P-93

EXTRACELLULAR REGULATED KINASE-MEDIATED PHOSPHORYLATION OF MYOMETRIAL CALDESMON DURING PREGNANCY AND LABOR

Li, Y.[1] Malek, S.[2] Morgan, K.G.[3] 1. Anesthesia and Critical Care, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; 2. Country Day High School, Newton, MA; 3. Boston Biomedical Research Institute, Watertown, MACaldesmon (CaD) is a major actin associated protein, regulating contraction and relaxation of smooth muscle (1). An increased level of CaD in term pregnant human myometrium compared to nonpregnant state suggests specific regulation of this protein during gestation (2). In the present study, we used a timed-pregnant rat model to track the dynamic changes during pregnancy and labor in (I) myometrial contractility; (II) content of contractile proteins and (III) the protein levels and phosphorylation state of CaD and Extracellular Regulated Kinase (ERK). Compared to contractility in nonpregnant myometrial strips (Force 0.34+/-0.04 g/mg in tissue dry weight, mean+/-SEM, n=8, frequency 10.85+/-0.81contractions/15min., n=7), although spontaneous contraction force amplitudes were significantly increased at 16 and 20-day pregnancy (1.11+/-0.12 and 1.25+/-0.15 g/mg respectively, n=7 and 6, $p<0.001$), frequencies of contraction were greatly inhibited (1.12+/-0.10 and 2.75+/-0.94contractions/15min. respectively, n=7 and 6, $p< 0.001$), reflecting myometrial quiescence during pregnancy. During the onset of labor, force amplitude and frequency reached the highest levels (1.12+/-0.10 g/mg and 12.61+/-1.51 contractions/15min. respectively, n=7 and 8). While the content of the 20kDa myosin light chain remains unchanged through pregnancy to labor, actin levels were significantly increased at 20-day pregnancy and during labor ($p<0.001$). The protein content of CaD was increased 3-4 fold in pregnancy (n=4). A 20-fold increase in CaD phosphorylation levels was observed during labor ($p<0.05$), compared to very minimal phospho-CaD in nonpregnant myometrium (n=4). The phospho-CaD antibody used is specific for phosphorylation at the ERK sites of CaD. Phosphorylation of CaD has been associated with increased contractility (3). ERK activation did not increase significantly during pregnancy until the onset of labor ($p<0.01$). We conclude that the increase in CaD protein content during pregnancy may contribute to a suppression of the contractility of the pregnant myometrium by raising the threshold for contraction. On the other hand, CaD phosphorylation, perhaps through an ERK-mediated signaling pathway, is suggested to reverse the inhibition by promoting the uterus to contract during labor. This work may point to new potential targets for therapeutic intervention. *1. Horowitz et al, Physiol Rev, 1996; 79:967 2. Word RA et al, J Clin Invest 1993; 92:29 3. Gangopadhyay & Morgan, J Appl Physiol, 2001; 91:953*

P-94

EPIDURAL BOLUS ADMINISTRATION AND CONTINUOUS EPIDURAL INFUSION OF FENTANYL DIFFER IN THEIR MECHANISM OF ACTION

*Ginosar, Y. Riley, E.T.; Angst , M.S. Department of Anesthesiology, Stanford University Medical School, Stanford, CA*Controversy exists as to whether epidural fentanyl acts predominantly by a spinal or systemic mechanism. This study tested the hypothesis that the predominant mechanism of fentanyl action depends upon the mode of its administration. **Method:** 10 healthy volunteers have completed this double-blind, randomized, cross-over study. Epidural catheters were placed at L3/4. On separate study days, subjects received either an epidural fentanyl bolus regime (0.03mg followed 210 min later by 0.1mg) or an epidural fentanyl infusion regime (0.03mg/h followed 210 minutes later by 0.1mg/hr for 200 min). Using both an experimental heat pain model and an experimental electrical pain model, analgesic effects of fentanyl were assessed at the leg and face 3 times before and 30, 60, 120, 180, 240, 270, 330, 390 min after first drug administration. Finally, an analgesic assessment was made after intravenous administration of 0.4mg naloxone. Plasma fentanyl was measured at each time point. **Results:** The figure depicts the change in heat (°c) necessary to cause maximum tolerable pain as a function of time after drug administration. The graph depicting the % change in electrical current required to cause maximum tolerable pain as a function of time after drug administration was almost identical and has not been represented here for lack of space. Fentanyl bolus administration caused significant analgesic effects at the leg (*) but not the head. Fentanyl infusion caused significant analgesic effects at both the leg (*) and the head (#). No difference could be detected between the magnitude of the analgesic effect at the leg and head for epidural infusion of fentanyl. **Conclusion:** Our data suggest that epidural bolus administration of fentanyl acts predominantly at the spinal site thereby providing segmental analgesia. Conversely, epidural infusion seemed to act significantly at supraspinal sites, so providing systemic analgesia.