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Milk-borne relaxin and reproductive system development

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Summary

A window of opportunity for maternal programming of neonatal development is open in the first few days of life as a consequence of nursing. Colostrum (first milk) supports neonatal development by providing a conduit for delivery of milk-borne bioactive factors, exemplified by relaxin, from mother to offspring as proposed in the lactocrine hypothesis. Relaxin, a prototypical milk-borne bioactive factor, is detectable in colostrum from multiple species, including the pig. Thus, relaxin serves as a model for understanding lactocrine signals that support development of neonatal tissues.

Key words

Relaxin, milk, uterus, lactocrine

Recent studies of female reproductive tract (FRT) development in the pig (*Sus scrofa domesticus*) implicate RLX as an effector of uterine and cervical development through a lactocrine-driven mechanism. Pro-relaxin is the primary, bioactive form of RLX found in porcine colostrum. Serum RLX, detectable in nursed gilts at birth (postnatal age = PND 0), is undetectable in neonatal gilts fed milk replacer (Yan et al, 2006). Thus, RLX is communicated from mother to offspring as a specific consequence of nursing. This is a prototypical example of lactocrine communication. In newborn gilts, nursing from birth is required for establishment of a normal developmental program in uterine and cervical tissues. When compared to pigs fed milk replacer over the same period, nursing for two days from birth induced expression of markers and mediators of uterine (Chen et al., 2008) and cervical (Frankshun et al., 2012) development on PND 2 including estrogen receptor-α (ESR1), vascular endothelial growth factor and pro-matrix metalloproteinase-9. Exogenous RLX altered expression of these proteins in nursed gilts while RLX alone failed to rescue FRT phenotypes in replacer-fed animals. Both neonatal porcine uterine and cervical tissues are RLX receptor (RXFP1) –positive at birth and are, therefore, targets for lactocrine-active RLX. In the cervix, a classic RLX target tissue, *RXFP1* expression increases from birth to PND 2 in both nursed and replacer-fed gilts and is reduced to a greater extent in RLX-supplemented nursed as compared to RLX-supplemented replacer-fed gilts. Observations of this kind, reported for both developing uterine and cervical

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tissues, suggest that effects of RLX on FRT development involve cooperating lactocrine-active factors. A feed-forward lactocrine driven mechanism was proposed to explain how milk-borne bioactive factors, exemplified by RLX, could support events central to endometrial adenogenesis in the neonatal pig (Bartol et al., 2009). In this scheme, lactocrine transmission of RLX allows this milk-borne bioactive factor to act via RXFP1 to induce and/or support endometrial ESR1 expression, required for initiation of uterine adenogenesis. In addition to the role of nursing in support of FRT development, we have evidence that male reproductive tract, cardiac, cerebral cortical and hypothalamic tissues are sensitive to lactocrine signaling. Thus, studies of RLX – a prototypical lactocrine-active factor in the pig – have opened a new research domain focused on identification of mechanisms through which factors of maternal origin, delivered in milk to nursing young, affect organizationally critical events in neonatal somatic tissues.

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