Nature Reviews Neuroscience | AOP, published online 15 January 2009; doi:10.1038/nrn2580

PRIONS

Getting a whiff of prion function

Although the role of the prion protein PrP^c in transmissible spongiform encephalopathies is well established, little is known about its normal physiological function. Now, Firestein and colleagues describe an unexpected role for PrP^c in the olfactory system based on studies carried out in three different PrP^c-deficient mouse lines.

PrP^c is abundantly expressed in the brain, but previous studies have found no overt phenotypes in PrP^c-knockout mice, suggesting that the protein might be dispensable. Here, the authors set out to determine whether PrP^c, which is localized in the axons of both peripheral sensory receptor neurons and central neurons of the olfactory system, has a functional role.

In an olfactory detection task, in which the time taken by mice to retrieve a reward that was buried under cage bedding was measured, they found that PrP^c-deficient mice took longer and sometimes failed to find the treat. Similarly, in a task in which the animals' investigatory behaviour towards an odour presented several times in succession was examined, the mice lacking PrP^c often failed to show interest in novel odours. These findings suggested an impaired ability to discriminate odours. In both tests, the ability was rescued by inducing neuron-specific expression of PrP^c in the knockout mice.

Electrophysiological recordings revealed that on odour stimulation PrP^c-knockout mice exhibited a smaller range, and subsequently a longer decay, of gamma and high-frequency gamma oscillatory activity in the olfactory bulb than wild-type mice. These oscillations have been postulated to facilitate odour coding in the olfactory cortex, leading the authors to examine dendrodendritic synapses between granule and mitral cells in the olfactory bulb of PrP^c-knockout mice. Using a paired-pulse stimulation protocol they found a facilitation of inhibitory postsynaptic potentials, which further suggests that synaptic transmission in the olfactory bulb is impaired in PrP^c-deficient mice.

Whether the altered paired-pulse plasticity is causally linked to the differences in oscillatory activity remains to be seen. However, this physiologically important function of PrP^c supports the idea that prion disease might result from the loss of PrP^c and not just from the build up of its pathological isoform.

Monica Hoyos Flight

ORIGINAL RESEARCH PAPER Le Pichon, C. E. *et al.* Olfactory behavior and physiology are disrupted in prion protein knockout mice. *Nature Neurosci.* **12**, 60–69 (2008)

© 2009 Macmillan Publishers Limited. All rights reserved