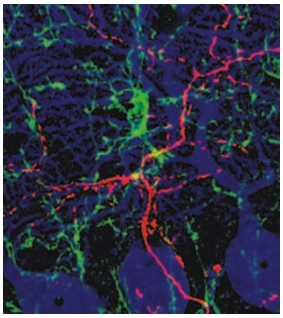
GLIA

Neurons and glia in close contact



Purkinje cells labelled with anti-calbindin (blue), NG2$^+$ cells labelled with anti-NG2 antibodies (green), and a climbing fibre labelled with Alexa-488 dextran (red) in the rat cerebellar cortex. Image courtesy of S. C. Lin, H. Nishiyama and D. E. Bergles, Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, USA.

Climbing fibres (CFs) from the inferior olive, one of the two main inputs to the cerebellum, make direct synaptic contacts with the cerebellum's output neurons, Purkinje cells. A new study shows that CFs also form conventional glutamatergic synapses with a population of glia in the cerebellar cortex. These glial cells, which express the proteoglycan NG2, might have an important part to play in the control of cerebellar function by CF inputs.

NG2-expressing (NG2$^+$) glia are oligodendrocyte precursor cells that are found throughout the developing and mature CNS. In the cerebellar cortex, they extend many processes around Purkinje cell dendrites. Like Bergmann glia, which ensheath excitatory synapses on Purkinje cells, NG2$^+$ cells express ionotropic glutamate receptors. But whereas Bergmann glia express uptake sites for glutamate and can, therefore, limit the spread of this neurotransmitter, NG2$^+$ cells do not express glutamate transporters. What is the role of NG2$^+$ cells in the cerebellum?

Lin and colleagues made whole-cell recordings from NG2$^+$ cells in mouse cerebellar slices. These non-excitable cells responded to CF stimulation with a transient inward current mediated by calcium-permeable AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors. The response seemed to be due to glutamate release at a conventional synapse rather than ectopic release, having rapid rise and decay kinetics and being remarkably stable with repeated stimulation. Paired recordings of Purkinje cells and NG2$^+$ cells showed that one CF can provide input to both cell types; however, unlike Purkinje cells, NG2$^+$ cells were found to receive input from more than one CF.

In an electron microscopic analysis, conventional synaptic junctions were seen between CFs and the processes of physiologically characterized NG2$^+$ cells. Synapses on NG2$^+$ cells were not wrapped by Bergmann glia, but the processes of NG2$^+$ cells were found in direct apposition with Bergmann glial lamellae.

PAIN

Great expectations

Placebos have been shown to relieve pain — a phenomenon known as placebo analgesia. A new study by Petrovic and colleagues has found that placebos can also affect emotion, alleviating the impact of unpleasant experiences.

Placebo analgesia and reward processing have similar characteristics: both involve anticipation of a positive outcome and are highly dependent on expectation. The authors conjectured that as emotion is closely associated with reward, it might also be affected by placebos. To test this, they used the so-called 'expectation manipulation' paradigm, in which a treatment expectation was induced in participants one day before the test day, using drugs that have well-established specific effects on emotion (that is, anxiolytic drugs and their blockers).

On day 1, participants were asked to rate the unpleasantness of neutral and disturbing pictures that were shown to them with or without the administration of an anxiolytic drug and its blocker. They were told in advance about the possible effect of the drug and its blockers on their perception of unpleasantness. As expected, the anxiolytic drug reduced the participants' perceived unpleasantness of the disturbing pictures, an effect that was reversed by administration of the drug's blocker. Neither the drug nor its blocker affected ratings of the neutral pictures.

On day 2, participants were told that the same treatments would be applied while their brains were scanned with functional MRI (fMRI). However, they were, in fact, treated with saline instead. The unpleasantness ratings of the disturbing pictures under the placebo condition (in which participants thought they had received the anxiolytic drug) were reduced by 29% compared with ratings under the control condition (in which participants thought they had received the drug followed by its blocker).

Interestingly, like placebo analgesia, the rostral anterior cingulate cortex (rACC) and the lateral orbitofrontal cortex (lObfc) — regions of the brain that are important in reward expectation — were activated by the emotional placebo. The increase in the activity of the rACC, but not that of the lObfc, correlated with the decrease in unpleasantness ratings of the pictures after the placebo treatment. In other words, the participants who reported the largest placebo response also showed the most extensive rACC activation.

These findings indicate that placebo analgesia — or the placebo effect in general — might be a special form of reward processing. This could shed new light on the evolutionary advantages of this powerful and fascinating phenomenon.

Jane Qiu

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INGVAR'S WEB SITE
http://www.cns.ki.se/en/research/martin_ingvar/martin_ingvar/

The cerebellum is involved in a range of motor and cognitive functions, but whether all aspects of the CF control of these functions can be attributed to the innervation of Purkinje cells has been unclear. Whereas Bergmann glia respond to the ectopic release of glutamate from CF terminals and are thought to isolate CF–Purkinje cell synapses, Lin *et al.* have shown that $NG2^+$ glial cells receive direct synaptic inputs from CFs and are well placed to influence cerebellar signalling. But the precise role of $NG2^+$ cells remains elusive. In future studies it will be important to determine whether rapid signalling between CFs and $NG2^+$ glia can affect the fate of these progenitor cells or the activity of surrounding neurons.

Rebecca Craven

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BIOPHYSICS

Signals and noise in tiny axons

What factors limit the minimum diameter of an axon? And what is that minimum diameter? Faisal and colleagues used biophysical theory and stochastic simulations to investigate these questions, and concluded that ion-channel noise sets a lower limit of ~0.1 μm on the diameter of axons that carry action potentials.

Action potentials are generated and propagated by ion channels, which open and close in response to changes in membrane voltage. However, the opening and closing of these channels is probabilistic, which means that random channel events introduce channel noise into the system. Because the effect of a single Na^+ channel on the membrane potential of an axon increases with decreasing axon diameter, in very thin axons the random opening of a single channel could, in theory, generate a spontaneous action potential. However, it is hard to record from the thinnest axons in the nervous system, so it has been difficult to determine the importance of this effect.

The authors investigated this issue by using stochastic simulations of axons. These simulations draw on empirical data on the responses of single channels to generate models of how a system containing these channels will behave. Simulating action potentials in axons is very demanding, but the authors developed a stochastic simulator, called Modigliani, that uses special routines to tackle this challenge.

Initially, the authors simulated the behaviour of two types of axon — pyramidal cell axons, which form most connections in cortical networks, and the squid axon, which has been extensively studied. They investigated how the generation of spontaneous action potentials by channel noise varied with axon diameter. Despite the differences between the two types of axon, both began to produce significant numbers of spontaneous action potentials at a critical diameter of about 0.15–0.30 μm — considerably lower than previous estimates. Below this point, the number of spontaneous action potentials increased exponentially as axon diameter decreased further.

Additional analysis and theoretical work led the authors to conclude that the critical diameter of an axon is relatively insensitive to its biophysical properties, and that most axons will have similar critical diameters — of the order of about 0.1 μm. When they studied published electron micrographs of axons from various species, Faisal and colleagues found that the minimum diameter of most axons was about 0.1 μm, with a few exceptions that might represent developing axons. However, on the basis of structural considerations alone, it should be possible to construct an axon with a diameter of as little as 0.06 μm, which indicates that channel noise is the limiting factor when it comes to axon miniaturization. Interestingly, neurites that do not conduct action potentials, such as those of *Drosophila* amacrine cells, can be as small as 0.05 μm in diameter, which indicates that the 0.1 μm limit applies only to axons that conduct action potentials.

Further simulations using this or similarly powerful systems should shed more light on the importance of channel noise in neuronal function, and on how the properties of axons might be fine-tuned to optimize signalling reliability.

Rachel Jones

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WEB SITES

Laughlin's laboratory: http://www.zoo.cam.ac.uk/zoostaff/laughlin/index.html

White's laboratory: http://www.bu.edu/ndl/

The Modigliani simulation framework: http://www.modigliani.co.uk/