SIGNAL TRANSDUCTION

Sink or swim

Although the precise signalling roles of nitric oxide (NO) in the nervous system are still controversial, few would dispute the fact that this labile molecule affects neuronal physiology. A lot of research has been devoted to discovering how NO influences brain function, but few studies have addressed the ways in which this gas is inactivated. As NO is so unstable, its existence in the cellular milieu is thought to be intrinsically short; a corollary of this idea is that cells do not need an inactivation mechanism for such a short-lived molecule. Now Griffiths and Garthwaite have tested this assumption, and obtained evidence for a cellular sink that can shape NO levels.

The authors prepared cell suspensions from rat cerebella, and measured their effect on the level of NO released by different donors. The cells reduced the concentration of the gas independently of other mechanisms known to consume NO, such as reaction with oxygen or with superoxide ions. Moreover, if the cells were challenged with a constant source of NO, they could actually clamp its concentration for several minutes; if NO release continued, the sink became saturated and the gas concentration rose in parallel.

NO signalling involves the activation of guanylyl cyclase. Does the NO sink affect this activation? Griffiths and Garthwaite measured the production of cyclic GMP in response to different clamped concentrations of NO, and found that the amounts of gas necessary to stimulate cGMP production were readily produced, despite the sink. At the same time, the authors wondered whether the sink might help to prevent any toxic effects of NO, focusing on its known influence on mitochondrial respiration. They found that if the clamp was not

NEURODEGENERATIVE DISORDERS

Targeting Aβ42

Why is it that people who regularly use nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are less likely to develop Alzheimer's disease? Some researchers have proposed that NSAIDs might reduce neurotoxic inflammation in the brain. However, Weggen *et al.* have found another potentially protective mechanism: a decrease in the production of amyloidogenic Aβ42 peptide in cultured cells or in transgenic mice that are treated with NSAIDs.

The Aβ42 peptide is the chief suspect in the pathogenesis of Alzheimer's disease. It is formed when γ-secretase cleaves the amyloid precursor protein (APP), and helps to form the amyloid plaques that are a characteristic feature of the disease. γ-Secretase activity can also produce a shorter peptide, Aβ40, which seems to be less damaging to nervous tissue. Weggen *et al.* treated cultured cells with three types of NSAID — ibuprofen, indomethacin and sulindac sulphide — and found that each of these compounds caused a decrease in the ratio of Aβ42 to Aβ40. However, a number of other NSAIDs, including aspirin, naproxen, and cyclooxygenase 1 (COX1)- and COX2-selective inhibitors, did not have this effect.

Another study recently showed that chronic treatment with ibuprofen can reduce neuropathology in transgenic mice that express APP. Weggen *et al.* showed that an acute treatment with the same drug could reduce the levels of Aβ42 in these mice, indicating that the reduction in Aβ42 might indeed be the mechanism by which pathology is decreased.

NSAIDs mediate their anti-inflammatory action by inhibiting the activity of COX. However, the ability of NSAIDs to reduce Aβ42 levels seems to be independent of COX activity. Weggen *et al.* found that when fibroblasts deficient in both COX1 and COX2, which have the same basal levels of Aβ42 and Aβ40 as normal fibroblasts, were treated with NSAIDs, the reduction in Aβ42 was still observed, showing that the ability of some NSAIDs to reduce Aβ42 levels does not rely on inhibiting COX activity.

When the group looked more closely at Aβ peptides in cell cultures treated with NSAIDs, they found that the decrease in Aβ42 was accompanied by an increase in the levels of a shorter peptide, Aβ38. Treatment with sulindac sulphide and other NSAIDs seems to subtly alter the activity of γ-secretase, producing a shift in the proportions of Aβ peptides produced. This selective action, unlike that of current γ-secretase inhibitors, does not seem to interfere with APP or Notch processing. Unfortunately, NSAIDs have other side effects, particularly gastrointestinal and renal toxicity, so they might not be suitable for long-term use in patients with Alzheimer's disease.

However, there is cause for optimism. As the Aβ42-lowering effect of NSAIDs is independent of their COX-inhibiting activity, it might be possible to develop derivatives that have a strong effect on Aβ42 levels, but do not have the present drawbacks of NSAIDs.

Rachel Jones

References and links

ORIGINAL RESEARCH PAPER Weggen, S. *et al.* A subset of NSAIDs lowers amyloidogenic Aβ42 independent of COX activity. *Nature* **414**, 212–216 (2001)

FURTHER READING Selkoe, D. J. Alzheimer's disease: genes, proteins and therapy. *Physiol. Rev.* **81**, 741–766 (2001)

ENCYCLOPEDIA OF LIFE SCIENCES Alzheimer disease

saturated, oxygen consumption was normal, but as soon as NO exceeded the capacity of the sink, respiration was inhibited.

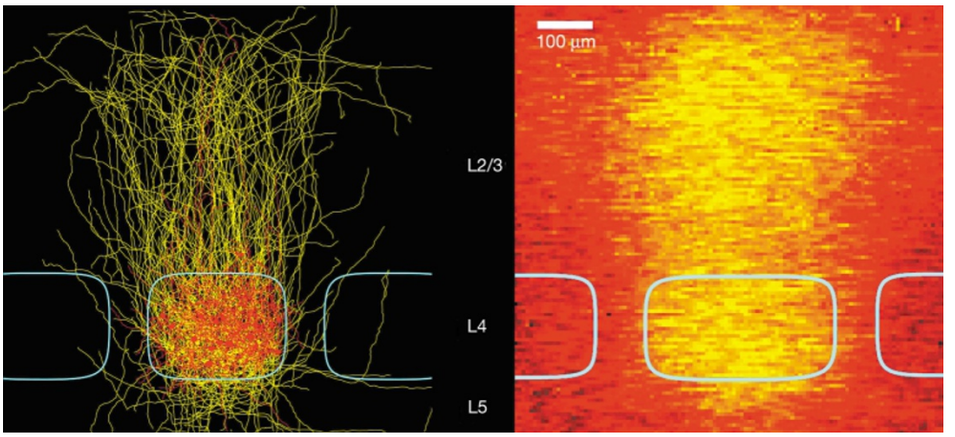
So cells can shape the levels of NO by means of a sink, the identity of which now needs to be established. Although this sink might have physiological and pathological relevance, the relationship between the NO concentrations measured in this study and those found *in vivo* is uncertain. It will therefore be necessary to embark on studies using more physiologically relevant systems to determine the actual role of this enigmatic sink in brain function.

Juan Carlos López

References and links

ORIGINAL RESEARCH PAPER Griffiths, C. & Garthwaite, J. The shaping of nitric oxide signals by a cellular sink. *J. Physiol. (Lond.)* **536**, 855–862 (2001)

FURTHER READING Thomas, D. D. *et al*. The biological lifetime of nitric oxide: implications for the perivascular dynamics of NO and O_2. *Proc. Natl Acad. Sci. USA* **98**, 355–360 (2001)



Left: the anatomically defined barrel column, delineated by the normalized barrel boundaries (cyan), dendrites (red) and axons (yellow) of the excitatory neurons of layer 4. Right: the spatial extent of excitation at the peak of the functional response evoked by stimulating the barrel, imaged using a voltage-sensitive dye. Courtesy of Carl Petersen, Max-Planck-Institute for Medical Research, Germany; © 2001 Society for Neuroscience.

CORTICAL IMAGING

Roll out the barrel

In rodents, each facial whisker is represented in layer 4 of the somatosensory cortex by a cylindrical array of neurons known as a barrel. The topographical organization of the barrels corresponds precisely to that of the whiskers, so the barrel cortex has proved to be extremely valuable for studying cortical responses to peripheral stimulation. Now, as reported in the *Journal of Neuroscience*, Petersen and Sakmann have devised an elegant *in vitro* system to investigate the functional anatomy of the barrel cortex.

Their experiments were carried out in slices of rat cortex, using a voltage-sensitive dye (vsd) to detect neuronal excitation. Following stimulation of a single barrel, the authors showed that the vsd response was initially confined to the stimulated barrel, but quickly spread vertically to an adjacent region of layer 2/3, of approximately the same width as the barrel. The signal decayed in the barrel and layer 2/3 simultaneously, and had disappeared entirely by 200 ms after stimulation.

Interestingly, *in vivo* studies have shown that stimulation of a single whisker activates an area of cortex much larger than the width of a barrel. What could account for this difference? A clue came from experiments in which Petersen and Sakmann treated their slices with bicuculline to inactivate GABA (γ-aminobutyric acid)-mediated inhibition. This treatment increased the lateral spreading of the vsd response in layer 2/3, whereas spreading in layer 4 was minimal and never extended into the adjacent barrel. So, GABA-mediated inhibition might limit the spread of activity in layer 2/3, but spread between barrels is more likely to be constrained by a lack of excitatory connections. The authors suggest that the reduced spread of activity in layer 2/3 in slices might reflect differences in the balance between inhibition and excitation *in vivo* versus *in vitro*.

To replicate the type of barrel activity observed when a rat is actively exploring, the authors stimulated a single barrel continuously at the frequency of normal whisker movement (10 Hz), or stimulated two adjacent barrels simultaneously. Although the amplitude of the vsd response decreased with repeated stimulation, the spatial pattern of activity was unchanged. Simultaneous stimulation of adjacent barrels did not change the extent of the response in the individual barrels, and caused only a slight increase in the spread of activity in layer 2/3. This indicates that the barrels function largely independently of one another.

In a slightly more complex protocol, Petersen and Sakmann paired the stimulation of a barrel and a region of layer 2/3 adjoining an adjacent barrel. After repeated paired stimulation, the area of layer 2/3 that was excited by stimulating the barrel alone was shown to be increased. The authors suggest that such pairing protocols could provide models for cortical plasticity that results from alterations in sensory input.

Petersen and Sakmann's system certainly holds a great deal of promise for modelling cortical activity *in vitro*. By designing different stimulation protocols, it might be possible to replicate a wide variety of manipulations of sensory input that have already been observed *in vivo*.

Heather Wood

References and links

ORIGINAL RESEARCH PAPER Petersen, C. C. H. & Sakmann, B. Functionally independent columns of rat somatosensory barrel cortex revealed with voltage-sensitive dye imaging. *J. Neurosci.* **21**, 8435–8446 (2001)

FURTHER READING Buonomano, D. V. & Merzenich, M. M. Cortical plasticity: from synapses to maps. *Annu. Rev. Neurosci.* **21**, 149–186 (1998)