Cyanide and uncoupling protein function: reply

We would like to thank Dr Eduardo Rial for the interest in our study and acknowledge his critical comment that sodium cyanide is not an appropriate compound to mimic the thermogenic properties of uncoupling protein 2 (UCP2). UCP2 uncouples adenosine triphosphate (ATP) production from mitochondrial respiration and thereby converts the loss of potential energy in heat production. In our study, we describe cyanide as a "well-known uncoupler of mitochondrial respiration", which assumes a similar mode of action as that of UCP2. As pointed out correctly by Dr Rial, sodium cyanide is not a classical uncoupling agent such as the carboxyl cyanide derivatives carbonyl cyanide m-chlorophenyl hydrazone (CCCP) and p-trifluoromethoxy carbonyl cyanide phenyl hydrazone (FCCP), but a respiratory chain inhibitor that binds to cytochrome c oxidase. In this regard, our terminology is indeed misleading. However, some textbooks in toxicology describe that the toxicity of cyanide results from inactivation of cytochrome oxidase, thus "uncoupling" mitochondrial oxidative phosphorylation.1,2

Given that cyanide inhibits mitochondrial respiration, the generation of a proton gradient across the inner mitochondrial membrane is inhibited. As a consequence, heat production via the uncoupling activity of UCP2 or non-protein membrane pores should be affected as well. We agree that this assumption contradicts the observed increase in temperature (ΔT = 0.13 ± 0.04°C) after administration of sodium cyanide to mice J774A.1 macrophages.2 Nonetheless, cyanide-mediated thermogenesis was highly reproducible in this type of cells. Interestingly, Prabhakaran et al.5 reported that treatment of mesenchymal cells with cyanide for 6 h or longer upregulated UCP2 expression. In our experiments, the increase in temperature after cyanide treatment was observed within 10 min, which rules out increased levels of UCP2 protein. However, cyanide might interfere with UCP2 by increasing its activity, resulting in an increase in temperature. One finding in favor of this theory is that cyanide induces a rapid burst of reactive oxygen species (ROS).1,6,7 Superoxide (or its products), in turn, activates UCPs, including UCP2, leading to an increase in mitochondrial proton conductance at the matrix side of the mitochondrial inner membrane.9,10 This effect is abolished by low concentrations of the mitochondrial targeted antioxidants mitoQ or mitoVIT E.10 It should be noted that the control of ROS production by UCP2 underlies a putative protective role against oxidative damage, as observed, for example, in vulnerable atherosclerotic plaques. Indeed, several lines of evidence suggest that the production of ROS by monocytes/macrophages, as main cellular component of the plaque, is at least in part regulated by UCP2 under various stress conditions.11,12 In this light, we recently reported that UCP2 in early atherosclerotic lesions probably fulfills an atheroprotective effect by reducing ROS production and/or by inhibiting monocyte recruitment.14 If the macrophage content of the plaque increases and the plaque progresses towards an unstable phenotype, ROS production is overwhelming, and possibly cannot be counteracted by the antioxidant properties of UCP2. In that case, the increasing number of UCP2-positive macrophages inside advanced plaques correlates with increased plaque temperature. This thermogenic effect can be detected by intravascular thermography, as outlined in our most recent study,2 and may be indicative of rupture-prone regions.

References


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