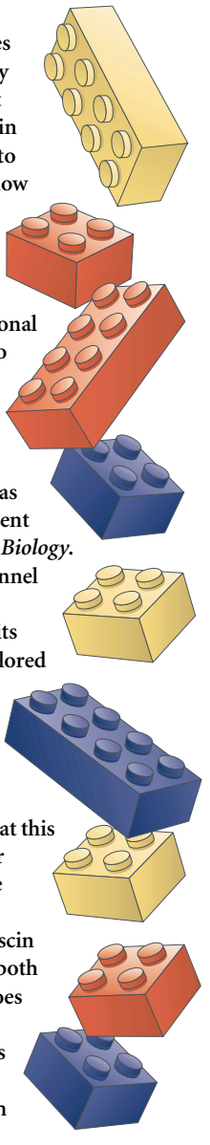
CELL BIOLOGY OF THE NEURON

Playing Lego at the nodes of Ranvier



The assembly of neuronal specializations is sometimes reminiscent of building structures with Lego blocks: some pieces can attach only to specific partners, and there are blocks that you cannot position until others are already in place. A big challenge for the cell biologist is to discover the rules of neuronal Lego, which allow the formation of structures as complex as a growth cone or the postsynaptic density. The nodes of Ranvier — gaps in the myelin sheath that allow the efficient propagation of action potentials — are neuronal specializations that are less heralded, but also contain proteins galore: different subunits of voltage-gated sodium channels, cytoskeletal elements and components of the extracellular matrix. But how do the nodes assemble? A new piece of this puzzle has fallen into place after the publication of a recent study by Ratcliffe *et al.* in *The Journal of Cell Biology*.

The extracellular domains of sodium channel β-subunits have an immunoglobulin-like domain, raising the possibility that β-subunits act as adhesion molecules. Ratcliffe *et al.* explored this idea by testing whether β-subunits interacted with neurofascin, an adhesion molecule that concentrates at prospective nodes of Ranvier. They found that the immunoglobulin-like domains of β1 and β3 subunits associated with neurofascin, and that this interaction did not involve their intracellular domains or their known association with the cytoskeletal protein ankyrin. Moreover, the association between β-subunits and neurofascin only occurred when the same cell expressed both molecules, indicating that this interaction does not mediate adhesion between neurons, but might be required for clustering heterologous molecules at specific membrane sites.

These data contribute to a model in which neurofascin clusters at prospective nodes of Ranvier before engaging ankyrin, and both molecules then recruit β-subunits through intra- and extracellular interactions. How are other proteins such as sodium channel α-subunits, tenascin R, NrCAM and spectrin then incorporated into the node? Many Lego blocks are left on the table.

Juan Carlos López

References and links

ORIGINAL RESEARCH PAPER Ratcliffe, C. F. *et al*. Sodium channel β1 and β3 subunits associate with neurofascin through their extracellular immunoglobulin-like domain. *J. Cell Biol.* **154**, 427–434 (2001)

FURTHER READING Isom, L. L. & Catterall, W. A. Na^+ channel subunits and Ig domains. *Nature* **383**, 307–308 (1996) | Ratcliffe, C. F. *et al*. A sodium channel signaling complex: modulation by associated receptor protein tyrosine phosphatase β. *Nature Neurosci.* **3**, 437–444 (2000)

NEUROTRANSMISSION

The chocoholic receptor?

Bingeing on chocolate — sometimes it refreshes the parts that other foods cannot reach. From Samuel Pepys, who noted his daily draught of chocolate in his seventeenth-century diary, to Henri de Toulouse-Lautrec, whose passion is said to have extended to inventing the chocolate mousse, most of us have experienced the rewards that overdosing on chocolate can bring. Several components of chocolate are potentially mood altering, including the 'trace amine' tyramine. Trace amines are closely related to biogenic amines, such as the classical neurotransmitters serotonin (5-HT), dopamine and noradrenaline, but are found at much lower levels in the body. Now, a study published in the *Proceedings of the National Academy of Sciences*, which reports the discovery of the first family of vertebrate G-protein-coupled receptors (GPCRs) for the trace amines, might explain how these molecules could mediate the addictive effects of chocolate. Much more importantly, the finding that trace amines are able to activate their own class of receptors indicates that, rather than simply interfering with neurotransmission by other biogenic amines, trace amines might be able to function as neurotransmitters in their own right. Trace-amine levels are known to be altered in a number of psychiatric disorders, and this makes their new receptors potentially exciting therapeutic targets.

Trace amines are hard to study, partly because of their low concentrations in the body. GPCRs for trace amines have long been known to exist in invertebrates, but no mammalian forms of such receptors had been found. Borowsky *et al.* discovered the new family of trace-amine receptors, which they named $TA_{1–15}$, while searching for new members of the 5-HT receptor family. By amplifying genomic DNA from humans, rats and mice using 'degenerate' primers in polymerase chain reactions — a technique that would allow the authors to find closely related DNA sequences — they hoped to fish out new 5-HT receptors that shared transmembrane domains with the 5-HT_1 receptor. Instead, they purified a group of 15 highly homologous receptors, some of which, on expression, were activated by trace amines, but not by 5-HT. Four of these TA receptors were identified in humans, and of these, only TA_1 seemed to be fully functional, responding most strongly to tyramine and β-phenylethylamine, two trace amines that are linked with depression and schizophrenia.

In the central nervous system, TA_1 is relatively heavily expressed in monoaminergic neurons in the dorsal raphe, locus coeruleus and ventral tegmental area — brain regions involved in mood regulation. The relatively strong level of expression of TA_1 in kidney might also help to explain why ingested trace amines can affect blood pressure: tyramine-containing foods such as cheese, red wine and chocolate are known to cause headaches in a subset of migraine patients, and to cause hypertension in those taking monoamine-oxidase-inhibitor antidepressants. And as for chocoholics? TA_1 is most concentrated in the amygdala, an area that is key to the associative processes, some leading to the emotional aspects of food reward, and others leading to dependence itself. It might, therefore, be the point at which chocolate works its own brand of magic.

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References and links

ORIGINAL RESEARCH PAPER Borowsky, B. *et al*. Trace amines: identification of a family of mammalian G-protein-coupled receptors. *Proc. Natl Acad. Sci. USA* **98**, 8966–8971 (2001)