HIGHLIGHTS

IN THE NEWS

Titter ye not

The news that scientists have located the region of the brain that responds to humour tickled the fancy of a variety of publications, ranging from *New Scientist* to the BBC's 'ComedyZone' web site (which referred to the researchers as 'laughter scientists'). In the MRI study, Vinod Goel and Raymond Dolan presented subjects with jokes and asked them to assess their funniness while their brains were scanned.

Commentators were particularly struck by the quality of the jokes, which included such gems as "Why did the golfer wear two sets of pants? ... He got a hole in one". However, the aim was apparently to produce a feeling of mild amusement rather than a belly laugh, and for a very good reason. As Goel told *New Scientist* (26 February 2001), "[we] didn't want the volunteers to laugh out loud and move their heads inside the scanner".

Several reports drew attention to the finding that humour stimulates the reward centres of the brain, perhaps explaining the sense of satisfaction that comes from 'getting' a joke. Asked to define the brain region involved, Dolan told *The Independent* (UK, 26 February) "You could say the funny spot, I would call it orbital prefrontal cortex".

As a control, subjects were given the same feedlines, but the punchlines were changed to make them logical rather than funny. For example, in the 'golfer' joke, the punchline was changed to "Because it was a cold day". However, the writer of a leader article in *The Independent* spotted a potential flaw in the experimental design, commenting "What the deliberately unfunny journal *Nature Neuroscience* fails to record ... is what happened to any of the 14 (subjects) who found this version of the joke much funnier than the original ..."

Heather Wood

SYNAPTIC PHYSIOLOGY

Calcium sensor identified ...

As the molecules involved in synaptic vesicle fusion began to be identified, synaptotagmin became the prime candidate to act as the calcium sensor — a crucial role in the exocytotic process. But despite structural considerations, genetic evidence and the ability of this protein to bind calcium, definitive evidence for the function of synaptotagmin as the calcium sensor has been difficult to obtain. By studying a mutant version of synaptotagmin, Fernández-Chacón and his colleagues have now provided the most compelling evidence yet that this is the molecule that triggers release upon binding of calcium.

The authors characterized a form of synaptotagmin I with a mutation in one of its calcium-binding domains.

This point mutation reduced calcium affinity of the protein by twofold, but did not cause significant changes in its three-dimensional structure. So, any influence of the mutation on transmitter release would be more likely to be related to its decreased affinity for the cation than to secondary effects such as misfolding or destabilization of the protein. Fernández-Chacón *et al.* then replaced the wild-type synaptotagmin I with the mutant form in mice and analysed release in cultured neurons. They found that release probability was reduced by two- to threefold and that this effect was not related to changes in the readily releasable pool of synaptic vesicles, but to a decrease in calcium sensitivity of the exocytotic machinery.

It therefore seems that the quest for the calcium sensor during synaptic exocytosis is finally drawing to a close. Although the exact mechanism by which calcium binding to synaptotagmin is followed by vesicle fusion remains to be defined more precisely, the answer might not be too far away. The well-established interaction of synaptotagmin with syntaxin, and our detailed structural understanding of the complex formed by syntaxin, synaptobrevin and SNAP25 — a SNARE complex critical for fusion — clearly tell us that we are on the right track.

Juan Carlos López

References and links

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FURTHER READING Jahn, R. & Südhof, T. C. Membrane fusion and exocytosis. *Annu. Rev. Biochem.* **68**, 863–911 (1999)
ENCYCLOPEDIA OF LIFE SCIENCES Calcium and neurotransmitter release

NEURODEGENERATION

... and β -secretase unmasked

Alzheimer's disease is characterized by the extracellular accumulation of amyloid- β (A β), a peptide generated from cleavage of the amyloid precursor protein (APP). Two different enzymatic activities — β - and γ -secretase — are responsible for A β production but the identity of the proteins that mediate these activities has remained elusive. In the case of γ -secretase, the presenilins and the recently identified protein nicastrin seem to be the culprits. Now, two papers published in *Nature Neuroscience* report that the molecule behind β -secretase activity is beta-site APP cleaving enzyme 1 (BACE1).

BACE1 had been suspected to be the β -secretase for some time. However, the subsequent identification of the close homologue BACE2 raised the question as to which of the two molecules actually cleaves APP in the brain. The new studies show that animals lacking BACE1 do not produce A β peptide even if APP is artificially overexpressed. This observation implies that BACE2 does not contribute to the generation of A β in the brain and point to BACE1 as the enzyme responsible for β -secretase activity.

BACE1 knockout mice are viable, can reach adulthood and do not

show any obvious abnormalities despite the fact that the protein is expressed in most tissues in wild-type animals. So, in contrast to the presenilins, which are also involved in phenomena as widespread as Notch signalling, BACE1 might be a more specific target for the development of drugs for preventing the abnormal extracellular accumulation of A β in Alzheimer's disease.

Juan Carlos López

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