Amino Acids (2013) 44:111–118
DOI 10.1007/s00726-011-1081-1

REVIEW ARTICLE

Possible involvement of transglutaminase-catalyzed reactions in the physiopathology of neurodegenerative diseases

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Received: 21 April 2011 / Accepted: 8 September 2011 / Published online: 22 September 2011

Abstract Transglutaminases are ubiquitous enzymes, which catalyze post-translational modifications of proteins. Recently, transglutaminases and tranglutaminase-catalyzed post-translational modification of proteins have been shown to be involved in the molecular mechanisms responsible for several human diseases. Transglutaminase activity has been hypothesized to be involved also in the pathogenetic mechanisms responsible for human neurodegenerative diseases. Neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, supranuclear palsy, Huntington's disease and other polyglutamine diseases, are characterized in part by aberrant cerebral transglutaminase activity and by increased cross-linked proteins in affected brains. In this review, we focus on the possible molecular mechanisms by which transglutaminase activity could be involved in the pathogenesis of neurodegenerative diseases, and on the possible therapeutic effects of selective transglutaminase inhibitors for the cure of patients with diseases characterized by aberrant transglutaminase activity.

Keywords Transglutaminases · Post-translational modifications of proteins · Nervous System · Neurodegenerative diseases

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Introduction

Transglutaminases (E.C. 2.3.2.13; TGs) are a family of related and ubiquitous enzymes, which catalyze post-translational modifications of proteins. These enzymes are also capable of catalyzing other reactions important for cell life. The distribution and the physiological roles of TGs have been widely studied in numerous cell types and tissues, and recently their roles in human diseases have begun to be identified. For example, the transglutaminase activity has been hypothesized to be involved in the pathogenetic mechanisms responsible for several human diseases, including neurodegenerative diseases. A recent wide range of studies has already clearly shown that the "tissue" transglutaminase (tTG or TG 2) is responsible for a very widespread human pathology, Celiac Disease (CD). This disease is due to intolerance to a food protein, gliadin, and is characterized by a very complex clinical syndrome, which includes gastrointestinal pathological manifestations, often associated with extra-intestinal manifestations. Interestingly, a subset of celiac patients develops neurological disorders. In this review, we describe the possible roles played by TGs in molecular mechanisms, which could be responsible for the physiopathology of neurodegenerative diseases.

Biochemistry of the transglutaminases

Transglutaminases are a family of enzymes (Table 1) which catalyze irreversible post-translational modifications of proteins. Examples of transglutaminase-catalyzed reactions include: (a) acyl transfer between the γ-carboxamide group of a protein/polypeptide glutaminyl residue and the ε-amino group of a protein/polypeptide lysyl residue;

Table 1 Transglutaminases and their biological roles when known

Transglutaminase	Biological role
Factor XIIIa	Blood clotting
TG 1 (Keratinocyte TG, kTG)	Skin differentiation
TG 2 (Tissue TG, tTG, cTG)	Apoptosis, cell adhesion, signal transduction
TG 3 (Epidermal TG, eTG)	Hair follicle differentiation
TG 4 (Prostate TG, pTG)	Suppression of sperm immunogenicity
TG 5 (TG X)	Epidermal differentiation
TG 6 (TG Y)	Unknown function
TG 7 (TG Z)	Unknown function

(b) attachment of a polyamine to the γ-carboxamide of a glutaminyl residue; (c) deamidation of the γ-carboxamide group of a protein/polypeptide glutaminyl residue (Fig. 1) (Folk 1983). The reactions catalyzed by TGs occur by a two-step mechanism (Fig. 2). The binding of Ca^{2+}, which exposes an active-site cysteine residue, activates the transamidating activity of TGs. This cysteine residue reacts with the γ-carboxamide group of an incoming glutaminyl residue of a protein/peptide substrate to yield a thioacyl-enzyme intermediate and ammonia (Fig. 2, Step 1). The thioacyl-enzyme intermediate then reacts with a nucleophilic primary amine substrate, resulting in the covalent attachment of the amine-containing donor to the substrate glutaminyl acceptor and regeneration of the cysteinyl residue at the active site (Fig. 2, Step 2). If the primary amine is donated by the ε-amino group of a lysyl residue in a protein/polypeptide, a N^{ε}-(γ-L-glutamyl)-L-lysine (GGEL) isopeptide bond is formed (Fig. 1a). On the other hand, if a polyamine or another primary amine (e.g. histamine) acts as the amine donor, a γ-glutamylpolyamine (or γ-glutamylamine) residue is formed (Fig. 1b). It is also possible for a polyamine to act as an N,N-bis-(γ-L-glutamyl)polyamine bridge between two glutaminyl acceptor residues either on the same protein/polypeptide or between two proteins/polypeptides (Piacentini et al. 1988). If there is no primary amine present, water may act as the attacking nucleophile, resulting in the deamidation of glutaminyl residues to glutamyl residues (Fig. 1c). As previously reported, it is worthwhile noting that two of these reactions, in particular, the deamidation of peptides obtained from the digestion of the gliadin, a protein present in wheat, and the N^{ε}-(γ-L-glutamyl)-L-lysine (GGEL) isopeptide formation between these peptides and the "tissue" transglutaminase (tTG or TG2), have been recently shown to cause the formation of new antigenic epitopes which are responsible of immunological reactions during the Celiac Disease (CD), one of the most common human autoimmune diseases (Kim et al. 2004; Fleckenstein et al. 2004). The reactions catalyzed by TGs occur with little change in free energy and hence should theoretically be reversible. However, under physiological conditions the cross linking reactions catalyzed by TGs are usually irreversible. This irreversibility partly results from the metabolic removal of ammonia from the system and from thermodynamic considerations resulting from altered protein conformation. Some scientific reports suggest that TGs may be able to catalyze the hydrolysis of N^{ε}-(γ-L-glutamyl)-L-lysine cross-links (GGEL) isopeptide bonds in some soluble cross-linked proteins. Furthermore, it is likely that TGs can catalyze the exchange of polyamines onto proteins (Lorand and Conrad 1984). In some TGs other catalytic activities, such as the ability to

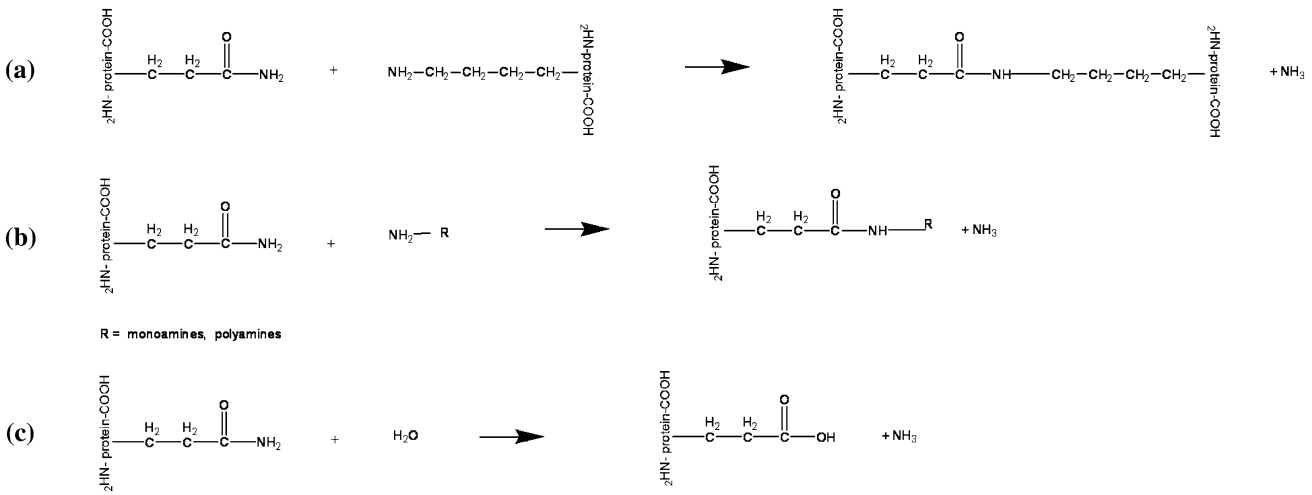

Fig. 1 Examples of transglutaminase-catalyzed reactions. **a** Acyl transfer between the γ-carboxamide group of a protein/polypeptide glutaminyl residue and the ε-amino group of a protein/polypeptide lysyl residue; **b** attachment of a polyamine to the γ-carboxamide group of a glutaminyl residue; **c** deamidation of the γ-carboxamide group of a protein/polypeptide glutaminyl residue

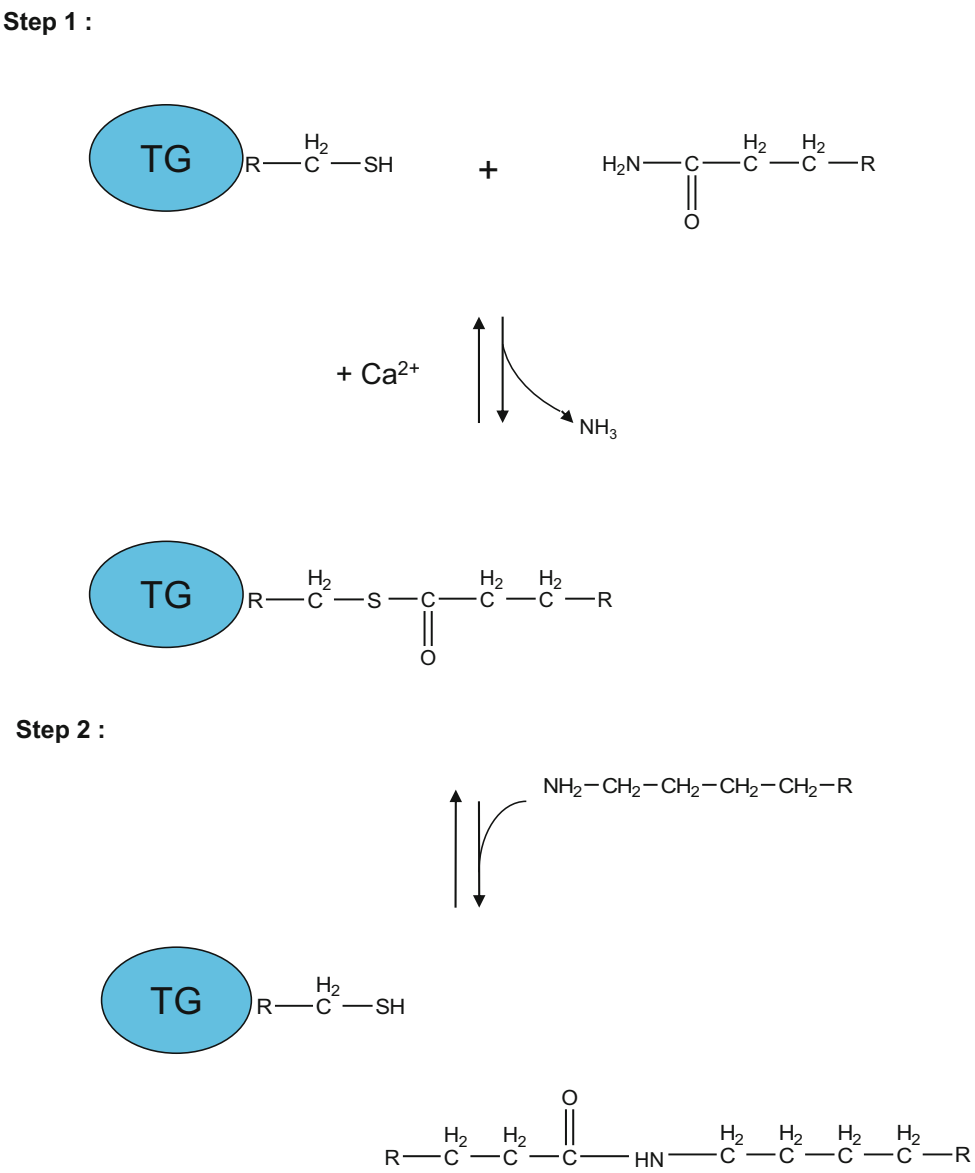

Fig. 2 Schematic representation of a two step transglutaminase reaction. *Step 1* In the presence of Ca^{2+}, the active-site cysteine residue reacts with the γ-carboxamide group of an incoming glutaminyl residue of a protein/peptide substrate to yield a thioacyl-enzyme intermediate and ammonia. *Step 2* The thioacyl-enzyme intermediate reacts with a nucleophilic primary amine substrate, resulting in the covalent attachment of the amine-containing donor to the substrate glutaminyl acceptor and regeneration of the cysteinyl residue at the active site. If the primary amine is donated by the ε-amino group of a lysyl residue in a protein/polypeptide, a N^{ε}-(γ-L-glutamyl)-L-lysine (GGEL) isopeptide bond is formed

hydrolyze GTP (or ATP) into GDP (or ADP) and inorganic phosphate, a protein disulfide isomerase activity, a serine/threonine kinase activity and an esterification activity, are often present (Achyuthan and Greenberg 1987; Lahav et al. 2003; Hasegawa et al. 2003). Therefore, several experimental evidences indicate that some TGs are multifunctional proteins with distinct and regulated enzymatic activities. In fact, under physiological conditions, the transamidating activity of TGs is latent (Smethurst and Griffin 1996), while other biochemical activities, more recently identified, could be present. For example, in some pathophysiological states, when the concentration of Ca^{2+} increases, the crosslinking activity of TGs may contribute to important biological processes. As previously described, one of the most intriguing properties of some TGs, such as TG2, is the ability to bind and hydrolyze GTP and furthermore, to bind to GTP and Ca^{2+}. GTP and Ca^{2+} regulate its enzymatic activities, including protein cross-linking, in a reciprocal manner: the binding of Ca^{2+} inhibits GTP-binding, while the GTP-binding inhibits the transglutaminase cross-linking activity of the TG2 (Achyuthan and Greenberg 1987). Interestingly, TG2 shows no sequence homology with heterotrimeric or low-molecular-weight G-proteins, but there is evidence that TG2 (TG2/Ghα) is involved in signal transduction, and, therefore, TG2/Ghα should also be classified as a large molecular weight G-protein. Other studies, along with ours, showed that TG2/Ghα can mediate the activation of phospholipase C (PLC) by the α_{1b}-adrenergic receptor (Nakaoka et al. 1994) and can modulate adenylyl cyclase activity (Gentile et al. 1997). TG2/Ghα can also mediate the activation of the δ1 isoform of PLC and of maxi-K

channels (Nanda et al. 2001). Interestingly, the signaling function of TG2/Ghα is preserved even with the mutagenic inactivation of its crosslinking activity by the mutation of the active site cysteine residue (Mian et al. 1995). Evidence of a pathophysiological role of the TGs in other biological functions, such as in cell signaling, in disulfide isomerase activity, etc., is still lacking to date.

Molecular biology of the transglutaminases

At least eight different TGs, distributed in the human body, have been identified (Table 1). Complex mechanisms regulating the gene expression of TGs, both at transcriptional and translational levels, determine a complex but precise distribution of these enzymes in a cell and/or a tissue (Thomazy and Fesus 1989). Such complex gene expression reflects the physiological roles that these enzymes play in both the intracellular and extracellular compartments. In the Nervous System, for example, several forms of TGs are simultaneously expressed (Kim et al. 1999). Moreover, several alternative splice variants of TGs, mostly in the 3′-end region, have been identified. Interestingly, some of them are differently expressed in human pathologies, such as Alzheimer's disease and others (Fig. 3) (Monsonego et al. 1997; Citron et al. 2001; Lai et al. 2007; Tee et al. 2010). Based on their ubiquitous expression and their biological roles, we may speculate that the absence of these enzymes would be lethal. However, this does not always seem to be the case, since, for example, null mutants of the TG2 are usually phenotypically normal at birth (De Laurenzi and Melino 2001). This result may be explained by the multiple expressions of other TGs genes that could be substituting the missing isoform.

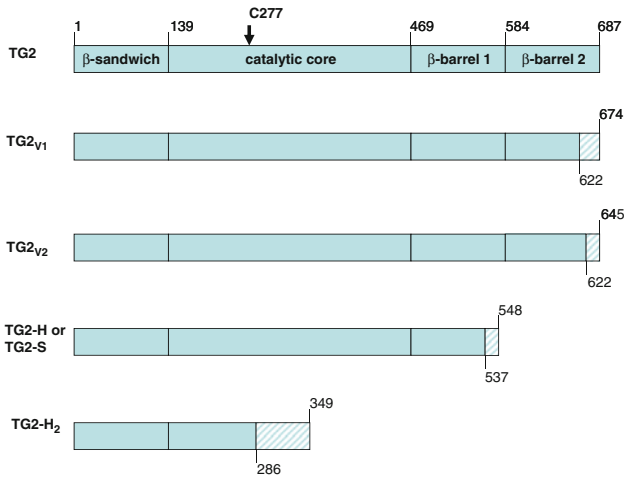

Fig. 3 Schematic diagram of TG2 and its different isoforms. Gray boxes represent TG2 protein sequences, and shaded boxes represent alternate aminoacid sequences due to changes in reading frames (see Refs. Citron et al. 2001; Lai et al. 2007; Monsonego et al. 1997)

Bioinformatic studies have shown that the primary structures of human TGs share some identities in only few regions, such as the active site and the calcium binding regions. However, high sequence conservation and, therefore, a high degree of preservation of residue secondary structure among TG2, TG3 and FXIIIa indicate that these TGs all share four-domain tertiary structures which could be similar to those of other TGs (Lorand and Graham 2003).

Transglutaminases and neurodegenerative diseases

Although several experimental data suggest that the transglutaminase activity could be involved in the pathogenesis of neurodegenerative diseases, up to now, however, conclusive experimental findings about the role of these enzymes in the development of these human diseases have not yet been obtained. Protein aggregates in affected brain regions are histopathological hallmarks of Alzheimer's disease and many other neurodegenerative diseases (Adams and Victor 1993). More than 20 years ago, Selkoe et al. (1982) suggested that transglutaminase activity might contribute to the formation of protein aggregates in AD brain. In support of this hypothesis, tau protein has been shown to be an excellent in vitro substrate of TGs (Dudek and Johnson 1993; Miller and Johnson 1995; Grierson et al. 2001) and GGEL cross-links have been found in the neurofibrillary tangles and paired helical filaments of AD brains (Appelt et al. 1996; Singer et al. 2002). In addition to these experimental findings, it has been shown that TGs and transglutaminase-catalyzed cross-links co-localize with pathological lesions in Alzheimer's disease brain (Appelt et al. 1996; Wilhelmus et al. 2009). Interestingly, a recent work showed the presence of *bis* γ-glutamyl putrescine in human CSF, which was increased in Huntington's disease (HD) CSF (Jeitner et al. 2008). These are important experimental data which demonstrate that protein/peptides cross-links and protein/peptides cross-linking by polyamines do indeed occur in brain, and that these transglutaminase-catalyzed reaction products are increased in AD and HD brains. More recently, transglutaminase activity has been shown to induce amyloid β-protein oligomerization and aggregation at physiologic levels in vitro (Dudek and Johnson 1994; Hartley et al. 2008). By these molecular mechanisms, TGs could contribute to AD symptoms and progression (Hartley et al. 2008). Moreover, there is evidence that TGs also contribute to the formation of proteinaceous deposits in Parkinson's disease (PD) (Citron et al. 2002; Junn et al. 2003) and in supranuclear palsy

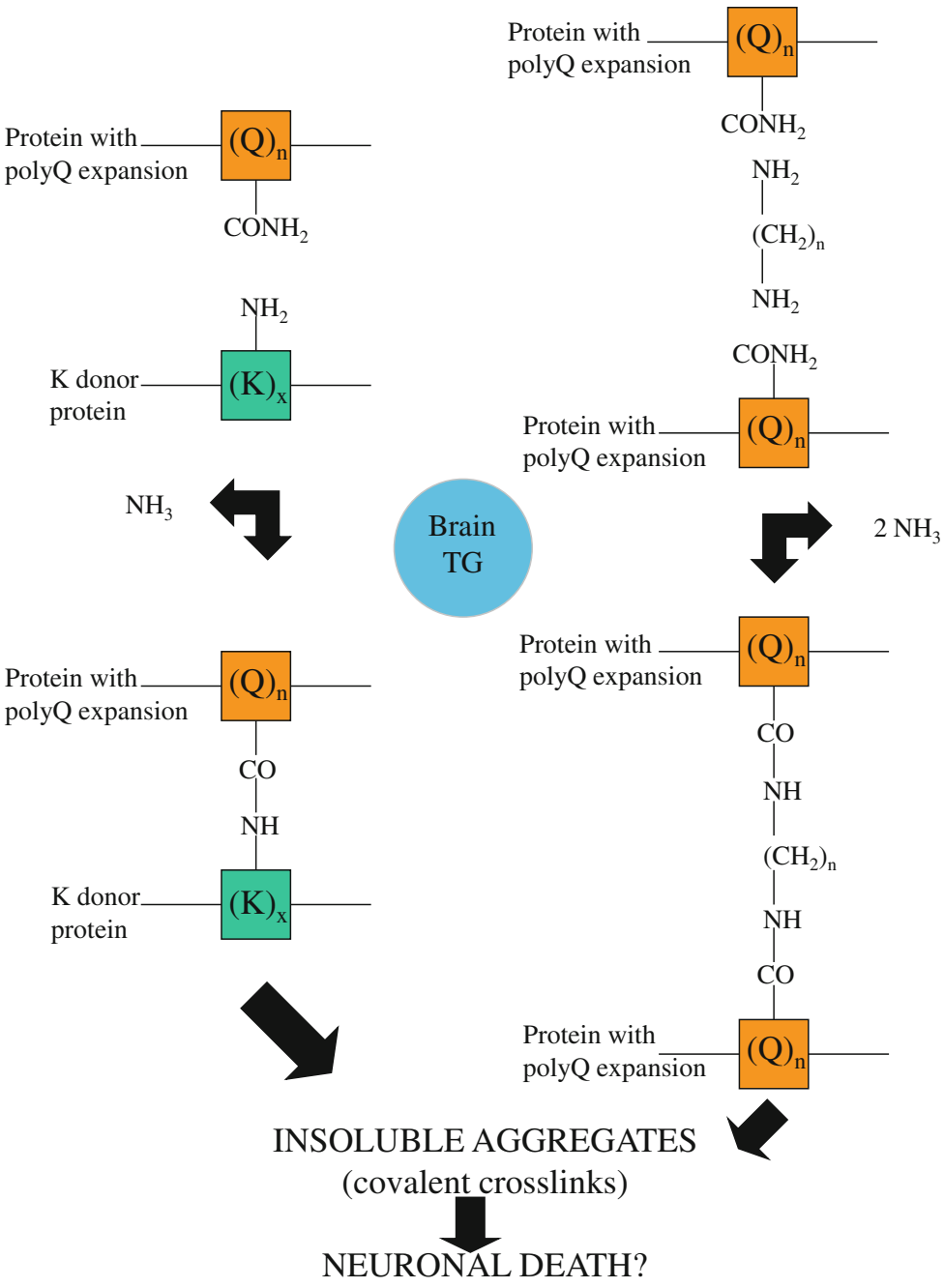

Fig. 4 Possible mechanisms responsible for protein aggregate formation catalyzed by transglutaminases

(Zemaitaitis et al. 2003). To support the role of the transglutaminase activity in the pathogenesis of neurodegenerative diseases, expanded polyglutamine domains, present in HD and other neurodegenerative diseases caused by a CAG expansion in the affected gene, have been reported to be substrates of TG2 in vitro (Gentile et al. 1998; Kahlem et al. 1998; Karpuj et al. 1999; Iuchi et al. 2003). Therefore, aberrant transglutaminase activity could contribute to the pathogenesis of neurodegenerative diseases, including Alzheimer's disease and other neurodegenerative diseases, by different molecular mechanisms, as described in Fig. 4. However, although all these studies suggest the possible involvement of the TGs in the formation of deposits of protein aggregates in neurodegenerative diseases, they do not indicate whether aberrant transglutaminase activity per se directly determines the disease's progression. In support of the hypothesis of a pathophysiological role for protein aggregates in neurodegenerative diseases, it is worth noting that the aggregate formation has been shown to inhibit the proteasome degradation of expanded polyglutamine

proteins (Verhoef et al. 2002) and that transglutaminase-catalyzed cross-linking of β-amyloid peptide may serve as trigger for rapid peptide aggregation (Schmid et al. 2011).

Transglutaminases as potential therapeutic targets of neurodegenerative diseases

Since up to now there have been no long-term effective treatments for human neurodegenerative diseases, then the possibility that selective TGs inhibitors may be of clinical benefit has been seriously considered. In this respect, some encouraging results have been obtained with TGs inhibitors in preliminary studies with different biological models of CAG-expansion diseases. For example, cystamine (Fig. 5) is a potent in vitro inhibitor of enzymes that require an unmodified cysteine at the active site (Griffith et al. 1977). Inasmuch as TGs contain a crucial active-site cysteine, cystamine has the potential to inhibit these enzymes by disulfide interchange reactions. A disulfide interchange reaction results in the formation of cysteamine and a cysteamine–cysteine mixed disulfide residue at the active site. Recent studies have shown that cystamine decreases the number of protein inclusions in transfected cells expressing the atrophin protein containing a pathological-length polyglutamine domain, responsible for the Dentato-Rubro-Pallido-Luysian Atrophy (DRPLA) (Igarashi et al. 1998). In other studies, cystamine administration to HD-transgenic mice resulted in an increase in life expectancy and amelioration of neurological symptoms (Karpuj et al. 2002; Dedeoglu et al. 2002). Neuronal inclusions were decreased in one of these studies (Dedeoglu et al. 2002). Although all these scientific reports seem to support the hypothesis of a direct role of the transglutaminase activity in the pathogenesis of the polyglutamine diseases, cystamine is also found to act in the HD-transgenic mice by mechanisms other than the inhibition of TGs, such as the inhibition of Caspases (Lesort et al. 2003), suggesting that this compound can have an additive effect in the therapy of HD. The pharmacodynamics and the pharmacokinetics of cystamine, therefore, should be carefully investigated in order to confirm the same effectiveness in patients with neurodegenerative diseases. Another critical problem in the use of TGs inhibitors in treating neurological diseases relates to the fact that, as previously reported, the human brain contains at least four TGs, including TG1, 2, 3 (Kim et al. 1999) and possibly TG6 (Hadjivassilou et al. 2008), and a strong non-selective inhibitor of TGs might also inhibit plasma Factor XIIIa, causing a bleeding disorder. Therefore, from a number of standpoints it would seem that a selective inhibitor, which discriminates between TGs, would be preferable to an indiscriminate TGs inhibitor. In fact, although most of the transglutaminase activity in mouse brain, at least as assessed by an assay that measures the incorporation of radioactive putrescine (amine donor) into N,N-dimethyl casein (amine acceptor), seems to be due to TG2 (Krasnikov et al. 2005), no conclusive data has been obtained by TG2 gene knock-out experiments about its involvement in the development of the symptoms in HD-transgenic models (Mastroberardino et al. 2002; McConoughey et al. 2010). However, a recent scientific report showed that cystamine reduces aggregate formation in a mouse model of oculopharyngeal muscular dystrophy (OMPD), in which also the TG2 knockdown is capable to suppress the aggregation and the toxicity of the mutant protein PABPN1 (Davies et al. 2010), suggesting this compound as a possible therapeutic for OMPD.

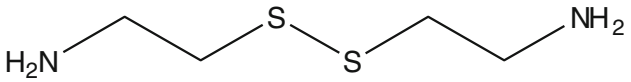

Fig. 5 Chemical structure of cystamine

Conclusions

Although many scientific reports have implicated aberrant transglutaminase activity in the pathogenesis of neurodegenerative diseases, still today we are looking for data which could definitely confirm the direct involvement of TGs in the pathogenetic mechanisms responsible for these diseases. The use of inhibitors of TGs could be then useful for therapeutical approaches. To minimize the possible side effects, however, selective inhibitors of the TGs should be required in the future. Progress in this area of research may be achieved also through pharmaco-genetic techniques.

Acknowledgments This work is supported by the Italian Education Department.

Conflict of interest The authors declare that they have no conflict of interest.

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