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COMMENTARY

Burn after feeding. An old uncoupler of oxidative phosphorylation is redesigned for the treatment of nonalcoholic fatty liver disease.

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Fatty liver

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Triacylglycerol

Abbreviations: BAT, brown adipose tissue; CYP, cytochrome P450; DAG, diacylglycerol; DNP, 2,4-dinitrophenol; FAO, fatty acid oxidation; DNPME, 2,4-dinitrophenol-methyl ether; NAFLD, nonalcoholic fatty liver disease; OXPHOS, oxidative phosphorylation; PKC ϵ , protein kinase C- ϵ ; ROS, reactive oxygen species; TAG, triacylglycerol; T2D, type 2 diabetes; UCP1, uncoupling protein-1; WAT, white adipose tissue

Summary

Uncoupling of oxidative phosphorylation (OXPHOS) in brown adipose tissue can be used by hibernating animals to produce heat at the expense of their fat mass. In a recent work, Dr Shulman and collaborators generated a liver-targeted derivative of the prototypical OXPHOS uncoupler 2,4-dinitrophenol (DNP) that alleviated steatosis, hypertriglyceridemia and insulin resistance in several model of nonalcoholic fatty liver disease and type 2 diabetes.

Oxidative phosphorylation (OXPHOS) is a fundamental biological process allowing the synthesis of mitochondrial ATP in most cells. During OXPHOS, energy production is coupled to the oxidation of endogenous substrates such as fatty acids and pyruvate. In some physiological situations, oxidation of these substrates can be uncoupled from ATP synthesis. This is for instance the case in brown adipose tissue (BAT) where OXPHOS uncoupling is a key mechanism whereby hibernators are generating heat to maintain a body temperature compatible with life[1,2]. OXPHOS uncoupling in BAT is mediated by the uncoupling protein-1 (UCP1), which is embedded within the inner mitochondrial membrane[1,2]. UCP1 facilitates proton entry into the mitochondrial matrix, and thus the energy of the proton-driven membrane potential ($\Delta\psi$) is dissipated into heat instead of being converted in ATP by the ATP synthase (Fig. 1A). Importantly, OXPHOS uncoupling is leading to a stimulation of substrate oxidation since this biochemical process is no longer controlled by ATP synthesis. In BAT, the preferred oxidative substrates are fatty acids that have been stored as triacylglycerol (TAG) molecules prior to hibernation[1,2] (Fig. 1A). At the end of the winter hibernating animals can lose as much as 40% of their body weight, mainly as fat mass, which has been burnt for thermogenesis[2-4].

Many researchers working in the field of mitochondria are using for different purposes synthetic OXPHOS uncouplers such as 2,4-dinitrophenol (DNP) or carbonyl cyanide m-chlorophenylhydrazone (CCCP). These compounds are also referred to as protonophoric uncouplers because their chemical structures allow the transport of protons across the inner mitochondrial membrane. Hence, DNP and CCCP can induce maximal mitochondrial respiration with different substrates including fatty acids, loss of the membrane potential $\Delta\psi$ and abolition of ATP synthesis in isolated mitochondria and intact cells [5-7]. It is also noteworthy that different pharmaceuticals currently on the market can uncouple OXPHOS. Indeed, this has been shown with the local anesthetic bupivacaine, the antiarrhythmic agent amiodarone, the nonsteroidal antiestrogen tamoxifen and different nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac, ibuprofen and salicylic acid [7-10]. Importantly, OXPHOS uncoupling can be an important mechanism whereby drugs can induce liver injury in some patients[10-12].

The treatment of obesity and related metabolic disorders such as type 2 diabetes (T2D) and nonalcoholic fatty liver disease (NAFLD) is a matter of extensive investigations because these diseases are a major burden for public health and medical care systems. Regarding NAFLD, reduction of *de novo* lipogenesis and stimulation of fat oxidation are two major

pharmacological strategies that are currently tested [13,14]. In particular, drug-induced increased fat utilization can be achieved by way of activation of peroxisome proliferator-activated receptor- α (PPAR α), PPAR δ , and AMP-activated protein kinase AMPK [13-17]. Another strategy under investigation is the stimulation of mitochondrial fatty acid oxidation (FAO) by the OXPHOS uncoupler DNP and its derivatives DNP-methyl ether (DNPME), as proposed by Dr Shulman and collaborators [18,19]. Indeed, this group already showed in 2004 that the treatment of obese rats for 3 days with low doses (16 mg/kg/day) of DNP alleviated fatty liver and hepatic insulin resistance [18]. Furthermore, amelioration of the latter metabolic disturbance was accompanied with a normalization of the activity of protein kinase C- ϵ (PKC ϵ) and c-Jun NH₂-terminal kinase-1 (JNK1), two kinases impairing insulin signaling [18].

Although these early results were encouraging and demonstrated the effectiveness of this pharmacological strategy, the authors wished to develop a safer compound for further investigations [19]. Indeed, DNP was used in the 1930's in different countries as a treatment of obesity but this remedy was rapidly withdrawn from the market due to significant toxicity [20]. For instance, severe hyperthermia, cardiovascular collapse and death were sometimes observed [21]. In addition, skin rashes, cataracts, agranulocytosis and neutropenia, deafness and liver injury with jaundice occurred in some patients [20,21]. Hence, although DNP-induced OXPHOS uncoupling and stimulation of mitochondrial FAO can alleviate obesity and fatty liver [18,20,21], its low therapeutic index and adverse effects preclude any registration to national drug agencies.

In order to develop a safer OXPHOS uncoupler, Dr Shulman and collaborators thus generated 5 derivatives of DNP that could be metabolized to DNP by cytochromes P450 (CYPs) [19]. Indeed, the working hypothesis was that hepatic biotransformation of the DNP derivatives to the parent compound would allow its local generation and consequently no (or minimal) OXPHOS uncoupling in extra-hepatic tissues (Fig. 1B). Hence, this strategy could minimize some side effects such as hyperthermia and cardiac dysfunction. These different compounds were screened for their ability to stimulate mitochondrial oxygen consumption in isolated hepatocytes with similar potencies to DNP. This screening allowed selecting 2 candidates but one of them was not retained because its physicochemical properties would not permit oral administration. Thus, DNP-methyl ether (DNPME) was selected for further *in vivo* investigations in rats.

A first set of investigations was performed in order to determine the safety profile of the selected molecule, as well as its ability to reduce liver TAG levels in rats fed a high-calorie diet[19]. From these experiments, it was found that a 5-day treatment with different doses of DNPME was far less toxic than DNP, in particular regarding liver and kidney injury as well as mortality. The dose of 5 mg/kg of DNPME was selected for further investigations since it was the lowest effective dose without significant toxicity. Importantly, other toxicological studies were carried out during 6 weeks and no deleterious effects were observed on the selected markers. Other investigations showed that after acute injection of 5 mg/kg of DNPME, DNP was found mainly in plasma, liver and kidney and to a lesser extent in heart, whereas much lower DNP levels were found in white adipose tissue (WAT), brain and skeletal muscles (quadriceps). In these experiments, it was noteworthy that DNPME was present at high levels in WAT compared to the other investigated tissues. Finally, a 7-day treatment with the same dose of DNPME showed a comparable kinetics profile with relatively high DNPME levels in WAT[19]. Thus, it appears that DNPME is metabolized mainly in liver to DNP, which undergoes renal excretion, and that DNPME accumulates in WAT.

In order to determine whether DNPME (5 mg/kg) could be effective for the treatment of NAFLD and associated metabolic disorders, additional investigations were carried out in rats fed a high-fat diet with sucrose-supplemented drinking water[19]. A first set of experiments showed that DNPME reduced preexisting hypertriglyceridemia, hyperglycemia and hyperinsulinemia, as well as TAG levels in liver and quadriceps. Moreover, DNPME induced an early increase in mitochondrial FAO in liver but not in heart, quadriceps, brain and kidney. Interestingly, the authors found a 50% reduction in hepatic very-low-density lipoprotein (VLDL) production with DNPME treatment. This could explain, at least in part, why TAG levels were reduced in skeletal muscle despite the absence of mitochondrial FAO stimulation in this tissue. Other investigations showed that hepatic and muscle levels of diacylglycerol (DAG) were significantly reduced and this was associated with lower PKC ϵ and PKC θ activity in liver and muscle, respectively. Moreover, DNPME-induced improvement of insulin sensitivity appeared to be related, at least in part, to the reduction of DAG levels since ceramide levels were unchanged in liver and muscle. Importantly, body weight, energy expenditure and food intake were unchanged during the 5-day period of DNPME treatment [19]. A second set of investigations was subsequently performed in two different rat models of T2D. In the first model, rats were fed a high-fat diet and treated with low doses of streptozotocin, an alkylating agent particularly toxic to the pancreatic beta cells [22]. In the

second model, Zucker Diabetic Fatty (ZDF) rats were fed a high-fat diet and sucrose-supplemented drinking water. In both models, DNPME treatment reduced fasting plasma glucose, insulin and TAG levels as well as liver and quadriceps TAG content with no signs of hepatic or renal injury [19].

Taking all these results into consideration, this study undoubtedly provides a major breakthrough in the treatment of NAFLD. Indeed, activation of mitochondrial FAO is currently considered as a major strategy to alleviate NAFLD [13-17,23], although the effects observed with some drugs stimulating FAO were somewhat disappointing in patients. For instance, treatment with fibrates afforded no (or minimal) effects on fatty liver in clinical studies [24,25], whereas these PPAR α activators were efficient in different rodent models of NAFLD [13]. It is still unclear why fibrates seem less efficient in alleviating NAFLD in humans, but possible hypotheses include lower basal PPAR α expression and/or lesser ligand-induced PPAR α transactivation activity [13]. Obviously, inter-species differences will not pose a problem with DNPME since the proton-driven membrane potential $\Delta\psi$ is a universal feature of mitochondria.

As previously mentioned, treatment with DNPME for 5 days did not modify the body's energy expenditure in treated mice [19]. Although this may suggest that DNPME has no major effect in BAT in the short term, it will be interesting to carry out further investigations in this tissue but also in beige adipose tissue (also referred to as inducible brown, brown-in-white, or brite adipose tissue). Indeed, recent investigations in adult humans showed that brown and beige adipose tissues could be interesting targets to treat obesity and related metabolic diseases [26,27].

Although the data presented by Dr Shulman *et al.* indicated that DNPME was devoid of apparent toxicity in the different rat models used in their study, further investigations will be required to better determine the safety profile of this molecule. Indeed, targeting DNP generation in the liver could avoid some side effects related to OXPHOS uncoupling such as hyperthermia and cardiac dysfunction, but not others that are more likely idiosyncratic reactions (e.g. skin rashes, neutropenia...). Regarding OXPHOS uncoupling, it is noteworthy that DNPME tended to increase oxygen consumption in isolated mouse heart and kidney mitochondria [19]. Moreover, DNPME significantly enhanced oxygen consumption in isolated mouse liver mitochondria [19]. These data thus indicate that DNPME is converted to DNP within mouse mitochondria, at least in some tissues. For a safety concern,

additional investigations would be warranted to find out whether DNPME could uncouple OXPHOS in mitochondria isolated from different human tissues.

It would also be important to determine whether long-term treatment with DNPME could favor oxidative stress in liver. Indeed, several studies showed that mitochondrial FAO can generate significant amount of reactive oxygen species (ROS) in different tissues including the liver [28-30]. ROS production during the mitochondrial FAO process seems to occur not only within the respiratory chain but also at the level of some FAO enzymes such as acyl-CoA dehydrogenases and ETF-ubiquinone oxidoreductase [30,31]. Importantly, ROS production by these mitochondrial FAO enzymes is relatively insensitive to the mitochondrial membrane potential $\Delta\psi$ and thus to OXPHOS uncoupling [30,31]. It is also noteworthy that FAO-driven ROS production could be higher in NAFLD, in particular in nonalcoholic steatohepatitis (NASH) [32]. Indeed, this liver lesion is associated with significant impairment of the respiratory chain activity, which greatly favors the leakage of electrons and thus ROS overproduction [32,33]. It should also be pointed out that OXPHOS uncoupling appears to be an important mechanism of drug-induced liver injury [10-12], as previously mentioned.

Another issue that would need further exploration with DNPME is the identification of metabolite(s) other than DNP. Indeed, CYP-mediated biotransformation can lead to numerous metabolites, even when the parent drugs are small-sized molecules [34,35]. Although most of drug metabolites are harmless, CYPs occasionally generate reactive metabolites that can be highly hepatotoxic [35,36]. It is noteworthy that DNPME is a structural analogue of anisole, which can be metabolized by CYPs to phenol and two different hydroxyanisole derivatives by way of O-dealkylation and aromatic hydroxylation, respectively [37]. Moreover, DNP has been shown to be metabolized to aminonitrophenol and diaminophenol, which could augment the activity of some CYP isoforms [38]. Hence, further investigations will be needed to identify the full spectrum of DNPME metabolites and to determine whether DNPME could interact with the biotransformation of some marketed drugs. This might be an important issue because obese patients are consuming on average more drugs than non-obese individuals [39], while polypharmacy increases the risk of drug-drug interactions [40]. Moreover, the activity of some CYPs are enhanced in NAFLD and this could favor drug-induced liver injury in some patients [36,41].

As already mentioned, DNPME administration in rats resulted in its accumulation in WAT, whereas little amount of DNP was detected in this tissue [19]. Importantly, investigations in

rodents and humans showed that CYPs are expressed at significant levels in WAT [42-44]. Moreover, CYP expression in this tissue can be increased by different lipophilic drugs such as phenobarbital and dexamethazone [42,43]. Thus, further studies should be carried out to determine whether such co-mediations could augment the biotransformation of DNPME to DNP in WAT, which might induce significant heat production and undesirable hyperthermia. Despite these potential issues, one can wish that DNPME will prove useful in obese patients for the treatment of fatty liver, a liver lesion that can progress to NASH, cirrhosis and hepatocellular carcinoma [45,46].

Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

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Legend of the figure

Figure 1: Consequences of oxidative phosphorylation uncoupling on fat metabolism and heat production. Panel A. In the brown adipose tissue (BAT), uncoupling of oxidative phosphorylation (OXPHOS) is mediated by the uncoupling protein-1 (UCP1), which is inserted within the inner mitochondrial membrane. UCP1 transfers protons (H^+) across the inner mitochondrial membrane, thus stimulating the mitochondrial fatty acid oxidation (FAO) and generating heat. Indeed, during OXPHOS uncoupling, mitochondrial FAO is uncoupled from ATP production and thus the energy of the proton-driven membrane potential $\Delta\psi$ is dissipated into heat instead of being used for ATP synthesis. This system is utilized by the hibernating animals to maintain a body temperature compatible with life. This is associated with a large decrease in the triacylglycerol (TAG) levels stored in adipose tissue because TAG are hydrolyzed into free fatty acids (FFA), which are subsequently used as fuel for the mitochondrial FAO pathway. Panel B. In liver, 2,4-dinitrophenol (DNP) is able to uncouple OXPHOS and stimulate mitochondrial FAO because this protonophoric uncoupler is able to transport protons across the inner mitochondrial membrane. In a recent work, Dr Shulman and collaborators generated a derivative of DNP, DNP-methyl ether (DNPME) that can be metabolized to DNP by cytochromes P450 (CYPs), thus allowing DNP formation principally in the liver [19]. This local OXPHOS uncoupling avoids an increase in body temperature but leads to a reduction of TAG and diacylglycerol (DAG) levels in fatty liver. Alleviation of steatosis is also associated to a reduction of plasma hypertriglyceridemia (not shown) and insulin resistance in liver and skeletal muscle.

