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Review Article

BLOOD METABOLOMICS FOR DETECTION OF METABOLIC DISORDERS IN DAIRY ANIMALS

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Abstract: The productive life span of a dairy cow largely depends on her metabolic health status. High disease incidences including fatty liver, ketosis, milk fever, mastitis, metritis, displaced abomasum, and downer cow syndrome cause a substantial decline in the profitability of most dairy operations. Most metabolic diseases have been related to perturbation of one specific metabolite. Milk fever has been linked to perturbation of calcium homeostasis; fatty liver has been explained with development of a negative energy balance (NEB) during peripartum and to increased release of non-esterified fatty acids (NEFA) from adipose tissue and subsequent storage in the liver in the form of triglycerides (TG); ketosis has been related to increased release of ketone bodies from liver hepatocytes as a result of oxidation of NEFA in mitochondria. Metabolomics has been introduced as part of 'omics' technology to better Understand interaction between nutrition and disease. A major advantage in the application of metabolomics stems from an improved ability to detect up to many hundreds of metabolites in parallel, which provides an efficient method for monitoring altered biochemistry.

Keywords: Blood metabolomics, metabolic disorders, dairy animals.

Introduction

Metabolomics is the detection of low molecular weight metabolites and their intermediates from biofluids or tissues. It is used widely in many fields, such as pharmacology, toxicology, and diagnostics, and its use and technological development have increased rapidly (Zhang *et al*., 2012). Metabolite changes that are observed in diseased individuals as a primary indicator have been an important part of clinical practice.

Many diseases are often discovered in an advanced stage because of the lack of specific symptoms and the diagnostic difficulties. The more advanced stage of diseases, the more invasive diagnostic and treatment interventions needed. An early molecular diagnosis is therefore of vital importance in order to increase the survival rate. A good diagnostic method should have the characteristics of high sensitivity, specificity, and functionality and meets the

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requirements of high throughput, portability, and low cost for subsequent clinical application (Nicholson *et al.*, 1999).

Tools for detection of metabolites in diseased animals

Common metabolomic technologies include GC-MS, nuclear magnetic resonance (NMR) and other chromatography coupled mass spectrometry, such as liquid chromatography-mass spectrometry (LC-MS) and capillary electrophoresis–mass spectrometry (CE-MS), metabolites chip are widely used as analytical tools (Nicholson *et al.*, 2002). Among the analytical techniques that can be employed for metabolomics applications, nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) are the most common.

Metabolomic evaluation

1. Milk fever

Milk fever (MF) is a complex metabolic disorder, usually of dairy cows, that occurs around parturition. The biochemical characteristic of this condition is severe hypocalcemia (usually <1.5 mmol/L), which most likely explains the clinical signs associated with milk fever. Investigation of this disease has chiefly focused on blood calcium, ionized calcium, or total calcium contents in the transition period because of the close connection between blood calcium and milk fever. Blood phosphorus status has also been researched because of the prominent interaction between calcium and phosphorus at the onset of lactation. Several other parameters, such as magnesium, alkaline phosphatase, hydroxyproline, osteocalcin, parathormone, calcitionin, and 1,25-dihydroxy-vitamin D, which are associated with the regulation of calcium metabolism.

Metabolites used for identification of milk fever

Serum amyloid A protein (SAA), Calcitonin-gene related peptide (CGRP), Endopin 2B, Serpin peptidase inhibitors (SPI), Downregulated proteins - fibrinogen beta chain, IGg heavy-chain C-region (IGg -CH), and albumin.

2. Fatty liver syndrome

The transition time around parturition and early lactation involves critical physiologic changes in dairy cows. An excessive demand for nutrients due to the increased performance required for milk production results in a negative energy balance (Mullins *et al.*, 2012). One major adjustment consists in the rapid mobilization of energy sources from tissue depots in the form of non-esterified fatty acids. Although in cattle the major site of fatty acid synthesis is the adipose tissue, the liver plays a central role in coping with sudden increases in the energy requirement (Kreipe and Deniz 2011).

Fatty liver disease develops when, during this critical transition period, the hepatic uptake of non-esterified fatty acids liberated from the adipose tissue exceeds their elimination from the liver, thus causing their hepatic storage as triacylglycerols (Bobe *et al*., 2004).

Hepatic parameter changes in cows suffering from FLD

Parameter	Changes	References
TAG	↑	(Kalaitzakis *et al*., 2007)
Total lipids	↑	
Glycogen	↓	(Veenhuizen *et al*., 1991)
Phospholipids	↓	Geelen and Wensing, 2006)
Cholesterol	↓	(Brumby *et al*., 1975)
Enzymes of the gluconeogenesis	↓	(Kuhla *et al*., 2009)
Enzymes of the β-oxidation	↓	
Enzymes of the glycolysis	↓	
Enzymes of the TAG-synthesis	↑	(Geelen and Wensing, 2006)

↑ Respective concentration or activity is elevated in cows with FLD

↓ Respective concentration or activity is reduced in cows with FLD

3. Ketosis

Ketosis is one of the most prevalent metabolic diseases of dairy cows during transition period. Metabolic disturbances of ketosis involve in multi-biochemical pathways such as glycolysis, gluconeogenesis, amino acids metabolism, fatty acids metabolism, pentose phosphate pathway.

Metabolites used for identification of ketosis

Metabolites	Remarks
B-hydroxybutyrate (BHBA), blood glucose levels (Glc), total triglycerides (TG), nonesterified fatty acids (NEFA) including palmitic acid (PA), heptadecanoic acid (HA), stearic acid (SA), trans-9-octadecenoic acid (T-9-OA), myristic acid (MA), cis-9-hexadecenoic acid (C-9-HA), long chain unsaturated fatty acids, and saturated acids and aspartate aminotransferase (AST)	Increased
Lactic acid (LA), glucuronic acid (GLCA), l-alanine (L-ala), glycolic acid (GA), ribitol, pyroglutamic acid (pglu), galactose (Gal), 2,3,4-trihydroxybutyric acid	Decreased

(THBA), and glucose (Glc)	
Up-regulated amino acids and their catabolic products – Glycine, lysine (2-piperidinecarboxylic acid), 3-hydroxyvaleric acid (3HV), 3-hydroxy-3-methylglutaric acid (HMG), isoleucine (2-methyl-3-hydroxybutyric acid (2Me3HB)),	Increased
Leucine (3-hydroxyisovaleric acid (3HIV)), 4-aminobutyric acid (GABA) - L-glutamic acid catabolism, melibiose from galactose metabolism, erythritol, a precursor of fructose 6-phosphate, and l-serine (L-ser)	Decreased

4. Abomasal displacement

Abomasal displacement [left (LDA), right (RDA) or anterioventral displacement of the abomasum] is an infrequent gastrointestinal disorder typically occurred in high producing dairy animals. The factors which responsible for the abomasal displacement are

1. Abomasal hypomotility due to mastitis, milk fever, metritis and genetic predisposition
2. Feed origin - High-concentrate, low-roughage diets
3. Other conditions – ketosis, fatty liver syndrome and phytobezoars.

Metabolites	Remarks
Valine, 3 β-hydroxybutyrate, alanine, glutamine and glutamate	Increased in RDA conditions
Succinate	Decreased in LDA condition

Conclusions

New biomarkers of metabolic disorders are urgently needed to facilitate diagnostic procedures, identify distinct stages of the disease, monitor the response to treatment regimens and allow for the design of prevention strategies. An important new paradigm in biomarker discovery research is to consider entire sets of molecular changes, instead of single parameters, that correlate with a particular disease. The results demonstrate that the ^{1}H NMR technique combined with multivariate statistical analysis can be used to access the changes and progression of ketosis, sub clinical ketosis, fatty liver, milk fever, abomasal displacement and to discover potential biomarkers for this disease in cows. In future, changes in the potential metabolites and metabolic pathways could present new strategies for the diagnosis and prevention of metabolic disorders in dairy cows.

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