracytoplasmic deposition of triglyceride-containing lipid droplets in the hepatocytes. This condition can be either self-limiting or evolve into nonalcoholic steatohepatitis (NASH), which is characterized by hepatocyte injury (hepatocyte ballooning and cell death), inflammatory infiltration and/or collagen deposits (fibrosis). NASH can progress to cirrhosis, at which point the hepatocytes are replaced by scar tissue, containing mainly collagen I. Liver cirrhosis can then progress to liver cancer (hepatocellular carcinoma) [65].

Currently, the treatment of NAFLD is limited to dietary and lifestyle changes. Additionally, the inhibition of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α by pentoxifylline, antioxidant therapy using vitamin E, insulin-sensitizing therapy using pioglitazone and ursodeoxycholedic acid, have shown some success in clinical trials in adults, although the use of vitamin E or metformin in children and adolescents with NAFLD was not superior to placebo [66]. Recently, a phase IIa trial was conducted in children with NAFLD using the enteric-coated formula of cysteamine bitartrate (a prototype of RP103). From 13 children included in the study, 11 completed the 24-week trial period. They started by taking 300 mg cysteamine twice daily, with dose increments over nine days to a maximum of 1000 mg twice daily. The primary endpoint, a normalization ($\leq$40 IU/L) or $\geq$50% reduction in baseline serum alanine aminotransferase (ALT) after 24 weeks, was achieved in seven patients. After treatment, a significant decrease in both ALT and aspartate aminotransferase (AST) was found, which remained below baseline levels 24 weeks after stopping cysteamine administration in all seven patients who achieved the primary endpoint. Given that there was no significant difference in body mass index (BMI), lifestyle changes were probably not responsible for these results. It was hypothesized that cysteamine administration might improve ALT and AST by increasing ROS scavenging and glutathione production, as well as by inhibiting transglutaminase activity, which might lead to decreased fibrin crosslinking, thus inhibiting fibrosis [67]. Furthermore, increased adiponectin production in patients treated with cysteamine, which has both insulin-sensitizing and anti-inflammatory effects, might further contribute to the positive effect of cysteamine in the treatment of NAFLD [68]. Currently, a phase IIb trial is being prepared to test the efficacy of enteric-coated cysteamine bitartrate in a tablet formula (called RP104) in patients with NAFLD.

Malaria

Malaria is caused by infection with the parasite *Plasmodium*. Mouse studies have shown that mutations in the *Char9* locus on chromosome 10 regulate the blood-stage replication of the parasite *Plasmodium chabaudi* AS (which most closely resembles infection by *Plasmodium falciparum* in humans), causing resistance against malaria. This resistance was attributed to the pantetheinase-encoding genes *Vnn1* (encoding vanin 1) and *Vnn 3* (encoding vanin 3) [69]. Given that pantetheinases produce cysteamine from pantetheine [70] (Fig. 1b), interest was sparked in the use of cysteamine as an antimalarial drug. In subsequent mouse studies, it was found that treatment with cysteamine markedly reduced parasite burden and significantly increased animal survival [69,71]. Furthermore, the addition of cysteamine to red blood cells infected with *P. falciparum*, diminished parasite replication and resulted in a dose-dependent delay and reduction in total parasitemia, after injection of these cells into mice that had not been treated with cysteamine; this indicated a direct antiparasitic effect of cysteamine as opposed to influencing the host inflammatory response [71].

However, the effect of cysteamine was still inferior to that of known antimalarial drugs. Therefore, concomitant administration of cysteamine and suboptimal doses of artemisinin derivates (artesunate or dihydroartemisinin) was studied. A dose-dependent synergistic effect between cysteamine and the artemisinin derivates was found. The combined administration of cysteamine and artesunate resulted in a delay of disease onset, a reduction in peak levels of parasitemia and an improved disease outcome [72]. Thus, the simultaneous administration of cysteamine with lower-dose artemisinin derivates, enabling the adverse effects of the latter drugs to be diminished, could be a new promising treatment option for patients with malaria.

Cancer

It was established in 1994 that the addition of cysteamine to astrocyte culture medium resulted in increased mitochondrial autophagy [73]. In 2011, it was found that cysteamine exerted a dose-dependent effect on the doxorubicin-induced death of cancer cells, measured in both HeLa cells and B16 cells (a mouse melanoma cell line), whereas cysteamine treatment alone had no influence on cell survival. In addition, in a doxorubicin-resistant breast cancer cell line, the addition of cysteamine to doxorubicin resulted in a dramatic increase in cell death. Moreover, in mice injected with B16 melanoma cells, the concomitant administration of both drugs led to additional tumor shrinking when compared to doxorubicin alone. Another *in vitro* study using HeLA cells showed that the downregulation of the gene encoding autophagy related 5 (*Atg5*), which is essential in autophagy, blocked the effect of cysteamine and enhanced the cytotoxicity of doxorubicin. Altogether, these studies indicate that cysteamine exerts a chemo-sensitizing effect on doxorubicin by influencing autophagy [74]. Furthermore, it was found in animal models that cysteamine inhibited the formation of gastric [75] and mammary [76] tumors that were induced chemically or after irradiation, respectively. Also, the administration of cysteamine inhibited the metastasis of pancreatic cancer in a mouse model by decreasing the expression and activity of metalloproteinases, which have an important role in cell invasion and metastasis [77]. These results indicate that cysteamine might be beneficial as an adjunct to chemotherapy.

Concluding remarks

Although cysteamine has been used for more than three decades for the treatment of cystinosis, it has been tested over the past 50 years with varying success in numerous *in vitro* and *in vivo* studies (Fig. 2). The mechanisms of action of cysteamine are summarized in Fig. 4 and can be generally classified as: (i) depleting lysosomal

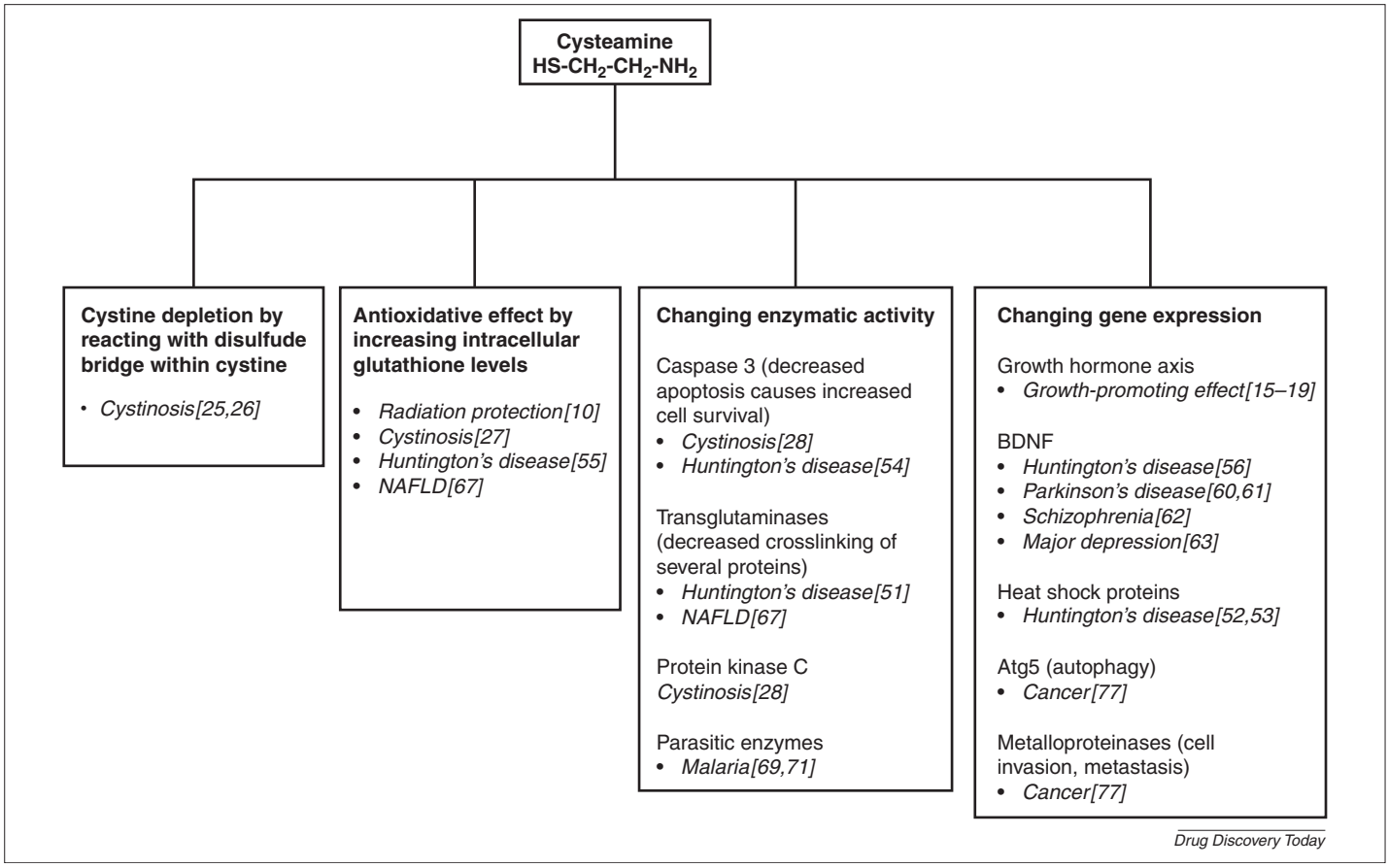

FIGURE 4

Mechanisms of action of cysteamine in different conditions. Cysteamine can exert a wide range of action, depending on the condition in which it is used. This list is not exhaustive. *Abbreviations*: Atg5, autophagy related 5; BDNF, brain-derived neurotrophic factor; NAFLD, nonalcoholic fatty liver disease.

cystine in cystinosis; (ii) antioxidative properties by increasing cellular glutathione levels; (iii) changing the enzymatic activity of several proteins as a result of binding to their thiol groups; and (iv) changing the expression of various genes.

The revival of cysteamine has recently been stimulated by the development of an enteric-coated cysteamine formulation that enables the drug to be given twice daily (instead of every six hours), possibly with a better pharmacokinetic and safety profile. Several clinical trials using this new formulation are underway and the first results are encouraging. The expectations are comparable to that of the old wine put in a new bottle: the taste remains the same, but the sales will go up.

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