Bezafibrate improves mitochondrial function in the CNS of a mouse model of mitochondrial encephalopathy

Natalie Noe, Lloye Dillon, Veronika Lellek, Francisca Diaz, Aline Hida, Carlos T. Moraes, Tina Wenz

A Institute for Genetics and Cluster of Excellence: Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Zülpicher Str. 47A, 50674 Cologne, Germany
B Department of Neurology, University of Miami School of Medicine, Miami, FL 33136, USA
C Department of Cell Biology and Anatomy, University of Miami School of Medicine, Miami, FL 33136, USA

Abstract

Mitochondrial dysfunction frequently affects the central nervous system. Here, we investigated the effect of bezafibrate treatment on neuronal mitochondrial function and its impact on the progression of a mitochondrial encephalopathy. We used a murine model with a forebrain-specific cytochrome c oxidase deficiency caused by conditional deletion of the COX10 gene. In this mouse model, bezafibrate-administration improved the phenotype of the mice associated with an increase in mitochondrial proteins and mitochondrial ATP generating capacity. Bezafibrate-treatment also attenuated astrogliosis and decreased the level of inflammatory markers in the affected tissues. Overall, bezafibrate had a neuroprotective effect in this mouse model of mitochondrial encephalopathy. These findings imply that bezafibrate might be a promising therapeutic agent for the treatment of neurodegenerative disease associated with mitochondrial dysfunction.

© 2012 Elsevier B.V. and Mitochondria Research Society. All rights reserved.

1. Introduction

Mitochondria supply the majority of cellular ATP by the process of oxidative phosphorylation (OXPHOS). Mitochondrial function is central to proper function of the nervous system and several neurodegenerative diseases have been linked to mitochondrial dysfunction (Beal, 2007). Particularly, mitochondrial disease, a class of inherited disorders caused by OXPHOS defects, frequently affects the nervous system resulting in seizures, stroke-like episodes, brain dysfunction and often premature death (DiMauro and Schon, 2008). Up to date, treatment of these mitochondrial encephalopathies is limited (Dimauro and Rustin, 2009).

A common feature of all classes of mitochondrial disease is that residual ATP generating capacity is still present. We have recently shown, that by boosting this residual OXPHOS capacity by increasing the mitochondrial mass prevents the bioenergetic crisis and ameliorates a mitochondrial myopathy (Wenz et al., 2008). The peroxisome proliferator-activated receptor (PPAR) and its co-activator α (PGC-1α) play an important role in activating mitochondrial biogenesis (Lin et al., 2002). PGC-1α expression and activity are controlled by the PPARs (Scarpulla, 2008) as well as by AMPK and Sirt1 (Canto and Mattson, 2009).

PGC-1α has recently emerged as a potential therapeutic target for neurodegenerative disease (McGill and Beal, 2006). In vitro experiments suggest that PGC-1α regulates mitochondrial and increases aerobic glucose metabolism in neuron mass (Izawa et al., 2009; Wareski et al., 2009). Moreover, PPAR agonists are able to prevent neuronal death in a metabolic crisis (Miglio et al., 2009). In neurons, PGC-1α also plays an important role in controlling the anti-oxidant response (St-Pierre et al., 2006), a feature associated with the pathogenesis of neurodegeneration (Gonzalez-Scarano and Baltuch, 1999; Minghetti and Levi, 1998). Other recent work shows that transgenic over-expression of PGC-1α in neurons is beneficial in a mouse models of ALS as well as in the MPTP-mouse model of Parkinson’s disease (Mudo et al., 2012; Zhao et al., 2011).

The PPAR and Sirt1 pathways can be activated pharmaceutically (Wenz et al., 2008). Bezafibrate, a PPAR agonist used for the treatment of hyperlipidemia (Tenenbaum et al., 2005), has been used in recent studies to evaluate its effects in mouse models with mitochondrial dysfunction (Table 1). While in most cases an improved phenotype was observed, the effects on the PPAR-PPG-1α pathway and on mitochondrial mass were variable and tissue specific. Some studies show that bezafibrate induces PGC-1α and increases mitochondrial mass in skeletal muscle (Johri et al., 2012; Wenz et al., 2008), while in other mouse models bezafibrate treatment did not have a significant effect in the same tissue (Dillon et al., 2012a; Viscomi et al., 2011; Yatsuga and Suomalainen, 2012). In liver, prolonged administration of bezafibrate resulted in decreased mitochondrial DNA levels as well as rodent-specific hepatomegaly (Dillon et al., 2012a; Viscomi et al., 2011; Yatsuga and Suomalainen, 2012).

With regard to neurodegenerative diseases, PPAR agonists such as fibrates and glitazone as well as the Sirt1 agonist resveratrol have been
shown to be neuroprotective, presumably by inducing anti-oxidant enzymes and decreasing inflammation (Ates et al., 2007; Besson et al., 2005; Luo et al., 2006; O’Rourke et al., 2004; Pallas et al., 2009; Ramanan et al., 2009; Yi et al., 2008). Bezafibrate administration has been recently shown to be neuroprotective in a mouse model of Huntington’s disease (Johri et al., 2012) as well as in the context of tau pathology (Dumont et al., 2012) (Table 1). In both animal models, an increase in mitochondrial mass markers was reported (Dumont et al., 2012; Johri et al., 2012).

Here we analyzed the effect of bezafibrate treatment on the progression of a mitochondrial encephalopathy in a mouse model and assessed the effect of the drug on neuronal mitochondrial metabolism.

2. Material and methods

2.1. Cell culture work

Human neuroblastoma SH-SY5Y was cultured at 37 °C in humidified 5% CO₂ and 95% air. Cells were pretreated with 250 and 400 μM bezafibrate for 5 days. Cells were then stressed with 6-hydroxydopamine (40 μM, 18 h) or NaN₃ (3 mM, 18 h) while bezafibrate supplementation