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COMMENTARY

Mitochondria as pharmacological targets

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In the last decade, mitochondria have provided a vast area of research for the pharmacologist, with a wealth of potential targets for drug action. Correct target identification and subsequent pharmacological manipulation might greatly help in the prevention and/or treatment of a number of the most prevalent diseases of our time including cancer, neurodegenerative disease and myocardial infarction. This is a commentary to accompany the publication of three papers in this issue of the *BJP* by Kurz *et al.*, Pravdic *et al.* and Puerta *et al.* on different aspects of pharmacology involving mitochondria.
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This article is a commentary on Pravdic *et al.*, pp. 220–232, Puerta *et al.*, pp. 233–245 and Kurz *et al.* pp. 246–257 of this issue. To view these papers visit http://dx.doi.org/10.1111/j.1476-5381.2010.00698.x http://dx.doi.org/10.1111/j.1476-5381.2010.00663.x and http://dx.doi.org/10.1111/j.1476-5381.2010.00656.x

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Abbreviations: Akt, serine/threonine kinase; ATP, adenosine triphosphate; MDMA, methylenedioxymethamphetamine; mPTP, mitochondrial permeability transition pore; NO, nitric oxide; NOS, NO synthase; ROS, reactive oxygen species

Mitochondria, from the Greek *mito* (thread) and *chondros* (little granules), are cellular organelles long known to be associated with the generation of energy via the formation of most of the ATP required by the cell. This is achieved through oxidative phosphorylation – a series of chemical reactions involving the oxidation of nutrients via the flow of electrons along an electrochemical gradient. The number of mitochondria in cells varies greatly, and their appearance, organization and distribution are constantly changing. Unlike other organelles, the mitochondria contain their own DNA, as well as their own transcriptional and translational machinery (Chen and Butow, 2005). Their 'bacteria-like' appearance and characteristics led to the suggestion that mitochondria might have evolved as a consequence of the incorporation of oxygen-consuming bacteria into the cytosol of other microorganisms, resulting in the development of multicellular organisms that are not only resistant to the oxidizing properties of oxygen, but can utilize them to generate energy (Lane, 2005).

Evolution over a billion years has led to the progressive loss of mitochondrial independence and to a relationship that can occasionally be detrimental to the cell. Indeed, mitochondria are known to play a role in cell death, specifically in apoptosis (Green and Reed, 1998). Mitochondrial permeability is controlled by proteins of the Bcl-2 family, the balance of whose opposing activities is fundamental in the 'life-or-death' decision of the cell (Dewson and Kluck, 2009). Mitochondria also contain a number of pro-apoptotic proteins that are released into the cytosol following mitochondrial stress and the formation of the so-called mitochondrial permeability transition pore (mPTP). Regulation of these processes might afford cell protection in different types of noxious conditions, including ischaemia and ischaemia–reperfusion damage.

Signalling with free radicals

Recently, mitochondria have been demonstrated to act as signalling organelles, through the release of free radicals or regulation of the oxygen concentration in their environment. In this way, they play a role in the activation of signalling cascades, physiologically, during host defence or in the initiation and development of pathophysiology. It has been known since the 1970s that a small proportion of the oxygen consumed by the mitochondria is converted to the superoxide radical, which itself can be converted, at least in part, to hydrogen peroxide by mitochondrial superoxide dismutase (Cadenas and Davies, 2000; Murphy, 2009). The precise mechanism by which these free radicals are released is still not clear. However, it has been proposed that they are generated during hypoxia (Guzy and Schumacher, 2006). Another

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possibility is that regulation of the redox state of the electron transport chain by nitric oxide (NO) may be the determinant factor in their release (Moncada and Erusalimsky, 2002; Taylor and Moncada, 2009). Furthermore, it is possible that in order to exert some of their actions, reactive oxygen species (ROS) generated during oxidative phosphorylation might require ROS produced by other enzymes, located either in the mitochondria or in the cytosol. Current knowledge suggests that free radicals in large quantities are cytotoxic, participating in the genesis of a number of conditions including cancer and the metabolic syndrome, as well as the ageing process. Free radicals in small concentrations, generated physiologically may, however, be beneficial because they might be involved in the maintenance of an antioxidant defence in tissues. Therefore, an area of particular research interest is the role of mitochondrially generated free radicals, together with the signalling cascades that lie downstream from them and the conditions in which they are activated. Such pathways include protein kinases, phosphoprotein phosphatases and redox-sensitive transcription factors.

Metabolic dysfunction and cancer

In addition to the electron transport chain, mitochondria contain a number of other enzymic systems, some of which are involved in the generation of key intermediates for the synthesis of proteins, lipids and nucleic acids required for cell growth and replication. Interest in this area of research is likely to increase exponentially in the next few years because it is possible that some of these enzymes might be targets for the prevention or treatment of cancer (Vander Heiden *et al*., 2009).

Mitochondrial biogenesis has been shown to be stimulated by endothelial NO synthase (eNOS)-derived NO acting on the soluble guanylate cyclase, and a major transcriptional regulator of mitochondriogenesis, peroxisome proliferator-activated receptor γ co-activator 1α. Mitochondriogenesis following cold exposure or caloric restriction is reduced in eNOS-deficient mice, providing further evidence that the NO–guanylate cyclase pathway modulates body energy consumption. In several animal models of obesity, eNOS expression and mitochondrial biogenesis have been shown to be reduced in a manner that can be reversed by preventing the signalling of the inflammatory mediator, tumour necrosis factor-α. This has led to the suggestion that defective mitochondriogenesis, resulting from the low-grade inflammation that characterizes obesity and metabolic syndrome, might be an early component of cardiovascular disease risk (Nisoli *et al*., 2007).

It is also becoming clear that there is a connection between metabolic diseases and neoplastic transformation, and that the predisposition to cancer associated with these conditions might be related to changes in metabolic pathways that alter nutrient utilization in cells. Indeed, a number of prototypes acting at different points in the phosphatidylinositol 3-kinase/Akt pathway, which is involved in energy sensing and modulation, are being investigated in cancer. Furthermore, drugs acting on this pathway that have been developed for the treatment of diabetes might be beneficial in cancer, either alone or as adjunct therapy to other treatments (Calle and Kaaks, 2004). It remains to be investigated whether early metabolic changes, including changes in mitochondrial pathways, predispose to both cancer and metabolic diseases, or whether the metabolic changes are a requirement for neoplastic transformation. Such studies are likely to suggest further targets for pharmacological intervention.

Mitochondrial pharmacology in the CNS and heart

The three papers on mitochondria published in this issue of the *British Journal of Pharmacology* illustrate yet other properties of mitochondria and the consequences of their manipulation, and demonstrate that mitochondrial pharmacology is as relevant to the CNS as it is to peripheral pathology. Thus, Puerta *et al*. (2010) show that methylenedioxymethamphetamine (MDMA, ecstasy), which causes loss of dopaminergic cell bodies, reduced the activity of complex I of the electron transport chain, and increased the generation of superoxide anion. Both MDMA-induced superoxide generation and neurotoxicity were reduced by α-lipoic acid. The authors conclude that complex I inhibition and generation of superoxide cause MDMA neurotoxicity. These results may also have relevance for other conditions with loss of dopaminergic neurones, as in Parkinson's disease. Another major neurodegenerative condition, Alzheimer's disease, is the setting of the work by Kurz *et al*. (2010). These authors show that the metabolic enhancer piracetam prevented the decrease in mitochondrial membrane potential and fall in ATP production associated with β-amyloid peptide, suggesting that improving mitochondrial function could protect against the neurodegeneration also induced by β-amyloid peptide. Finally, Pravdic *et al*. (2010) return to the periphery and show that the anaesthetic isoflurane, given at the onset of reperfusion (anaesthetic post-conditioning), inhibited mitochondrial respiration, depolarized mitochondria and acidified mitochondrial pH. These events may lead to inhibition of mPTP opening and preservation of mitochondrial membrane potential and ATP production, so that anaesthetic post-conditioning may derive from protection of mitochondrial function rather than blockade of neuronal transmission.

We look forward to many more of these exciting observations.

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