Turning off the anxiety master switch

Anxiety is a natural adaptive behavioral state controlled by specific neuronal circuits and endocrine systems that are activated by real or perceived danger. However, with the ever increasing pace of modern societies, prolonged and unnecessary anxiety has become a major problem for many people. Although neurotransmitter and neuroendocrine pathways that either stimulate or suppress anxiety pathways have been identified during the past three decades, resulting in the development of several drugs that can relieve anxiety, a recent flurry of studies on the neuropeptide corticotropin-releasing hormone (CRH) has propelled a resurgence of excitement in the field of anxiety research. CRH was first identified as the neuropeptide produced by hypothalamic neurons, which is released into the portal vessels and stimulates production of adrenocorticotropin, an action critical for activation of the brain-hypothalamic-pituitary-adrenal (HPA) axis that controls production of glucocorticoids. However, CRH is also produced by neurons in several other regions of the brain, as are two different CRH receptors (CRHR-1 and CRHR-2) coupled to adenylate cyclase and cyclic AMP production. Studies in rodents had provided evidence that CRH plays an important role in activating anxiety pathways in the brain.

Habib *et al.*[1] report on the effects, in a primate model of psychosocial stress, of a highly specific antagonist of CRHR-1 called antalarmin. The authors characterized the pharmacokinetics of antalarmin in blood and brain after oral administration in rhesus macaques. They then performed a double-blind placebo-controlled study of the effects of antalarmin on behavioral and neuroendocrine responses to an acute psychosocial stress paradigm in which two monkeys unfamiliar with each other are placed in adjacent cages separated by a transparent plexiglass screen. Antilarmin inhibited an array of anxiety- and fear-related behaviors including grimacing, teeth gnashing, urination, body tremors and cage shaking. Monkeys given antalarmin exhibited sexual and exploratory behaviors normally inhibited by psychosocial stress. Moreover, antalarmin suppressed stress-induced increases in plasma levels of adrenocorticotropin, cortisol and epinephrine. The authors' findings establish an essential role for CRH acting on CRHR-1 as a 'master switch' that triggers a complete psychological and endocrine anxiety response in primates. Interestingly, recent analyses of stress responses in CRHR-2 knockout mice suggest that CRHR-2, whose endogenous ligand might be urocortin rather than CRH, mediates a central anxiolytic response[2,3]. Thus, two highly homologous receptors linked to the same second messenger system serve opposite roles in stress responses, presumably as the result of selective activation by different ligands and/or differential cellular localization of the receptors.

The implications of the powerful control of stress responses by CRH receptor signaling are profound. A variety of clinically important disorders might benefit from selective antagonism of CRHR-1 including not only anxiety and panic disorders, but also serious cardiovascular, reproductive and gastrointestinal disorders in which psychosocial stress plays a major role.

References

1 Habib, K.E. *et al.* (2000) Oral administration of a corticotropin-releasing hormone receptor antagonist significantly attenuates behavioral, neuroendocrine, and autonomic responses to stress in primates. *Proc. Natl. Acad. Sci. U. S. A.* 97, 6078–6084

2 Bale, T.L. *et al.* (2000) Mice deficient for corticotropin-releasing hormone receptor-2 display anxiety-like behaviour and are hypersensitive to stress. *Nat. Genet.* 24, 410–414

3 Kishimoto, T. *et al.* (2000) Deletion of crhr2 reveals an anxiolytic role for corticotropin-releasing hormone receptor-2. *Nat Genet.* 24, 415–419

Mark P. Mattson

Laboratory of Neurosciences, National Institute on Aging Gerontology Research Center, 5600 Nathan Shock Drive, Baltimore, MD 21224, USA

The Journal Club section of TINS *features short synopses of current research in neuroscience. The summaries are written by scientists, for scientists and appear daily in the* ***Commentaries*** *section of BioMedNet at http://www.bmn.com*

Nerves – the silent but strong type

The central nervous system contains billions of neurones, yet there is a strict order to the patterns of connections made by these neurones. Although this order underlies our normal everyday functions, there appears to some trial and error in the formation of the synapses – the pattern we end up with is not always the same as the one we begin with. This is evident in the primary visual cortex where an initial diffuse pattern of visually related inputs from the thalamus is transformed to ordered, alternating ocular-dominance columns. A similar organization of synaptic connections is apparent throughout the nervous system, usually as a result of a decrease in overlap of connectivity. However, the mechanisms by which some synapses are removed and others are favoured are unclear.

It is thought that activity in terminals competing for favour at a single postsynaptic target is essential in determining connectivity, because active terminals and synaptic boutons have widely been shown to have a competitive advantage over inactive ones. However, a recent paper by Costanzo *et al.*[1] shows that activity at a synaptic connection is not necessary for competition. They used the neuromuscular junction as a model for the genesis of synaptic connections because these nerves can regenerate following injury, permitting controlled experimental intervention and identification of the origin of individual terminals. They selected a muscle that is normally innervated by two nerves. Crush or section of one of the nerves leads to degeneration of its terminals at the endplate and sprouting of the other nerve to occupy the vacant endplates. Normally, blockade of conduction in the sectioned nerve would be expected to result in reduced or failed re-innervation by terminals from the sectioned nerve. Therefore, activity itself might be considered to be essential for synapse elimination and consolidation. However, in this report Costanzo *et al.* blocked the activity in both the sectioned and intact nerve, as well as the postsynaptic receptors, and found that there was significant re-innervation by the sectioned nerve. Therefore, activity at the synaptic junction is not necessary for the regenerating nerve to displace pre-existing synaptic connections.

These findings stress that we do not know exactly what confers the ability to survive on one synapse in favour of another. Specifically, this is important at the neuromuscular junction because paralysed muscles can be re-innervated. Identification of the factors that influence nerve regeneration might be clinically useful in promoting the return of muscular function following injury. More generally, the factors that govern re-modelling of synapses at the neuromuscular junction might apply elsewhere in the nervous system and this could therefore provide a good model in which to establish the requirements for synaptic consolidation and elimination.

Reference

1 Costanzo, E.M. *et al.* (2000), Competition at silent synapses in reinnervated skeletal muscle. *Nat. Neurosci.* 3, 694–700

Jim Deuchars

Dept of Physiology, Worsley Medical and Dental Building, University of Leeds, Leeds, UK LS2 9NQ