Animal Reproduction Science 179 (2017) 10–19

Contents lists available at ScienceDirect

Animal Reproduction Science

journal homepage: www.elsevier.com/locate/anireprosci

Extra and intracellular calcium signaling pathway(s) differentially regulate histamine-induced myometrial contractions during early and mid-pregnancy stages in buffaloes (*Bubalus bubalis*)

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ARTICLE INFO

Article history:
Received 8 July 2016
Received in revised form 18 January 2017
Accepted 25 January 2017
Available online 7 February 2017

Keywords:
Histamine
Buffalo myometrium
Stages of pregnancy
Calcium
PL-C
SERCA

ABSTRACT

This study examines the differential role of calcium signaling pathway(s) in histamine-induced uterotonic action during early and mid-pregnancy stages in buffaloes. Compared to mid pregnancy, tonic contraction, amplitude and mean-integral tension were significantly increased by histamine to produce myometrial contraction during early pregnancy with small effects on phasic contraction and frequency. Although uterotonic action of histamine during both stages of pregnancy is sensitive to nifedipine (a L-type Ca^{2+} channels blocker) and NNC55-0396 (T-type Ca^{2+} channels blocker), the role of extracellular calcium seems to be more significant during mid-pregnancy as in this stage histamine produced only $9.38 \pm 0.96\%$ contraction in Ca^{2+} free-RLS compared to $21.60 \pm 1.45\%$ in uteri of early pregnancy stage. Intracellular calcium plays major role in histamine-induced myometrial contraction during early pregnancy as compared to mid pregnancy, as in the presence of cyclopiazonic acid (CPA) Ca^{2+}-free RLS, histamine produced significantly higher contraction in myometrial strips of early-pregancy in comparison to mid-pregnancy ($10.59 \pm 1.58\%$ and $3.13 \pm 0.46\%$, respectively). In the presence of U-73122, the DRC of histamine was significantly shifted towards right with decrease in maximal effect (E_{max}) only in early pregnancy suggesting the predominant role of phospholipase-C (PL-C) in this stage of pregnancy.

1. Introduction

Mast cells are the main source of endogenous histamine in the endometrium and myometrium (Massey et al., 1991; Pap, 2004) and the density of mast cells is significantly higher in pregnant than in non-pregnant women (Garfield et al., 2006). Quantity and activity of mast cells is influenced by hormonal status of the organism (Szelag et al., 2002a). Histamine is a potent uterotonic and increases contractility of isolated myometrium from pregnant and non-pregnant women (Cruz et al., 1989; Martinez-Mir et al., 1990; Rudolph et al., 1993; Castelli and Vadora, 1993), non-pregnant guinea pigs (Goyal and Verma, 1981) and pregnant and non-pregnant mice (Rudolph et al.,

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http://dx.doi.org/10.1016/j.anireprosci.2017.01.011
0378-4320/

1992; Rubio et al., 1999) and non-pregnant buffaloes (Sharma et al., 2014). Release of endogenous histamine may activate uterine contractility during pregnancy and consequently result in preterm labour and delivery (Bytautiene et al., 2002, 2003, 2004), but it has physiological significance too as it may regulate embryo–uterine interactions during implantation. Expression of histamine-producing enzyme histidine decarboxylase (HDC) is about 1000 times higher in the placenta than in other organs (Pap, 2004). Murine preimplantation blastocysts have been found to express histamine receptors-2 (H_2R) (Zhao et al., 2000) and conversely, histamine seems to promote cytotrophoblast invasiveness specifically through activation of histamine receptor-1 (H_1R) in humans (Liu et al., 2004) which are expressed in syncytiotrophoblasts of placental villi and play an important role in exchange of substances.

Histamine produces a contractile effect on isolated myometrial strips from majority of the mammalian species through activation of H_1 histamine receptors, but in rats, the predominant response of uterus is relaxation through activation of H_2 histamine receptors (Szelag et al., 2002b). Therefore, the effect of histamine depends on the dominance of histaminergic receptors (H_1 or H_2) and their response changes during pregnancy due to alterations in calcium signaling pathway(s) involved in uterine contractions during pregnancy (Coleman et al., 2000). There are species-specific differences in the relative importance and timing of myometrial contractions; and in general, the components of signaling pathways favouring contraction and parturition are enhanced in myometrium during pregnancy or in labour (Challis and Lye, 1994; Fuchs, 1995; Sanborn et al.1998; Challis et al., 1999).

Pregnancy-dependent alterations in histamine levels in blood and reproductive tissues have been documented in cattle and buffaloes (Matta et al., 1999, 2001). Maternal total blood histamine levels are highest during first trimester (Dubois et al., 1977) and these do not significantly differ from the non-pregnant state (Haimart et al., 1985; Kimura et al., 1999; Brew and Sullivan, 2006) while they decrease during the second (Dubois et al., 1977; Clemetson and Cafaro, 1981) and third trimesters of pregnancy (Achari et al., 1971; Dubois et al., 1977; Sharma et al., 1984) showing a nadir in the second trimester (Brew and Sullivan, 2006).

Histamine exerts its effects through H_1, H_2, H_3 and H_4 receptors on target cells in various tissues. Histamine receptors (H_1 and H_2) are expressed in both decidual and placental components (human amnion, chorion, decidua, villous cytotrophoblast and stromal cells) of the feto–maternal interface (Fukui et al., 1994; Brew and Sullivan, 2001) and play an important role at the feto–maternal interface after implantation (Brew and Sullivan, 2001; Pap, 2004).

Myometrium is a phasic smooth muscle, although tonic contractions may develop with high-frequency electrical stimulation during labour or after use of some agonists such as oxytocin, prostaglandins, or endothelin. Elucidation of signaling mechanisms involved in histamine-induced myometrial contraction may facilitate identification of some selective therapeutic targets for addressing myometrial patho-physiological states during pregnancy in human beings and animals, especially in buffaloes. Mechanistic pathway(s) of oxytocin and $PGF_{2\alpha}$-induced myometrial contractions have been elucidated in women (Burghardt et al., 1999; Luckas et al., 1999; McKillen et al., 1999; Parkington et al., 1999; Tribe, 2001), laboratory animals (Luckas et al., 1999; Coleman et al., 2000) and in buffaloes (Sharma et al., 2016) and it has been found that calcium regulatory pathways differentially modulate myometrial activity during non-pregnant and pregnancy states. Calcium signaling pathways in histamine-induced myometrial contractions during non-pregnant state in buffaloes have been reported by us (Sharma et al., 2014) and our present communication describes the differential involvement of extra and intracellular calcium regulating pathways during early and mid-pregnancy stages in buffaloes which have an average gestation period of 10 months and 10 days.

2. Materials and methods

2.1. Collection of buffalo myometrium

Uteri along with the ovaries were collected from pregnant buffaloes from the local abattoir, depending on availability, immediately after slaughter and transported to laboratory in chilled ($4.0 \pm 0.5\,^{\circ}C$) Ringer-Locke solution (RLS) having pH of 7.4. The uteri were cut open to identify about the pregnancy status and stage of pregnancy was determined by measuring the curved-crown versus rump (CRV) length of foetus (Soliman, 1970).

When CVR length was below 20 cm,

$$Y = 28.66 + 4.498x$$

When CVR length was 20 cm or above,

$$Y = 73.544 + 2.256x$$

Where Y = days of gestation, X = curve crown rump length in centimeters.

2.2. Preparation of myometrial strips

Myometrial strips were prepared from uteri of pregnant buffaloes as per the method described earlier (Choudhury et al., 2010) and mounted in thermostatically controlled ($37.0 \pm 0.5\,^{\circ}C$) organ bath (Ugo Basile, Italy) of 10 ml capacity containing RLS continuously aerated with carbogen (95% O_2 + 5% CO_2) under a resting tension of 2 g. During the equilibration period of at least 2 h, bath fluid was changed after every 10 min.

2.3. Chemicals

Histamine, oxytocin, nifedipine (a L-type Ca^{2+} channel blocker), NNC55-0396 [a specific T-type Ca^{2+} channel blocker (Huang et al., 2004)], ruthenium red (IP3/ryanodine receptor blocker), U-73122 (1-(6[([17-]-3-methoxyestra 1,3,5(10)-trien-17-yl) amino]hexyl)-1H-pyrrole-2,5 dione) (a PL-C blocker) and cyclopiazonic acid (CPA, a sarcoendoplasmic reticular Ca^{2+}-ATPase inhibitor) were sourced from Sigma–Aldrich (USA). Except U-73122(dissolved in DMSO) and nifedipine (dissolved in ethanol), all other