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Preterm Labour: Tsunami Waves?

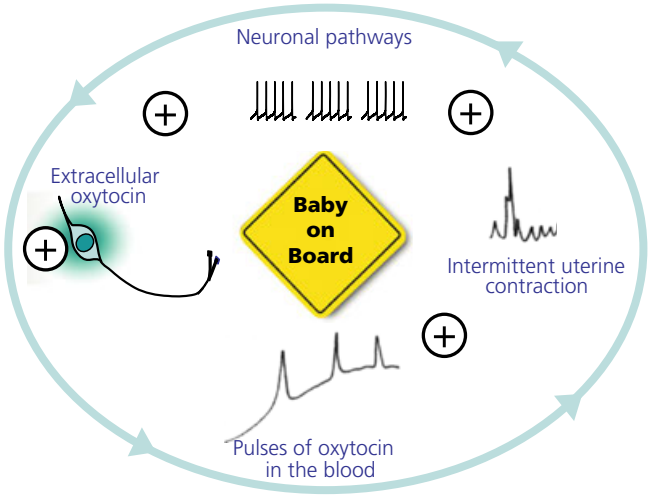
SUMMARY
Preterm labour and birth can be delayed but are generally unstoppable, threatening the health of the mother–baby duo. This may be a result of peripheral signals prematurely recruiting the oxytocin neurones that co-ordinate the timing of birth and, via specialised activity and secretion patterns, drive uterine contractions. Once sensitised, these neurones respond with waves of activity, even to weak stimuli, resulting in a positive-feedback loop that escalates towards inevitable birth.

Baby on board

Late gestation is an important time for mothers and their babies. The mother's brain and pituitary are adapting to perform many new tasks, perhaps never before experienced. For example, neuroendocrine neurones must, almost simultaneously, be able to facilitate birth, initiate maternal care, and control the provision of milk during lactation. The near-term foetus is also undergoing dramatic changes; many of its organs still developing and maturing, including its brain and lungs. These changes must occur when the baby is wholly supported in the maternal environment, and they will ensure life support after birth, even though the baby will not be independent from its mother for several years. Without these co-ordinated adaptations, the health and welfare of the mother and baby duo are at risk, and inadequate preparation for life after pregnancy often results in adverse consequences. This occurs especially when birth takes place before the allotted time.

Baby 'overboard'?

Researchers have known for over 70 years that the hormone oxytocin is important for normal birth in mammals, and the process has been studied extensively in rodents. Oxytocin is synthesised in magnocellular neurones in the hypothalamus whose axon terminals in the posterior pituitary secrete oxytocin into the blood in distinctive pulses first observed during birth. These pulses drive intermittent myometrial contractions that facilitate delivery of the foetus. Oxytocin is commonly administered to women during labour to accelerate the birth process, and this can even help to overcome protracted labour as a result of stress. The pulses of oxytocin secretion are driven by a unique burst firing pattern of activity of oxytocin neurones, which are



The unstoppable positive feedback loop in labour: oxytocin neurones become sensitized to incoming signals from the uterus which results in ever-increasing oxytocin secretion and uterine contraction, terminating in birth.

synchronised at this time. The oxytocin neurones have a specialised auto-control mechanism, whereby they also release oxytocin from their dendrites into the extracellular space around them. This local oxytocin acts on oxytocin receptors whose expression by the neurones is increased at birth. Local oxytocin plays a key positive-feedback role in co-ordinating the neuronal activity; it primes its own release, enhancing oxytocin neurone sensitivity to incoming stimuli.

> *'The pulses of oxytocin secretion are driven by a unique burst firing pattern of activity …'*

Signals from the term-pregnant uterus, placenta and foetus evidently initiate the labour process. Although the exact intra-uterine mechanism for this is different in different species, preliminary uterine contractions in early labour appear to engage the brain and oxytocin neurones in particular. Ferguson, in 1941, first described the reflex explaining this: uterine contraction sets up oxytocin secretory pulses, which drive further uterine contractions. We now know that this is partly mediated by a brainstem noradrenergic pathway, and the noradrenaline released onto oxytocin neurones excites them and plays a role in the morphological and neurochemical adaptations necessary for the burst firing to occur. Intriguingly, dendritically-released oxytocin can control transmitter release from the noradrenergic terminals, either directly or via other local signals such as endogenous cannabis-like substances (cannabinoids). Many other local factors are likely to be involved, but strong evidence points to the major role for oxytocin itself. This is further reinforced by the recent finding of an important mechanism controlling local oxytocin concentration because it appears that specialised enzymes made by the oxytocin neurones themselves can degrade oxytocin. As enzyme activity is physiologically-regulated, it can determine oxytocin access to its receptors. It remains to be determined whether, as in the uterus, decreased activity promotes oxytocin action (i.e. if reduced oxytocin degradation by neurones facilitates their auto-excitation at birth). Together, these networks of neurones and their inputs ensure appropriate timing of birth under normal circumstances.

The inescapable tsunami

However, preterm labour is common (>12.5% in the developed world; defined as regular uterine contractions combined with cervical maturation) and it is difficult to attenuate for more than a few days. Clinicians usually attempt to delay birth during preterm labour so that maternal and fetal physiology can be optimised. Preterm labour is associated with inappropriate, premature activation of the oxytocin system, further driving contraction and risking birth. Thus, one of the most effective treatments for preterm labour is the administration of an oxytocin antagonist (Tractocile, in current UK guidelines). This is an effective tocolytic, temporarily preventing uterine contraction with very few side-effects, although it often needs to be repeatedly given and does not typically delay birth until full-term. A premature baby is likely to exhibit increased morbidity and mortality and all the associated adverse consequences.

Several peripheral mechanisms can trigger uterine contractility and preterm labour, including inappropriate activity of cytokines and prostaglandins. But why is birth difficult to delay long enough to reach term? The answer may lie in the recruitment of the oxytocin neurones which, once primed by the initial signals, then respond to any small trigger (including uterine factors/contraction and or psychological situations such as stress that activate parallel brain pathways). This results in an ever-increasing positive feedback that promotes oxytocin secretion in larger pulses, which inevitably precipitate further uterine contraction and birth. So, far from uterine mechanisms sustaining labour, brain activity is crucial, and drugs targeting oxytocin neurone priming mechanisms may be an appropriate way forward for therapeutic intervention in preterm labour.

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