Nature Reviews Neuroscience | AOP, published online 1 June 2006; doi:10.1038/nrn1951

NEUROLOGICAL DISORDERS

Changing channels

DOI:
10.1038/nrn1951

> “Hemichannels represent a promising therapeutic target in the treatment of ischaemic injury.”

Ischaemic injury involves a pronounced reduction in oxygen and glucose around the affected area, which leads to rapid cell death that is associated with Ca^{2+}, Na^{+}, K^{+} and Cl^{-} dysregulation. But which channels mediate these changes? Writing in *Science*, Thompson and colleagues report the surprising finding that the ionic dysregulation seen in ischaemia results from the opening of hemichannels — sets of proteins that form one half of large conductance channels, known as gap junctions, that allow molecules and ions to flow directly between most cell types.

Thompson and co-workers created ischaemic-like conditions in which there was oxygen and glucose deprivation (OGD) in isolated rat hippocampal pyramidal neurons. Voltage-clamp recordings revealed that OGD activated a current with a large amplitude, a linear current–voltage relationship and a reversal potential close to 0 mV — key features of hemichannel activation when Na^{+}, Ca^{2+} and K^{+} currents were blocked. Selective blockage of hemichannels using carbenoxolone (Cbx) or lanthanum chloride confirmed their involvement in OGD-activated current. Prolonged (>20 min) OGD led to irreversible current activation, neuronal swelling and breakdown of cell membranes.

Further investigations showed that blocking the ion channel ASIC1a or the purinergic $P2X_7$ receptor (previously implicated in ischaemia-related ionic dysregulation) failed to affect the large current triggered by OGD activation, although there was a minor effect of blocking the transient receptor potential channels TRPC4 and TRPC5 on the small residual current that remained after blockage of hemichannels. Nevertheless, the large amplitude current attributable to hemichannels indicated that they are the major contributors to the OGD-activated current, so these researchers explored their role in ionic dysregulation in more detail.

Thompson and colleagues separately assessed the movement of two types of small fluorescent molecule that can permeate gap junctions: calcein AM and sulphorhodamine (SR101). Under normal conditions calcein AM remains inside neurons, whereas SR101 is absent from neurons. But during OGD there was a steady reduction in calcein and an increase in SR101 in neurons. The ability of these molecules to cross the membrane was prevented by Cbx, indicating that hemichannel opening was responsible for their movement.

Gap junctions are formed from two hemichannels that comprise connexin or pannexin (PX) proteins. Pannexins, but not connexins, are expressed in pyramidal neurons and were therefore likely to form the hemichannels under scrutiny here. The single-channel biophysical properties — including amplitude, conductance, opening probability, current–voltage relationship and reversal potential — were consistent with those of PX1 hemichannels.

This comprehensive set of studies provides compelling evidence that the opening of PX1 gap junction hemichannels is crucial for the ionic dysregulation and consequent neuronal death that follows ischaemia. Hemichannels therefore represent a promising therapeutic target in the treatment of ischaemic injury.

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ORIGINAL RESEARCH PAPER Thompson, R. J., Zhou, N. & MacVicar, B. A. Ischemia opens neuronal gap junction hemichannels. *Science* **312**, 924–927 (2006)
FURTHER READING Sohl, G., Maxeiner, S. & Willecke, K. Expression and functions of neuronal gap junctions. *Nature Rev. Neurosci.* **6**, 191–200 (2005)