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Altered Cholesterol and Fatty Acid Metabolism in Huntington Disease

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Abstract

Huntington disease is an autosomal dominant neurodegenerative disorder characterized by behavioral abnormalities, cognitive decline, and involuntary movements that lead to a progressive decline in functional capacity, independence, and ultimately death. The pathophysiology of Huntington disease is linked to an expanded trinucleotide repeat of cytosine-adenine-guanine (CAG) in the IT-15 gene on chromosome 4. There is no disease-modifying treatment for Huntington disease, and novel pathophysiological insights and therapeutic strategies are needed. Lipids are vital to the health of the central nervous system, and research in animals and humans has revealed that cholesterol metabolism is disrupted in Huntington disease. This lipid dysregulation has been linked to specific actions of the mutant *huntingtin* on sterol regulatory element binding proteins. This results in lower cholesterol levels in affected areas of the brain with evidence that this depletion is pathologic. Huntington disease is also associated with a pattern of insulin resistance characterized by a catabolic state resulting in weight loss and a lower body mass index than individuals without Huntington disease. Insulin resistance appears to act as a metabolic stressor attending disease progression. The fish-derived omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid, have been examined in clinical trials of Huntington disease patients. Drugs that combat the dysregulated lipid milieu in Huntington disease may help treat this perplexing and catastrophic genetic disease.

Keywords

Huntington disease; cholesterol; triglycerides; insulin resistance; omega-3 fatty acids

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HUNTINGTON DISEASE NATURAL HISTORY AND PATHOPHYSIOLOGY

Huntington disease is an autosomal dominant neurodegenerative disorder characterized by behavioral abnormalities, cognitive decline, and involuntary movements including chorea and dystonia, that lead to a progressive decline in function and independence.¹ The onset of illness is typically in middle-age with a prevalence in most Caucasian populations is about 10 per 100,000.² Its prevalence is much less in African and Japanese populations where it affects about 0.5 individuals per 100,000. The course of illness is uniformly fatal and only one symptomatic treatment (tetrabenazine) for the involuntary choreic movements of Huntington disease has been approved in the U.S.³ Although the neurologic manifestations are incapacitating and patients are at high risk of suicide, cardiovascular disease, after pneumonia, is the leading cause of death in afflicted individuals.⁴ More recent and detailed data regarding the exact etiology of cardiovascular disease deaths are not available. We hypothesize that disordered lipid metabolism may contribute to neurological dysfunction and degeneration in Huntington disease.⁴

The pathophysiology of Huntington disease is linked to an expanded trinucleotide repeat of cytosine-adenine-guanine (CAG) in the IT-15 gene on chromosome 4.¹ Individuals who have inherited the Huntington disease genetic mutation are healthy on average for the initial two-thirds of life before the insidious emergence of motor, cognitive and behavioral disturbances. Neuronal dysfunction in the clinically pre-manifest stages of disease evolves eventually into neuropathological changes including prominent cell loss and atrophy in the putamen and caudate (neostriatum) and the accumulation of cytoplasmic and nuclear inclusions that contain the mutant protein *huntingtin*. Despite the known genetic etiology of the disease, the exact function of the *huntingtin* protein and its role in the pathogenesis of Huntington disease is not clear. Mitochondrial dysfunction and bioenergetic defects may be contributing mechanisms.¹

LIPID METABOLISM IN HUNTINGTON DISEASE

Cholesterol is crucial for myelin membrane growth, and mice that cannot properly synthesize cholesterol manifest tremor and ataxia.⁵ In addition to its central nervous system-specific role, cholesterol is an essential component of all cell membranes, acting as a structural component, organizing signal transduction in lipid rafts of cell membranes, playing a role in synaptogenesis, and in neurotransmitter release within synapses.⁶ Cholesterol also plays a vital role as a cofactor for signaling molecules, and a precursor of steroid hormones. Despite the fact that the central nervous system constitutes only two percent of total mammalian body mass, it has the highest concentration of cholesterol of all organs.⁶ This correlates with an estimated concentration of cholesterol of 15-20 mg/g of fresh tissue and 8-10 times the concentration found in the whole mammal. The majority of brain cholesterol is unesterified and localized in myelin sheaths produced by oligodendrocytes.⁷ Brain cholesterol homeostasis is primarily determined by local synthesis as cholesterol does not easily cross the blood-brain barrier. Since local cholesterol synthesis is highest in neonates and much lower in the adult brain, levels in adults may more accurately reflect prior production years. spines.

Although cholesterol turnover has been shown to be very slow in the adult central nervous system, abnormalities in cholesterol homeostasis have been associated with neurodegenerative disorders that include Huntington disease, Alzheimer disease, and Niemann-Pick type C.⁶ The biosynthesis of cholesterol and fatty acids is impaired in cell cultures that include the Huntington disease genetic mutation (Figure 1) and in animal models of Huntington disease.⁷ The hypothesis that lipid dysregulation is pathogenic in Huntington disease is supported by the observations that the mRNA transcription of key genes in the cholesterol and fatty acid biosynthetic pathways is downregulated in human postmortem Huntington disease striatal and

cortical tissue as well as in murine models of Huntington disease.⁸ The molecular mechanism that has been linked to impaired lipid biosynthesis is a mutant *huntingtin*-dependent reduction in active sterol regulatory element response protein 2 (SREBP-2). Figure 1 outlines several points along the biosynthetic pathways of cholesterol (SREBP-2), and fatty acids (SREBP-1c). Since fatty acids are precursors of triglyceride and phospholipid synthesis, the normal synthesis of all these important lipids require regulation by these sterol regulatory element binding proteins.⁷

Consistent with the reduced synthesis of cholesterol in cells affected by mutant *huntingtin* protein, total cholesterol mass is reduced in the central nervous systems of mice with a model of Huntington disease and in human cells in which the expression of mutant *huntingtin* has been activated.⁷ Individuals with Huntington disease also have total serum cholesterol concentrations approximately 40 mg/dL lower than healthy individuals without Huntington disease.⁹ Although the correlation of cholesterol levels in the central nervous system and blood are not well defined, levels of 24 hydroxycholesterol are approximately 10% of those in human plasma.¹⁰ Twenty-four hydroxycholesterol is formed from cholesterol in the brain and is important for cholesterol central nervous system homeostasis.¹¹ The reduced synthesis of cholesterol and precursors in the pathway may help explain why ubiquinone (coenzyme Q10), a nutritional supplement synthesized from intermediary metabolites within the cholesterol pathway, is under investigation for the treatment of Huntington disease.⁶

Fatty acid metabolism also appears disordered in individuals with Huntington disease (Figure 1).⁷ SREBP-regulated genes affect both fatty acid and cholesterol metabolism (Figure 1), influencing the elongation and desaturation of fatty acids. Fatty acid dysregulation is also supported by the fact that fibroblasts in Huntington disease patients grow more slowly than those from healthy individuals when they are in a lipid-deprived medium but their growth normalizes when a mixture of linoleic and linolenic acids is added to the medium.¹² Evidence that fatty acid composition has been implicated as a factor affecting the fluidity of cell membranes¹³ and preliminary data suggesting that freshly isolated cells from diseased patients have altered membrane fluidity⁶ also suggest that dysregulated fatty acid pathways exist.

The compartmentalization of fatty acids may also be altered in patients with Huntington disease. Palmitoylation is the process by which fatty acids, such as palmitic acid, covalently attach to residues of membrane proteins, such as cysteine.¹⁴ The precise function of palmitoylation depends on the protein under consideration. However, this process enhances the hydrophobicity of proteins and contributes to their membrane association and the subcellular trafficking of proteins between membrane compartments.⁶ The palmitoylation of *huntingtin* by *huntingtin*-interacting protein is crucial for its normal function and transport but this process is impaired in those with Huntington disease.¹⁵ *Huntingtin*-interacting protein is enriched in normal brain and co-localizes with *huntingtin* in the striatum and in the medium spiny projection neurons, a subset of neurons affected in Huntington disease. Reduced interaction between *huntingtin* and *huntingtin*-interacting protein may contribute to the neuronal dysfunction in Huntington disease by dysregulating normal neuronal intracellular transport pathways.

A striking feature of Huntington disease is an impressive alteration in nutritional status characterized by increased appetite and caloric intake.⁶ Paradoxically, this increase in energy intake is usually accompanied by increased sedentary energy expenditure and weight loss. The metabolic profile of transgenic mice with a model of Huntington disease and those of humans with the disease appears to be distinct and indicates a change from normal to one of a catabolic phenotype, particularly early in the disease. One striking feature of this hypercatabolic state is that fatty acid and amino acid catabolism has been shown to be abnormal.¹⁶ Of importance is the fact that this hyper-catabolic state which occurs in Huntington disease patients is associated

chronologically with more rapid progression of the neurologic symptoms.¹⁶ Despite this interesting phenomenon, the etiology for increased sedentary energy expenditure with subsequent weight loss and more rapid disease progression in these patients is unknown.⁶

INSULIN RESISTANCE IN HUNTINGTON DISEASE

Insulin resistance is a pathophysiologic state associated with obesity and aging and characterized by hyperglycemia and dysfunctional lipid metabolism.¹⁷ It is associated with an increased risk of cardiovascular disease and diabetes mellitus as well as certain neoplasms including those of the breast and colon. The lipid disorder tends to consist of high triglycerides and small, dense LDL, with an accompanying high number of atherogenic (apoB) particles. The primary concerns regarding the increased frequency of insulin resistance in populations globally have been those related to macro- and microvascular disease events. Not as much attention has been devoted to its relationship to neurodegenerative diseases.

A puzzling feature of Huntington disease patients is that, despite having a lower-than-normal body mass index, they tend to have insulin resistance in peripheral tissues and an increased risk for developing type 2 diabetes mellitus.¹⁸ These issues have been investigated in 620 probands (278 living, 332 deceased) with Huntington disease and their first and second degree relatives participating in the National Huntington Disease Research Roster. In the probands, 65 individuals (10.5%) were identified as diabetic. In this population, the prevalence of diabetes, particularly for those less than 50 years of age, was significantly greater than corresponding figures among the general U.S. Caucasian population. Specifically, analysis of these families indicates that Huntington-affected relatives of a diseased proband with diabetes are seven times as likely to have diabetes over the proband's non-Huntington disease affected relatives. So, a family history of diabetes in individuals with Huntington disease is associated with a very high risk for diabetes mellitus.

Insulin resistance may be a pathogenic factor in Huntington disease. One hypothesis for a relationship between insulin resistance and neurodegeneration is that insulin resistance represents a metabolic stressor that influences an underlying neurobiologic template in a way that leads to a pathologic phenotype.¹⁹ Such a phenomenon has been suggested in the InCHianti study in which individuals with cognitive impairment involving subcortical features were more likely to suffer from insulin resistance than those without cognitive impairment or those with cognitive impairment without subcortical features. In another study, 29 nondiabetic patients with Huntington disease and 22 control participants without Huntington disease or diabetes were matched by age, sex, and socioeconomic status.¹⁹ Those individuals with Huntington disease had higher levels of insulin resistance manifested by an increased homeostasis model assessment (HOMA index) and lower insulin sensitivity. The acute insulin response was blunted and the insulinogenic index (the ratio of plasma insulin to plasma glucose) was also reduced in those with Huntington disease compared to the healthy controls. Although the association of insulin resistance with neurodegeneration in these studies may not be causal, a dose-response relationship is suggested by the fact that the number of CAG repeats in the mutant Huntington disease gene correlated in the latter study with reduced acute insulin response. Participants with Huntington disease in this study notably had a lower body mass index than the healthy individuals. In addition, insulin resistance in these individuals was not associated with the lipid abnormalities that typically are present in those without Huntington disease who have insulin resistance or diabetes mellitus.^{19, 20}

A link between reduced insulin secretion and Huntington disease is also suggested by the R6/2 transgenic mouse model characterized by 150 CAG repeats.²¹ These mice develop glycosuria and glucose intolerance at the age of 9 weeks and more than 70% develop diabetes by 14 weeks. In this same murine model of Huntington disease, intranuclear inclusions, a histopathologic

hallmark of Huntington disease, are present not only in brain tissue but also in pancreatic cells.²¹ These data are consistent with the intriguing finding that neurons share functional similarities with insulin-secreting pancreatic cells and that these similarities have been hypothesized to be due to islet cell evolution from an ancestral insulin-secreting neuron.²²

THE ROLE OF OMEGA-3 FATTY ACIDS IN CENTRAL NERVOUS SYSTEM HEALTH

The state of insulin resistance is characterized by hyperglycemia, abnormal lipoprotein metabolism, and elevated levels of circulating free fatty acids.¹⁷ The intake and concentrations of long-chain polyunsaturated fatty acids, including the fish-derived omega-3 fatty acids docosahexaenoic (DHA) and eicosapentaenoic acids (EPA), are negatively correlated with insulin resistance and its manifestations whereas intake and concentrations of saturated fatty acids are positively correlated.²³ A specific effect of these marine vertebrate-derived omega-3 fatty acids on the pathophysiology of neurodegenerative diseases has been suggested by prior studies. An extensive review of the literature has concluded that an increase in brain concentrations of DHA are positively associated with improvements in cognitive or behavioral performance.²⁴ Although an exact mechanism of action by which ethyl-EPA may be beneficial in individuals with Huntington disease is not known, it may improve neuronal dysfunction and stabilize mitochondrial integrity.²⁵ This could occur directly and/or indirectly via several mechanisms, which have been shown to be affected by EPA in preclinical studies. EPA has been implicated in various studies to trigger the expression of certain enzymes and regulatory factors though the exact relevance of these studies to its potential use as a therapeutic in Huntington disease is not yet known. However, ethyl-EPA can stabilize membranes important in oxidative metabolism,²⁶ modulate mitochondrial metabolism by increasing beta oxidation²⁷ and prevent mitochondrial apoptosis.²⁸ Ethyl-EPA has been shown to suppress apoptosis by affecting the phosphorylation of p38 MAPK²⁹ 30 and the activation of p53.³⁰ Ethyl-EPA also has direct effects on COX-2, PPAR receptors, and prostaglandin synthesis³¹ which may also lead to beneficial effects on the cellular metabolism of the central nervous system. Beyond inflammation, numerous mechanisms have been offered to explain the effect of enhanced omega-3 polyunsaturated fatty acid status on central nervous system function, including alteration in dopaminergic function³² and an increase in serotonin-mediated neurotransmission.³³ In a murine model of Huntington disease, supplementation with essential fatty acids such as eicosapentaenoic acid (EPA) is associated with improved motor manifestations.³⁴ However, in the TREND-HD randomized clinical trial, ethyl-EPA 2g/day over 6 months did not result in improved motor performance in Huntington disease patients.²⁵ It may be that six months of observation may be too short to detect potential salutary effects of EPA on disease progression. Thus, beneficial effects of EPA and DHA remain speculative and await investigation. Preliminary data suggest that a mechanism of action of ethyl-EPA on processes of neurodegeneration may be in the stabilization of the integrity and function of the mitochondria of “suffering neurons”.

The central nervous system (CNS) accumulates large amounts of polyunsaturated fatty acids during development, particularly docosahexaenoic acid (DHA-an omega-3 fatty acid) and arachidonic (an omega-6 fatty acid) which compose greater than 10% of fatty acids in gray matter.³⁵ The central nervous system avidly retains polyunsaturated fatty acids once central nervous system development is complete such that frank omega-3 deficiency is observed in developing primates and rats deprived of omega-3s, but effects in adults are not obvious.³⁶ Unlike docosahexaenoic acid, the concentration of EPA is well below 1% of fatty acids possibly mediated by oxidation upon entry into the brain in the same way that alpha-linolenic acid and linoleic acid are oxidized.³⁷ Were this to be confirmed, it would not be an efficient DHA precursor.

In animal studies, central nervous system phospholipid EPA rises with EPA feeding,³⁸ however its biochemical role in the central nervous system is not well understood. It has long been thought to be a precursor of eicosanoids that oppose the inflammatory action of arachidonic acid-derived eicosanoids, and more recently as a precursor for compounds that signal for the resolution of inflammation.³⁹ These recently discovered compounds are endogenous potent lipid mediators and are referred to as resolvins. A unique feature of *resolvins* is that they are lipid mediators that have effects which lead to the active *resolution* of inflammation and help to restore homeostasis at the tissue level. Resolvins exert these effects by inhibiting leukocyte infiltration while stimulating non-phlogistic phagocytosis of apoptotic neutrophils by macrophages. These effects occur at least partially via G-protein-coupled receptors, which are a large group of receptors that bind an extensive set of molecules including neurotransmitters and biologically active amines. Similar potent lipid mediators termed neuroprotectins are produced from DHA and have similar active inflammation-resolution effects which have been most notable in the central nervous system and in the vasculature. Neuroprotectins also stimulate non-phlogistic phagocytosis of apoptotic neutrophils and, in addition, has been shown to protect epithelial cells from oxidative-stress-induced apoptosis. In humans with Alzheimer disease, the production of neuroprotectin D1 has been shown to be reduced. In animals, this potent lipid mediator has demonstrated effects which are protective against ischemic injury in the central nervous system. Interestingly, some of the lipid mediators in this family of molecules are synthesized from EPA and DHA in the presence of aspirin due to the acetylation of cyclooxygenase 2 (COX2). Although a role of these lipid mediator products of omega-3 fatty acids in protecting the central nervous system from neurodegenerative diseases such as Huntington disease has not yet been a focus of research, the possibility that they are important regulators of neurodegeneration (an inflammatory process) should be explored in humans. Their effects suggest a potential link between the depletion of polyunsaturated fatty acids in the brain of Huntington disease patients and the etiology for a progressive, disabling, and inevitably fatal disease.

IMPLICATIONS OF DISTURBED LIPID METABOLISM IN HUNTINGTON DISEASE

EPA's potential neuroprotective effects and the disrupted fatty acid metabolism in Huntington disease raise the question of whether targeting lipid metabolism may be useful therapies for individuals with Huntington disease. The fact that EPA has beneficial effects on triglycerides is not novel. However, since Huntington disease is characterized by insulin resistance and hypertriglyceridemia is one characteristic of insulin resistance, a beneficial effect of EPA on triglycerides in Huntington disease may be a manifestation of this omega-3 fatty acid's protective effects on the central nervous system. Although the exact mechanisms by which omega-3 fatty acids reduce triglycerides are unknown, insights can be derived from information at the gene transcriptional level. Important lipid regulation targets include liver $\times$ receptor, farnesol $\times$ receptor, hepatocyte nuclear factor-4alpha (HNF-4alpha), and peroxisome proliferator-activated receptors (PPARs).⁴⁰ Each of these receptors is modulated by the primary genetic regulator of lipogenesis: sterol receptor element binding protein-1c (SREBP-1c). By simultaneously downregulating DNA encoding proteins that stimulate lipid synthesis and upregulating DNA encoding proteins that stimulate fatty acid oxidation, EPA and DHA are potent hypotriglyceridemic agents. The fact that omega-3 fatty acids alter SREBP regulation, which is disrupted in Huntington disease (SREBP downregulation leads to reduced synthesis of long-chain fatty acids), suggest that they, as well as long-chain omega-6 fatty acids, could potentially exert beneficial effects in these patients by altering the metabolism of other lipids.

The fish-derived omega-3 fatty acids EPA and DHA have exhibited mechanisms by which they directly inhibit insulin resistance. For instance, both EPA and DHA induce mitochondrial

biogenesis and beta-oxidation in adipocytes.⁴¹ Current evidence suggests that the turning on of this 'metabolic switch' in adipocytes may lead to a reduction in adiposity. EPA and DHA also ameliorate low-grade inflammation in adipose tissue which is associated with obesity and induce changes in the pattern of secreted adipokines. These effects all result in improved systemic insulin sensitivity. The effects of EPA and DHA in ob/ob mice, an obesity model of insulin resistance and fatty liver disease, have also been studied.⁴² In this model, dietary intake of EPA and DHA had insulin-sensitizing effects in adipose tissue and liver. EPA and DHA activated genes involved in insulin sensitivity (PPAR γ), glucose transport (GLUT-2/GLUT-4), and insulin receptor signaling (IRS-1/IRS-2). These fatty acids also increased levels of adiponectin, an anti-inflammatory and insulin-sensitizing cytokine and activated AMPK phosphorylation, a fuel-sensing enzyme and a gatekeeper of energy balance. At the same time, EPA and DHA reduced hepatic steatosis. These omega-3 polyunsaturated fatty acids (PUFA) reduce the formation of omega-6 fatty acid-PUFA-derived eicosanoids, while triggering the formation of omega-3-PUFA-derived resolvins and protectin metabolites. Some of these resolvins and protectins have potent insulin-sensitizing and antisteatotic effects. Therefore, EPA and DHA and some of their metabolites exert beneficial actions in preventing obesity-induced insulin resistance and hepatic steatosis.

Although very current data do not exist regarding the most common causes of death of Huntington disease patients, the evidence available suggests that cardiovascular disease is the second leading cause of mortality.⁴ Therefore, since a large body of evidence exists regarding the effects of omega-3 fatty acids on cardiovascular risk, their beneficial effects on lipid metabolism could potentially be associated with improved clinical outcomes in individuals with Huntington disease. Previous studies of omega-3 fatty acids derived from fish oil, including EPA and docosahexanoic acid (DHA), have demonstrated that supplementation does not significantly alter total cholesterol levels but reduces triglyceride concentrations by 25-30%.⁴³ Several studies have demonstrated an association between EPA+DHA intake or tissue levels with reduced risk for fatal and non-fatal coronary heart disease in individuals with and without coronary heart disease.⁴⁴

FUTURE DIRECTIONS FOR THE TREATMENT OF HUNTINGTON DISEASE

Since Huntington disease is characterized by a pattern of impaired insulin secretion and insulin resistance in the setting of hypercatabolism and weight loss, the presentation of insulin resistance and diabetes appears to be very different than that for the majority of individuals with type 2 diabetes mellitus and the metabolic syndrome. Reductions in insulin secretion suggest a pathophysiology similar to type 1 diabetes mellitus but this form of diabetes is immunologic, not degenerative, in nature and individuals affected suffer from very high mortality without insulin replacement therapy. Nonetheless, it may be useful to consider the possibility that a mechanism by which omega-3 fatty acids exert a beneficial effect on the central nervous system is linked to the beneficial effects of these long-chain dietary fats on insulin resistance.

The potential for drugs that enhance insulin sensitivity to improve the prognosis in Huntington disease patients is a topic that may warrant investigation. In the R6/2 mutant mouse model, metformin treatment has been associated with prolonged survival⁴⁵ and rosiglitazone treatment has been associated with increasing mitochondria mass levels and reduced oxidative stress through a PPAR- γ -mediated mechanism in mutant *huntingtin*-expressing striatal cells.⁴⁶ No current published data exist regarding the effects of fibrates on the pathophysiology of Huntington disease. The derangement of lipid metabolism in Huntington disease and potential for drugs that affect lipid metabolism to be beneficial suggest that research of drugs such as thiazolidinediones and metformin may be fruitful in this genetic disorder.

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Fig. 1.

The cholesterol and triglyceride-phospholipid biosynthesis pathways. The genes in green were found to be decreased in the inducible Huntington disease cell model by microarray analysis; the genes in blue were not present on the microarray filters. All of the genes bearing an SRE in their promoter, and regulated by sterol regulatory element binding proteins (SREBP), are tagged with a red asterisk. Sterol C14-reductase, sterol C4-methyl oxidase, NAD(P)H steroid dehydrogenase, 17 β -hydroxysteroid dehydrogenase-7, 3 β -hydroxysteroid- Δ^8 - Δ^7 -isomerase, sterol C-5-desaturase and desmosterol reductase, localized between Cyp51 and 7DHCRd, are likely also SREBP-dependent genes. The triglyceride-phospholipid biosynthetic pathway has

not yet been carefully analysed in Huntington disease but, based on the findings from Sipione et al. herein summarized, it may well be affected. From 6