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Adrenomedullin (AM) and adrenomedullin binding protein (AM-BP) in the bovine mammary gland and milk: Effects of stage of lactation and experimental intramammary *E. coli* infection☆

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Abstract

Adrenomedullin (AM) has been characterized as an endogenous tissue survival factor and modulator of many inflammatory processes. Because of the increased susceptibility of the mammary gland to infection during the time surrounding parturition in the cow, we investigated how milk and tissue content of AM and its binding protein (AM-BP) might be affected by the stage of lactation and the udder health status. Milk and mammary biopsy samples were obtained from Holstein cows 21 days prior to and at various times after calving to represent the dry period and early and mid-stages of lactation. Additional cows received an intramammary challenge with *Escherichia coli* for immunohistochemical characterization of AM and AM-BP. Milk AM concentrations were relatively constant across the stages of lactation while AM-BP increased two-fold ($P < 0.04$) between early and

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mid-lactation. Milk AM ($P < 0.04$) and AM-BP ($P < 0.03$) increased as somatic cell counts (SCCs) increased within a given stage of lactation. Tissue content of both (AM and AM-BP) were significantly affected by stage of lactation, lowest in the dry period and progressively increasing to peak at mid-lactation as well as increasing in association with higher levels of SCCs. Following *E. coli* challenge, AM increased in epithelial cells surrounding mammary alveoli presenting high levels of SCCs. The data suggest that AM and AM-BP are cooperatively regulated in the mammary gland during lactation; changes in localized tissue AM and AM-BP content reflect a dynamic regulation of these tissue factors in the bovine mammary gland consistent with their protective effects within inflamed tissue.
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Keywords: Adrenomedullin; Adrenomedullin binding protein; Mammary gland; Inflammation; Lactation

1. Introduction

Adrenomedullin (AM) is a 50-to-52 amino acid peptide, present in a myriad of tissues and is a member of the calcitonin gene-related (CGRP) family of bioactive peptides [1–3]. Following its discovery and characterization as a potent regulator of cardiovascular function [4,5], AM is now credited with a multiplicity of effects including autocrine growth regulation, angiogenesis and neoplasia, tissue differentiation and development, and regulation of metabolism [3]. More recently AM has been called a tissue survival factor [6] in that its upregulation during periods of proinflammatory stress has been linked to decreased apoptotic events [7], maintenance of tissue perfusion [8], localized antimicrobial peptide effects [9,10] and modulation of immune function [6,11]. Many actions of AM are tied to its interaction with the proinflammatory cytokine cascade including its regulation by endotoxin (LPS) and tumor necrosis factor-α (TNF-α, [12,13]), as well as the generation of nitric oxide via several of the isoforms of nitric oxide synthase (NOS, [13–15]). We recently characterized a circulating protein that functions as a transport binding protein for AM (AM-BP, [16]). Further research into this binding protein revealed it to be a member of the complement cascade, namely, complement factor-H (C-F_H, [17]). The interaction of AM with AM-BP/C-F_H results in the modulation of the bioactivity of each component of the complex [17–19].

Cooperative work between our laboratories indicated that AM was present in several biofluids including human and bovine milk [20]. Because of its multiple effects on tissue function and survival as well as its properties as an antimicrobial peptide, we were interested to determine whether AM levels in bovine milk and mammary tissue might be associated with or reflective of the changes in udder health status and general mammary physiology that have been documented with regard to the impact of stage of lactation, especially around calving and presence of mammary infection [21–23]. Employing immunohistochemical image analysis techniques as well as RIA and Western blot approaches, we report here for the first time quantified localized changes in tissue AM and AM-BP in mammary tissue of cows, as well as changes in concentrations of AM and AM-BP in milk as a function of lactational status, milk somatic cell count, or presence of intramammary infection.

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