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Neuroprotective and metabolic effects of resveratrol: Therapeutic implications for Huntington's disease and other neurodegenerative disorders

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Abstract

Resveratrol is a naturally occurring polyphenolic compound associated with beneficial effects on aging, metabolic disorders, inflammation and cancer in animal models and resveratrol is currently being tested in numerous clinical trials. Resveratrol may exert these effects by targeting several key metabolic sensor/effector proteins, such as AMPK, SIRT1, and PGC-1 α . Resveratrol has also received considerable attention recently for its potential neuroprotective effects in neurodegenerative disorders where AMPK, SIRT1 or PGC-1 α may represent promising therapeutic targets. A recent study published in *Experimental Neurology* (Ho et al., 2010) examined the therapeutic potential of a micronised proprietary resveratrol formulation, SRT501 in the N171–82Q transgenic mouse model of Huntington's disease (HD). HD is a progressive and devastating genetic neurodegenerative disorder that is associated with downregulation of PGC-1 α activity. The Ho et al. study found that SRT501 treatment did not lead to significant improvement in weight loss, motor performance, survival and striatal atrophy. However, other studies have reported neuroprotective effects of resveratrol and a distantly related polyphenol, fisetin, in HD models. HD has been associated with diabetes mellitus. Interestingly, evidence from the Ho et al. study suggests a resveratrol formulation induced beneficial anti-diabetic effect in N171–82Q mice. This commentary summarizes the pertinent outcomes from the Ho et al. study and discusses the further prospects of resveratrol and other polyphenols, including novel grape-derived polyphenols, in the treatment of HD and other neurodegenerative disorders.

Introduction

A large body of literature has shown that the naturally occurring polyphenol resveratrol (*trans*-3,4',5-trihydroxystilbene) exerts beneficial effects on the age-related metabolic deterioration that is characteristic of certain metabolic diseases, such as type 2 diabetes and obesity (Baur et al., 2006; Lagouge et al., 2006). Resveratrol mimics calorie restriction by extending the lifespan of several small organisms (Baur and Sinclair, 2006; Greer and

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Brunet, 2009), and by delaying specific age-related phenotypes in mice (Pearson et al., 2008).

The direct molecular target of resveratrol *in vitro* and *in vivo* is unknown. The compound has been suggested to modulate cellular processes by activating key metabolic sensor/effector proteins, including AMP-activated protein kinase (AMPK), sirtuin 1 (SIRT1), and peroxisome proliferator-activated receptor γ co-activator-1 α (PGC-1 α) (Canto and Auwerx, 2009; Um et al., 2009; Vingtdoux et al., 2010). It was initially proposed that resveratrol binds *in vitro* to SIRT1 and activates the deacetylase activity of this enzyme (Howitz et al., 2003). Recent studies have challenged these data by showing that the reported direct interaction between resveratrol and SIRT1 *in vitro* was likely an artifactual observation, implying that resveratrol might act *in vivo* by targeting other proteins (Borra et al., 2005; Pacholec et al., 2010). Nevertheless, SIRT1 appears to be required for resveratrol metabolic functions *in vivo* by contributing to an energy sensing network involving AMPK and PGC-1 α (Canto and Auwerx, 2009; Ruderman et al., 2010).

Resveratrol has been shown to have beneficial effects in *in vitro* models of epilepsy, Alzheimer's disease (AD), Parkinson's disease (PD), HD, amyotrophic lateral sclerosis (ALS), and nerve injury (Rocha-Gonzalez et al., 2008). AMPK, SIRT1, and PGC-1 α were all thought to be involved in the etiology of these neurological disorders. Based on evidence that resveratrol modulates these proteins, it was proposed that resveratrol has therapeutic potential in the abovementioned neurodegenerative diseases. The therapeutic potential of resveratrol in neurodegenerative disorders is supported by multiple studies demonstrating neuroprotective effects of resveratrol in different cell culture and *in vitro* systems (see review (Vingtdoux et al., 2008)). In a recent study published in this journal, Ho et al. examined the therapeutic potential of oral administration of a proprietary resveratrol formulation (SRT501-M from Sirtris Pharmaceuticals) in the N171–82Q mouse model of HD (Ho et al., 2010). The following commentary summarizes the results of the SRT501-M study and discusses the potential development of resveratrol and other grape-derived polyphenols for treating neurodegenerative disorders.

In search of a therapy for Huntington's disease

HD is an autosomal-dominant neurological disorder that is caused by an unstable trinucleotide CAG repeat expansion at the N-terminus of the IT15 gene encoding the ~350 kDa huntingtin (htt) protein (MacDonald et al., 1992). The mutation leads to the production of htt protein with an abnormal length of polyglutamine (polyQ) repeats. It is hypothesized that the polyQ repeats cause a gain of function resulting in abnormal protein-protein interaction underlying HD neuropathology (Davies et al., 2007; Trotter et al., 1995). HD is associated with neuronal intranuclear inclusions as well as cytoplasmic inclusions containing truncated polyglutamine fragments (Davies et al., 2007; DiFiglia et al., 1997). Progressive neuronal loss in the caudate and putamen is a hallmark of HD (Vonsattel et al., 1985), affecting the medium spiny projection neurons. HD is estimated to affect five to seven people in 100,000 throughout the world (Walker, 2007). However, the prevalence rate of HD is quite different among races — the frequency of HD is very high in Caucasians, but it is ten times lower in Asians. Clinical manifestation of the disease is characterized by

severe cognitive decline and personality changes (Duff et al., 2007; Johnson et al., 2007; Solomon et al., 2007), accompanied by progressive loss of coordination and motor functions that eventually lead to immobility (Penney et al., 1990). Currently, there is no cure for this devastating neurodegenerative disorder, and treatments are mainly focused on alleviating cognitive and psychological symptoms.

Bioavailability and clinical trials of resveratrol in neurodegenerative diseases

Bioavailability of resveratrol has received considerable attention (Wale, 2011). The oral bioavailability of resveratrol is rather low, less than 1%. Micronised resveratrol also has low systemic availability, although it can reach levels 3.6 times higher than the standard form (Howells et al., 2011). Although *in vivo* evidence is emerging in animal models that resveratrol is bioavailable (Vingtdeux et al., 2010) and bioactive (Karuppagounder et al., 2009; Vingtdeux et al., 2010) in the brain, conclusive results in human trials are still lacking. Because resveratrol has very low bioavailability and is rapidly metabolized, it has been suggested that some of its metabolites are responsible for its biological activity. In particular, resveratrol-3-sulfate and resveratrol-3-O-glucuronide are major metabolites, and di- and tri-sulfated derivatives have been also detected in substantial concentrations in vivo (Wenzel et al., 2005).

There are currently as many as 35 clinical trials listed in the NIH clinicaltrials.gov registry that investigate the effect of resveratrol on diverse conditions. Selected clinical trials are listed in Table 1. These include clinical trials focusing on AD, Friedreich Ataxia, traumatic brain injury, cognitive performance (memory) in the elderly, and a trial to assess cerebral blood flow and cognitive performance in young, healthy volunteers. The latter trial showed that after consuming 500 mg resveratrol, levels of total hemoglobin were significantly higher in the frontal cortex during cognitive task completion, compared to placebo. However, cognitive performance was not affected. It is also of note that Sirtris Pharmaceuticals (now GlaxoSmithKline), developer of the SRT501 formulation of resveratrol, suspended a clinical trial in multiple myeloma patients due to cases of kidney failure (Clinicaltrials.gov). According to a GlaxoSmithKline spokesperson, an internal analysis of the kidney failure cases has concluded that they “most likely were due to the underlying disease.” However, the formulation of SRT501 was not well tolerated, and side effects of nausea / vomiting / diarrhea may have indirectly led to dehydration, which exacerbated the development of the acute [kidney] failure” (<http://pipeline.corante.com>).

Does resveratrol work through activation of SIRT1?

Resveratrol and SIRT1 are best known for their pro-longevity properties. Studies in *S. cerevisiae*, *C. elegans*, and *Drosophila* have established SIRT1 orthologs as key determinants of longevity (Finkel et al., 2009). In several models, the effect of calorie restriction on lifespan extension was proposed to be SIRT1-dependent (Finkel et al., 2009). Resveratrol was also found to mimic calorie restriction at the molecular level and to extend longevity in both yeast and worm (Baur and Sinclair, 2006; Greer and Brunet, 2009). SIRT1 was thought to be the molecular target of resveratrol, based on *in vitro* studies showing that the polyphenol can enhance SIRT1 deacetylase activity (Howitz et al., 2003). Concerns have been raised, however, about the validity of the enzymatic assay used in this study. Indeed,

consecutive studies have shown that resveratrol does not activate SIRT1 *in vitro* and thus is likely to work through direct interaction with one or several other proteins *in vivo* (Beher et al., 2009; Borra et al., 2005; Pacholec et al., 2010). Resveratrol is a relatively potent activator of AMPK in cell cultures and *in vivo* in mice (Canto and Auwerx, 2010; Dasgupta and Milbrandt, 2007; Hawley et al., 2010; Vingtdoux et al., 2010). Resveratrol's effect on AMPK activity was proposed to be indirect as well, either by increasing cytosolic calcium levels (Vingtdoux et al., 2010) or by facilitating AMP-dependent activation of AMPK (Hawley et al., 2010). Nevertheless, AMPK activation by resveratrol is dependent on sirtuin function. Also, SIRT1 appears to be required for resveratrol metabolic functions in skeletal muscle *in vivo* by contributing to the activation of AMPK as well as PGC-1 α , which is a downstream substrate of SIRT1 (Canto and Auwerx, 2009; Canto et al., 2009; Ruderman et al., 2010). Nonetheless, in spite of evidence implicating resveratrol as having the potential to modulate the AMPK/SIRT1/PGC-1 α signaling network, the direct *in vivo* molecular target(s) of resveratrol remain(s) elusive.

Resveratrol: a novel Huntington disease treatment?

In 2005, Parker et al. reported that increased gene dosage of Sir2 (the SIRT1 ortholog in worm) or treatment with resveratrol prevented early neuronal dysfunction phenotypes in a transgenic *C. elegans* model expressing mutant polyglutamines (Parker et al., 2005). Moreover, the authors showed the *in vitro* efficacy of resveratrol to protect against mutant polyglutamine-mediated cell death in striatal neuronal cultures isolated from the HdhQ111 knock-in mice model of HD (Parker et al., 2005). In addition, the authors also demonstrated resveratrol may neuroprotect HdhQ111 striatal neuron cultures through promotion of SIRT1-related mechanisms (Parker et al., 2005). In line with this study, Kumar et al. showed that oral administration of resveratrol reversed motor and cognitive impairments induced by 3-nitropropionic acid in mice, another model for neurotoxicity and HD (Kumar et al., 2006). SIRT1 overexpression and resveratrol treatment were also found to protect against toxicity in HEK293T cells transfected with polyglutamines (Li et al., 2007). The authors proposed that SIRT1 and resveratrol worked by deacetylating Ku70, a multifunctional protein involved in DNA repair and cell survival (Li et al., 2007).

Recent evidence suggests that PGC.1 α deregulation may be essential in the pathogenesis of HD (Chaturvedi et al., 2010; McGill and Beal, 2006). Based on this, together with *in vitro* evidence that resveratrol promotes SIRT1 deacetylase activity (Howitz et al., 2003) and additional *in vitro* studies suggesting that resveratrol may protect against HD-type neurotoxicity (Kumar et al., 2006; Li et al., 2007), Beal and colleagues investigated the therapeutic potential of resveratrol in the N171–82Q transgenic mouse model of HD. In a recent article in *Experimental Neurology* (Ho et al., 2010) they describe testing of SRT501 (also termed SRT501-M), a proprietary micronised resveratrol formulation from Sirtris Pharmaceuticals (now GlaxoSmithKline)). After oral dosing by gavage of the SRT501-M preparation at 25 mg/mouse/day for 45 days (5 days a week), Ho et al. assessed both the metabolic effect at the periphery and the CNS effect on several HD hallmarks. In the brain, a small but significant elevation of PGC-1 α and NRF-1 mRNA expression was reported in the cerebral cortex of HD mice following SRT501-M treatment. Additional studies will be necessary to clarify whether SRT501-M treatment might modulate the activity of PGC-1 α .

(or SIRT) in the brain. Nonetheless, this modest increase in PGC-1 α and NRF-1 mRNA expression is likely to have a limited impact on mitochondrial function in the cerebral cortex as SRT501 treatment had no effect on the expression of the mitochondrial transcription factor (Tfam), another downstream target of NRF-1 involved in mitochondrial DNA replication and transcription. In the striatum, oral SRT501-M treatment resulted in a non-significant trend of increase in PGC-1 α mRNA levels, whereas NRF-1 and Tfam expression were unchanged. In line with the lack of clear transcriptional response in the striatum, no effect on striatum atrophy and spiny neuron size and numbers were observed. Finally, SRT501-M treatment failed to rescue motor performance, prevent weight loss, or promote survival in the HD mice. Together these data show that oral administration of the SRT501-M resveratrol formulation beneficially modulated metabolic effects at the periphery. However, SRT501-M treatment does not prevent or improve HD-type neurotoxicity in the striatum, the primary brain region affected in these mice and in HD, and does not attenuate the development and progression of HD clinical phenotypes in the N171–82QHD mouse model. The present results raise doubts about the therapeutic potential of the SRT501-M resveratrol preparation in HD (Scheme 1).

The observation that oral SRT501-M treatment induced biological responses in the cortex but not in the striatum is consistent with previous studies showing that orally administered resveratrol can cross the blood-brain barrier (BBB) and accumulate in the cerebral cortex but not in the hippocampus (Karuppagounder et al., 2009; Vingtdeux et al., 2010). This selective accumulation of resveratrol in different brain regions remains unexplained, but could be due to the diffusion rate of the compound or its specific metabolism in the brain. Nevertheless, the Ho et al. (2010) study indicates that if resveratrol has to be tested further in HD, improved administration and formulation methods should be implemented, or more potent resveratrol metabolites or analogues should be identified prior to evaluation in animal models. A recent study by Maher et al. (2011) in HD models reported neuroprotective effects of two polyphenols, fisetin and resveratrol, *in vitro* and fisetin *in vivo*. Resveratrol was found to be ineffective in the N171–82Q HD mouse model, whereas fisetin was neuroprotective *in vivo* in the R6/2 mouse model of HD. However, fisetin is rather distantly related to resveratrol and thus the *in vivo* fisetin data cannot be extrapolated towards resveratrol. It remains to be established if other formulations or dosing regimens of the compound would have efficacy in animal models and human clinical trials for HD.

SIRT1 and Alzheimer disease

A main pathogenic event in AD is the cerebral aggregation of the neurotoxic peptide β -amyloid (A β) (Citron, 2010). A β is generated from the sequential endoproteolysis of a longer precursor, amyloid precursor protein (APP), by the action of two enzymes, (β - and γ -secretase. Another enzyme, α -secretase, precludes A β production by cleaving APP in the A β sequence (Selkoe, 2001). Several proteases of the ADAM family, such as ADAM10, have been implicated in the α -secretase cleavage of APP. In 2006, we showed that calorie restriction attenuates A β production, in part by promoting α -secretase through mechanisms involving activation of SIRT1 (Qin et al., 2006b). Calorie restriction was found to increase SIRT1 expression and NAD⁺ levels in the brain of the Tg2576 transgenic mouse model of AD. Furthermore, we showed that SIRT1 expression in primary Tg2576 neurons and in

APP-transfected CHO cells reduces the generation of A β from APP by facilitating α -secretase activity (Qin et al., 2006b). Additional work demonstrated the implication of the Rho kinase ROCK1 in SIRT1-mediated α -secretase activity (Qin et al., 2006b). Moreover, studies in squirrel monkeys demonstrated that calorie restriction in primates also effectively reduces the contents of cortical A β peptides, and that this decrease is inversely correlated with SIRT1 protein concentrations in the same brain region (Qin et al., 2006a).

These results by Qin et al. were recently confirmed in SIRT1 transgenic and knockout mice (Donmez et al., 2010). The authors showed that A β production and the resulting amyloid deposition is decreased in the brains of SIRT1 transgenics. In contrast, both A β production and amyloid deposition in the brain are elevated in SIRT1 knockouts when crossed with APP-transgenic mice. Mice overexpressing SIRT1 also showed a reduction in brain inflammation, tau phosphorylation (another hallmark of AD), and in cognitive defects specific to the APP-transgenic mice. Conversely, SIRT1 deficiency exacerbated A β -linked pathology in the mice. In this study, SIRT1 was proposed to activate α -secretase by directly activating ADAM10 expression. The authors further showed that SIRT1 can deacetylate and coactivate the retinoic acid receptor β , a known modulator of ADAM10 transcription (Donmez et al., 2010). Collectively, the original discovery from Qin et al. (2006a, 2006b) and the confirmatory studies from Donmez et al. (2010) suggest that pharmacological activation of SIRT1 may represent a promising approach to prevent amyloid deposition and neurodegeneration in AD (Wang et al., 2010a, 2010b).

A novel possible pathway for resveratrol-mediated responses in the brain via AMPK activation and increased protein clearance

We and others have recently shown that resveratrol controls A β accumulation by facilitating its proteolytic clearance in neuronal cells (Marambaud et al., 2005; Vingtdeux et al., 2008, 2010) and reduces cerebral amyloid deposition *in vivo* in APP transgenic mice (Karuppagounder et al., 2009; Vingtdeux et al., 2010). We demonstrated for the first time that AMPK activation is responsible for the anti-amyloidogenic effect of resveratrol (Vingtdeux et al., 2010). AMPK is a heterotrimeric Ser/Thr protein kinase activated by different upstream kinases such as LKB1 or CaMKK β , a kinase predominantly expressed in neural tissue (Carling et al., 2008; Fogarty et al., 2010; Viollet et al., 2009). AMPK controls protein degradation by inhibiting the protein kinase mTOR and by activating autophagy (Hardie, 2007). Our work revealed that resveratrol can activate AMPK by increasing CaMKK β -dependent phosphorylation of AMPK. Activation of AMPK by resveratrol led to mTOR inhibition, autophagy induction, and proteolytic clearance of A β (Vingtdeux et al., 2010). Importantly, we also demonstrated that orally administered resveratrol in mice can cross the BBB to activate brain AMPK and reduce A β levels and deposition in the cerebral cortex (Vingtdeux et al., 2010). These studies underscored the therapeutic potential of AMPK activation as an anti-amyloidogenic strategy in AD, but also motivate the search for resveratrol metabolites/analogues or other polyphenolic compounds (or polyphenolic preparations) with improved potency and brain penetration properties as anti-neurodegenerative molecules (Vingtdeux et al., 2008; Wang et al., 2010a, 2010b).

Caloric restriction, resveratrol and neurodegeneration

Resveratrol is known to have beneficial metabolic effects and is considered a mimetic of dietary/caloric restriction. Since resveratrol is being considered as a treatment for HD, it is of interest that Ho et al. found beneficial anti-diabetic effects of resveratrol in the mouse model of HD. Chaturvedi et al. recently demonstrated that administration of SRT501-M could benefit metabolic impairments observed in N171–82Q mice by reducing levels of brown adipose tissue (BAT) vacuolation and blood glucose, two metabolic parameters that are abnormally elevated in this HD mouse model, although not all the HD mice responded to SRT501-M treatment (Chaturvedi et al., 2010). In BAT, a transcriptional response was observed in treated HD mice with an increase in the expression of PGC-1 α and two of its downstream effectors, nuclear respiratory factor-1 (NRF-1) and uncoupling protein-1 (UCP-1). Also, impaired PGC-1 α function has previously been shown to play a role in muscle dysfunction (Chaturvedi et al., 2009) and mitochondrial dysfunction (Weydt et al., 2006) in HD. It is possible that resveratrol may improve the HD phenotype via metabolic benefits. However, since CNS-related indicators of HD were not improved in the resveratrol-treated N171 mice, it appears that the metabolic effects of resveratrol would not ameliorate CNS neurodegeneration. Moreover, an implication of the Ho et al. study is that caloric restriction is unlikely to ameliorate central HD symptoms. In contrast to HD, Wang et al. (2005) demonstrated that caloric restriction attenuates β -amyloid neuropathology in a mouse model of AD.

Grape-derived polyphenols as a potential alternative to resveratrol

Resveratrol is found naturally in low concentrations among certain food sources such as peanuts, some berries, red grapes and grape by-products such as red wines and red grape juices. Prospective studies have shown that moderate red wine consumption is associated with lower relative risk of dementia (Orgogozo et al., 1997). More recently, James Joseph and colleagues demonstrated that dietary supplementation with a Concord purple grape juice significantly improves memory function in subjects with mild cognitive impairment (Krikorian et al., 2010). Consistent with these observations, we demonstrated that moderate red wine consumption beneficially modulates AD-type cognitive deterioration in the Tg2576 transgenic mouse model of AD by attenuating A β neuropathology (Wang et al., 2006; Ho et al., 2009). Moreover, we demonstrated that total polyphenolics isolated from red wine significantly attenuate the generation of A β peptide in primary corticohippocampal neuron cultures generated from Tg2576 mice (Wang et al., 2006). While red wine and grape juice are among some of the richest dietary sources of resveratrol, we found the contents of resveratrol in red wines or grape juices cannot account for the neurological benefits derived from normal consumption of red wine (or grape juice). For example, while resveratrol has been found to promote A β clearance (Marambaud et al., 2005), the content of resveratrol in the red wine we used in the Wang et al. (2006) study is approximately 10-fold lower than the minimal effective concentration shown to promote A β clearance *in vitro* (Marambaud et al., 2005). Thus, our studies suggest that grape-derived polyphenolic components other than resveratrol may also exert neurological health benefits. Consistent with this, we demonstrated that a red wine polyphenolic preparation containing no detectable contents of resveratrol significantly attenuates the development of β -amyloid neuropathology and cognitive deterioration in Tg2576 AD mice (Ho et al., 2009).

Aside from modulating A β generation, we found polyphenolics from red wine (Ho et al., 2009) and Concord purple grape juice (Ho and Pasinetti, unpublished observation) may also potentially interfere with the aggregation of A β peptides into neurotoxic high-molecular weight A β oligomers, which is now considered central to neurotoxicity in AD. More recently we identified a number of polyphenolic metabolites that accumulate in the brain following oral administrations of red wine and grape juice (Ho, Ferruzzi and Pasinetti, unpublished observation). More importantly, we found that some of these braintargeting grape-derived polyphenolic compounds are capable of attenuating the generation of A β peptides from primary neuron cultures, and/or promote cellular pCREB signaling, which has been associated with memory consolidation (Ho and Pasinetti, unpublished observation). Collectively, our observation raises an intriguing possibility that a combination of grape-derived polyphenolics may modulate AD by simultaneously reducing A β generation, interfering with aggregations of A β peptides and/or promoting molecular mechanisms involved in memory consolidation.

Our observation that certain red wine polyphenolic preparations potentially interfere with aberrant aggregations of A β peptides also has implications in other neurodegenerative disorders. Abnormal aggregation of certain proteins in susceptible brain cells is a common feature of a number of neurodegenerative disorders, including AD, PD, ALS and HD. As discussed, recent evidence indicates that mutant htt aggregation in susceptible brain cells may be responsible for the onset and progression of HD-type phenotype (MacDonald et al., 1992; Yamamoto et al., 2000), implicating abnormal htt protein aggregation as a novel target for HD treatment. We recently found that a grape-derived polyphenolic preparation interferes with abnormal aggregation of htt protein in an *in vitro* cell model of HD degeneration (Wang et al., 2010a, 2010b). More importantly, we found that this polyphenolic preparation is physiologically bioavailable and significantly attenuates HD-type phenotype in the R6/2 mouse model of HD, as well as significantly extends lifespan in the *UAS-Q93htt exon1* drosophila model of HD (Pfleger et al., 2010; Wang et al., 2010a, 2010b).

Collectively, accumulating evidence from our group and others provides the impetus to suggest further investigations to explore, pre-clinically, the suitability of alternative grape-derived polyphenols as a potential novel agent for the treatment of HD and other neurodegenerative conditions caused by abnormal protein aggregation.

Conclusions

The study by Ho et al. (2010) shows that oral administration of the SRT501 resveratrol formulation does not significantly improve HD-type pathology in the N171–82Q mouse model. The authors also found no effect of SRT501-M treatment on striatal expression and activity of PGC-1 α , a potential drug target for HD. However, the study confirms that the SRT501-M resveratrol preparation can lower blood glucose levels in metabolically impaired mice. While these results support the ongoing clinical trials on the effect of resveratrol on type 2 diabetes, this work suggests that there is no link between prevention of metabolic deterioration in N171–82Q mice and striatal neurodegeneration since the beneficial effect of the SRT501-M resveratrol preparation on hyperglycemia in these mice did not lead to any improvement of the HD-type pathology. Despite the accumulating encouraging *in vitro* and

in vivo evidence implicating that resveratrol might protect against HD-type neurotoxicity (e.g., Maher et al., 2011), presently there is no conclusive preclinical evidence suggesting that resveratrol might exert beneficial disease-modifying activity in HD. Nevertheless, further testing of resveratrol and other polyphenols in HD is warranted, although the field suffers from a lack of unified logic as to the mechanism of action of these compounds. The high-level dosing of resveratrol necessary for its *in vivo* bioactivities, together with its pleiotropic biological effects, may suggest that more attention should be focused on sulfated resveratrol derivatives, as these possess biological activity and somewhat resemble sulfated heparin mimetics (e.g., suramin, 3-aminopropanesulfonic acid [Alzhemed/tramiprosate]), a class of broadly active substances with overlapping biological effects on cancer, inflammation and neurodegeneration.

Although recent reports have shown that resveratrol or its metabolites can cross the BBB and lead to some biological responses in the brain after oral dosing (Abd El-Mohsen et al., 2006; Ho et al., 2010; Karuppagounder et al., 2009; Vingtdeux et al., 2010), the important question of how to improve resveratrol bioavailability in the brain remains to be addressed. Indeed, if resveratrol has to be tested further in HD or in any other brain conditions, improved administration and formulation methods should be implemented, and more potent resveratrol metabolites or analogues should be identified prior to evaluation in animal models.

Another line of research is to focus on novel, brain-targeting grape-derived polyphenols with promising anti-neurodegenerative properties (Ho and Pasinetti, 2010; Wang et al., 2008), which is the main topic of the NCCAM-funded center for Complementary and Alternative Medicine in Research in Alzheimer's disease. Outcomes from these studies should lead to further development of grape-derived polyphenol preparation for treating neurodegenerative conditions.

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Scheme 1.

Schematic summary of SRT501-M treatment on the development of HD phenotypes in N171–82Q mice. SRT501-M treatment improved metabolic parameters in the periphery, but did not modulate pathologic responses in the striatum, a brain region central for HD. Most importantly, SRT501-M treatment did not modulated HD clinical phenotypes. These observations do not support potential development of the SRT501 resveratrol preparation for treating HD. Additional preclinical studies will be need to explore whether other resveratrol preparation might be efficacious for modulating HD phenotypes. Abbreviation: BAT, brown adipose tissue.

Table 1

Selected human clinical trials with resveratrol.

Sponsor	Indication	Dosing mg/day	Stage	Status
Northumbria University	Cognition	250–500	Phase II	Completed
University of Florida	Memory and physical performance in elderly	300–1000	Phase I/II	Ongoing
Murdoch Childrens Research Institute	Friedreich Ataxia	1000–5000	Phase I/II	Ongoing
Kaleida Health	NIDDM and obesity	120–500	Phase II/III	Ongoing
GlaxoSmithKline	Colorectal Cancer and hepatic metastases	5000 (SRT-501)	Phase I	Completed
University of Texas Southwestern Medical Center	Traumatic brain injury	500	Phase II	Ongoing
University of Aarhus	Obesity, Metabolic syndrome and inflammation	1500	Phase II	Ongoing
GlaxoSmithKline	Multiple myeloma	5000 (SRT-501)	Phase II	Terminated
Medical College of Wisconsin	Mild to moderate Alzheimer's disease	215	Phase III	Unknown
Veterans Affairs	Alzheimer's disease	Glucose, malate and resveratrol	Phase III	Ongoing
Maastricht University Medical Center	Dislipidemia	150	Phase I/II	Ongoing