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Setting the pace for labour

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During labour the uterus changes from relative quiescence, with infrequent, uncoordinated, localised, ineffective contractions to the strong, rhythmic, coordinated contractions of labour necessary for vaginal delivery of the fetus. Full relaxation between labour contractions is essential for the wellbeing of the fetus during labour. Since the arteries supplying the uterus and placenta are located within the muscle mass of the uterine wall, tonic uterine contractions without regular periods of relaxation would reduce placental perfusion, depriving the fetus of oxygen. This raises the question, how are labour contractions paced and coordinated throughout the uterus so as to direct the fetus through the birth canal?

Coordinated contraction of the smooth muscle cells in the wall of, for example, the gastrointestinal and urogenital tracts (Sanders et al., 2014) and the vasculature (Hashitani & Lang, 2016) is essential for optimal function in these systems. In these organs, the role of specialized cells such as interstitial cells or pericytes and autonomic and sensory nerves interact with the smooth muscle to achieve the coordination required for complex, direction-oriented contraction.

In the early days of smooth muscle electrophysiology (1950s and 60s), prominent depolarizing pacemaker potentials were identified in intestinal smooth muscle. It was established that interstitial cells of Cajal (ICCs, and other IC-like and fibroblast-like cells) play a major role in the complex peristalsis of the gastrointestinal tract. ICCs possess ion channels and signalling systems that give rise to significant depolarizing pacemaker potentials which are relayed to the smooth muscle cells via gap-junction connections. Failure of ICCs to develop, results in dysfunction of gut motility in humans and animal models. Jean Marshall, the first to record intracellular potentials in myometrium, reported a lack of similar large pacemaker events in uterus, an observation that stands today (Marshall, 1959). While in occasional impalements, small depolarisations occurred, in most cells, activity arose abruptly from the resting potential. Functional (contractility and electrophysiology)

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and histological (electronmicroscopy and immunohistochemistry) studies have failed to provide convincing evidence for gut-like ICCs or ICC markers in myometrium from pregnant women or rodents. In addition, attempts to demonstrate directionality of labour contractions, such as occurs in the gastrointestinal tract during peristalsis, have failed.

Enteric and autonomic efferent nerves form intimate contacts, as close as 20nm, with the ICC pacemaker cells within the gut, playing an important role in peristalsis. In the upper urinary tract, atypical smooth muscle cells are involved in pacemaking, and the evidence indicates that sensory neurons may be involved in modulating their activity. Sustained elevated progesterone levels, essential for pregnancy maintenance, lead to the disappearance of efferent autonomic innervation to the uterus during pregnancy in all species studied. Quadriplegic women can conceive, carry their pregnancy to term and go into labour. While an efferent innervation may not be involved, sensory nerves persist and their contribution to potential pacemaking cannot be discounted. However, no evidence exists for the involvement of sensory nerves in modulating uterine contractility during pregnancy.

An elegant study by Lutton and colleagues in this edition strove to provide some answers in a rat model as to where uterine contractions might be initiated. The detailed histology, electromyographical recording and mathematical modelling provide evidence that activity occurs first in the smooth muscle cells in the immediate vicinity of the placenta, establishing this location as a (the) pacemaker region. The “myometrial- placental pacemaker zone” described consists of strands of smooth muscle cells in very close proximity to the placentae. Their electromyographic (EMG) activity suggests that they may be responsible for generating coordinated labour contractions. The unresolved question is the mechanism(s) mediating this role. Are they merely smooth muscle cells that are close to activating secretions from the placenta? Or have they been earlier “groomed” as pacemakers through phenotypic plasticity, to possess altered ion channel and/or signalling pathways and thus become atypical smooth muscle cells? Are they close to nerves (they are close to blood vessels)? These intriguing possibilities are now on the menu for further experimentation.

A final consideration is the fact that this study was of labour in rats, where each uterine horn contains up to 7-8 pups, and pups are born randomly from the two horns. From the birth of the first pup, labour takes 2-3 hours in rats. Maximal survival of all pups would be facilitated if the placentae of pups closest to the cervix became detached from the uterine wall earlier in the labour process, while those closer to the oviduct remained firmly attached to the uterine wall. It is unclear from the study of Lutton et al, whether and to what extent this might have occurred. In other words, a sophisticated contraction gradient along the uterus might be required. On the other hand, in species carrying a single or very few fetuses, such as humans, these considerations may be redundant. In an early study, we implanted 8 pairs of (EMG) electrodes within the uterus of ewes pregnant with single fetuses. The ewes were freely moving, enabling recording for several weeks before and continuing during labour and delivery. While EMG activity became larger and bursts were more frequent during labour, the electrode in which activity “commenced” for each burst was completely random. In other words, no pacemaker region could be identified (Parkington et al., 1988). It may be that labour contractions are not initiated at a particular site(s), but arise spontaneously at varying sites such that the overall effect is a general increase in tension in the wall of the uterus. The weakening of the

structural components around the cervix provides an “escape” route along which the fetus moves under the increased tension in the uterine wall.

While the study of Lutton and colleagues is novel and makes important conceptual advances, it is the beginning, not the last word on setting the pace for labour contractions, especially in humans.

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Additional information:

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