ENDOCANNABINOID SYSTEM AND MOUSE UTERINE CONTRACTILITY

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Cannabis and cannabinoids have been reported to be involved in controlling the activity of the female reproductive system (Sun and Dey, 2012; Brents, 2016). However, the role of the endocannabinoid system in mouse uterine contractility in the dioestrus and oestrus phases has not been previously investigated. The present study aimed at filling this omission. Endocannabinoid (anandamide and 2-arachidonoylglycerol) levels were measured in mouse uterus at dioestrus and oestrus phases by liquid chromatography-mass spectrometry; quantitative reverse transcription-PCR measured mRNA expression of cannabinoid receptors and enzymes involved in the metabolism of endocannabinoids. Contractility was evaluated in vitro either on the spontaneous contractions or by stimulating the isolated uterus with exogenous spasmogens. The tissue concentrations of endocannabinoids were reduced in the oestrus phase, compared to dioestrus. Uteri obtained in the dioestrus, but not oestrus, phase showed spontaneous phasic prostaglandin-mediated contractions that were reduced by ACEA (CB1 receptor agonist) and to a lower extent by JWH133 (CB2 receptor agonist). These inhibitory effects were counteracted by the corresponding selective antagonists. Both ACEA and JWH133 did not affect the contractions induced by exogenous PGE2 in the uterus from the oestrus phase. The FAAH inhibitor JNJ1661010 and, to a lower extent, the MAGL inhibitor JZL184 also reduced spontaneous contractions. It is concluded that the endocannabinoid system undergoes to adaptive changes between the oestrus and dioestrus phases. CB1 and, to a lower extent, CB2 receptor activation results in selective inhibition of myometrial contractility, without un-specific relaxing effects on the uterine smooth muscle. The inhibitory effect of cannabinoid agonists was shared by a FAAH inhibitor, although with a cannabinoid receptor-independent mechanism. A MAGL inhibitor also exerted a much smaller but still significant effect. Our study, by revealing the involvement of the endocannabinoid system in uterine motility, provides novel molecular targets to achieve tocolysis through activation of CB1 and/or CB2 receptors, for example by arresting the progression of spontaneous preterm labor or facilitating sperm transport disrupted by uterine hypercontractility in adenomyosis patients.

Sun X, Dey SK. Endocannabinoid signaling in female reproduction. ACS Chem Neurosci. 2012;3:349-55.

Brents LK. Marijuana, the Endocannabinoid System and the Female Reproductive System. Yale J Biol Med. 2016;89:175-91.