cells — insulinoma-1 (INS-1) cells that respond to glutamate application with a rapid elevation in their intracellular calcium concentration owing to the expression of NMDA receptors. The authors showed that the flashes of fluorescence at the astrocyte membrane were followed by an NMDA receptor-dependent increase in intracellular calcium in the INS-1 cells, confirming that glutamate was being released through regulated exocytosis.

Although the astrocytic glutamate-releasing vesicles are similar to synaptic vesicles in many ways, there are also some intriguing differences. For example, the groups of vesicles were often smaller and less well-organized than the vesicles at presynaptic terminals. Also, they express the v-SNARE cellubrevin, whereas synaptic vesicles mostly express VAMP2 (vesicle-associated membrane protein 2). In the future, it will be interesting to explore the implications of these similarities and differences for neuron–glia communication.

Heather Wood

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those that contain NR2B. The idea is also consistent with previous findings, such as the fact that the NR2A/NR2B ratio increases during development, and LTD is more difficult to induce in more mature animals. However, there are also some problems for the theory. For example, a previous study by Tang *et al.* found that overexpression of NR2B subunits in the forebrain of mice increased levels of LTP, not LTD. Furthermore, different rules might apply in different parts of the brain.

Further work will no doubt help to clarify such issues, and should establish how different stimulation protocols might preferentially activate receptors that contain different types of subunit. It should also investigate what might happen downstream of receptor activation: there is already evidence that NR2A-containing receptors might couple to different signalling pathways from NR2B-containing receptors, and this provides a potential mechanism for their different effects on long-term plasticity.

Rachel Jones

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ION CHANNELS

Crystal-clear interactions

Calcium channels are the latest family to give in to the power of crystallography and reveal their structural details. Three recent papers have disclosed the atomic structure of the interacting domains between α- and β-subunits of voltage-gated calcium channels, challenging some previous ideas about the workings of the channel.

Voltage-gated calcium channels comprise different subunits — the α_1-subunit forms the pore of the channel, and the α_2-, β- and γ-subunits modulate channel function. The β-subunit, in particular, has a profound effect on several channel properties, including activation and inactivation rates and surface expression. Previous studies had narrowed down the α_1- and β-regions that mediate their interaction — the so-called α_1-interaction domain (AID) and a conserved core of the β-subunit, which includes what was regarded as the β-interaction domain (BID). The three papers report on the crystal structure of the conserved core of several β-subunits on their own and bound to the AID.

Perhaps the most surprising result from the three papers is that the BID does not really interact with the α-subunit. Instead, it is largely buried within the β-core and is more relevant for the structural integrity of the actual binding site, which, as it turns out, is structurally reminiscent of another protein family — membrane-associated guanylate kinases (MAGUKs).

MAGUKs are known to function as scaffolds at the synapse, a function for which their several PDZ domains are critical. The PDZ domains, which are absent in the core of the β-subunit, precede an SH3 domain and a guanylate kinase domain. A linker domain joins these two regions and, together, these three domains constitute the region of homology between MAGUKs and the conserved β-core. The structural analysis showed that the domain of the β-subunit that binds the AID is a hydrophobic cleft within the region homologous to the guanylate kinase domain of MAGUKs; the BID, by contrast, lies in the linker domain.

From the functional perspective, the structural results provide good clues about the way in which the β-subunit can affect channel inactivation. The interaction between the two subunits places the β-region near the intracellular end of a pore-lining segment of the α-subunit that is important for switching the channel off, raising the possibility that the β-subunit can affect the movement of this segment through electrostatic or physical interactions.

Last, the AID seems to occupy a small part of the region of homology between MAGUKs and the β-subunit. As this region contains other protein–protein interaction modules, such as the SH3 domain, it is conceivable that additional molecules bind to this region, potentially increasing the complexity of calcium channel modulation.

Juan Carlos López, Chief Editor,
Nature Medicine

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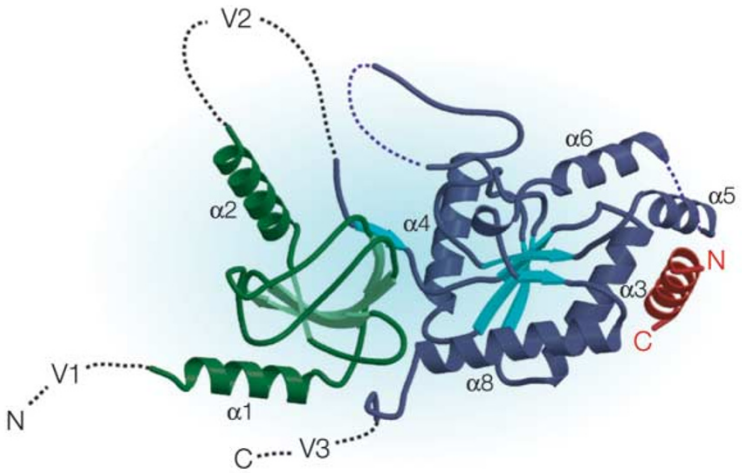

A ribbon diagram of the structure of the $Ca_V\beta_{2a}$–$Ca_V1.2$ α-interaction domain complex. Reproduced, with permission, from *Nature* © Macmillan Magazines Ltd.