Therapeutic Prospects for the Prevention of Neurodegeneration in Huntington's Disease and the Polyglutamine Repeat Disorders

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Abstract: Huntington's disease (HD) is a dominantly inherited neurodegenerative disorder caused by expansion of a polyglutamine (polyQ) tract in the huntingtin protein, resulting in intracellular aggregate formation and neurodegeneration. Biochemical pathways leading from polyQ expansion to disease pathogenesis are largely unknown. Recent approaches using genetic models systems have begun to uncover nuclear and cytoplasmic pathologies that represent potential targets for therapeutic intervention.

Key Words: Axonal transport, neurodegeneration, vesicle trafficking, protein aggregation, polyQ, huntington's disease.

INTRODUCTION

Huntington's disease is an autosomal-dominant neurodegenerative disorder characterized by motor dysfunction, psychiatric symptoms, cognitive decline and shortened lifespan [1, 2]. HD belongs to a family of at least nine inherited neurodegenerative diseases caused by an expansion of CAG triplet repeat within the coding region of otherwise-unrelated genes, resulting in an elongated polyQ stretch in the responsible proteins. The polyQ disease family includes spinocerebellar ataxia 1 (SCA1), SCA2, SCA3/MJD, SCA6, SCA7, SCA17, spinal bulbar muscular atrophy (SBMA), and dentatorubral pallidoluysian atrophy (DRPLA) (Table **1**). In each polyQ disease, longer CAG repeat lengths are correlated with increased disease severity and earlier age of onset. The huntingtin (Htt) protein, affected in HD, normally has a stretch of 6-35 glutamines in the amino-terminal portion of the protein in normal individuals, whereas an expansion in the range of 36-121 is observed in patients.

The expansion of a polyQ tract within Htt generates an abnormal conformation that leads to globular and protofibrillar intermediates [3, 4] that assemble into SDS-resistant aggregates rich in β-sheets [5]. Abnormal amyloid structures are found in a variety of late-onset neurodegenerative diseases, including Alzheimer's, Parkinson's, and prion diseases [2]. PolyQ-containing intracellular aggregates are the prominent pathological hallmark in brain samples of patients with polyQ disease, as well as in model organisms expressing polyQ-containing proteins. Mice expressing an expanded polyQ portion show insoluble polyQ-containing aggregates as well as neurodegeneration [6]. Transgenic HD mice expressing human Htt exon 1 (81 a.a.) with a 150 polyQ stretch also exhibit an HD-like phenotype, indicating the polyQ tract alone is sufficient to cause neurodegeneration [7]. Htt exon 1 proteins with expanded polyQ tracts form aggregates autonomously *in vitro* in a polyQ-length, polyQ-concentration, and time-dependent manner [8]. Aggregates *in vitro* can have a fibril amyloid-like structure with extensive β-pleated sheets that can be stained by amyloid-binding dyes [5, 9] (for review [2]).

The ability of the polyQ-containing protein to cause toxicity is closely linked with its ability to form aggregates, supporting the theory that polyQ aggregation is intimately associated with the severity of polyQ diseases. For example, blockage of mutant Htt exon I expression in symptomatic transgenic mice results in the disappearance of aggregates and the amelioration of motor dysfunction [10]. In addition, the polyQ threshold for *in vitro* aggregation and the threshold for disease manifestation are strikingly similar [8, 11]. Longer polyQ tracts undergo rapid aggregate formation, correlating with early onset pathology [8, 12]. In support of a pathological role for aggregate formation, various manipulations that suppress aggregation, including overexpressing chaperone proteins, small-anti-aggregation peptides, intracellular anti-aggregation antibodies, or anti-aggregation drugs often suppress polyQ toxicity. However, the presence of aggregates does not consistently correlate with cell death. Real-time analysis of fluorescent aggregate formation suggests increased aggregates correlate with improved survival [13]. Therefore, whether aggregates are toxic, beneficial or simply a byproduct remains controversial and may depend on the subcellular localization of the developing aggregate. Htt aggregates that form in small diameter neurites may block axonal transport and contribute to toxicity [14], while aggregates present in the cell body may serve to sequester normally toxic monomeric or intermediate forms of polyQ proteins [15, 16].

MODELING HD IN GENETICALLY TACTABLE ORGANISMS

To characterize the pathogenic mechanisms underlying HD and other polyQ diseases, model systems expressing polyQ-containing proteins have been developed. Research performed with these models include overexpression studies

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Table 1. Summary of the Proteins Affected in the Polyglutamine Diseases. The Number of Polymorphic Repeats Found in Normal and Diseased Individuals is Indicated in the Right Column

Disease	Protein	Mol. Weight (kDa)	Number of CAG repeats	
			Normal	Disease
HD	huntingtin	348	6-34	36-121
SMBA	androgen receptor	99	7-34	38-68
DRPLA	atrophin-1	124	5-35	49-85
SCA1	ataxin-1	87	6-39	41-82
SCA2	ataxin-2	90	14-31	35-59
SCA3/MJD	ataxin-3/MJD1	42	13-44	65-84
SCA6	calcium channel	large	4-16	21-27
SCA7	ataxin-7	95	7-17	48-130
SCA17	TATA-binding protein	41	25-42	47-63

in mice, nematodes (*Caenorhabditis elegans*), flies (*Drosophila melanogaster*), yeast and cell culture. In all model systems examined so far, the expression of polyQ-containing protein causes aggregate formation and neuronal toxicity.

Of these systems, *Drosophila* transgenic models have proven to be excellent organisms to characterize the pathology of HD and other polyQ diseases [17-19]. The *Drosophila* model replicates most features of polyQ diseases including late onset, progressive nuerodegeneration, reduced life span, and the accumulation of aggregates where polyQ-containing proteins are expressed. When polyQ-containing proteins are expressed in the retina under regulation of an eye-specific promoter, progressive neurodegeneration of photoreceptor neurons occurs [17, 18, 20]. When polyQ proteins are expressed in all neurons, shortened life span and abnormal motor behavior are observed (for review, see [19]). The short life cycle and ease of genetic analysis in *Drosophila* allow identification and characterization of pathogenic mechanisms of polyQ diseases in a more timely fashion than most mammalian models. As such, large-scale genetic screens in *Drosophila* polyQ models have identified many genes and molecular pathways that are involved in polyQ disease pathogenesis [20-22].

PATHOLOGICAL MECHANISM OF POLYQ DISEASES

Although the misfolding of polyQ in mutant proteins appears to be an important step in pathogenesis, the resulting pathogenic events are not well understood and likely encompass multiple cellular processes. Several pathogenic mechanisms have been proposed, and it appears that the expression of polyQ-containing proteins can alter distinct cellular functions in both the nucleus and cytoplasm.

(1) Pathological Functions of Mutant Htt and polyQ-containing Proteins in the Nucleus

The expression of mutant Htt exon 1, which causes an HD–like phenotype in mice, results in the formation of aggregates in the nucleus [7]. In addition, the presence of nuclear aggregates derived from a cleaved Htt fragment have been reported in HD patients [23], and nuclear localization of mutant Htt increases toxicity [24]. Based on these findings, pathogenic mechanisms of polyQ diseases involving nuclear pathology have been proposed. One potential causation mechanism is the ability of polyQ-containing proteins to impair gene transcription by sequestration of transcription factors, which often contain small polyQ tracts within their sequence. Transcriptional factors and cofactors, such as TATA binding protein (TBP), CREB binding protein (CBP), TATII130, Sp1, and p53 have been shown to be sequestered in nuclear polyQ-containing aggregates (for review [25]). It has also been demonstrated that mutant Htt exon 1 inhibits the acetyltransferase activity of transcriptional co-activators, causing additional transcriptional dysregulation [26]. Mutant Htt exon 1 binds the acetyltransferase domains of CBP and P/CAF, and a recombinant mutant Htt inhibits the acetylating activity of CBP, p300 and P/CAF *in vitro* [26]. In cultured cells expressing mutant Htt exon 1, acetylated levels of histones H3 and H4 are reduced [26]. In support of a nuclear pathology, mutations of Sin3A and Rpd3, a catalytic histone deacetyl transferease (HDAC) protein and its co-regulator, were isolated in genetic screens for enhancers of neurodegeneration in *Drosophila* expressing pathogenic SCA1 [21]. Finally, an interaction of p53 with mutant Htt has recently been shown to increase the stability and transcriptional activity of p53 in neuronal cells, resulting in mitochondrial membrane depolarization and downstream effects on neuronal function [27].

(2) Pathogenic Effects of Mutant Htt and polyQ-containing Proteins in the Cytoplasm

Given the observation that small polyQ fragments localize to the nucleus, early studies in HD pathogenesis focused almost entirely on pathogenic roles of mutant Htt in the nucleus. However, both normal and pathogenic full-length Htt largely localize to the cytoplasm of neurons [28], with nu-

clear localization restricted to small Htt fragments that have undergone intracellular cleavage [23] (Fig. (**1**)). The normal Htt protein localizes to several subcellular compartments, including the cell body, neurites and synapses [29, 30]. Htt function is essential for mouse embryogenesis and required throughout development and in adulthood [31]. Although the *in vivo* function of Htt is not well known, there is mounting evidence that the normal cytoplasmic localization and function of Htt can be disrupted by polyQ expansion.

In support of cytoplasmic pathology, transgenic mice expressing full-length mutant Htt show early electrophysiological abnormalities prior to the formation of nuclear aggregates [32]. In addition, the expression of mutant MJD protein with a nuclear export signal can still induce neurodegeneration in *Drosophila* [15]. Expression of a 548 a.a. fragment of human Htt with an expanded polyQ in *Drosophila* results in aggregates that are found exclusively in the cytoplasm, generating HD-like phenotypes [14]. These observations have made it clear that mutant Htt exhibits pathogenic functions not only in nucleus, but also in the cytoplasm.

One of the more recently described pathogenic mechanisms of polyQ-containing proteins in the cytoplasm involves defective axonal transport [14-16]. When recombinant polyQ-containing proteins, including mutant Htt and SMBA, are perfused into isolated squid axoplasm, they robustly inhibit fast axonal transport in both anterograde and retrograde directions [16]. This inhibition occurs in the absence of microscopically visible aggregates, suggesting that soluble forms of polyQ-containing proteins are toxic for axonal transport. In addition, polyQ-containing aggregates have been shown to physically block axonal transport of vesicles [14]. When mutant Htt is expressed in *Drosophila* neurons, Htt aggregates form at synapses and along axons, causing the accumulation of synaptic vesicle proteins such as synaptotagmin at sites of axonal aggregation. Axonal transport defects may also result from depletion of important components of the transport machinery by polyQ-containing proteins. Expression of polyQ-containing proteins in *Drosophila* neurons reduces the expression of multiple trafficking components, including dynein heavy chain, dynein light chain, $p150^{Glued}$, kinesin heavy chain and kinesin light chain [15]. Together, these studies have emphasized the importance of cytoplasmic pathology in the polyQ diseases, with inhibition of axonal transport at several stages and by multiple mechanisms.

In the case of HD, an additional pathogenic mechanism may involve loss of the normal function of Htt, in addition to a toxic gain of function from polyQ expansion. Because a conditional deletion of Htt in adult mouse brain causes neurodegeneration, the loss of normal Htt function might be predicted to contribute to HD pathogenesis (for review [31]). Htt has been shown to interact with various proteins, including several involved in transcription, signaling, endocytosis, and vesicle trafficking (see reviews [31, 33]). Among them, Htt interaction with huntingtin-associated protein 1 (HAP1), a component of the dynactin complex, has suggested a role for Htt function in vesicular transport. Indeed, *Drosophila* expressing transgenic RNAi against endogenous Htt show defective axonal transport [15]. Moreover, normal Htt has been shown to enhance, and mutant Htt function to reduce, vesicular transport of the neurotrophin BDNF *via* direct interactions between Htt and HAP1 [34]. Therefore, defects of axonal transport in HD models may be caused by toxic effects of polyQ in the mutant Htt and by a loss of normal Htt function.

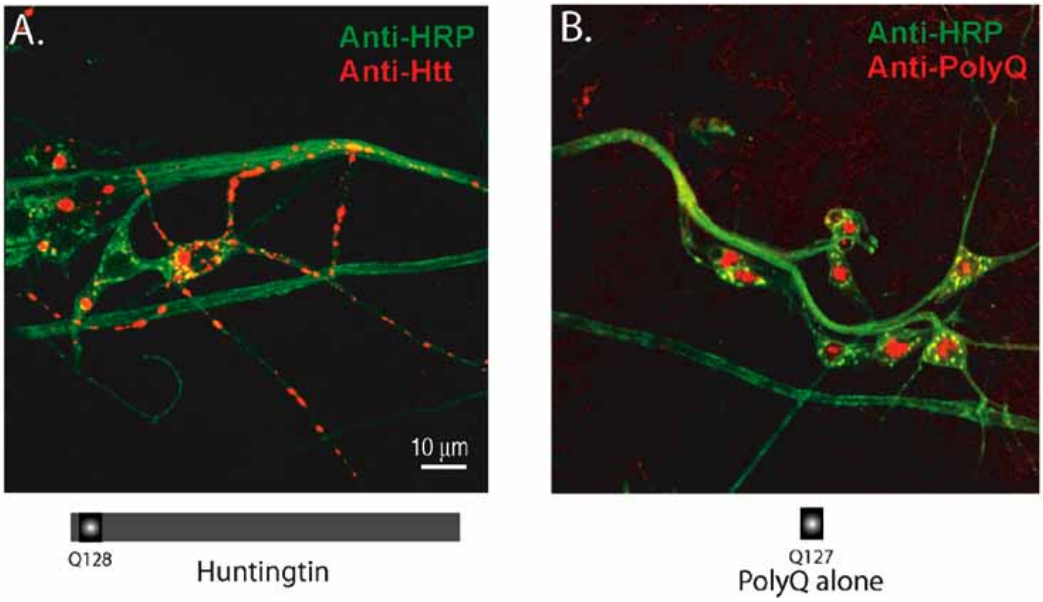

Fig. (1). Localization of overexpressed polyQ proteins in *Drosophila* demonstrate that protein context is important for subcellular distribution of the aggregated protein. Immunolocalization of aggregates in 3rd instar larvae expressing Htt-Q128 (A) or Q127 alone (B) in PNS neurons driven by the neuronal elav-GAL4 driver are shown. Htt-Q128 aggregates are exclusive to the cytoplasm, while expression of the polyQ tract alone leads to aggregate formation in the nucleus. In mammals, smaller fragments of Htt that are cleaved have also been observed in the nucleus.

An additional pathogenic mechanism involving cytoplasmic dysfunction is suggested by the observation that mutant Htt inhibits mitochondrial trafficking [35]. Alterations in mitochondrial levels at synapses may lead to a variety of synaptic defects secondary to altered metabolism and oxidative damage. It has been recently shown that mutant Htt may cause abnormal mitochondrial function as well, providing additional avenues for metabolic defects in HD [36]. In summary, recent experimental data has provided strong evidence for a role for Htt in axonal transport, and a dysregulation of axonal trafficking in HD models.

(3) Impairment of Cellular Protein Quality Control Pathways

PolyQ-mediated aggregates have been shown to contain ubiquitin and proteasome components, as well as components such as transcription factors and molecular chaperones [37]. Treatment with proteasome inhibitors enhances polyQ-mediated aggregate formation in model systems [38]**.** Transgenic mice expressing a dominant-negative form of ubiquitin-proteasome system (UPS) components such as Ubc/Cdc34 enhance polyQ-mediated toxicity. In addition, loss-of-function mutations in ubiquitin and two ubiquitin conjugating enzymes (dUbcD1 and dUbc-E2H) enhance SCA1 toxicity in *Drosophila* [21]. Besides UPS, the autophagy-lysosome pathway appears to protect neurons from polyQ toxicity [39]. These observations have suggested that cellular degradation systems play an important role in the clearance of toxic polyQ proteins.

Disruption of the normal cellular degradation machinery can also contribute to polyQ toxicity. Proteasome activity is reduced in cells expressing mutant ataxin-1 or Htt exon 1, with the proteasome sequestered in polyQ-containing aggregates [40-42]. *In vitro* analysis has shown that proteasomes degrade polyQ-containing proteins partially and slowly [42]. These results indicate polyQ expansion may prevent degradation of other substrates *via* its prolonged occupation of the proteasome, leading to the accumulation of aberrant proteins within neurons.

As mentioned above, conformational changes of polyQ in the diseased proteins appear to be a necessary step to pathogenesis for all of the polyQ diseases. Members of the cellular folding machinery, such as Hsp70 and Hsp40, function to prevent misfolding of various proteins. Consistently, overexpression of molecular chaperones, including Hsp70, Hsp40, and Hsp104, suppress toxicity caused by the expression of polyQ-containing proteins in various model systems [37, 43-45]. Recently, it was shown that unrelated temperature-sensitive nematode mutants become more susceptible to phenotypes at lower restrictive temperatures when polyQ-proteins are co-expressed, suggesting that polyQ expression can cause destabilization of partially misfolded proteins [46].

(4) Activation of the Cell Death Pathway

Expression of a dominant-negative caspase-1 mutant has been demonstrated to reduce aggregate formation of mutant Htt exon 1 and subsequent disease progression in HD transgenic mice [47]. The accumulation of caspase-8 into insoluble aggregates is required to induce cell death in primary rat neurons, while prevention of caspase-8 recruitment into aggregates blocks polyQ-mediated cell death [48]. In addition, treatment with polycaspase inhibitors, such as zVAD.fmk, inhibits polyQ-mediated ATP depletion [4]. These findings indicate that caspase-mediated apoptosis pathways may play an important role in HD pathogenesis. Mutations in *Drosophila dark*, a homolog of mammalian caspase activator Apaf-1, inhibit progression of polyQ-mediated neurodegeneration and aggregation [49]. Moreover, mutations of *ter94*, a homolog of VCP/p97, a member of AAA superfamily, were isolated in genetic screens for loci that prevent neurodegeration in polyQ expressing *Drosophila* [22]. In *C. elegans*, the Apaf-1 homolog CED4 binds to MAC-1, a VCP/p97 family member, suggesting that these proteins function in a complex to trigger apoptosis in polyQ-expressing cells. In the case of *dark* mutants, caspase-3-like activity is suppressed, [49], consistent with an essential role for caspase-mediated apoptotic pathways in polyQ diseases.

INHIBITORS OF POLYQ DISEASE PATHOLOGY

Based on the proposed pathogenic mechanisms so far, a range of small molecules or compounds have been screened for their ability to prevent or retard polyQ disease progression. In particular, small molecules with effects on aggregation, protein folding and degradation, transcription, and cell death are prime targets for candidate drugs that may alter at least one aspect of polyQ pathology.

(a) Compounds that Prevent Misfolding or Aggregate Formation of polyQ

Benzoquinone ansamycins such as geldanamycin are specific inhibitors of Hsp90 [50] (Fig. (**2**)). Hsp90 binds and represses heat shock factor 1 (HSF1), a transcription factor for various stress inducible proteins. Geldanamycin treatment triggers the release of HSF1 from Hsp90 and induces HSF-1 mediated expression of several molecular chaperones, including Hsp40 and Hsp70. When geldanamycin is added to cultured cells expressing mutant Htt exon 1, a reduction in Htt aggregation occurs [51], suggesting Hsp90 might serve as a relevant drug target for polyQ pathology. Besides geldanamycin, radicicol, another Hsp90 inhibitor, was shown to delay earlier stages of Htt exon 1 aggregate formation in organotypic slice cultures [52].

In addition to Hsp90 as an indirect target, several groups have screened chemical compounds that can directly alter polyQ aggregation. Wanker and collegues assessed the aggregation of Htt exon 1 with expanded polyQ *in vitro* by testing known inhibitors of amyloid-like proteins [53]. Congo red and thioflavine S, which are histological dye compounds used to detect amyloid deposits, were found to be effective at preventing aggregation (Fig. (**2**)). Moreover, chrysamine G and direct fast yellow have also been shown to be effective in disrupting aggregation. Congo-red-treated HD mice show improved survival and preserved motor function [4], suggesting a potential efficacious role *in vivo*. Although the direct target for Congo red action is unknown, the molecule binds to β-sheet structures and may slow down aggregation by interfering with nucleus formation and subsequent growth of fibrils, an essential step in the process of aggregate formation. Wanker and colleagues further developed an automated filter retardation assay to assess aggregation of mutant Htt exon I *in vitro* and screened a chemical library of 184,000

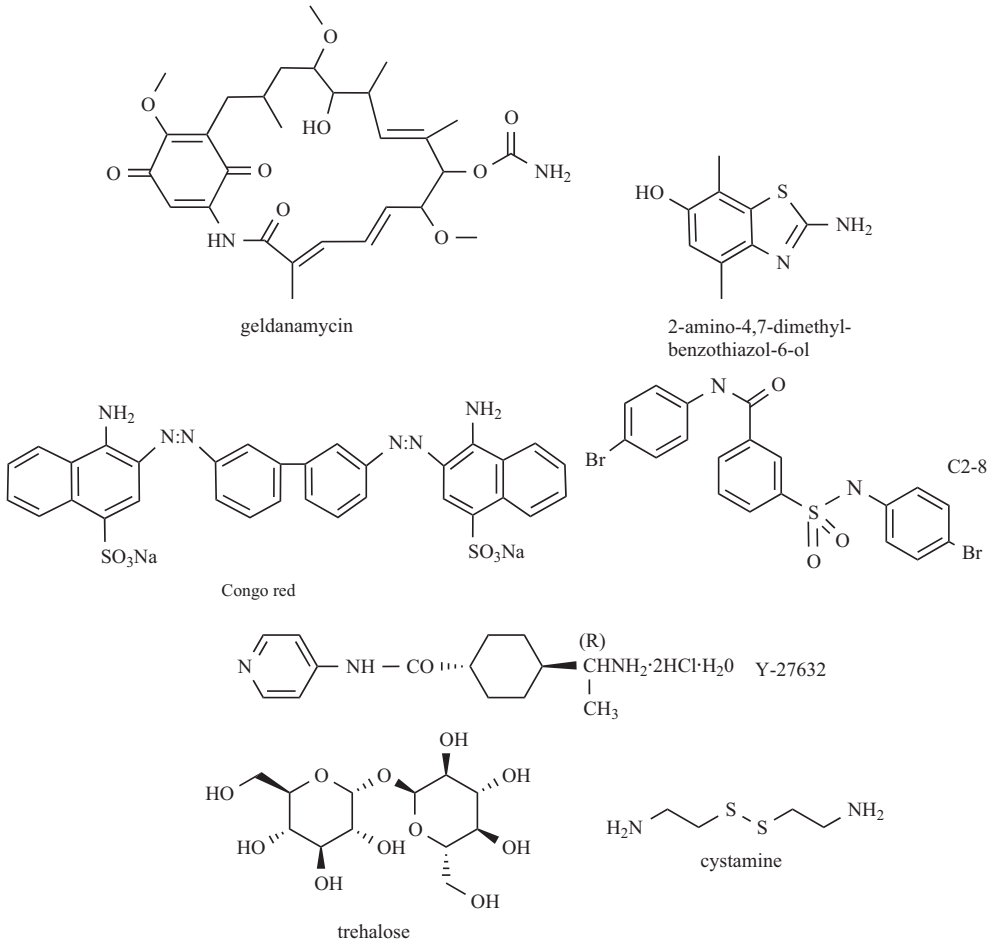

Fig. (2). Structures of selected polyQ pathogensis inhibitors. Structures of geldanamycin, 2-amino-4,7-dimethyl-benzothiazol-6-0l, Congo red, C2-8 (N-(4-bromophenyl)-3-{[(4-bromophenyl)amino]sulfonyl}benzamide), Y-27632 ((R)-(+)-trans-4-(1-aminoethyl)-N-(4-pyridyl) cyclohexanecarboxamide dihydrochloride monohydrate), trehalose, and cystamine are shown.

compounds. They identified ~300 compounds that reduced aggregation, of which 25 were benzothiazole derivatives [54]. In particular, 2-amino-4,7-dimethyl-benzothiazol-6-ol not only reduced the formation of aggregates in cultured cells expressing a mutant Htt exon 1, but was also non-toxic to cells (Fig. (**2**)). The discovery of benzothiazole derivatives as anti-aggregation molecules is consistent with the observation that oral administration of riluzole (2-amino-6-trifluoromethozybenzothiazole), a derivative benzothiazole originally identified as a potent antagonist of glutamate release, ameliorated chorea of HD patients in clinical tests [55]. However, riluzole did not improve other motor, cognitive, and behavioral aspects of HD [56].

Using a different FRET-based screening methodology, a compound originally identified as an inhibitor of Rho activated serine/threonine kinase (Y-27632, (R)-(+)-trans-4-(1-aminoethyl)-N-(4-pyridyl)cyclohexanecarboxamide dihydrochloride monohydrate) was found to reduce aggregation of polyQ-containing proteins in mammalian cells [57, 58] (Fig. (**2**)). This inhibitor was effective *in vivo* in a *Drosophila* HD model, suppressing neurodegeneration of photoreceptor neurons compared with non-treated flies. The direct target of Y-27632 that blocks polyQ aggregation has not been identified. However, analysis of rho-GTPase family mutants suggests that the Y-27632 target(s) indirectly modulate polyQ aggregation by controlling cytoskeleton function mediated by the rho-GTPase family.

About 16,000 compounds were tested in screens for reduced cell toxicity and polyQ aggregation in yeast [59]. Secondary screening using a mammalian cell culture assay to test polyQ aggregation identified four chemical compounds ((C1, C2, C3, C4) with unique chemical scaffolds. Although all four compounds did not inhibit aggregation of polyQ-containing proteins in a cell-free system, compound C2 -8 (N-(4-bromophenyl)-3-{[(4-bromophenyl)amino]sulfonyl} benzamide) a derivative of C2, did (Fig. (**2**)). Moreover, C2-8 had an inhibitory effect on polyQ-mediated aggregation in hippocampal slice cultures expressing mutant Htt exon I, and relieved neurodegeneration *in vivo* in a *Drosophila* HD model.

Several dissaccharides have also been shown to prevent aggregation of polyQ-containing proteins by stabilizing partially unfolded polyQ proteins *in vitro* [60]. Of these disac-

charides, trehalose is the most effective in preventing aggregation (Fig. (**2**)). Trehalose is produced in a variety of organisms such as yeasts and insects and is often found in human food. When trehalose was orally administered to transgenic HD mice, a decrease of aggregate formation of mutant Htt protein, improvement of motor activity and extended lifespan were observed. Further studies of the potential for disaccharide-mediated aggregation inhibition should be informative given the relatively benign *in vivo* nature of the primary compounds.

Cystamine is a putative inhibitor of transglutaminase, which catalyzes a calcium-dependent covalent linkage of glutamines to lysines. Cystamine also inhibits caspase activity and increases glutathione production. Cystamine increases the life span and improves motor function in HD transgenic mouse models [61, 62].

(b) Compounds that Prevent Transcriptional Dysregulation

As mentioned previously, expanded polyQ stretches can inhibit acetylation of transcription cofactors, contributing to cellular toxicity. SAHA (suberoylanilide hydroxamic acid) and butyrate are known inhibitors of HDAC, which remove acetyl groups from histones and other proteins. The administration of SAHA and butyrate has been shown to be effective in HD flies [26]. These observations suggest further analysis of target molecules that alter transcriptional activity might have some efficacy in polyQ disorders.

(c) Compounds that Disrupt Cleavage or Up-regulate Protein Degradation Systems

Htt contains several well-characterized caspase consensus cleavage sites and calpain cleavage sites (for review [63]). Mutant Htt has been shown to be more susceptible to caspase-and calpain-mediated cleavage, which generates toxic N-terminal Htt fragments [23]**.** Proteolytic processing may facilitate HD pathogenesis, as disruption of caspase and calpain activity can reduce Htt toxicity and delay pathogenesis [47]. As such, candidate molecules that disrupt caspase- or calpain-dependent cleavage of Htt might be effective in altering HD pathology.

In addition to direct effects on Htt cleavage, target molecules that can alter general cellular degradation pathways have been found to be efficacious in HD. Rapamycin (sirolimus) is a specific inhibitor of mTOR, a kinase that inhibits autophagy, and can induce autophagy following application to cells (Fig. (**3**)). Rapamycin has been shown to protect against neurodegeneration in *Drosophila* HD models [64], suggesting a potential *in vivo* drug candidate. Its water-soluble analog, CCI-779 (temsirolimus), enhances clearance of polyQ aggregates in cultured cells [64]. CCI-779 also improves motor tasks and tremors in HD mice, suggesting efficacy in mammals as well. However, rapamycin is effective only when it is administered in early stages of aggregate formation, and does not show efficacy when given later in disease progression.

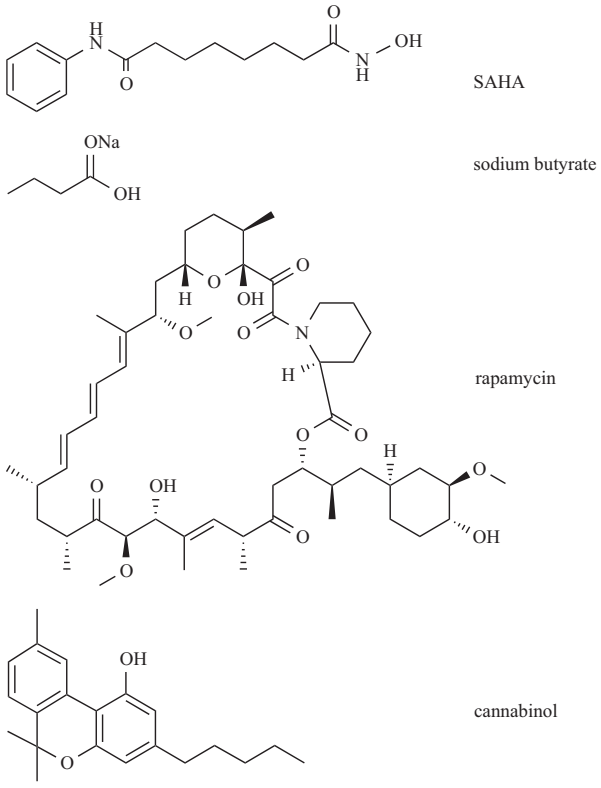

Fig. (3). Structures of inhibitors of polyQ pathology. Structures of SAHA, sodium bytyrate, rapamycin (sirolimus), and cannabinol are shown.

(d) Compounds that Prevent Cell Death

Inhibitors of neuronal cell death would seem an obvious target for candidate therapies of polyQ-mediated neurodegeneration. Blocking apoptosis has been shown to be neuroprotective in *Drosophila* retinal degeneration mutants, suggesting a therapeutic benefit of altering late-stage apoptotic processes [65]**.** Compound libraries have been screened for their ability to prevent cell death following expression of a mutant Htt exon I [66]. Several effective compounds were identified, including caspase inhibitors and cannabinoids (Fig. (**3**)). The loss of cannabinoid receptors were previously reported in the HD patients [67]. The mechanism for cannabinoid protection is unknown, but cannabinoids were reported to have an antioxidant effect [67].

In addition to direct inhibitors of the apoptotic machinery, candidate drugs have also been identified that alter other cytoplasmic pathologies that lead to cell death. Creatine, dichloroacetate and co-enzyme Q target metabolic and mitochondrial defects observed in HD and are effective in altering pathogenesis of transgenic HD mice [68-70]. In particular, creatine and co-enzyme Q are currently in clinical trials in humans. Other pathologies, including HD excitotoxicity, can be targeted with NMDA receptor antagonists and metabotropic glutamate receptor agonists [71].

Interestingly, compounds identified in anti-apoptotic screening did not inhibit polyQ aggregation, raising the possibility that combinatorial therapy targeting multiple cellular pathogenic mechanisms may be beneficial. Combinations of at least two drugs that target different mechanisms have been tested based on the idea that polyQ expression affects multiple cellular activities [72]. Indeed, several drug combinations, such as SAHA and cystamine, SAHA and Congo red, or cystamine and Congo red, were shown to have enhanced effectiveness in *Drosophila* HD models. Further studies using such combinatorial therapy are likely to yield valuable insights into synergistic effects of drug therapy in HD and other polyQ disease models.

CONCLUSION

Based on recent studies into polyQ pathogenesis, multiple cellular mechanisms involving both nuclear and cytosolic biology are disrupted by polyQ proteins. In this review, we have discussed several pathogenic mechanisms and test compounds that have been characterized to have some therapeutic value in model systems of polyQ disease. At present, no effective treatments are yet available for humans with HD and other polyQ diseases. Transitional studies with currently identified neuroprotective compounds, as well as additional studies into the pathogenic mechanisms of polyQ diseases will be required to expand therapeutic treatment into humans.

ABBREVIATIONS

AAA = ATPases associated with diverse cellular activities

BDNF = Brain derived neurotrophic factor

CBP = CREB (cAMP responsive element binding protein) binding protein

DRPLA = Dentatorubral pallidoluysian atrophy

FRET = Fluorescence resonance energy transfer

HD = Huntington's disease

HDAC = Histone deacetyl transferase

HSF1 = Heat shock factor 1

Hsp = Heat shock protein

Htt = Huntingtin

MJD = Machado Joseph Disease

NMDA = *N*-methyl-D-aspartate

P/CAF = p300/CBP associated factor

PolyQ = Polyglutamine

SAHA = Suberoylanilide hydroxamic acid

SCA = Spinocerebellar ataxia

SMBA = Spinal bulbar muscular atrophy

Ubc = Ubiquitin conjugating enzyme

UPS = Ubiquitin proteasome system

VCP = Valosine containing protein

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