Os agonista dos PPARs lesam o Complexo I da cadeia de elétrons mitocondrial a NADH citocromo-c redutase provocando aumento da geração de radicais livres de oxigênio, lesão do DNAmt e diminuição da produção de ATP mitocondrial o que desvia o metabolismo para glicólise anaeróbia, motor da proliferação celular maligna.

Este efeito de lesão do Complexo I é leve com os fibratos – agonistas alfa (clofibrato, bezafibrato, gemfibrozil) e forte com as thiazolidinedionas – agonistas gama (rosiglitazona- “Avandia”, pioglitazon – “Actos”, ciglitazone ) e provoca os conhecidos efeitos colaterais destes medicamentos: lesão hepática, cardíaca, muscular e renal. Os fibratos se ligam fortemente à hemoglobina e podem provocar hipoxia tecidual, o que agrava a hipoxia já existente nos tumores sólidos.

Antes se pensava que os agonistas dos PPARs induziam câncer somente em camundongos e ratos, entretanto tal fato ocorre também em humanos. De fato, o gemfibrozil aumenta a incidência de carcinoma baso-cellular e raises nos trabalhos onde não há aumento da incidência encontra-se aumento da mortalidade por câncer.

Entretanto, vários trabalhos mostram que os agonistas dos PPARs provocam inibição do crescimento, indução da diferenciação e morte de células tumorais por mecanismos extra-receptores (ou por provocar aumento da biogênese tumoral??).

A diferenciação celular pelos fibratos e as glitazonas é parcialmente inibida por antioxidantes como a acetil-cisteína e a microscopia eletrônica nestes casos mostra lesão mitocondrial. (Scatena R. Mitochondria,PPARs,and Cancer: Is Receptor-Independent Action of PPAR Agonists a Key?. PPAR Research, volume 2008, article ID 256251, 10 pages.Italy)

Como no câncer já existe aumento dos radicais livres na mitocondria e impedimento de sua função não é aconselhável usar drogas que certamente provocam lesão do Complexo I, para tratar o câncer.

José de Felippe Junior

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The effect of the hypocholesterolemic drug clofibrate on liver mitochondrial biogenesis. A role for neutral mitochondrial proteases.


**SUMMARY**

The hypocholesterolemic drug clofibrate raises hepatic levels of mitochondria by over 100%, with maximum increase at 2 to 4 days after drug administration, and a slow rise continuing at 10 days. This time response was similar to that seen after partial hepatectomy. However, several clear differences exist. During the doubling in mitochondrial content, no change in particle size or specific content of DNA or RNA was observed, whereas during liver regeneration the former decreases by 50% and the latter increases by 300%. The half-life of 5.8 days for normal mitochondria was not altered significantly by clofibrate, using [guanidino-WLarginine. However, the initial rate of short term incorporation of [35S]methionine into control mitochondria in vivo was 60% of that for drug-tested animals, while the in vitro efficiency of WLeucine incorporation was reversed; mitochondria from drug-treated animals were about 61% as active as those from controls. Enzyme activity of drug-treated animals was not significantly altered for inner membrane or matrix enzymes. However, a 30 to 40% fall in specific activity of three outer membrane enzymes was noted from 2 to 15 days. This resembles changes seen during early liver regeneration. One striking action of clofibrate was to inhibit the neutral protease activity of mitochondria. Even at 2 days on clofibrate, neutral protease activity was inhibited to 62% of the control value of 0.334 pmole of amino acid per hour per mg of protein. Inhibition was a maximum of 50% at 6 days, and was still at 63% at 20 days. Clofibrate added in vitro had negligible influence on neutral protease activity. _ The inhibition was independent of lysosomes since the protease activity of purified lysosomes was neither inhibited, nor was acid phosphatase activity in whole homogenates or the purified mitochondrial fractions changed during drug treatment. The endogenous amino acid content of 0.032 pmole per mg protein remained constant during the stimulation in biogenesis. The results of this study on clofibrate support a hypothesis that net levels of hepatic mitochondria may be controlled by the activity of their own neutral proteases. A possible action is to degrade newly synthesized mitochondrial proteins, which may be structural or binding, such that a lowered protease activity would raise their levels and thereby increase mitochondrial content.

Since the introduction of the hypocholesterolemic drug clofibrate in 1962 (1, 2), an enormous volume of literature has described its useful clinical ability to lower serum levels of both cholesterol and triglycerides. Various hypotheses have been proposed for rationalizing this role. However, none are completely
satisfactory. For example, explanations of the mode of action of clofibrate range from decreased absorption of cholesterol and enhanced excretion (3, 4), through accelerated conversion of cholesterol to bile acids, inhibition of cholesterol synthesis (5), and a redistribution of cholesterol between plasma and tissue compartments (6, 7).

An early observation that hepatomegaly occurred during clofibrate administration (8) stimulated interest in liver function, particularly since this organ is so vitally concerned with lipid and cholesterol transport, as well as cholesterol oxidation to bile acids. Subsequent to this, a useful study was reported by Hess et al. (9), on some specific enzyme changes. They noted a dramatic g-fold increase in hepatic levels of glycerol phosphate dehydrogenase specific activity, a significant (74%) rise in cytochrome c oxidase, as well as a smaller 27% increase in catalase. Strangely, the latter microbody enzyme did not parallel urate oxidase, which fell by 58%. These observations correlated with an early electron microscopy study by Paget (10) who showed an elevated number of normal-sized, but denser mitochondria. More lysosomes were thought to exist, but this could have resulted from staining problems, since the later electron micrographs of Hess et al. (9) strongly supported an elevated number of microbody profiles, not lysosomes. Enzyme estimations (7) supported these latter conclusions. Interestingly, the lack of crystallloid in the acidophilic area correlated with the depressed urate oxidase activity seen after clofibrate treatment.

In 1970 Kurup et al. (11) reported a detailed study on the specific ability of clofibrate to raise hepatic levels of mitochondria. They demonstrated that most of the increase in liver weight could be accounted for by mitochondrial protein alone, and that apart from the dramatic stimulation of glycerol phosphate dehydrogenase activity (9), mitochondrial "quality" was not altered by the drug. A subsequent study with the related compound clofenapate (12), also demonstrated clearly that only hepatic levels of mitochondria were increased, not those of the nuclear, microsomal, or supernatant fractions.

This striking ability of clofibrate to raise levels of hepatic mitochondria provides a basis for a general hypothesis of the hypcholesterolemia and hyperlipidemic properties of the drug. It is known that although cholesterol conversion to bile acids occurs primarily in the cytoplasm, the final side chain cleavage to propionyl-CoA and choolyl-CoA is a mitochondrial step (13, 14).

Thus Kritchevsky et al. (15) described how clofibrate dramatically increased the ability of rat liver to oxidise [14C26]cholestero l 4CO2. However, when their data were normalized per mg of mitochondrial nitrogen, there was no difference between mitochondrial fractions derived from control or clofibrate-treated rats. Consequently, the explanation for these observations probably lies in the ability of the drug to cause a net increase in the amount of mitochondrial protein per animal.

The above experiments might help explain the hypcholesterolemica tion of clofibrate by increase in mitochondrial cholesterol oxidation to bile acids and salts, and has been confirmed by others (16), but remains controversial (3). The former study in dogs was by analysis of bile obtained from a Thomas camilla, whereas the latter (3) involved analysis of fecal steroids and bile salts in humans. Another rationalization, still related to increased hepatic cholesterol synthesis. Several observations support such an idea (5, 17) and specifically pointed to cholesterol synthesis from acetate and not mevalonate as being inhibited, but these findings have been questioned for a discussion, see ef. (5). Since he biosynthetic steps occur extramitochondrially (15), it could be asked how changes in the amount of mitochondria might influence cholesterol synthesis. Recently, however, Burch and Curran (18) found that the activity of mitochondrial acetocetyl-CoA deacylase was markedly increased in rats fed a clofibrate diet. The increase was a surprisingly 65% on a total liver basis, a nd was quantitatively significant in terms of the net cholesterol synthesised.

The authors pointed out that the consequence of the deacylase increase could be a reduced cholesteryl C-acyl-CoA necessary for mevalonate formation, and would fit in with the early observations of Gould et al. (5). They also presented evidence for a strong relationship between a reduction in digitoinsinprecipitably terols and increased eacylase activity. The result could not be demonstrated in vitro, and thus depended on either a metabolite of clofibrate or some time-dependent induction of mitochondria. A recent report, however, describes separate pathways for ketone body formation and cholesterol synthesis (19).

A final involvement for the hypothesis of altered hepatic levels of mitochondria relates to the known hypotriglyceridemic action of clofibrate. One of the earliest known enzymes tivity was that of mitochondrial glycerol-3-phosphate dehydrogenase, high
rose -fold during drug administration (7, 9). A consequence of this rise could be to reduce cytoplasmic levels of glycerol 3-phosphate needed for triglyceride and phospholipid synthesis. Indeed, Fallon et al. (20) reported a 46% lowering of hepatic levels for rats 2 weeks on clofibrate treatment, although these workers thought the best hypolipemic explanation lay in an inhibition of the acyltransferase enzyme, and not with simple lack of necessary substrate.

This brief survey provides good evidence that the hypolipemic activity of clofibrate could well follow from a net increase in hepatic mitochondria. The effect of this could be either to accelerate cholesterol breakdown to bile acids, or inhibit its synthesis, or both, and to decrease glycerol 3-phosphate availability for triglyceride and phospholipid synthesis needed for very low density lipoprotein formation.

The research to be reported here was undertaken to investigate how clofibrate might act in altering levels of liver mitochondria, and to provide a firm basis for the hypothesis that the hypolipemic action of clofibrate is correlated with an increased liver content of mitochondria. The results of this study support the conclusion that clofibrate inhibits mitochondrial eutrial protease activity, and thereby raises the synthesis of newly synthesized protein for incorporation into mitochondria.