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A dynamic model to simulate potassium balance in dairy cows

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ABSTRACT

High-performing dairy cows require a particular composition of nutritional ingredients, adapted to their individual requirements and depending on their production status. The optimal dimensioning of minerals in the diet, one being potassium, is indispensable for the prevention of imbalances. Potassium balance in cows is the result of potassium intake, distribution in the organism, and excretion, and it is closely related to glucose and electrolyte metabolism. In this paper, we present a dynamical model for potassium balance in lactating and nonlactating dairy cows based on ordinary differential equations. Parameter values were obtained from clinical trial data and from the literature. To verify the consistency of the model, we present simulation outcomes for 3 different scenarios: potassium balance in (1) nonlactating cows with varying feed intake, (2) nonlactating cows with varying potassium fraction in the diet, and (3) lactating cows with varying milk production levels. The results give insights into the short- and long-term potassium metabolism, providing an important step toward the understanding of the potassium network, the design of prophylactic feed additives, and possible treatment strategies.
Key words: dairy cow, potassium balance, mathematical model, ordinary differential equation, network

INTRODUCTION

Potassium is quantitatively the third most present monovalent cation in the body. It is fundamental for cell functioning, being involved in regulation of osmotic pressure, signal transduction, acid-base regulation, nerve impulse transmission, and muscle contraction. Potassium needs to be taken up continuously with the diet (NRC, 2001). After absorption from the intestinal tract, potassium is distributed dynamically between intra- and extracellular space in all tissues. Its main excretion pathway is via urine through the kidneys. However, our knowledge about detailed mechanisms and regulation of potassium balance in mammals is still incomplete (Youn and McDonough, 2009).

High-performing dairy cows require a particular composition of nutritional ingredients depending on their production status. The optimal dimensioning of minerals in the diet, including potassium, is indispensable for the prevention of imbalances. Current nutritional recommendations propose a low-potassium diet before calving (Goff, 2006). In cattle and other mammals, the serum potassium concentration is maintained in the narrow range between 3.5 and 5.8 mmol/L (Sejersted and Sjøgaard, 2000); however, with an intracellular potassium concentration between 7 and 70 mmol/L in erythrocytes (Christinaz and Schatzmann, 1972), minor damage of cells can lead to a large overestimation of serum potassium content (Sejersted and Sjøgaard, 2000). In recent years, measurement methods have been improved and hypokalemia has increasingly been diagnosed in cows linked with metabolic and mineral imbalances, abomasal displacement, ketosis, and recumbency (Sattler et al., 1998; Peek et al., 2000; Mokhber Dezfouli et al., 2013); this motivates our research on this topic.

Potassium balance closely interacts with glucose and electrolyte metabolism (Grünberg et al., 2006). That is, elevated glucose blood levels lead to a rise in blood insulin, which favors the potassium shift to the intracellular space. Postpartum veterinary treatments frequently intervene in glucose metabolism by administration of dextrose and corticosteroids, both of which have been shown to favor hypokalemia (Sattler et al., 1998; Peek et al., 2000; Grünberg et al., 2006). Sodium, potassium, and chloride are important players in the maintenance of osmotic pressure and acid base homeostasis. Changes in their concentration affect potassium homeostasis; that is, acidosis leading to potassium shifts from intracellular fluid (**ICF**) to extracellular fluid (**ECF**) and vice versa for alkalosis (Adrogué and Madias, 1981). Clinical relevance and application is reviewed in Russell and Roussel (2007) and Palmer and Clegg (2016).

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Studying veterinary and mathematical viewpoints, we developed a quantitative, dynamic model for potassium balance in dairy cows. We focused on the whole organism instead of narrowing to the cellular level, with an emphasis on metabolic flows between components (e.g., gastrointestinal tract, milk). We compared the outcome of the model simulations with experimental data in a qualitative manner, as the interindividual variability was too large to reproduce the data exactly.

To our knowledge, no published work has presented a biomathematical model of potassium balance in dairy cows or in another livestock species. Mathematical modeling of the involved mechanisms generates quantitative knowledge of the underlying biological processes enabling predictions about the intake and outputs and the distribution of potassium within the body. A preliminary model was published in a technical report (Plöntzke et al., 2013).

The long-term goal behind developing such a model is to gain more insight into the mechanistic background to assist the development of feed additives and effective treatment strategies. The model will be open access available in Systems Biology Markup Language (SBML) format on BioModels Database (www.ebi.ac.uk/biomodels-main/) where it can be used by the scientific community and industry to support ration calculation as well as herd and individual cow management.

MATERIALS AND METHODS

Model Description

The modeling objective was to obtain a system of ordinary differential equations (**ODE**) and algebraic equations, which are able to simulate the dynamics of potassium balance in dairy cows. Practical mathematical tools for modeling stimulatory or inhibitory effects are positive and negative Hill functions (H):

$$\mathrm{H}^{+}(S,T;n)=\frac{(S/T)^{n}}{1+(S/T)^{n}}, \text{ and}$$

$$\mathrm{H}^{-}(S,T;n)=\frac{1}{1+(S/T)^{n}},$$

where $S \geq 0$ denotes the influencing substance, $T \geq 0$ the threshold, and $n \geq 1$ the Hill coefficient. A Hill function is a sigmoidal function between 0 and 1 that switches at the threshold $S = T$ from one level to the other with a slope specified by n and T.

To build up essential components for potassium balance, the model was designed on a whole organism level, based on clinical study data and scientific knowledge. The model consists of 12 ODE, 4 algebraic equations, and 63 parameters. All simulations were conducted in the software Celldesigner (Ver. 4.4; Systems Biology Institute, Tokyo, Japan) using the solver SOSlib. The mechanisms of the model are pictured in the flowchart in Figure 1. Model components and their units are summarized in Table 1. Table 2 contains the list of parameter values and units.

Experimental Data

In the Clinic for Ruminants of Freie Universität Berlin, a clinical study was conducted to study potassium balance in 6 nonlactating dairy cows. Experimental data from the current study were available for parameter estimation, which was performed with the algorithms NLSCON (Deuflhard, 2004) and simulated annealing (Kirkpatrick et al., 1983). In the data set from the clinical study, we noticed strong interindividual variations between the 6 study cows, most notably in intracellular potassium and insulin measurements. In the preliminary model of potassium balance in Plöntzke et al. (2013), we set some parameters to cow-specific values. Thus, we obtained specific parameter sets that adapt the model behavior to the considered cow. The default condition of the advanced model was based on this data set in a quantitative way, as well as on values from literature. Finally, we obtained a deterministic model that reproduced the potassium balance of an average cow.

Units

To obtain a model for potassium balance with uptake and excretion and to account for distribution inside the organism, the model needs to handle masses and concentrations and convert between those. The in- and output components potassium taken up with diet ($\mathbf{K_{FEED}}$; Table 1) and potassium excreted with urine ($\mathbf{K_{URIN}}$; Table 1) are specified in gram per hour and gram (accumulated), respectively. The amount of potassium taken up from $\mathrm{K_{FEED}}$ is dissolved in the noncellular compartment of the cow blood, potassium in the extracellular blood fluid ($\mathbf{K_{ECF}}$; Table 1).

For the conversion of mass to concentration, we required the volume in which the substances were dissolved. Blood volume calculation was made on the base of 55 mL of blood/kg of BW, as reported by Reynolds (1953). The BW was set to 600 kg in the default condition. The intra- and extracellular volume of blood