The importance of adrenergic receptors in the bovine udder for milk removal

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Presence of adrenergic receptors in the bovine mammary gland

Alpha- and β-adrenergic receptors are present in most mammalian organs. They are mediating the tissue-specific activity of the sympathetic nervous system with noradrenalin as neurotransmitter or the systemic endocrine action of adrenalin released from the adrenal medulla. Adrenergic receptors belong to the family of G-protein-coupled receptors which are located in the cell membrane and have seven stretches of hydrophobic transmembrane spanning domains (Gether, 2002). Alpha- and b-adrenergic receptors are pharmacologically classified into the receptor types α1 and α2, and β1, β2 and β3, respectively. Between these receptor types there are functional differences and often antagonistic effects, e.g. vasoconstriction mediated by α1 and α2-receptors and vasodilation mediated by β2-receptors (Bruckmaier et al. 1991; Inderwies et al. 2003b, c).

Within the bovine mammary gland, adrenergic receptors have first been detected in the teat smooth muscle layer (Roets et al. 1984; Roets & Peeters, 1985; Roets & Peeters, 1986). Later, α- and β-adrenergic bindings sites were also found in the tissue surrounding the gland cistern and the large milk ducts whereas almost no binding was detected in the secretory parenchyma free of larger milk ducts (Hammon et al. 1994). Based on quantitative analysis of the mRNA encoding for the different receptor types and subtypes eight of nine currently known receptor subtypes could be detected in the udder of dairy cows (Wellnitz et al. 2001; Inderwies et al. 2003a). mRNA expression of α1 and α2 receptors was highest for the α1A and α2A subtypes, respectively. Within the β receptors, the β2 receptor type was most highly expressed.

Alpha-adrenergic receptor stimulation inhibits milk ejection and milk removal

Experiments demonstrated an inhibition of milk ejection and milk flow in response to the administration of adrenalin or noradrenalin (Cochrane, 1949; Naito et al. 1964; Vorherr, 1971; Sibaja & Schmidt, 1975). These results led to the hypothesis that catecholamines and amongst them mainly adrenalin are responsible for disturbed milk ejection under practical conditions which was clearly contradicted in several investigations in the 1990th.

The importance of α- and β-adrenergic receptors for this inhibitory effect could not be evaluated in these studies because the natural catecholamines adrenalin and noradrenalin stimulate both receptor types albeit the respective effect is dose-dependent and the experimentally administered dosages were always in a supraphysiological range. Therefore, additional studies were necessary where adrenalin was administered together with receptor-type specific blocking agents or receptor-type specific agonists were administered as far as available (Blum et al. 1989; Bruckmaier et al. 1991). These studies proved that the inhibitory effect on milk ejection and thus reduction of milk yield was mediated by α-adrenergic receptor stimulation, whereas β-adrenergic receptor stimulation caused an increased milk flow, however, without any effect on milk yield. The inhibition of milk ejection as induced by α-adrenergic receptor stimulation could not be overcome by oxytocin administration even in very high pharmacological dosages but by an α-receptor blocking agent (Bruckmaier et al. 1997). In addition, it could be shown that despite inhibition of milk ejection, α-adrenergic receptor stimulation does not inhibit but rather augment the milking-related release of oxytocin from the posterior pituitary (Bruckmaier et al. 1997). Thus, the experimental inhibition of milk ejection via α-adrenergic receptor stimulation is not based on a suppression of oxytocin release or on an interaction with the oxytocin receptors of the myoepithelial cells. Obviously, the inhibition of milk ejection occurs on the level of the milk duct system where many subtypes of adrenergic receptors have been detected in high density (Hammon et al. 1994; Wellnitz et al. 2001; Inderwies et al. 2003a). Smooth muscles of the milk ducts have the potential to close the ducts in response to intensive α-adrenergic stimulation (Inderwies et al. 2003b). Surprisingly, the longitudinal contraction of the teats which is also visible in response to α-adrenergic stimulation seems to have almost no inhibitory effect on milk ejection and milk flow (Bruckmaier et al. 1997; Inderwies et al. 2003b). In conclusion, the inhibitory action of α-adrenergic stimulation is solely located in the milk duct system and acts in a dose-dependent manner (Inderwies et al. 2003b; 2003c).

Beta-adrenergic receptor stimulation increases milk flow but not milk yield

Selective β-adrenergic receptor stimulation either by a β-adrenergic agonist (Bruckmaier et al. 1991) or by adrenalin administered together with an α-adrenergic blocking agent (Blum et al. 1989) caused an augmentation of milk flow rates, most pronounced of peak flow rate, but no simultaneous increment of milk yield. Obviously, β-adrenergic receptor stimulation facilitates the transfer of milk from the alveolar tissue into the cisternal cavities to be available for milk removal. It has been demonstrated that milk ejection is a continuous process throughout the entire milking (Bruckmaier et al. 1994). Most likely, the milk ejection rate can be a limiting factor for milk flow rate. Consequently, a relaxation of the large milk ducts may result in increased milk flow rates. Because adrenergic receptors are not present in the secretory tissue (Hammon et al. 1994) the β-adrenergic stimulation does obviously not interact with myoepithelial contraction thus explaining a lack of effect on milk yield.

Adrenergic receptors and milkability

Based on the effects of pharmacological stimulation of α- and β-adrenergic receptors it seems likely that the distribution of α- and β-adrenergic receptors and their various subtypes influences the course of milk ejection and hence milk flow during machine milking. Studies by Roets et al. (1989) showed that milkability traits are correlated with the ratio of β2/α2 receptors in the teat muscle layer and in blood cells. Further studies even showed a significant correlation between the b2/a2 receptors on blood cells of bulls and the milkability of their daughters (Roets et al. 1995). Recently it could be demonstrated that the peak flow rate is negatively correlated with the expression level of the α2A receptor in the tissue around the large milk ducts both on a mRNA and a protein level whereas no relation between the expression of other adrenergic receptor subtypes and peak flow rate could be found (Inderwies et al. 2003c). Without adrenergic drug treatment the adrenergic receptors are stimulated by the neurotransmitter noradrenalin from the sympathetic neurons or by circulating catecholamines released from the adrenal medulla. Thus, the sympathetic tone of the milk duct system seems to have a considerable influence on the milk ejection rate and thus availability of alveolar milk for the milking machine and milk flow.

Adrenergic receptors in the udder do not mediate spontaneous inhibition of milk ejection in practical dairy farming

Despite contradictory reports in many text books it has to be clearly stated that spontaneous inhibition of milk ejection in dairy farms was never shown to be related with adrenergic receptor stimulation in the mammary gland. All types of disturbed milk ejection under practical conditions such as in primiparous cows after parturition and during milking in unfamiliar surroundings (Bruckmaier et al. 1992; 1993, 1995; Macuhova et al. 2001) are based on reduced or lacking release of oxytocin from the pituitary. This effect is not induced by catecholamines such as adrenalin because they would rather stimulate than inhibit the release of oxytocin (Blum et al. 1989; Bruckmaier et al. 1997). Expectedly, during spontaneously disturbed milk ejection in unfamiliar surroundings with lacking oxytocin release, the administration of α- and β-adrenergic blocking agents were without any beneficial effect on the milk ejection (Bruckmaier et al. 1997). However, there may be an evolutionary advantage in the possibility of immediate total milk duct closure in response to very high concentrations of adrenalin in wild animals. In contrast to the situation on dairy farms, wild animals can come in the situation of a “fight and flight” response, also called the „acute stress response“ which was first described by the Harvard physiologist Walter Cannon in the 1920s as a theory that animals react to threats with a general discharge of the sympathetic nervous system. This reaction is related to the release of huge amounts of adrenalin. If such conditions should occur during suckling the offspring, it is a clear advantage to interrupt immediately the transfer of milk from the ventral to more proximally located regions and to simultaneously contract the teats in longitudinal direction in order to gain more distance between the mammary gland and the ground.

In conclusion, under practical conditions in dairy farms, the distribution of adrenergic receptor types and blood concentration of catecholamines or sympathetic activity may influence the rate of milk ejection and hence milkability. Contrary reduced or lacking milk ejection is not induced by adrenergic receptor stimulation.

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