oligosaccharides or the glycosylphosphatidylinositol anchor of the prion, these parts are not required for infectivity, although this does not mean that they have no influence on infectivity.

The authors conclude that all that seems to be required for the spontaneous formation of prions in any mammal is host prion protein. They propose that no additional agent is needed, which would explain the pathogenesis of sporadic Creutzfeld–Jakob disease. However, tangible evidence to back up these theories and prove the prion hypothesis requires further research. The real test is whether synthetic prions can cause disease when injected into wild-type mice, which express a much lower level of PrP^{C} than the transgenic mice used here.

Sarah Archibald

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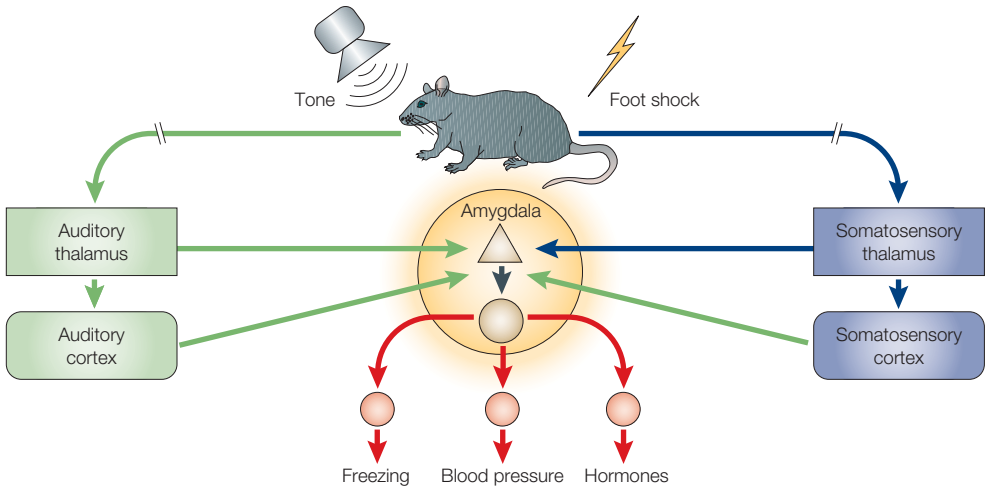

LEARNING AND MEMORY

Learning to fear

A new study, published in the *European Journal of Neuroscience*, shows that NMDA (*N*-methyl-D-aspartate) receptors are essential for the acquisition of both fear conditioning and the associated neurophysiological changes in the lateral amygdala, but not for the expression of these changes.

In Pavlovian fear conditioning, animals learn to associate a conditioned stimulus (for example, a tone) with an aversive, unconditioned stimulus (such as a shock). After a single training trial (one experience of the paired stimuli), the conditioned stimulus itself becomes able to elicit fear responses, such as increases in heart rate or freezing. Because learning in this protocol takes just one session, it is ideal for differentiating the mechanisms of learning from those of expression (or remembering).

Long-term potentiation — a cellular model of associative learning — occurs in the amygdala and requires NMDA-receptor activation, and NMDA-receptor blockade can attenuate fear learning in conditioned fear experiments. However, pharmacological manipulation of other receptors in the amygdala, such as metabotropic glutamate receptors or AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors, also alters fear conditioning, making it unclear whether plasticity in the amygdala related to fear conditioning is mediated solely by NMDA receptors. So Goosens and Maren investigated the effects that blocking NMDA receptors had on neuronal plasticity in the amygdala of awake, behaving rats, and the effects on both learning and expression of conditioned fear. They used a competitive NMDA-receptor antagonist, CPP (±3-(2-carboxypiperazin-4-yl) propyl-1-phosphonic acid), and single-unit recording of neurons in the lateral amygdala.

When rats were treated with CPP just before the training session, they did not subsequently show conditioned fear responses, such as freezing, to the conditioned stimulus. Unlike control rats, treated rats also showed no significant increase in neuronal spike firing in the lateral amygdala in response to the conditioned stimulus after training. These results support the idea that NMDA receptors are required for acquisition of both fear conditioning and associative plasticity in the lateral amygdala.

To investigate the role of NMDA receptors in the expression of conditioned fear and associative plasticity, Goosens and Maren treated rats with CPP just before testing, rather than before training. This treatment reduced the amount of conditioned fear behaviour shown by the rats in response to the conditioned stimulus, but did not completely abolish it. By contrast, CPP treatment did not affect the expression of associative plasticity in the lateral amygdala — neurons here still showed increased firing in response to the conditioned stimulus, regardless of whether the rats had been treated with CPP.

So, non-NMDA receptors in the amygdala seem not to be able to support either conditioned fear learning or associative neuronal plasticity after training, but they are sufficient for the expression of the conditioned fear response (albeit reduced) and of associated spike firing. Because CPP has a particular affinity for the NR2A and NR2B subunits, it would seem that NMDA receptors containing these subunits are important for conditioned fear learning and for the plasticity that is associated with it.

Rachel Jones

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WEB SITE

Maren's laboratory: http://marenlab.org/