PERSPECTIVES

Steroidal influences on oxytocin neurones

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Oxytocin is essential for successful lactation. Without it, a babe that sucks at a nipple will go hungry, even if the breast at which it sucks is engorged with milk. In lactating rats, oxytocin cells respond to suckling with brief, explosive, synchronous bursts of electrical activity (Lincoln & Wakerley, 1974). This behaviour is not observed in virgin rats even in response to stimuli that strongly excite oxytocin cells, and is not even observed in lactating rats in response to any stimulus other than suckling.

Many have thus felt that oxytocin cells must be 'conditioned' in some way by pregnancy to enable them to display this unusual behaviour, and recent interest has focused on the influence of ovarian steroids. Pregnancy in mammals is accompanied by high plasma concentrations of progesterone that are maintained until shortly before term, when in most mammals the concentration of progesterone falls abruptly, and that of oestrogen surges. The surge of oestrogen is only transient; the stimulus of suckling suppresses the hypothalamo-gonadal axis, and, in rats, ovarian cyclicity is restored only once the pups are weaned.

Recent work indicates that the fall in progesterone concentration at term may indeed influence the oxytocin neurones. Oxytocin cells secrete oxytocin not only from nerve terminals in the posterior pituitary gland, but also from their dendrites within the hypothalamus, where released oxytocin can act both presynaptically upon afferent nerve endings and postsynaptically upon the oxytocin cells themselves. Brussard *et al.* (2000) have now shown that postsynaptic actions of oxytocin attenuate the efficacy of GABA – but strikingly, this action is blocked by the progesterone metabolite allopregnanalone. Moreover, as already shown by Brussard *et al.* (1999), in late pregnancy, oxytocin cells express $GABA_A$ receptors with a subunit composition that confers sensitivity to allopregnanalone; as the concentration of progesterone falls, the neuronal sensitivity to GABA also falls (see Leng & Russell, 1999). Thus, taking these findings together, the fall in progesterone at term may precipitate a state of 'positive feedback disinhibition' in the oxytocin cells, which favours the expression of bursting.

If the bursting behaviour of oxytocin cells is thus initiated by the fall in progesterone at term, is it terminated by the increase in oestrogen at weaning? Israel & Poulain (this issue of *The Journal of Physiology*) recorded from oxytocin cells in hypothalamic slices taken from rats in early lactation and from rats at the end of lactation. The electrophysiological characteristics of the cells differed at these two stages in several respects, and at the end of lactation, but not in early lactation, these characteristics were influenced by the presence of oestrogen. The authors looked in particular at neuronal sensitivity to kainate. They have previously reported that, in a monolayer organotypic culture of neonatal rat hypothalamus, oxytocin cells display bursts that are driven by glutamatergic interneurones acting through non-NMDA receptors, and they have proposed that such a mechanism may underlie milk-ejection bursts *in vivo* (Jourdain *et al.* 1998).

So does the rise in oestrogen at weaning precipitate a fall in neuronal sensitivity to glutamate, terminating the phase of lactational hyperexcitability? Sadly, the converse appears to be the case. Neuronal sensitivity to kainate is reduced in late lactation, but this reduction is abolished in the presence of oestrogen. Thus the authors speculate that, far from terminating lactational hyperexcitability, the increasing oestrogen titre may allow the milk-ejection reflex to 'linger on' in the face of a progressively diminishing frequency of suckling.

Glutamate is the predominant excitatory transmitter influencing oxytocin cells, and is present in many pathways, including those from anterior circumventricular structures involved in osmoregulation. However, while osmotic stimuli strongly excite oxytocin cells, they do not induce bursting, even in lactating rats. There is no direct evidence regarding the identity of the afferent transmitters released during suckling, and the best evidence that glutamate may mediate the milk-ejection reflex is alluded to above – the bursting behaviour of organotypic cultures. However, these bursts are generally much longer, less intense, and occur much more frequently than typical milk-ejection bursts. These may be merely quantitative differences, reflecting the sort of difference that might be expected from a reduced subset of the normal neuronal network. Alternatively, though, neonatal cells in culture may retain immature membrane properties that are absent in adult neurones, or they may establish a pattern of synaptic connectivity that is not present *in vivo*. Interestingly, in the study by Israel & Poulain (2000), although kainate produced an intense depolarisation of supraoptic neurones, the peak firing rates that resulted were well below the firing rates seen in milk-ejection bursts, because of the apparent effect of an intrinsic post-spike hyperpolarising after-potential (HAP). Even if glutamate is involved in triggering milk-ejection bursts, it may be that other factors are necessary; it may be that, before oxytocin cells are capable of firing at the high frequencies typical of milk-ejection bursts, the HAP mechanism that normally limits discharge frequency must first be 'disenabled'.

Thus the work of Israel & Poulain (2000) and that of Brussard *et al.* (1999, 2000) clearly shows that ovarian steroids have an important influence on the behaviour of oxytocin cells, and indeed it seems conceivable that these influences determine the expression of bursting behaviour in lactation. However, there remain major conceptual gaps to be closed, and interesting challenges lie ahead for electrophysiologists.

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