BJP British Journal of Pharmacology

DOI:10.1111/bph.12679
www.brjpharmacol.org

Themed Issue: Mitochondrial Pharmacology: Energy, Injury & Beyond

EDITORIAL

Mitochondrial pharmacology: energy, injury and beyond

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Keywords
mitochondria; energetics; cell death; mitochondrial diseases; models for mitochondrial disorders; drug targets

While the mitochondrion has long fascinated biologists and the sheer diversity of druggable targets has made it attractive for potential drug development, there has been little success translatable to the clinic. Given the diversity of inborn errors of metabolism and mitochondrial diseases, mitochondrially mediated oxidative stress (myopathies, reperfusion injury, Parkinson's disease, ageing) and the consequences of disturbed energetics (circulatory shock, diabetes, cancer), the potential for meaningful gain with novel drugs targeting mitochondrial mechanisms is huge both in terms of patient quality of life and health care costs. In this themed issue of the *British Journal of Pharmacology*, we highlight the key directions of the contemporary advances in the field of mitochondrial biology, emerging drug targets and new molecules which are close to clinical application. Authors' contributions are diverse both in terms of species and organs in which the mitochondrially related studies are performed, and from the perspectives of mechanisms under study. Defined roles of mitochondria in disease are updated and previously unknown contributions to disease are described in terms of the interface between basic science and pathological relevance.

LINKED ARTICLES

This article is part of a themed issue on Mitochondrial Pharmacology: Energy, Injury & Beyond. To view the other articles in this issue visit http://dx.doi.org/10.1111/bph.2014.171.issue-8

Themed Issues take time to come to fruition and in this case, because of the complexity of the topic, progress was dependent upon the assembly of an interactive team of editors. While the initial idea for a Themed Issue focused on mitochondria arose in 2011, real progress was not achieved until three editors met in December 2012 and conceptualized the Aims and Scope for the BJP website. Our scope was deliberately broad from molecules in drug development and targets to mechanisms, models and disease to capture the great contemporary interest in mitochondrial biology. As authors' contributions were beginning to enter the editorial pipeline in June 2013 the topic of mitochondrial disease hit the British and international press – the British National Health Service announced plans to create babies with the DNA of three people involving 'mitochondrial replacement' therapy. How timely for a BJP Themed Issue!

This topic of inborn errors of metabolism features here within contemporary reviews (Kanabus *et al.*, 2014; Komen and Thorburn, 2014). Molecular diagnosis and how we discover novel and rare mitochondrial diseases is also covered with insights into the strategies of next-generation sequencing and bioinformatics (Carroll *et al.*, 2014). A key goal in mitochondrial disease, be it an inherited disorder, neurodegenerative condition or cancer, is turning up energy production (Komen *et al.*, 2014; Swerdlow, 2014). Here gene therapy and pharmacological approaches rate mentions as possible treatments. An intriguing gene therapy proposal is to bypass the defective mitochondrial complex by expression of the alternative oxidase gene (El-Khoury R *et al*, 2014). Pharmacological approaches include the use of benzafibrate, resveratrol and AlCAR – currently available molecules that may be useful because of their actions on mitochondrial biogenesis. This concept introduces us to perhaps the hottest topic in mitochondrial biology, 'mitophagy' or mitochondrial autophagy where PubMed identifies 582 articles in 2013 with mitochondria scoring 7161 'hits'. Mitophagy in its broader context of

mitochondrial quality control features strongly here with perspectives from basic (Baker *et al.*, 2014), cardiovascular (Hall *et al.*, 2014; Jimenez *et al.*, 2014), diabetic (Higgins and Coughlan, 2014) and neurological (Celardo *et al.*, 2014; Osellame and Duchen, 2014) fields.

Exciting developments in drug design and application receive appreciable attention. Using a cheminformatic screening approach, Ivanes *et al.* (Ivanes *et al.*, 2014) were able to identify a compound which could protect against ischaemic injury by selectively inhibiting reverse mitochondrial F_1F_o-ATPase activity without compromising ATP synthesis. Interestingly, this also rescued the defective haemoglobin synthesis in zebrafish mutants lacking an endogenous ATPase inhibitor. Of great interest are drugs aimed at mitochondrial targets regulating key events in 'death' cascades of programmed cell death, including the redistribution of the key death signalling factor cytochrome c. Amongst numerous attractive targets are Bcl-2 family proteins whose members regulate the life/death decision determining the survival of threatened cells. There have been major advances in this area, including the use of *in silico* molecular analyses and medicinal chemistry to develop drugs targeting Bcl-2 family proteins (Roy *et al.*, 2014) which hold therapeutic potential for various types of cancers, autoimmune and neurodegenerative conditions. Clerc *et al.* (Clerc *et al.*, 2014) analysed the actions of a high-affinity, Bcl-2 antagonist (ABT-737) to explore the interface between mitochondrial fission, apoptosis and cytochrome c release. Other forms of programmed cell death offer promising therapeutic possibilities and, with inhibitors of poly (ADP-ribose) synthetase 1 (PARP-1) having entered clinical trials, Fatokun *et al* (Fatokun *et al.*, 2014) offer a timely review of parthanatos, a novel form of programmed cell death occurring through overactivation of PARP-1.

Cytochrome c and energy production raise their heads again via cardiolipin (Birk *et al.*, 2014), which is an attractive target since modulation of its function on the inner mitochondrial membrane enables restoration of bioenergetics in aging and diseased tissues. Indeed a fascinating cardiolipin-protective compound which has been developed shows promise as a novel therapeutic agent (Szeto, 2014). Integral to such considerations are the alterations in lipid environment, which affect the mitochondrial membrane potential and the efficiency of the electron transport. In fact, fatty acids and lipids can act either directly or indirectly to modulate various aspects of mitochondrial function, including to disrupt energy metabolism perhaps via hexokinase detachment, and as such are of great interest as anti-cancer drugs (Murray *et al.*, 2014). Conversely, the degree of mitochondrial localization of hexokinase has major metabolic consequences, not only by inhibiting fatty acid oxidation but also by elevating energy metabolism. To this end, ischaemic pre-conditioning, metformin and microRNAs are being explored as means of stimulating mitochondrial hexokinase localization in the settings of myocardial infarction, stroke, elective surgery and transplantation (Nederlof *et al.*, 2014). Fillmore *et al.* (Fillmore *et al.*, 2014) address how targeting fatty acid oxidation to therapeutically regulate cardiac energy metabolism is beneficial for treating heart disease. Another strategy offering a new approach for cardioprotection is that of enhancing drug accumulation in mitochondria by its conjugation to the triphenylphosphonium cation – Nadtochiy *et al.* (Nadtochiy *et al.*, 2014) demonstrate the effectiveness of this approach using conjugated nitro-linoleate, which they demonstrate protects cardiac cells in a mitochondrial-dependent manner. Obviously, bioenergetics is a key consideration in mitochondrial biology whatever the system under investigation, and in a comprehensive review, Szabo *et al.* (Szabo *et al.*, 2014) discuss the paradoxical actions of H_2S which can exert anti- or pro-oxidant effects with consequent changes in cellular ATP generation, in accordance with its concentration. These issues are highly pertinent to the pathophysiological and therapeutic consequences of H_2S production on circulatory shock, diabetes, cancer and, perhaps more unexpectedly, on its possible application in the development of therapeutic 'suspended animation' (Módis *et al.*, 2014).

Mitochondrial dysfunction and its consequence, oxidative stress, have long been considered contributory factors in many acute and chronic disorders of the CNS. Indeed, Pfeiffer *et al.* (Pfeiffer *et al.*, 2014) suggest that mitochondrial and metabolic adaptations play an important role in neuronal resistance against chronic oxidative stress. Grubman *et al.* (Grubman *et al.*, 2014) point out that transition metals (Cu^{2+}, Zn^{2+}, Mn^{2+} & Fe^{2+}) are localized to various mitochondrial compartments, with Fe^{2+} and Cu^{2+} particularly important for the electron transport chain and ATP production. Loss of homeostasis of discrete metal pools contributes to numerous neurodegenerative conditions and there have been notable advances in the therapeutic targeting of metal-modulating compounds, which act by a common theme of protecting mitochondrial function through anti-oxidant mechanisms. Anzovino *et al.* (Anzovino *et al.*, 2014) focus on Friedreich's ataxia, an inherited disorder in which decreased expression of frataxin, a mitochondrially-encoded iron binding protein, results in dysfunctional autophagy and iron homeostasis of the mitochondrial redox environment. In amyotrophic lateral sclerosis, an adult-onset neurodegenerative disease of rapidly advancing pathology, new evidence suggests impairment of mitochondrial fission/fusion, trafficking and autophagic/lysosomal processing (Muyderman and Chen, 2014). Markham *et al.* (Markham *et al.*, 2014) link the limitations that energy availability places on brain function to dysfunction, and point out that brain-derived neurotrophic factor (BDNF) not only has plastic and neuroprotective roles, but also possesses a capacity to improve respiratory efficiency that may be advantageous in neurodegenerative and psychiatric disorders. This theme is continued by Villaseñor *et al.* (Villaseñor *et al.*, 2014) who report in a ground-breaking metabolomic study that the anti-depressant effects of ketamine, an NMDA receptor modulator, in patients with bipolar depression involve important mitochondrial metabolism of fatty acids.

The articles in 'Mitochondrial Pharmacology: Energy, Injury and Beyond' reflect not only the dynamic nature of this diverse topic of research, but also the enthusiasm of the many authors for this rapidly advancing field. When the issue was planned it was never imagined the volume would grow to this size, but the number of contributors reflects the vibrancy of ongoing work across different problems and organs, and their internationality reflects its global relevance to health, and hence pharmacology and therapeutics. The coverage provided will be of broad interest to academic and commercial researchers, and students alike. The editors thank the authors

and reviewers for their efforts in making the Themed Issue a roaring success. The parents of this particular mitochondrial 'baby' are delighted.

Acknowledgements

Constant and enthusiastic support of Michael Curtis is gratefully acknowledged. PMB acknowledges receipt of Research Fellowship (APP1019833) from National Health and Medical Research Council (Australia).

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