



Quantitative Analysis of Uterine Action Potentials

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A fundamental problem in developing therapeutic interventions for uterine dysfunction is that the electrical profile of the myometrium, and how it changes in physiological, let alone pathophysiological, situations is unknown. Excitation-contraction coupling of the myometrium is a central component of healthy functioning of the uterus. Even though proper function of this smooth muscle is fundamental in women's health, the electrical activity of the uterus is much understudied, and poorly understood. What is needed is a comprehensive quantitative electrophysiological approach involving experimentation and computer modeling, similar to that developed to understand excitation-contraction coupling in the heart.

The uterus contains myogenic smooth muscle, i.e., muscle that contracts in the absence of neuronal or hormonal input [1]. Although the hormonal and biochemical events play a key role in regulation of the uterus, uterine contraction, like all smooth muscle contraction, is primarily an electromechanical event [2]. Abnormalities in excitation-contraction coupling in the non-pregnant uterus are associated with to dysmenorrhea, endometriosis, and infertility [3-6]. In most women with dysmenorrhea, there is uterine hyperactivity and irregular contractions [7-9]. Abnormalities in the timing of excitation-contraction coupling (whether drug-induced or spontaneous) in the pregnant uterus can lead to abortion, preterm labor, dystocia or dysfunctional labor, or post-term labor [10,11].

Abnormal timing of the development of excitation-contraction coupling associated with parturition can lead to preterm birth. However, it is not clear whether preterm birth merely involves abnormal timing in the development of the electrical profile of the uterus, or development of an electrically active uterus with a differing molecular basis. Preterm birth is a significant health problem which accounts for as much as 85% of neonatal and infantile morbidity and mortality (excluding congenital defects). Although there has been significant decrease in mortality, prematurity is still associated with a significantly higher risk of developing long term complications such as mental retardation, neurodevelopmental disabilities, cerebral palsy, blindness, deafness and respiratory diseases, as well as communication and behavioral difficulties [12-14]. In addition to the medical, social and emotional problems, preterm birth also results in significant healthcare costs. This is a significant, long term, clinical problem. Identifying the molecular basis of changes in ion channel activity and in excitation-contraction coupling during pregnancy is of critical importance. Determining the exact sequence of physiological and pathophysiological changes in the electromechanical profile of the uterus offers the opportunity of identifying new targets for therapeutic intervention, which are desperately needed.

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The action potential is the fundamental unit of electrical activity in the myometrial cell. The action potential depolarizes the membrane, and results in an influx of calcium ions, which is the trigger for uterine contraction [15,16]. Transmembrane calcium flux is an important controller of intracellular calcium, and thus contraction, which emphasizes the importance of understanding the myometrial action potential. Calcium influx is strongly dependent on the properties of the action potential. Understanding the shape and duration of the myometrial action potential is therefore a critical step in understanding excitation-contraction coupling in the myometrium.

The nature of the uterine action potential is complex [17]. A variety of ion channels contribute to electrical activity in the myometrium (for reviews, see [18-20]). Myometrial ion channels can be grouped according to their functional roles, i.e.: excitatory, repolarizing, membrane-stabilizing, background currents, and pacemakers. This is remarkably similar to the components of other better studied smooth muscle types and the cardiac action potential. The complex nature of multiple interacting membrane currents with cellular, multicellular and subcellular components has required extensive use of computer models to be able to understand and interpret data. In heart, this type of modeling has been a critical part of research since the 1960s. Computer models of electrical activity have played a crucial role in understanding defects in excitation and contraction, movement of timed impulses through the heart, treatment and identification of potential therapeutic targets for intervention. In the uterus, such models require information concerning depolarizing or excitatory currents, which are responsible for the upstroke of the action potential, as well as repolarizing currents, which are responsible for the return of the membrane potential to the resting potential. In addition, the uterine muscle model must contain membrane stabilizing currents, which hold the potential near the resting potential, which work in contrast to pacemaker currents, which are membrane destabilizing, and initiate electrical activity. Finally, a uterine muscle will model require information on intracellular calcium transients, and their relationship to the action potential. Few details of the molecular basis or the electrophysiological profile of these currents are known in uterine muscle. In this respect, our knowledge of excitation contraction coupling in uterine muscle resembles the early days of cardiac electrophysiological modeling and analysis. Because of the constrained relationship between currents and the action potential, a computer model, even an erroneous one, will give guidance as to key missing factors that can be identified experimentally. This interplay between models and experiments has been very fruitful in understanding the role of excitation and contraction in heart and will prove equally powerful in advancing our understanding of myometrial function in health and disease.

What can we learn from such efforts? As one example, identification of pacemaker mechanisms and how they mature in uterus will identify the "uterine pacemaker" which initiates contraction during delivery and provides regular, steady well directed waves of excitation. Such knowledge has the potential to provide new molecular targets for modulating contractions. Although the nature and even the existence of a uterine "pacemaker" is hotly debated, the fact that rhythmic contractions exist in the myometrium necessitates

them to arise somewhere (i.e., by definition, a pacemaker site), even if it is not a fixed anatomical point. Similar to cardiac muscle, abnormal contractions may result from ectopic foci initiating contractile behavior due to injury, or inflammation. Computer models of excitation-contraction coupling, and the currents governing it, has the potential to provide new insights into potential targets for the treatment of a host of dysfunctions such as dysmenorrhea, endometriosis, preterm labor, dystocia and infertility.

In short, it is vital that substantial efforts are directed towards rigorous quantitative analysis and modeling of the molecular mechanisms and electrophysiological profile of the myometrium in order to move our understanding of this critical area of women's health forward.

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