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Phenotypic and genetic relationships of bovine natural antibodies binding keyhole limpet hemocyanin in plasma and milk

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ABSTRACT

To improve the health status (resilience) of dairy cows, levels of natural antibodies (NAb) might be useful. The objective of the present study was to compare levels and to estimate genetic parameters for NAb measured in milk and plasma samples. Titers of NAb IgM and IgG isotype-binding keyhole limpet hemocyanin of 2,919 cows, in both plasma and milk, were measured using ELISA. Analysis revealed that NAb levels in milk significantly increased with parity, whereas they remained constant in plasma. Moderate positive phenotypic correlations were found between NAb levels in milk and in plasma: 0.18 for IgG and 0.40 for IgM. This indicates that NAb from milk and plasma might reflect different aspects of dairy cow health status. However, high genetic correlations were found for NAb in milk and plasma: 0.81 for IgG and 0.79 for IgM. Heritabilities (SE in parentheses) for NAb measured in plasma [0.15 (0.05) for IgG and 0.25 (0.06) for IgM] were higher than heritabilities of NAb measured in milk [0.08 (0.03) for IgG and 0.23 (0.05) for IgM]. Our results indicate that NAb measured in milk and plasma are heritable and likely have a common genetic background, suggesting that NAb levels measured in milk might be useful for genetic improvement of disease resistance.

Key words: dairy cattle, natural antibody, genetic parameter

INTRODUCTION

Genetic selection for improved disease has become more important because of the limitation of usage of antibiotics. Selection for animal health status is a challenging task due to the lack of reliable, cheap, and easy to measure parameters. Natural antibodies (**NAb**) might be a novel parameter that enables selection of cows with an improved ability to stay healthy and to remain productive over a longer period.

In mammals, NAb represent an important component of innate immunity, forming a first line of defense and linking innate and specific immunity (Ochsenbein and Zinkernagel, 2000). Natural antibodies are defined as immunoglobulins derived from self-renewing CD5+ B-1 cells (Casali and Notkins, 1989; Baumgarth et al., 2005). They have been found in all animals tested so far without intentional antigenic stimulation (Avrameas, 1991; Ochsenbein and Zinkernagel, 2000) and have been proposed to reflect the ability of an animal to stay healthy and prolong survival (Boes, 2000; Star et al., 2007).

Natural antibodies are suggested to play an essential role in induction of a primary immune response and improve immune responsiveness to protect individuals against viral and bacterial pathogens (Thornton et al., 1994; Ochsenbein et al., 1999; Kohler et al., 2003; Lammers et al., 2004). In chicken, NAb-binding keyhole limpet hemocyanin (**KLH**) was indicative for a higher probability of survival during the laying period (Star et al., 2007; Sun et al., 2011). In cattle, NAb were found in both plasma and milk (van Knegsel et al., 2007; Ploegaert et al., 2011) and NAb levels increased with age (Srinivasan et al., 1999; van Knegsel et al., 2007). A positive phenotypic relationship was suggested in dairy cattle between NAb measured in plasma and their energy balance, milk yield, and DMI (van Knegsel et al., 2007). However, in milk, negative relations were found between NAb levels and energy balance, milk yield, and DMI (van Knegsel et al., 2007). Furthermore, Ploegaert (2010) suggested that NAb (especially isotype IgG1) protect against clinical mastitis and high SCC. Heritabilities of KLH-binding NAb levels measured in plasma were 0.18 for IgM and 0.32 for IgG (Thompson-Crispi et al., 2013). Heritabilities of KLH NAb measured in milk were 0.32 for IgG and 0.41 for IgM (Wijga et al., 2013).

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Together these results show that NAb give information on the health perspective of animals and might also be used for genetic selection to improve health traits.

Measurement of NAb levels in milk, rather than in plasma, is noninvasive and cheap. Natural antibodies measured in milk may thus be a promising parameter reflecting innate immunity, which might be predictive for disease resistance of dairy cows. As a first step in determining the value of NAb measured in milk as a parameter of disease resistance, phenotypic and genetic relationships of NAb measured in plasma and milk is useful. Knowledge of this relationship is currently lacking. The objective of our study was to estimate phenotypic and genetic parameters for NAb measured in plasma and milk. Genetic parameters will reveal whether NAb levels in plasma and in milk reflect the same trait.

MATERIALS AND METHODS

Animals and Samples

Data used are from the Dutch project WeerbaarVee (resilient livestock). In February and March 2011, plasma and milk samples of 3,034 dairy cows were simultaneously collected from 29 Dutch dairy farms spread over the country. Animals with an unknown ID number or with missing values were excluded from the data set; thus, 2,919 cows were used for the final analyses. To ensure that the results would be representative of future farming conditions, farms were required to have at least 60 cows in milk recording and farms with a mean production level in the lowest quartile were excluded. The farms were chosen from the group of farms with either a high herd age (mean = 4.73 yrs; farm type 1) or an average herd age (mean = 4.16 yrs; farm type 2) in the year before the start of the study. All selected farms needed to participate in the national milk production registration system (**MPR**) and were required to agree to sampling of plasma and milk from cows and detailed disease recording. Most (72.5%) of the cows included in the study were purebred Holstein Friesians. Furthermore, preliminary results showed no significant effect of breed and it was therefore left out for further analyses. Milk samples were collected in conjunction with MPR from all lactating cows. Plasma samples were taken from about 70 cows per farm: both lactating and nonlactating (dry cows and heifers before calving). The aim of the data set was to keep the distribution of cows over different parities and lactation stage as equal as possible; therefore, cows were selected for plasma sampling based on their parity and lactation stage. Clinically sick animals were not included in MPR and therefore have no milk samples. In total 2,610 milk samples and 2,032 plasma samples were collected. The pedigree file for estimating genetic parameters was provided by CRV (Cooperative Cattle Improvement Organization, Arnhem, the Netherlands), and included 30,436 animals. Cows used within this study originated from 994 sires and 2,367 dams.

NAb

Natural antibody isotypes IgM and IgG binding *Megathura crenulata*-derived KLH were determined in individual plasma and milk samples by an indirect 2-step ELISA. Flat-bottomed 96-well medium binding plates were coated overnight at 4°C with 1 μg/mL of KLH (MP Biomedicals Inc., Aurora, Ohio), 100 μL/well, in coating buffer (5.3 g/L of Na_2CO_3 and 4.2 g/L of $NaHCO_3$, pH 9.6). After washing, plasma and milk samples were diluted in 4 steps with a dilution buffer (PBS; 10.26 g/L of $Na_2HPO_4{\cdot}H_2O$, 2.36 g/L of KH_2PO_4, and 4.50 g/L of NaCl, pH 7.2, containing 0.05% Tween 20 and 0.5% normal horse serum). Plates were incubated for 1.5 h at room temperature with the samples 1:3 diluted (1:30, 1:90, 1:270, and 1:810). Binding of the antibodies to KLH was visualized using a 1:20,000 diluted rabbit anti-bovine IgGFc labeled with peroxidase (RABo/IgGFc/peroxidase, Nordic, Tilburg, the Netherlands) and 1:20,000 diluted rabbit anti-bovine IgM (RABo/IgM/peroxidase, Nordic). After washing, substrate (tetramethylbenzidine and 0.05% H_2O_2) was added. After 10 min, the reaction was stopped with 2.5 N H_2SO_4. Extinctions were measured with a Multiskan (Labsystems, Helsinki, Finland) at a wavelength of 450 nm. Antibody levels (titers) were expressed as log2 values of the highest dilutions giving an extinction closest to 50% of EMAX, where EMAX represents the highest mean extinction of a standard positive reaction present on each flat-bottomed ELISA-plate (Ploegaert et al., 2010b). The EMAX was calculated based on a plasma-calibrated line for each ELISA plate, for both milk and plasma samples. An amount of 3 titer units was added to all obtained NAb titers to create positive values.

Statistical Analyses

Descriptive statistics were calculated using SAS (version 9.2). Variance components for levels of different NAb isotypes in milk and plasma samples were estimated with a linear animal model:

$$Y_{ijklm} = \mu + PAR_i + LAC_j + HERD_k + animal_l + e_{ijkl}, \quad [1]$$

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