

Fenofibrate as a treatment for Huntington's disease

Abstract

Huntington's disease (HD) is a devastating neurodegenerative disease that typically strikes in the prime of life and for which no disease modifying treatment is currently available. The disease is caused by a CAG repeat expansion that translates into an expanded polyglutamine repeat stretch within the Huntingtin protein. Symptoms include movement abnormalities, psychiatric disability and cognitive dysfunction, with multiple regions of the brain affected.

PGC-1 α is a transcriptional co-activator and key regulator of mitochondrial biogenesis. Recent work has highlighted that PGC-1 α links mitochondrial dysfunction and transcriptional dysregulation in many neurodegenerative diseases, including HD. In HD, Alzheimer's disease (AD) and other neurodegenerative diseases, PGC-1 α activity and downstream gene expression is significantly reduced with disease progression. PGC-1 α can partially reverse the toxic effects of mutant Huntingtin (HTT) expression in cultured striatal neurons and neuroprotection elicited by lentiviral-mediated delivery of PGC-1 α in the striatum of transgenic HD mice. Further, PGC-1 α null mice show demonstrable striatal neurodegeneration reminiscent of HD pathology. PGC-1 α protein content in AD is negatively correlated with both neuritic plaque pathology and A β content. Importantly, reconstitution of PGC-1 α expression attenuates hyperglycemic-mediated beta-amyloidogenesis through attenuation of the forkhead-like transcription factor 1 (FoxO3a) expression and promotion of the alpha-secretase processing of APP. These data strongly promote PGC-1 α as a promising target for therapeutic modulation for HD and other neurodegenerative diseases. The therapeutic potential of PGC-1 α up-regulation lies in its ability to increase mitochondrial biogenesis and protect against oxidative stress-mediated cell death.

Because supra-physiologic overexpression of PGC-1 α may cause clinically adverse effects, PGC-1 α levels must be optimized for efficacy. PGC-1 α levels need to be normalized when pathologically down-regulated, as in HD. Thus, pharmaceutical PGC-1 α gene modulation, which allows small molecule-mediated temporal and dose-dependent regulation, will be an attractive treatment option. After screening several thousand FDA-approved drugs for potential PGC-1 α up-regulation, the Federoff group has identified fenofibrate, a well-tolerated, anti-dyslipidemic, as a molecule that can robustly induce PGC-1 α gene expression in central nervous system (CNS) cells. The data suggests that fenofibrate increases PGC-1 α in a dose-dependent manner in the MN9D neuronal cell line and the BV2 microglial cell line. Moreover, fenofibrate robustly protects MN9D cells from induced oxidative injury and prevents lipopolysaccharide (LPS)-induced inflammation in BV2. The neuroprotective effect of fenofibrate has been demonstrated in rodent models of Parkinson's disease, Huntington's disease, schizophrenia, and stroke. The group has also shown that the fenofibrate-mediated anti-inflammatory effect in BV2 cells requires PGC-1 α . Overall, fenofibrate-mediated PGC-1 α up-regulation is posited to be a safe and effective intervention for neurodegenerative diseases, associated with PGC-1 α deficiency and mitochondrial dysfunction. The molecular mechanisms through which fenofibrate regulates PGC-1 α in CNS cells has begun to be elucidated and fenofibrate increases the small heterodimer partner (SHP) in liver by activating the adenosine monophosphate-activated protein kinase (AMPK) signaling pathway in a PPAR α -independent manner. AMPK is an energy sensor and can phosphorylate PGC-1 α and fenofibrate is able to elicit phosphorylation of AMPK. **Here we propose to evaluate pharmacodynamics of fenofibrate in HD cells and safety and efficacy in a pilot study in HD subjects.**

A series of induced pluripotent stem cells from Huntington's disease fibroblasts with CAG repeats ranging from adult onset (40-60 Qs) to juvenile onset (60 and above) alleles will be differentiated into neuronal populations. Differentiated cells will be treated with fenofibrate to assess whether the compound can modulate mutant HTT mediated phenotypes. The mechanistic insights gleaned in these studies will inform anticipated pharmacodynamic readouts in peripheral PMBCs in the planned fenofibrate clinical trial.

We will examine the disease-modifying potential of the PGC-1 α activating agent fenofibrate in a pilot Phase IIa randomized, double-blind, placebo-controlled clinical trial for 6-months in 20 HD subjects. The goal of this pilot trial is to provide preliminary evidence of efficacy and effect sizes for a future Phase IIb trial. The main hypothesis being tested is that fenofibrate increases PGC-1 α levels and slows the progression of HD. Subjects who meet our entry criteria will be randomized (3:1) to either 145mg daily fenofibrate or placebo. Our primary outcome will be change in PGC-1 α levels in leukocyte RNA and protein over the 6-month trial. In secondary analyses, we will examine drug effects on motor, cognitive, psychiatric, and functional outcomes.