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TRACKING CALCIUM

An understanding of calcium dynamics in the cell may point the way toward new therapeutics.

Calcium signalling underpins everything from fertilisation to muscle contraction. Several groups' work this year has significantly advanced our understanding of how calcium flows are finely tuned in the cell.

Three small chemical messengers are crucial to calcium signalling: two (InsP₃ and cADPR) trigger release from endoplasmic reticulum (ER) stores; a third, NAADP, was discovered only recently but has turned out to be the most potent stimulant of calcium release.

Antony Galione and John Parrington in Oxford, Mark Evans in Edinburgh and colleagues in the USA and China have made an important step forward in understanding the NAADP system, identifying its receptor and the location of the NAADP-sensitive calcium store.¹ Surprisingly, calcium is released from acidic compartments such as lysosomes, not previously known as major calcium stores. This initial burst of calcium can trigger further calcium release through the InsP₃ and cADPR systems, amplifying the original signal.

Calcium is a versatile signalling system: a wide range of signals can be generated, from local 'puffs' to global 'waves' spreading across the cell. Colin Taylor in Cambridge and colleagues have found that 'tuning' of InsP₃ receptors can generate complex spatiotemporal patterns of calcium release.

Their research has shown that InsP₃ receptors are initially randomly distributed in the ER membrane. When InsP₃ first binds, receptors aggregate into small clusters, which alters their sensitivity to both InsP₃ and calcium. The signal generated will therefore depend on levels of InsP₃ and calcium (and other inputs). InsP₃ can thus generate a hierarchical set of responses – initially from single channels, then puffs from clusters of channels and then waves as multiple puffs coalesce.²

Ultimately, modulating calcium signalling could be a way to modify the behaviour of cells involved in disease processes. The receptors that mediate calcium release are obvious targets. Working with Professor Taylor and others, Barry Potter in Bath has developed a range of chemical analogues that mimic or interfere with the triggers of calcium signals; these agents have been used to provide detailed insight into the mechanics of InsP₃ receptor activation.³ Working with groups in Germany, Professor Potter has also designed other agents to block NAADP signalling and modulate the activation of T cells⁴ – opening up a possible route to the treatment of autoimmune diseases.

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¹ Calcrafft PJ et al. *Nature* 2009;459(7246):596–600.

² Taufiq-Ur-Rahman et al. *Nature* 2009;458(7238):655–9.

³ Rossi AM et al. *Nat Chem Biol* 2009;5(9):631–9.

⁴ Dammermann W et al. *Proc Natl Acad Sci USA* 2009;106(26):10678–83.

ALL IN THE BRAIN

Infections can cause a variety of physical symptoms, but they also make us feel bad. How these feelings are triggered in the brain is now becoming clear.

Ever since the Ancient Greeks, the mind and emotions have been cordoned off from the body. Recently, however, there has been a flourishing of research into the neural correlates of emotions and 'subjective' feelings. In work begun at University College London and continued at the University of Sussex, Hugo Critchley and Neil Harrison are examining how inflammation in the body affects mood and brain function.

We all recognise the sensation of feeling 'under the weather' when laid low by an infection. Yet while the immune system's response to infection receives close scrutiny, much less attention is given to the attendant mental symptoms – collectively known as 'sickness behaviour'.

To get a better handle on the brain's response to systemic infection, Professor Critchley, Dr Harrison and their colleagues have explored the effects of artificially induced inflammation on brain activity, brain function and mood. Volunteers were injected with either typhoid vaccine, to induce inflammation, or a saline placebo, then given a battery of tests while their brain activity was being monitored by functional magnetic resonance imaging.

Participants who received the vaccine suffered a notable deterioration of mood.¹ Functional imaging revealed corresponding changes in brain activity:

IMAGE

'Sickness behaviour' illustrates how systemic infection can affect the brain.

images of emotional faces, for example, triggered abnormally high activity in an area of the brain known to be involved in depression, while connectivity between this area and other regions of the brain was reduced. Such findings could explain why feeling ill has much in common with feeling depressed.

In addition, participants suffered greater fatigue, confusion and impaired concentration when undertaking a cognitively demanding task. Doing the test activated 'interoceptive' brain regions – those implicated in sensations of internal body states.² The extent to which these areas were activated was a good match for the levels of fatigue and confusion reported. Those who did well on the test tended to recruit additional prefrontal areas of the cortex.

The results thus provide direct evidence of how an immune response can influence brain activity, performance and subjective feelings. In the long term, an understanding of these processes may suggest ways to overcome the negative impact of infection on our brains and behaviour.

¹ Harrison NA et al. *Biol Psychiatry* 2009;66(5):407–14.

² Harrison NA et al. *Biol Psychiatry* 2009;66(5):415–22.



FLUKE OF NATURE

The genome sequence of a schistosome parasite is of interest to medical researchers and evolutionary biologists alike.

Schistosomes – flukes or parasitic flatworms – are responsible for a huge global health burden. Over 200 million cases of schistosomiasis occur every year, disabling millions and killing hundreds of thousands. The genome sequence of *Schistosoma mansoni*, sequenced by Matt Berriman and colleagues at the Wellcome Trust Sanger Institute,¹ is suggesting new ways to break the transmission cycle but is also providing clues to pivotal stages of evolution: the development of organs and of the bilateral body plan.

The *S. mansoni* genome consists of some 360 million bases, and shows some curious features. Within its 12 000 genes, the gaps in its coding regions (introns) are small near the starts of genes and much larger towards their ends. The genome sequence also revealed families of genes with very small exons (chunks of coding sequence) that seem to be mixed and

matched in multiple combinations – possibly a mechanism to increase protein variability and help the parasite to evade the host immune system.

A detailed analysis of the genome has identified many possible avenues for drug development, such as proteins not seen in vertebrates and new members of protein families typically targeted by drugs. Indeed, some *S. mansoni* proteins resemble those for which potential drugs already exist.

Schistosomes are an important evolutionary stepping-stone. Comparisons with more simple organisms such as sea anemones have shed light on the new genetic features that led to anatomical innovations maintained throughout the evolution of higher animals – such as the three-layered body plan and the formation of organs. Similarly, comparisons up the family tree are providing insight into the steps needed to create the complex anatomical structures seen in higher animals.

¹ Berriman M et al. *Nature* 2009;460(7253):352–8.

IMAGE

The head of the parasitic flatworm *Schistosoma mansoni*.