Neurophysiology of labour pain

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The purpose of this lecture is to discuss four fundamental aspects of obstetric analgesia and pain of labour:

- anatomy of pain fibres important in the first stage of labour
- neurophysiology and sensitization of these pain fibres during labour
- effects of analgesia on the progress of labour
- tissue trauma of labour: production of chronic pain

Anatomy of pain fibres important in the first stage of labour

Pain arising from the first stage of labour is carried through afferents which course through the paracervical plexus and hypogastric nerve, co-mingle with sympathetic efferents along the paravertebral sympathetic chain and enter the spinal cord at the T10 to L1 dermatomes. Near the end of the first stage and during the remaining phases of labour there is also input from somatic efferents in the pudendal nerve which innervate the vaginal surface of the cervix, the vagina, and the perineum. As such, analgesia can be accomplished during the first stage of labour by paracervical, paravertebral, or lumbar epidural administration of local anaesthetics.

It is widely stated that uterine innervation underlies the pain of uterine contractions during labour. Uterine afferents clearly respond to distension, can be sensitized by inflammatory mediators and irritant chemicals, and may play an important role in chronic pelvic pain. Yet their role in obstetric pain is unlikely, since afferents which innervate the myometrium regress in pregnancy [1]. Additionally, anecdotal observations by Bonica, in which vigorous manual palpation of the uterine body during Caesarean section under field block anaesthesia failed to mimic the pain of labour [2], argue that it is not the uterine corpus which signals obstetric pain.

In contrast to myometrial afferents, those which innervate the lower uterine segment and cervix sprout near the end of pregnancy, with a massive increase in neuronal fibre staining in the day preceding the onset of labour in the rat [3]. Cervical afferents are conceivably stimulated during the first stage of labour by uterine contractions, resulting in increased deformation and tension on cervical tissue. Experimental cervical distension is painful in non-pregnant women, with pain referred to low thoracic dermatomes [4], similar to that of labour and consistent with a role for these afferents in signalling obstetric pain. Bonica also noted that manual distension of the uterine cervix in women undergoing Caesarean section with field block anaesthesia reproduced the pain of labour [2].

Neurophysiology and sensitization of these pain fibres during labour

In humans, experimental visceral pain by distension of the oesophagus results in a wider area of referred pain to the body surface than experimental somatic pain from noxious heat applied to the skin to an equivalent level of pain report [5]. This broader, more diffuse representation of visceral pain has been recognized for many years, and is thought to reflect the considerable rostro-caudal and deep arborization of visceral afferent input into the spinal cord dorsal horn compared with somatic afferent input. Cessation of noxious stimulation of the skin results in a rapid disappearance of pain, whereas considerably longer is required for pain to fall to zero after cessation of noxious stimulation of the oesophagus.
The small amount of human psycho-physical study of pain from uterine cervical distension in humans generally reflects these observations of pain from other visceral organs. As such, distension of the cervix in non-pregnant women results in an increase in pain which is dependent on the increase in cross-sectional area of the distending device [4]. Pain from experimental uterine cervical distension is referred to the low thoracic dermatomes, similar to the pain of labour, and there is a slow return of pain to zero following abrupt cessation of distension.

As with other abdominal visceral nociceptive stimuli, uterine cervical distention results in activation of spinal cord dorsal horn neurons, not only in the superficial laminae, but also deep and surrounding the central canal. This activation, as measured by expression of the neuronal marker for activation, cFos, occurs in lower thoracic and upper lumbar dermatomes in a stimulus duration dependent manner after uterine cervical distension, and is blocked by instillation of lidocaine into the cervix prior to distension [6]. The location and pattern of spinal cord cFos expression after experimental uterine cervical distension is similar to that observed following labour and delivery in the rat [7], consistent with uterine cervical afferent activation during labour in this species.

Braxton Hicks contractions, which occur with increasing regularity near term pregnancy, are similar in intensity to those during the first stage of labour, but are typically not perceived as painful. Yet nearly one-third of women in early labour experience severe pain with uterine contractions. We have speculated that sensitization of uterine cervical afferents just prior to and during labour results in this discrepancy in pain between Braxton Hicks contractions and those during labour. It has long been recognized that sensitization occurs during labour, as indicated by hyperalgesia to mechanical stimuli to the skin of the lower abdomen, whose afferents converge on those receiving input from the uterine cervix [8].

Beginning approximately 1 day before the onset of labour, a state of inflammation of the uterine cervix is established. Inflammation progresses as part of the process described above, exacerbated by intermittent ischaemia during contractions and frank injury to tissue late in the first stage of labour. Inflammatory mediators are known to sensitize nociceptors in the skin and the colon, and it would be surprising if they did not sensitize nociceptors in the uterine cervix during this process. Nonetheless, there has been no systematic examination of the effect of inflammatory mediators on cervical afferents, either in the non-pregnant or term pregnant state.

Oestrogen could also conceivably sensitize uterine cervical afferents, since oestrogen signalling increases just prior to the onset of labour. We recently observed an increase in spontaneous activity of single hypogastric units innervating the uterine cervix in ovariectomized rats receiving oestrogen in a dose that produced physiologic concentrations observed in the non-pregnant animal [9]. Interestingly, oestrogen treatment sensitized the response to uterine cervical distension in high-, but not low threshold mechano-sensitive units, consistent with sensitization to nociceptive input.

**Effects of analgesia on the progress of labour**

Delivery requires the sequential activation of two processes – cervical ripening to allow dilatation, and regular, co-ordinated, strong contractions of the myometrium. Most work regarding the normal physiologic mechanisms regulating these processes has focused on maternal or maternal-foetal hormonal causes. The role of uterine innervation has received much less attention. Regression of sympathetic efferents and sensory afferents to the myometrium during pregnancy has been suggested to maintain uterine quiescence by eliminating catecholamine and neuropeptide uterine stimulation from these fibres, respectively. Re-innervation of the myometrium does not occur until several days following delivery, arguing against a role of these fibres in the progress of labour.

Uterine cervical afferents, in contrast, sprout in the days preceding the onset of labour [3]. Although such sprouting could conceivably increase the sensation of pain during labour, normal innervation of the cervix is quite capable of transducing pain from distension, since uterine cervical dilatation is painful in the nonpregnant state. As such, this sprouting is unlikely to serve an important role for sensation. Denervation of the cervix, but not the uterus, produces dystocia in rats [10], but the mechanisms by which these nerves participate in the process of labour have not been investigated.

Uterine cervical afferents express sP and CGRP, and the expression of these neuropeptides increases in lumbar DRGs in the last days of pregnancy, coinciding with the time of onset of cervical ripening [11-13]. Similarly, NK1 receptor expression increases in cervical tissue at this same time, and administration of sP or CGRP induces extravasation in cervix at this time [11-13]. Vascular endothelial growth factor (VEGF) is also expressed in cervical tissue and increases prior to and during the ripening process, likely increasing access
of circulating immune cells to the cervical stroma. Denervation of the cervix prevents this increase in VEGF [14]. These data suggest that uterine cervical afferents may participate in cervical ripening and the birth process by depolarization-induced release of vasoactive neuropeptides.

Afferent function is altered, at least as regards nociceptive neurotransmission, by spinal or epidural administration of analgesics, and these may affect the progress of labour. Spinal administration of lipophilic opioids provides analgesia during the first stage of labour [15] primarily by actions on afferent terminals in the spinal cord, whereas epidural administration of local anaesthetics provides analgesia primarily by axonal blockade of spinal nerve roots. These differing mechanisms of action could presumably alter axon reflex depolarization in a different manner, and hence differentially alter neuropeptide release in the cervix. This may explain the considerably more rapid progress of labour observed with intrathecal opioid administration compared with epidural local anaesthetic injection [16] or compared with systemic opioid administration [17].

Tissue trauma of labour: production of chronic pain

Animal models of neuropathic pain include physical trauma to peripheral nerves, and surgical trauma to ilioinguinal and iliohypogastric nerves presumably underlies chronic neuropathic pain following abdominal hysterectomy. Surgery and physical trauma are increasingly recognized as sources of chronic pain, and the incidence of persistent pain following abdominal hysterectomy or inguinal herniorrhapsy is 15-20%. We recently completed a large multi-national study demonstrating that similar nerve trauma produces nearly no chronic pain at Caesarean section, and animal studies indicate that pregnancy and delivery are protective of generation of neuropathic pain following peripheral nerve trauma. Although the reasons for the apparent protective effect of pregnancy on the development of persistent pain after trauma are unknown, recent work from our laboratory suggests a role for spinally released oxytocin.

Key learning points

- Pain from the first stage of labour arises from sensory nerves in the uterine cervix and lower uterine cervix, rather than from the uterine corpus
- Sensory fibers to the uterine corpus regress during pregnancy, whereas those to the uterine cervix sprout, become sensitized, and are spontaneously active
- Pain during labour can diminish frequency and intensity of uterine contractions due to increased circulating adrenaline and may also increase cervical ripening due to release of substances into the cervix
- Unlike surgical trauma, vaginal and Casarean delivery have an extremely low incidence of subsequent chronic pain
References


