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Substantial replacement of lactose with fat in a high-lactose milk replacer diet increases liver fat accumulation but does not affect insulin sensitivity in veal calves

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ABSTRACT

In veal calves, the major portion of digestible energy intake originates from milk replacer (MR), with lactose and fat contributing approximately 45 and 35%, respectively. In veal calves older than 4 mo, prolonged high intakes of MR may lead to problems with glucose homeostasis and insulin sensitivity, ultimately resulting in sustained insulin resistance, hepatic steatosis, and impaired animal performance. The contribution of each of the dietary energy sources (lactose and fat) to deteriorated glucose homeostasis and insulin resistance is currently unknown. Therefore, an experiment was designed to compare the effects of a high-lactose and a high-fat MR on glucose homeostasis and insulin sensitivity in veal calves. Sixteen male Holstein-Friesian calves (120 ± 2.8 kg of BW) were assigned to either a high-lactose (HL) or a high-fat (HF) MR for 13 consecutive weeks. After at least 7 wk of adaptation, whole-body insulin sensitivity and insulin secretion were assessed by euglycemic–hyperinsulinemic and hyperglycemic clamps, respectively. Postprandial blood samples were collected to assess glucose, insulin, and triglyceride responses to feeding, and 24-h urine was collected to quantify urinary glucose excretion. At the end of the trial, liver and muscle biopsies were taken to assess triglyceride contents in these tissues. Long-term exposure of calves to HF or HL MR did not affect whole-body insulin sensitivity (averaging $4.2 \pm 0.5 \times 10^{-2}$ [(mg/kg·min)/(μU/mL)]) and insulin secretion. Responses to feeding were greater for plasma glucose and tended to be greater for plasma insulin in HL calves than in HF calves. Urinary glucose excretion was substantially higher in HL calves (75 ± 13 g/d) than in HF calves (21 ± 6 g/d). Muscle triglyceride content was not affected by treatment and averaged 4.5 ± 0.6 g/kg, but liver triglyceride content was higher in HF calves (16.4 ± 0.9 g/kg) than in HL calves (11.2 ± 0.7 g/kg), indicating increased hepatic fat accumulation. We conclude that increasing the contribution of fat to the digestible energy intake from the MR from 20 to 50%, at the expense of lactose does not affect whole-body insulin sensitivity and insulin secretion in calves. However, a high-lactose MR increases postprandial glucose and insulin responses, whereas a high-fat MR increases fat accumulation in liver but not muscle.
Key words: veal calves, lactose, fat, insulin sensitivity

INTRODUCTION

Veal calves are fed milk replacer (**MR**) and solid feed (consisting of concentrates and roughages). Despite the tendency in recent years to increase the amount of solid feed, the vast majority (60–70%) of the digestible energy intake originates from MR. After feeding, MR bypasses the calf's rumen and directly enters the abomasum because of closure of the esophageal groove. Milk replacer typically contains highly digestible nutrients such as lactose, fat, and proteins, which provide approximately 45%, 35%, and 20% of the digestible energy intake, respectively.

Prolonged intakes of high amounts of MR have been shown to induce problems with glucose homeostasis and insulin sensitivity in heavy (>4 mo of age) veal calves, characterized by high incidences of hyperglycemia and hyperinsulinemia and increased urinary glucose excretion (Hostettler-Allen et al., 1994; Hugi et al., 1997; Pantophlet et al., 2016a). These problems may result in metabolic and pro-inflammatory diseases as seen in humans (Hotamisligil, 2006; Shoelson et al., 2006) and in hepatic steatosis (Gerrits et al., 2008).

Dietary factors contributing to the disturbed glucose homeostasis and insulin sensitivity in heavy calves have been studied (Hugi et al., 1997, 1998; Pantophlet et al.,

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2016a), and results indicate that high amounts of lactose may be a factor. Ingesting high amounts of lactose in only 2 daily meals and for a prolonged period (i.e., ~6 mo of life) deviates from the ontogenetic background of calves. In nature, calves between 4 and 6 mo of age are grazing, and feedstuffs from plant origin are fermented in the rumen, along with short-chain fatty acids being produced as a major energy source. Thus, in nature, a gradual shift occurs from glucose and long-chain fatty acids from milk as main energy sources to short-chain fatty acids originating from rumen fermentation during the first months of the calf's life. In general, problems with glucose metabolism and insulin sensitivity appear to be age dependent in veal calves (Hugi et al., 1997, 1998; Pantophlet et al., 2016b). Heavy veal calves produce very little fatty acids from glucose (Roehrig et al., 1988; van den Borne et al., 2006), and ingestion of large quantities of glucose perturbs their glucose homeostasis for a substantial period after feeding. This circumstance could explain why a high lactose intake negatively affects glucose metabolism and insulin sensitivity in veal calves (Hugi et al., 1997, 1998) and leads to significant amounts of glucose being excreted in urine (Hugi et al., 1997; Pantophlet et al., 2016a).

Alternatively, the high dietary fat content in MR for calves could affect glucose homeostasis and insulin sensitivity. The composition of the digestible energy in veal calves (i.e., high fat and high carbohydrate content) resembles that of the adult Western human diet (Schwarz et al., 2003), and such high dietary fat intake has consistently been associated with the development of insulin resistance (Randle et al., 1963; Storlien et al., 1996; Frayn, 2003; Müller and Kersten, 2003). In rodents, fat-induced problems with insulin sensitivity may operate via several mechanisms, including triglyceride accumulation in skeletal muscle and adipocytes, which impairs GLUT-4 translocation (Storlien et al., 1996), and reduction of the number of insulin receptors in adipocytes (Harris, 1992; Harris and Kor, 1992). However, weaned nonruminant animal species, such as pigs and rodents, do not commonly develop insulin resistance, although they consume higher amounts of glucose (but less fat) than veal calves. We therefore hypothesize that, apart from species differences, interactions between fatty acids and glucose may play a role in perturbing glucose homeostasis and inducing the development of insulin resistance in veal calves.

Standardized studies in which lactose and fat are exchanged (isoenergetically) may reveal the contribution of the dietary energy source to the development of insulin resistance in calves. The objective of the current study was therefore to assess effects of a large isoenergetic exchange of lactose and fat intake on insulin sensitivity in veal calves.

MATERIALS AND METHODS

Animals and Housing

Sixteen male Holstein-Friesian calves (120 ± 2.8 kg of BW; 99 ± 2.0 d old) were purchased. During the first 6 wk of the 13-wk study, calves were housed in pens of 4 calves each (2 m^2 per calf) that were fitted with a wooden slatted floor and galvanized fencings. Calves were then transferred to metabolic cages (dimension: 0.80 × 1.8 m) for the next 7 wk. During this period, several measurements were performed (see Experimental Procedures). Ventilation occurred by ceiling fans, and illumination was by natural light and artificial (fluorescent lamps) light between 0700 and 1900 h. Temperature was controlled at 18°C and humidity at 65%.

Experimental procedures complied with the Dutch Law on Experimental Animals and the ETS123 (Council of Europe 1985 and the 86/609/EEC Directive) and were approved by the Animal Care and Use Committee of Wageningen University.

Experimental Design, Diets, and Feeding

Calves were assigned to either a high-lactose diet (**HL**; n = 8) or a high-fat diet (**HF**; n = 8), and to 1 of 8 blocks (pairs of calves) with 1 HL calf and 1 HF calf per block. Body weight and age did not differ between treatments at the start of the trial. Because of health problems in 2 HF calves, block 7 consisted of 2 HL calves, and block 8 (with the 2 remaining HF calves) was not included in the insulin sensitivity, insulin secretion, postprandial blood metabolites, and urinary glucose excretion measurements. Between treatments (Table 1), fat and lactose were exchanged isoenergetically based on digestible energy. Energy values of 39.0 kJ/g fat and 16.5 kJ/g lactose and ileal digestibilities of 95% for fat and 94% for lactose were assumed (Hof, 1980). High-lactose diet calves received 25% more feed than HF calves to obtain isoenergetic and isonitrogenous feeding strategies. Apart from fat and lactose, the daily allowance of protein and micronutrients was similar for the 2 treatments. The feeding level for both MR diets was 2.25 times the digestible energy requirements for maintenance, which was set at 473 kJ/$kg^{0.75}$ per day (Van Es et al., 1967). At the start of the study, calves received a commercial MR. Introduction of the experimental MR occurred gradually within the first 3 d of the study. The feeding schedule was adjusted according to the calf's metabolic weight ($kg^{0.75}$), which was measured weekly. Milk replacer was prepared at a concentration of 167 g of MR/L and provided in a bucket at a temperature of 40–42°C at 0800 and 1630