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Evidence for behavioral benefits of early dietary supplementation with CoEnzymeQ10 in a slowly progressing mouse model of Huntington's disease

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ABSTRACT

Controversies surround the usefulness of Coenzyme Q10 (CoQ10) in Huntington's disease (HD), an autosomal dominant, fatal, neurodegenerative disease with no cure or disease modifying treatment. CoQ10, an endogenous substrate for electron transport and an anti-oxidant, has been shown in some but not all studies to improve symptoms and survival in mouse models of HD. Previous studies have been conducted in fast-progressing models that better mimic the juvenile forms of HD than the much more common middle-age onset form, possibly accounting for mixed results. Establishing the usefulness of CoQ10 to alter HD disease course in a model that better recapitulates the progressive features of the human disorder is important because clinical trials of CoQ10, which is safe and well tolerated, are being planned in patients. The CAG140 knock-in (KI) mouse model of HD in which an expanded (approximately 120) CAG repeat is inserted in the mouse gene provides a model of the mutation in the proper genomic and protein context. These mice display progressive motor, cognitive and emotional anomalies, transcriptional disturbances and late striatal degeneration. Homozygote mutant CAG140 KI mice and wild-type littermates were fed CoQ10 (0.2%, 0.6%) in chow, and behavioral and pathological markers of disease were examined. CoQ10 improved early behavioral deficits and normalized some transcriptional deficits without altering huntingtin aggregates in striatum. The lower dose (0.2%) was more beneficial than 0.6%. Similar to previous studies, this low dose also induced deleterious effects in open field and rotarod in WT mice, however these effects are of unclear clinical significance in view of the excellent safety profile of CoQ10 in humans. These data confirm that CoQ10 may be beneficial in HD but suggest that maximum benefit may be observed when treatment is begun at early stages of the disease and that dosage may be critical.

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Introduction

Much work has been devoted over the last decade in performing clinical trials for potential neuroprotective therapies for Huntington's disease (HD), a progressive neurological disorder with no cure or effective treatment. The disease is inherited in an autosomal dominant manner and is caused by a single mutation in the N terminus of the *huntingtin* (htt) gene (The Huntington's Disease Collaborative Research Group, 1993). Many functions have been attributed to htt and it is thought that the mutation causes both a toxic gain in function, and a loss of function of the wild type (WT) protein (Cattaneo et al., 2005; Lee et al., 2007; Miller et al., 2010).

CoenzymeQ10 (CoQ10), also known as ubiquinone, is found in nearly all cell membranes, especially in the inner mitochondrial membrane where it acts as an anti-oxidant, in addition to its role in electron transport (Chaturvedi and Beal, 2008; Kwong et al., 2002). These properties, and evidence for oxidative stress in several neurological disorders, have led to the use of CoQ as a potential treatment for many disorders including amyotrophic lateral sclerosis (Ferrante et al., 2005) and Parkinson's disease (Shults et al., 1998, 2004). In HD, CoQ10 administration increases patient CoQ10 serum levels significantly when compared to untreated patients, and levels are no longer different to controls (Andrich et al., 2004) and CoQ also decreases cortical lactate (Koroshetz et al., 1997). In a large clinical trial, CoQ10 treatment (300 mg twice daily) slowed the decline of total functional capacity in HD patients; however the improvement was non-significant (The Huntington Study Group, 2001). Importantly, much higher doses of CoQ10 are safe and well tolerated in HD (Feigin et al., 1996; The Huntington Study Group Pre2CARE Investigators, 2010),

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opening the path for further investigation in humans. Notably, recent studies have highlighted the importance of titrating therapies to disease duration (Okamoto et al., 2009).

Several studies have reported beneficial effects of CoQ10 on behavior and pathology in mouse models of HD (Ferrante et al., 2002; Schilling et al., 2001, 2004; Smith et al., 2006; Stack et al., 2006; Yang et al., 2009). However, a recent study in the fast-progressing murine model of HD, the R6/2 mouse, has failed to confirm these data when testing mice in an enriched environment and using actual end of life as an additional endpoint (Menalled et al., 2010). Together with the minimal effect in the early clinical trials in patients, these data indicate that more studies are required to better define the context in which CoQ might be beneficial in HD. In particular, it is possible that CoQ may improve only some aspects of the disorder, or be more effective at early stages, before multiple pathological processes come into play. This is difficult to assess in fast-progressing models of the disease, where extensive pathology and dysfunction are observed early on and animals progress to death in a few months (Hickey et al., 2005). Therefore, we have re-examined CoQ effects, using a regimen similar to that used in the negative study in R6/2 mice, in a slowly progressive model of HD, the CAG140 KI mouse, which expresses the full length protein in the proper genomic context and may better reproduce human pathology (Hickey et al., 2008; Menalled et al., 2003).

CAG140 homozygote KI mice present behavioral, neuropathological, electrophysiological and molecular changes that emerge at 1–2 months of age and progress slowly towards loss of striatal neurons, a canonical feature of HD, at approximately 2 years of age (Cui et al., 2006; Cummings et al., 2010; Hickey et al., 2008; Hickey et al., 2011; Menalled et al., 2003; Phan et al., 2009; Simmons et al., 2009). Specifically, these mice first show behavioral deficits at 1 month of age, with nuclear staining and microaggregates of htt appearing in striatum and other brain regions by 2 months of age. By 4 m, the mice exhibit changes in striatal transcripts for several receptors and neuropeptides and nuclear inclusions form in striatal and other neurons. At 12 months KI mice show striatal atrophy (Lerner et al., submitted), profound loss of DARPP-32 (by optical density) and cortical gliosis, with striatal gliosis and striatal neuronal loss by 2 years (Hickey et al., 2008).

Here, we examined the effects of 0.2% and 0.6% CoQ10 in chow in CAG140 KI mice, at an early stage in disease, with the aim of developing therapeutics for treating early disease and neuronal dysfunction. Thus, we have examined pathological endpoints such as transcription and mutant protein aggregation rather than neurodegeneration. CoQ10 was administered in chow, from conception to 4.5 months and we monitored the effects of the treatment on behavioral deficits at 1–4 months of age as well as mutant htt aggregates and striatal transcripts at 4.5 months. Both doses markedly improved behavioral deficits, with the lower dose (0.2%) providing more extensive benefits. In addition, both doses normalized some of the striatal transcriptional deficits induced by mutated htt. These data support the potential usefulness of CoQ10 in HD but stress the need for early treatment to achieve benefits.

Results

Husbandry

Mice were fed control or the same dose of CoQ used in a recent study in R6/2 mice (Menalled et al., 2010): 0.2% or 0.6% CoQ10 in chow, however, here 0.6% chow was not supplemented with gamma-cyclodextrin. In the present study CoQ was administered from conception to maximize exposure to the dietary supplement at the earliest stages of the disease. Therefore, we monitored breeding success to ensure normal fecundity. There was no difference between treatment groups in size of litters at birth and weaning (Table 2; no effect of treatment $F(2,54)=0.24$, ns; no interaction of treatment with age $F(2,54)=0.8$, ns). The percentage of pups brought through to weaning age was also similar between groups (control, $58.4\pm14.6\%$; 0.2%, 75.4 ± 17.2; 0.6%, 82.4 ± 10.7; effect of treatment $F(2,30)=0.65$, ns), as was the proportion of genders and genotypes represented within each treatment group (males–females group sizes in WT, HET and KI groups: control 7–9; 0.2% 8–14; 0.6% 6–15). Chi square independence tests were used to compare number of WTs and KIs within treatment groups (control ns; 0.2% ns, 0.6%, ns). Pups from each group gained weight, and over the course of the study there was no significant difference in body weight profiles of control-treated mice compared to CoQ10-treated mice (Figs. 1a–d, body weights of WT and KI mice were compared, HETs were also used for analysis of body weights, but were not used for subsequent behavioral testing, males: genotype × treatment × timepoint $F(64,1027)=0.84$, ns; females: genotype × treatment × timepoint $F(64,1020)=0.6$, ns). These data are in agreement with the safety profile of CoQ10, which is an over-the-counter dietary supplement (Bhagavan and Chopra, 2006). Thus, treatment with CoQ10 from conception did not have any deleterious effects on the pups or success of breeding.

Table 1
Sequences of primers used for mRNA quantification analysis.

Gene	Primer sequence
Eif4a2	F: TACTGACTTGTTGGCCCGTG
	R: ATTCATGGGCATTTCCTCC
Atp5b	F: TCCTAAATGCCCTGGAAGTG
	R: GCCTCAGCATGAATAGGAGC
Substance P	F: ACCCAAGCCTCAGCAGTTCTTTG
	R: TTCTGCATCGCGCTTCTTTCATA
DARPP-32	F: AAGGACCGCAAGAAGATTCAGTTCT
	R: CTCTCCAGAGGTTCTCTGATGTGGA
Dopamine receptor 1	F: AGAAGCAAATCCGGCGCATC
	R: GGAGCCAGCAGCACACGAATAC
Dopamine receptor 2	F: GGTCTACTCCTCCATCGTCTCGTTC
	R: TAACGGTGCAGAGTTTCATGTCCTC
Cannabinoid receptor 1	F: CGGCCTTGCAGATACCACCTTC
	R: GGAACCAACGGGGAGTTGTCTC
Preproenkephalin	F: CCTGAGATAGAGAAAAGATACGGG
	R: GATGTTTCGTCAGGAGAGATGAGG

Behavioral effects of treatment with CoQ10

Mice were tested for rearing and locomotor activity in the open field at 1 month of age. Control-fed KI mice reared less than control-fed WT mice (Fig. 2a). Demonstrating a beneficial effect, 0.2% CoQ10 rescued this reduced rearing in KI mice (Fig. 2a, gray stippled bars), while 0.6% (black stippled bars) had no effect. Interestingly, the effect of CoQ10 was opposite in WT mice, with 0.2%-fed WT mice rearing less (gray bars) than control-fed WT mice (Fig. 2a), while 0.6% (black bars) had no effect (genotype × treatment interaction $F(2,106)=3.2$, $p<0.05$). The lower dose of CoQ10 also improved initial exploration of the open field, since the reduced locomotion during the first 5 min was rescued in 0.2%-treated KI mice (Fig. 2b, effect of timebin $F(2,198)=127.2$, $p<0.0001$). Mice were tested for spontaneous climbing activity two weeks later, at 1.5 months, and as previously shown (Hickey et al., 2008), in control-fed groups, KI mice climbed less than WT mice (Fig. 3; overall effect of genotype $F(1,107)=9.7$, $p<0.01$). There was no significant difference in climbing between KI groups (Fig. 3), however CoQ10 0.2% abolished the decreased climbing in KI versus control-treated WT (Fig. 3). At 4 months of age, mice were tested for performance on the pole task and rotarod. Both doses of CoQ10 rescued the impaired pole performance of KI mice (Fig. 4a, interaction of genotype and treatment, $F(2,105)=3.2$, $p<0.05$) and neither dose had any effect on WT performance.

For rotarod analysis, mice were trained for 4 days using an accelerating protocol and smooth axle (4–40 rpm over 10 min, 3 trials per day), followed by 1 day of constant speeds using a smooth axle (10, 20, 30 rpm, 1 trial per speed) and a final day of constant speeds with a

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