Cell Metabolism

Correspondence

Species Differences in the Effects of Bezafibrate as a Potential Treatment of Mitochondrial Disorders

Dear Editor,

Genetic defects of mitochondrial respiratory chain (RC) form an expanding family of rare diseases, whose number and global incidence increase constantly, whereas treatment options remain extremely limited. In line with recent literature data (Bastin et al., 2008) suggesting a potential of bezafibrate for correction of RC defects in human fibroblasts, Viscomi et al. recently published in *Cell Metabolism* the results of in vivo experiments aimed at evaluating the effects of bezafibrate in RC-deficient knockout mice (Viscomi et al., 2011). The conclusions from this study appeared in marked contrast with those drawn from in vitro studies in patient cells and apparently cast doubt on therapeutic properties of bezafibrate in RC deficiencies. However, we consider that limitations in the study design could explain the apparent inefficacy and toxic effects of bezafibrate reported by the authors. Furthermore, based on clinical data obtained in individuals treated with bezafibrate, we present data showing that this drug can stimulate the RC function in the human skeletal muscle.

One of the most questionable points in the study of Viscomi et al. (2011) is the bezafibrate dosage tested in the knockout mice (0.5% drug added to standard diet for 1 month), for several reasons. At first, when using this diet, it is easy to calculate that the daily drug supply is in considerable excess compared to the pharmacological dose used in humans. Indeed, assuming a mouse body weight of 25–30 g and a 4 g/day food intake, 0.5% bezafibrate in chow is equivalent to 666–800 mg/kg/day bezafibrate, i.e., represents up to 80-fold the dose used for the treatment of dyslipidemia (10 mg/kg/day). The second and main concern is the known toxicity and carcinogenic potential of such high doses of fibrate in rodents, established in the early 1980s. Indeed, it is known that a 2-fold increase in liver weight is already observed in mice after 1 week on a diet containing 0.5% bezafibrate, likely due to PPAR-α-mediated induction of genes involved in hepatocyte proliferation (cyclin D1, CDK4, and c-Myc), whereas mice kept on this regimen will develop hepatocarcinoma in the long term (Hays et al., 2005). Importantly, recent studies also show that clinically relevant doses of bezafibrate elicit triglyceride-lowering effects in mice, and no toxic effects (Nakajima et al., 2009).

Taking into account these literature data, there is no rationale to use 0.5% bezafibrate in diet when investigating pharmacological properties of this drug. Furthermore, it appears likely that liver hepatomegaly reported both in treated *Surf 1*$^{-/-}$ and wild-type animals reflects a classical toxic response to high doses of bezafibrate. PPAR agonists at high doses can also induce muscle damages (myofibril degeneration and inflammatory cell infiltration). Accordingly, worsening of muscle damages in *ACTA-Cox15*$^{-/-}$ mice treated by bezafibrate could also be ascribed to toxic effects of bezafibrate overdosage. Under these conditions, conclusions on the therapeutic potential of bezafibrate in RC-deficient mouse models cannot be drawn, and extrapolation to the treatment of RC-deficient patients appears irrelevant.

Importantly, the hepatotoxicity and carcinogenic activity of fibrates are clearly rodent specific. Indeed, it has long been known that humans are resistant to the development of hepatocarcinoma after chronic exposure to fibrates, and large-scale studies performed since the 1980s consistently established that bezafibrate is a safe drug, with limited side effects (Tenenbaum et al., 2005, cited in Bonnefont et al., 2010).

Regarding the possible use of this drug in patients with inborn metabolic myopathies, we tested bezafibrate in patients with the myopathic form of carnitine palmitoyltransferase 2 (CPT2) deficiency, one of the most common inborn mitochondrial fatty acid β-oxidation defects. In contrast with the assumption made by Viscomi et al. (2011) on the basis of their study in mice, this pilot trial did not reveal contraindications in the use of bezafibrate in myopathic patients. On the contrary, CPT2-deficient patients treated by bezafibrate for 6 months at 10 mg/kg/day generally experienced a clear decline in muscular pain and rhabdomyolysis episodes, and less limitation in physical activity. Furthermore, follow up of these patients for 3 years indicated stable beneficial effects of the treatment in the long term, without adverse effects (Bonnefont et al., 2010).

Importantly, as reported here (see Figure S1 available online), we established in the course of this trial that bezafibrate treatment led to an increase in RC capacity in the human skeletal muscle. Indeed, stimulation of RC capacities was reflected by the rise in maximal O_2 consumption observed in muscle mitochondria of treated patients. Thus, as shown in Figure S1A, the oxidation rates of pyruvate + malate (a RC complex I substrate) or of succinate (a RC complex II substrate) markedly increased ($p = 0.028$, two-sided Wilcoxon signed-rank test) after 6 months of bezafibrate treatment in patient muscle mitochondria. Consistent with this, the levels of key RC proteins, i.e., NDUFV1 (complex I) and COX4 (complex IV), encoded by nuclear genes, or COX2, a mitochondrial DNA-encoded gene, were found strongly increased in the muscle of bezafibrate-treated patients (Figure S1B). Finally, cytochrome *c* oxidase (complex IV, COX) and citrate synthase (mitochondrial matrix protein) enzyme activities measured in muscle homogenates significantly increase after bezafibrate treatment (Figures S1C and S1D).

Altogether, our in vivo data, as well as in vitro studies performed in patients' cells, reinforce the notion that activation of the PPAR-PGC1 signaling pathway by bezafibrate could be a promising approach for pharmacological correction of partial FAO or RC deficiencies. Clinical trials will be needed to assess the possible beneficial effects of bezafibrate in various RC disorders and the absence of adverse effects.

SUPPLEMENTAL INFORMATION

Supplemental Information includes one figure and can be found with this article online at doi:10.1016/j.cmet.2011.11.003.

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