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EDITORIAL

Coupling cellular metabolism to neuronal signalling

Derek Bowie[1] and David Attwell[2]
[1]*Department of Pharmacology and Therapeutics, McGill University, Montréal, Québec, Canada, H3G 1Y6*
[2]*Department of Neuroscience, Physiology and Pharmacology, University College London, Gower Street, London, UK*
E-mail: derek.bowie@mcgill.ca

Although it has long been appreciated that much of the brain's energy is devoted to neuronal signalling, it is unclear if and how these two processes are coupled. To explore this emerging area of neuroscience, *The Journal of Physiology* sponsored a symposium at The Physiological Society's annual meeting, Physiology 2014, in London to bring together five researchers (see Fig. 1) whose work is at the forefront of this rapidly developing field of study. This issue of *The Journal of Physiology* brings together six timely review articles from some of these speakers and other researchers whose work captures some of the ideas, discussions and debates that arose during the 2014 Symposium on 'Coupling cellular metabolism to neuronal signalling'.

Derek Bowie from McGill University presented recent data from his lab demonstrating that mitochondrial derived reactive oxygen species (ROS) strengthen inhibitory transmission by $GABA_A$ receptors in cerebellar stellate cells (Accardi *et al.* 2014). Although often associated with oxidative stress in neurodegenerative disease, these observations suggest that ROS act as a putative homeostatic signalling molecule at central synapses. An additional surprise was that ROS strengthen GABAergic synapses by recruiting α3-containing GABA receptors rather than accumulating more α1-containing receptors resident to stellate cell synapses. Since α3-receptors are targeted to postsynaptic sites that are functionally distinct from those for α1-receptors, it was concluded that ROS strengthen only a subset of all inhibitory synapses. In keeping with this, recent work from their lab has shown that insulin strengthens GABAergic synapses of cerebellar granule cells by a similar mechanism (Accardi *et al.* 2015). Taken together, a general mechanism is proposed whereby α1-containing GABA receptors resident to inhibitory synapses form the hardwiring of neuronal circuits with receptors of a different subunit composition fulfilling a fundamental but unappreciated role in synapse strengthening.

Engl and Attwell from University College London review the non-signalling or house-keeping energy expenditure of the brain (Engl & Attwell, 2015). The Attwell lab has already developed a metabolic budget for the cost of signalling in the brain, estimating that as much as 80% is consumed on reversing sodium ion gradients generated by action potential firing and glutamatergic transmission (Attwell & Laughlin, 2001; Harris *et al.* 2012). Although the brain is thought to spend less than half of its total energy on non-signalling tasks, it remains to be established how energy usage is distributed amongst the different processes. To better understand this distribution, the authors reviewed published experimental data on energy use by the major subcellular processes involved in housekeeping such as actin treadmilling, protein and lipid synthesis, and proton leak in mitochondria. An unexpected challenge was that results from different studies were often incompatible due to differences in animal models used and differences in their developmental stage and experimental protocols therein. As a result, these confounding factors introduced a degree of uncertainty in drawing firm conclusions about each housekeeping activity. The authors conclude by highlighting the need for more research on this topic to better define how the brain expends energy on non-signalling tasks.

Lee and colleagues from New York University School of Medicine examine the emerging idea that ROS lie at the hub of a number of signalling pathways in the brain (Lee *et al.* 2015). The authors focus on the role of hydrogen peroxide (H_2O_2) which the Rice lab has shown to be an endogenous modulator of dopamine release in the striatum (Chen *et al.* 2001). This observation is clinically relevant since the loss of dopaminergic innervation from the substantia nigra to the striatum is a key pathology that underlies early symptoms of Parkinsonism (Lotharius & Brundin, 2002). The authors describe how an elevation in the concentration of H_2O_2 derived from the mitochondria inhibits dopamine release by acting on ATP-sensitive K^+ channels (Avshalumov *et al.* 2005). In contrast, H_2O_2 enhances the activity of the non-selective cation channel TRPM2 expressed by GABAergic projection neurons in the dorsal striatum and projecting neurons from the substantia nigra pars reticulata (Lee *et al.* 2013). Accordingly, mitochondrial H_2O_2 plays a key role in establishing the balance between inhibitory and excitatory input into and within the striatum. Given that the striatum is a key target in the treatment of Parkinson's disease, further insight into the role of H_2O_2 in this CNS region may provide clues into how to treat this most debilitating disease.

The role of cytosolic and mitochondrial calcium (Ca^{2+}) in shaping the cell's bioenergetics is the focus of the review by Llorente-Folch and colleagues (Llorente-Folch *et al.* 2015) from the Universidad Autónoma de Madrid and University College London. Although the

Figure 1. Photograph of the speakers at the symposium on 'Cellular metabolism and neuronal signalling' at the 2014 Physiological Society meeting in London
Left to right are Dr David Attwell, Dr Margaret Rice, Dr Irene Llorente-Folch from the Satrustegui and Duchen labs, Nicholas Wellinger from the Thompson lab and Dr Derek Bowie.

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mitochondria have long been associated with buffering cytosolic Ca^{2+} (Miller, 1991), the authors point out that a key role of sequestered Ca^{2+} is to stimulate ATP production. Newly synthesized ATP is then used to meet the cell's energy demands during periods of heightened activity. Intracellular Ca^{2+} achieves this in a number of ways. Elevations in cytosolic Ca^{2+} stimulate the transfer of metabolites, such as pyruvate, across the inner mitochondrial membrane whereas the citric acid cycle and ATP synthase activity are upregulated by $[Ca^{2+}]$ rises within the mitochondrial matrix. A further complication is that different Ca^{2+} loads alter mitochondrial bioenergetics by distinct mechanisms. For example, the aspartate–glutamate exchanger Aralar/AGC1 (Slc25a12), a component of the malate–aspartate shuttle (MAS), responds to small and modest workloads through changes in cytosolic Ca^{2+}. In contrast, large workloads stimulate ATP production in the absence of the MAS and rely upon stimulating cellular respiration by elevating matrix $[Ca^{2+}]$. The authors conclude by providing examples of how deficits in Ca^{2+} handling impact mitochondrial bioenergetics that in turn lead to pathology and disease.

Roger Thompson from the University of Calgary reviews the role played by pannexin channels in the neurotoxicity and ensuing cell death accompanying cerebral ischaemia (Thompson, 2015). Pannexin channels are a family of membrane-bound proteins that are homologous to innexins found in invertebrates (Dahl & Muller, 2014). In vertebrates, pannexins form transmembrane channels that permit the transfer of small and large molecules between intracellular and extracellular space (Dahl & Muller, 2014). Although the overactivation of NMDA-type ionotropic glutamate receptors (NMDARs) is one of the primary triggers of ischaemic cell death (Choi, 1992), the author presents a compelling argument linking NMDAR signalling to the activation of pannexin channels via Src family kinases (Thompson *et al.* 2006, 2008). In the hippocampus, the C-terminal region of pannexin1 (Panx1) is the main target of Src kinases, which may directly regulate channel gating by phosphorylation or through allosteric coupling between the channel and the kinase. Since an interfering peptide can disrupt the regulation of Panx1 by NMDARs, it is proposed that understanding this mechanism may lead to novel therapies for cerebral ischaemia.

The article by Brisco and Hass from the University of British Columbia examines emerging data that link mitochondria and the transcription factor myocyte enhancer factor 2 (MEF2) to the structural and functional plasticity of glutamatergic synapses (Brusco & Haas, 2015). The Haas lab first identified a MEF2 signalling pathway in sculpting neuronal circuits of the optic tectum of the developing *Xenopus* brain (Chen *et al.* 2012). As its name implies, MEF2 was originally discovered because of its role in differentiating myocytes (Lilly *et al.* 1994) before its widespread expression was noted in the vertebrate brain and subsequently linked to synapse development (Flavell *et al.* 2008). The authors argue that MEF2 and mitochondrial function are closely aligned since MEF2 is a target of mitochondrial apoptotic caspases and also controls mitochondrial genome transcription responsible for the production of ROS. Most unexpectedly, the authors conclude that numerous mitochondrial pathways normally associated with apoptotic cell death are, in fact, also important players in the normal physiology of healthy neurons where they mediate plasticity and metaplasticity mechanisms.

Finally, Bagriantsev and Gracheva from Yale University review the complex molecular mechanisms that give rise to temperature adaptation in many vertebrate species (Bagriantsev & Gracheva, 2015). The authors highlight the central role of the transient receptor potential (TRP) family of ion channels in the sensory perception of temperature. Some TRP channels, such as TRPM8, contribute to the detection of cold in somatosensory neurons, whereas others, such as TRPV1, detect hot temperatures in excess of 42°C. A major challenge in understanding how somatosensory systems have adapted during evolution is limited by the available experimental models. For example, most studies have attempted to understand temperature adaptation by focusing on TRP channel biology in mouse and rat animal models. Though valuable, the authors argue that the way forward is to seek out evolutionarily distant vertebrate species. Only then will it be possible to pinpoint the general principles by which all species sense and regulate their temperature.

References

Accardi MV, Brown PM, Miraucourt LS, Orser BA & Bowie D (2015). α6-containing $GABA_A$ receptors are the principal mediators of inhibitory synapse strengthening by insulin in cerebellar granule cells. *J Neurosci* **35**, 9676–9688.

Accardi MV, Daniels BA, Brown PM, Fritschy JM, Tyagarajan SK & Bowie D (2014). Mitochondrial reactive oxygen species regulate the strength of inhibitory GABA-mediated synaptic transmission. *Nat Commun* **5**, 3168.

Attwell D & Laughlin SB (2001). An energy budget for signaling in the grey matter of the brain. *J Cereb Blood Flow Metab* **21**, 1133–1145.

Avshalumov MV, Chen BT, Koos T, Tepper JM & Rice ME (2005). Endogenous hydrogen peroxide regulates the excitability of midbrain dopamine neurons via ATP-sensitive potassium channels. *J Neurosci* **25**, 4222–4231.

Bagriantsev SN & Gracheva EO (2015). Molecular mechanisms of temperature adaptation. *J Physiol* **593**, 3483–3491.

Brusco J & Haas K (2015). Interactions between mitochondria and the transcription factor myocyte enhancer factor 2 (MEF2) regulate neuronal structural and functional plasticity and metaplasticity. *J Physiol* **593**, 3471–3481.

Chen BT, Avshalumov MV & Rice ME (2001). H_2O_2 is a novel, endogenous modulator of synaptic dopamine release. *J Neurophysiol* **85**, 2468–2476.

Chen SX, Cherry A, Tari PK, Podgorski K, Kwong YK & Haas K (2012). The transcription factor MEF2 directs developmental visually driven functional and structural metaplasticity. *Cell* **151**, 41–55.

Choi DW (1992). Excitotoxic cell death. *J Neurobiol* **23**, 1261–1276.

Dahl G & Muller KJ (2014). Innexin and pannexin channels and their signaling. *FEBS Lett* **588**, 1396–1402.

Engl E & Attwell D (2015). Non-signalling energy use in the brain. *J Physiol* **593**, 3417–3429.

Flavell SW, Kim TK, Gray JM, Harmin DA, Hemberg M, Hong EJ, Markenscoff-Papadimitriou E, Bear DM & Greenberg ME (2008). Genome-wide analysis of MEF2 transcriptional program reveals synaptic target genes and neuronal activity-dependent polyadenylation site selection. *Neuron* **60**, 1022–1038.

Harris JJ, Jolivet R & Attwell D (2012). Synaptic energy use and supply. *Neuron* **75**, 762–777.

Lee CR, Machold RP, Witkovsky P & Rice ME (2013). TRPM2 channels are required for NMDA-induced burst firing and contribute to H_2O_2-dependent modulation in substantia nigra pars reticulata GABAergic neurons. *J Neurosci* **33**, 1157–1168.

Lee CR, Patel JC, O'Neill B & Rice ME (2015). Inhibitory and excitatory neuromodulation by hydrogen peroxide: translating energetics to information. *J Physiol* **593**, 3431–3445.

Lilly B, Galewsky S, Firulli AB, Schulz RA & Olson EN (1994). D-MEF2: a MADS box transcription factor expressed in differentiating mesoderm and muscle cell lineages during *Drosophila* embryogenesis. *Proc Natl Acad Sci USA* **91**, 5662–5666.

Llorente-Folch I, Rueda CB, Pardo B, Szabadkai G, Duchen MR & Satrustegui J (2015). The regulation of neuronal mitochondrial metabolism by calcium. *J Physiol* **593**, 3447–3462.

Lotharius J & Brundin P (2002). Pathogenesis of Parkinson's disease: dopamine, vesicles and α-synuclein. *Nat Rev Neurosci* **3**, 932–942.

Miller RJ (1991). The control of neuronal Ca^{2+} homeostasis. *Prog Neurobiol* **37**, 255–285.

Thompson RJ (2015). Pannexin channels and ischaemia. *J Physiol* **593**, 3463–3470.

Thompson RJ, Jackson MF, Olah ME, Rungta RL, Hines DJ, Beazely MA, MacDonald JF & MacVicar BA (2008). Activation of pannexin-1 hemichannels augments aberrant bursting in the hippocampus. *Science* **322**, 1555–1559.

Thompson RJ, Zhou N & MacVicar BA (2006). Ischemia opens neuronal gap junction hemichannels. *Science* **312**, 924–927.

Additional information

Competing interests

None declared.