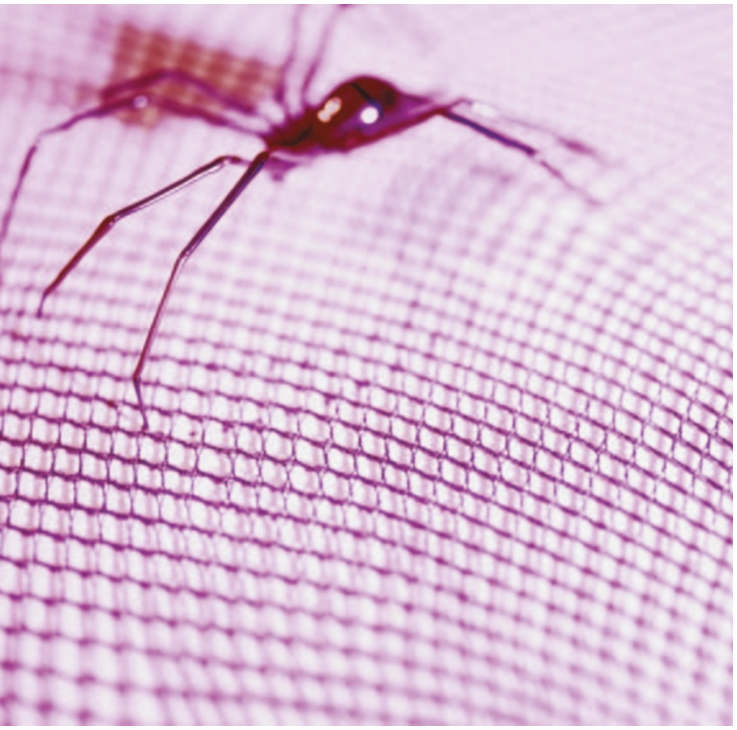
NEUROPEPTIDES

Understanding our fears



It has long been recognized that the amygdala is involved in the expression of fear in mammals, and that vasopressin and oxytocin can modulate this response. Huber and colleagues have now shown, for the first time, that two distinct neuronal populations in the amygdala are excited by either vasopressin or oxytocin, and that their interactions might represent a neurophysiological mechanism for regulation of the fear response.

The central amygdala (CeA) triggers autonomic fear expression by signalling to the brainstem and hypothalamus, and is known to express various neuropeptide receptors, including those for vasopressin and oxytocin. Vasopressin enhances aggression, anxiety and stress levels, and the consolidation of fear memory. Conversely, oxytocin decreases stress and anxiety, and facilitates maternal care and other social interactions. Both neuropeptides increase neuronal activity in the CeA, but, until now, their mechanism of action was unclear.

The authors first determined the positions of vasopressin and oxytocin receptors within previously defined regions of the CeA — vasopressin receptors in the medial part and oxytocin receptors in the lateral and capsular areas — using autoradiography of rat brain sections. Next, by applying different oxytocin and vasopressin receptor agonists, they discovered two types of responsive neuron: those excited by oxytocin-receptor activation, and those inhibited by oxytocin-receptor activation but excited by a specific vasopressin-receptor type, V1a.

Using sharp-electrode intracellular recordings, the authors determined the precise locations of these neurons in the CeA, and found that vasopressin-excited cells were restricted to the medial CeA whereas oxytocin-excited cells were found in the lateral CeA. This correlated with the autoradiographic map of the receptors. The inhibitory effects of oxytocin on vasopressin-excited cells were caused by the enhanced excitability of neurons in the lateral CeA areas, which led to an increase in GABA (γ-aminobutyric acid) release in the medial region of the CeA.

NEUROENDOCRINOLOGY

Obesity's sleepy link

Recent epidemiological studies have noted a link between obesity and insufficient sleep, but the underlying mechanisms are not clear. Now, two reports provide genetic and physiological evidence of how the regulation of circadian rhythm, sleep and metabolism might be tightly coordinated.

Turek and colleagues investigated whether disruption of the circadian system could affect an animal's eating and sleeping behaviours. The circadian system, which controls the timing of almost every aspect of physiology, relies on the so-called 'clock' genes such as clock (*Clk*), period (*Per*) and timeless (*Tim*). The authors found that mice that lacked a functional *Clk* gene — the primary driver of the circadian machinery — slept less and ate more than their wild-type counterparts. Such mice are heavier and show a significant increase in body fat compared with control animals: 35% when fed a normal diet and 75% when fed a high-fat diet. In addition, they show various tissue and biochemical abnormalities that are hallmarks of metabolic disorders, such as high levels of blood glucose and cholesterol, and low levels of insulin. These phenotypes might be related to a decrease in the production of the appetite-regulating hypothalamic hormones leptin and ghrelin in the mutant mice.

In the second study, Hovath and Diano showed that the hypocretin (also called orexin) neurons in the lateral hypothalamus might be a crucial integrator of sleep and metabolism regulation. These neurons secrete hypocretin — a key regulator of both feeding and arousal — and project to many regions of the brain, including the hypothalamus, cerebral cortex, brain stem and spinal cord. Overnight food deprivation promotes the formation of excitatory synapses onto hypocretin neurons and leads to an increase in miniature excitatory postsynaptic currents in these neurons. These effects can be blocked by leptin administration during fasting and are reversed when feeding is subsequently resumed. The results point towards the intriguing possibility that obesity-associated metabolic defects, such as reduced production of leptin, and leptin dysfunction, could render hypocretin neurons more excitable and result in an increased level of arousal and insomnia.

Therefore, genes, hormones and the ability of neurons to undergo synaptic changes can all affect both sleep and metabolism. Further research on the relationships between the two processes and their molecular underpinnings should provide guidelines for the development of new therapeutic approaches to treat obesity and sleep disorders.

Jane Qiu

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These findings show that, in the medial CeA, oxytocin and vasopressin modulate activity in opposite ways. Through the activation of distinct elements of this inhibitory network, the two neuropeptides can integrate the different signals entering the CeA into a single output to the autonomic nervous system, thereby regulating the expression of fear. The authors argue that the distribution of oxytocin and vasopressin receptors throughout the larger, extended amygdala indicates that this system might also be involved in the control of anxiety, stress, motivation and addiction in mammals. Furthermore, they suggest that these neuropeptide receptors could be future targets for the pharmacological treatment of stress and anxiety in humans.

David Stevens

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NEUROTRANSMITTER RECEPTORS

A new role for stargazin

Two recent studies have revealed that the protein stargazin, which is involved in the trafficking of glutamate receptors, can also influence their functional properties. This finding offers new insights into how receptor function can be regulated at excitatory synapses.

Stargazin, which interacts with AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)-type glutamate receptors (AMPARs), is a member of the TARP (transmembrane AMPAR regulatory proteins) family. The interaction of stargazin with AMPARs is important for the correct localization of the receptors at synapses, and this process is involved in synaptic plasticity. The authors of these two studies investigated whether stargazin also influences the gating of AMPARs.

Both Tomita *et al.* and Priel *et al.* used co-expression of glutamate receptor subunits and stargazin in cells such as *Xenopus laevis* oocytes to investigate this question. They found that, as well as increasing the surface expression of AMPARs, stargazin reduced the desensitization and deactivation of the receptors, and speeded up their recovery from desensitization. Stargazin thereby increased the response of cells that expressed AMPARs to glutamate. In addition, the co-expression of stargazin with AMPARs greatly increased the sensitivity of these receptors to the partial agonist, kainate. Tomita and colleagues used this potentiation to quantify the effects of stargazin on channel properties.

Tomita *et al.* then went on to investigate the mechanism by which stargazin influences AMPAR function. They generated stargazin mutants in which specific domains of the protein were substituted with the equivalent domains from another TARP, γ-5, which does not enhance the receptor's response to glutamate or its trafficking. Whereas the trafficking functions of stargazin are mediated by its cytoplasmic tail, they found that an extracellular loop of stargazin was crucial for its effects on AMPAR channel properties.

How does the extracellular domain of stargazin mediate these effects? Tomita and colleagues used a fast glutamate perfusion system to investigate the effects of stargazin on the channel kinetics of AMPARs. In patches from cells transfected with the GluR4 subunit, stargazin greatly increased the steady-state current that could be evoked by glutamate, and specifically increased the frequency of large single-channel openings and the duration of channel bursts. The fundamental effect of stargazin on AMPAR function seems to involve an increase in the rate constant for channel opening.

Finally, Tomita *et al.* investigated whether these biophysical effects of stargazin are physiologically relevant at synapses. They expressed a stargazin–γ-5 chimaera that does not affect channel gating in neurons to disrupt the effects of the endogenous TARP. Overexpression of this chimaera reduced the peak amplitude and increased the decay rate of miniature excitatory postsynaptic potentials, which indicates that stargazin does regulate glutamatergic transmission in intact neurons.

The finding that a receptor trafficking protein can also influence the biophysical properties of AMPARs adds new complexity to the regulation of synaptic responses in the nervous system. The functional importance of this effect, and the molecular mechanisms by which it is mediated, will undoubtedly come under scrutiny in the near future.

Rachel Jones

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