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TRANSCERVICAL ARTIFICIAL INSEMINATION (AI) IN SHEEP: AN OVERVIEW

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Abstract

Within sheep industry artificial insemination (AI) is a very valuable tool for rapid genetic progress. AI is performed to maximise the use of superior rams and contain certain contagious diseases within flocks. In the sheep breeding industry three methods of AI are prevalent: vaginal, cervical and laparoscopic intrauterine. Commercially acceptable fertility rates, however, can be achieved by laparoscopic intrauterine insemination using both fresh and cryopreserved semen but with cervical AI using fresh semen only. The most successful method, therefore, seems to be Laparoscopic AI but it is an expensive, invasive surgical procedure and is not considered to be welfare-friendly. A practical solution is, therefore, transcervical intrauterine (TCAI). However, due to the convoluted nature of the sheep cervix, penetration of the inseminating pipette to enable TCAI is rarely achievable. This review describes some of the work that has been done to understand the mechanism(s) of cervical relaxation with the ultimate objective of performing transcervical AI in sheep.

Keywords: Trans-cervical artificial insemination, Sheep, Cervical relaxation

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1. Introduction

Studies at the RVC are focussed at investigating the anatomical and/or technical factors that affect the passage of an insemination pipette through the cervix, particularly the basic mechanism(s) involved in the cervical relaxation. The ultimate aim of research on AI, at the RVC, is to have a greater understanding of the regulation of cervical relaxation in the sheep during the oestrous cycle that may facilitate the development of therapeutic treatments, and develop a method by which semen could be deposited into the uterus through a trans-cervical route.

2. Overview

Preliminary work in our laboratory showed that there is a degree of natural relaxation of the cervix at the time of oestrus and that led us to hypothesise that "the periovulatory changes in oestrogen and progesterone decrease the glycosaminoglycans (GAGs) content of the cervical stroma via a cervical cyclo-oxygenase-2 (COX-2) dependent mechanism, to dilate the cervix at the time of oestrus".

The results of the studies on ovine cervices collected at different stages of the oestrous cycle (luteal, pre- and post-LH surge) have shown that the cervices collected at the pre-LH surge time of the oestrous cycle have maximum expression of COX-2 mRNA. This expression was seen predominantly at the uterine region and was greatest in

the irregular smooth muscle layer of the cervix (Kershaw et al., 2007). Moreover, EP2 mRNA expression was significantly higher in the cervices collected at the time of pre-LH surge compared to other stages of the oestrous cycle (Kershaw-Young et al., 2009). In addition, we also found that almost all the GAGs in cervix were Hyaluronan-like (HA-like), and pre-LH surge cervices contained most HA-like GAG, predominantly at the uterine region and in the luminal epithelium (Kershaw-Young et al., 2009).

Pre-LH cervices also had a greater percentage area occupied by collagen compared to smooth muscle particularly at the uterine region (Kershaw et al., 2007). These studies led us to conclude that the major impediment to TCAI in sheep is anatomy of the cervix, in particular the arrangement of cervical rings. The enhanced penetrability of the cervix at the oestrus is not associated with a change in the gross anatomy of the cervix but is instead associated with molecular and structural changes in the cervical ECM. Oestradiol in synergy with FSH increases COX-2 expression in fibroblasts and smooth muscle cells, possibly through an oxytocin-mediated mechanism and the fall in progesterone concentrations may increase the expression of PGE_2 receptor EP_2.

The increase in COX-2 leads to increase in PGE2 synthesis, which after binding to its receptors EP2 and EP4 initiates cervical relaxation. It is a possibility that activation of EP2 and EP4 receptors stimulates adenylate cyclase and cAMP/protein kinase pathway stimulating the relaxation of smooth muscle. In addition, activation of EP4 stimulates the synthesis of GAGs, particularly HA. HA increases the uptake of water into the sheep cervix decreasing relative concentrations of sulphated GAGs like chondroitin sulphate (CS) and dermatan sulphate (DS) that form cross-links with collagen bundles. The reduction in CS and DS concentrations is associated with a reduction in cross-links between collagen bundles and collagen fibres, enabling collagen fibres to move across one another, separate and become disorganised. Separation of collagen bundles and fibres reduces the tensile strength of the sheep cervix and in combination with the relaxation of smooth muscle through the activation of EP2 and EP4 culminates in relaxation of sheep cervix at oestrus.

Considering the increase in HA content of the cervix at the time of oestrus, the main aim of further studies was to investigate the other role(s) that HA may play in the cervical relaxation of the ewe. In this respect, HA content, the expression of its receptor CD44, regulation of HA synthesis by hyaluronan synthases (HAS), and components of the CD44 signalling cascade, including ras-related C3 botulinum toxin substrate 1 (Rac1), actin-related protein 2/3 (Arp 2/3) and Capping protein-Z (Cap Z), along with their hormonal regulation were studied. In addition, it was investigated whether a topical application of HA would affect penetration through the cervix by an inseminating pipette and/or help in achieving the commercially acceptable fertility rates with frozen-thawed semen.

At oestrus, the hormone profile in the ewe is one of higher oestradiol (E_2), luteinising hormone (LH) and follicle stimulation Hormone (FSH) and lower progesterone (P_4). So using the cervices collected at the luteal, at oestrus (pre-LH surge) and post-LH surge stages of the oestrous cycle, the results of our studies have demonstrated that Pre-LH (at oestrus) surge animals had significantly higher HA content of the cervix compared to the luteal and post-LH groups.

Moreover, there were significantly more cervices containing only small HA fragments in the luteal stage, and containing only large HA fragments in the post-LH surge stage of the oestrous cycle. However, there were significantly more cervices containing both small and large HA fragments at the Pre-LH stage of the oestrous cycle (Perry et al., 2010a). The HA content of the cervices was increased along with a temporal expression of Hyaluronan synthase-3 (HAS3) that only produces low molecular weight (LMW) HA (Perry et al., 2012).

This increase in LMW HA might be responsible for the significant increase in its receptor CD44 in the pre-LH group (Perry et al., 2010a) and the down-stream signalling cascade resulting in an increased expression of Rac1 and ARP2/3 and a decreased expression in CapZ in the cervical tissues. We propose that down-stream signalling cascade is then likely to initiate cellular remodelling through F-actin polymerisation and cellular reorganisation, and result in cervical remodelling. This proposed model of cervical remodelling is confirmed by the results of our further studies, which demonstrated that topical application of LMW HA to the cervix does increase cervical penetrability to facilitate the passing of an inseminating pipette in sheep (Perry et al., 2010b).

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Conflict of interest

The author declare that there is no conflict of interest.

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