J. Dairy Sci. 99:1–10
http://dx.doi.org/10.3168/jds.2016-11084

Insulin sensitivity in calves decreases substantially during the first 3 months of life and is unaffected by weaning or fructo-oligosaccharide supplementation

A. J. Pantophlet,*[1] M. S. Gilbert,† J. J. G. C. van den Borne,† W. J. J. Gerrits,† M. G. Priebe,* and R. J. Vonk‡
*Department of Pediatrics; Center for Liver, Digestive and Metabolic Diseases, University Medical Centre Groningen, PO Box 30001, 9700 RB Groningen, the Netherlands
†Animal Nutrition Group, Wageningen University, PO Box 338, 6700 AH, Wageningen, the Netherlands
‡Medical Biomics, University Medical Centre Groningen, PO Box 30001, 9700 RB, Groningen, the Netherlands

ABSTRACT

Veal calves at the age of 4 to 6 mo often experience problems with glucose homeostasis, as indicated by postprandial hyperglycemia, hyperinsulinemia, and insulin resistance. It is not clear to what extent the ontogenetic development of calves or the feeding strategy [e.g., prolonged milk replacer (MR) feeding] contribute to this pathology. The objective of this study was therefore to analyze effects of MR feeding, weaning, and supplementation of short-chain fructo-oligosaccharides (FOS) on the development of glucose homeostasis and insulin sensitivity in calves during the first 3 mo of life. Thirty male Holstein-Friesian calves (18 ± 0.7 d of age) were assigned to 1 of 3 dietary treatments: the control (CON) group received MR only, the FOS group received MR with the addition of short-chain FOS, and the solid feed (SF) group was progressively weaned to SF. The CON and FOS calves received an amount of MR, which gradually increased (from 400 to 1,400 g/d) during the 71-d trial period. For the SF calves, the amount of MR increased from 400 to 850 g/d at d 30, and then gradually decreased, until completely weaned to only SF at d 63. The change in whole body insulin sensitivity was assessed by intravenous glucose tolerance tests. Milk tolerance tests were performed twice to assess changes in postprandial blood glucose, insulin, and nonesterified fatty acid responses. Whole-body insulin sensitivity was high at the start ($16.7 \pm 1.6 \times 10^{-4}$ [μU/mL]$^{-1}$), but decreased with age to $4.2 \pm 0.6 \times 10^{-4}$ [μU/mL]$^{-1}$ at the end of the trial. The decrease in insulin sensitivity was most pronounced (~70%) between d 8 and 29 of the trial. Dietary treatments did not affect the decrease in insulin sensitivity. For CON and FOS calves, the postprandial insulin response was 3-fold higher at the end of the trial than at the start, whereas the glucose response remained similar. The SF calves, however, showed pronounced hyperglycemia and hyperinsulinemia at the end of the trial, although weaning did not affect insulin sensitivity. We conclude that whole body insulin sensitivity decreases by 75% in calves during the first 3 mo of life. Weaning or supplementation of short-chain FOS does not affect this age-related decline in insulin sensitivity. Glucose homeostasis is not affected by supplementation of short-chain FOS in young calves, whereas postprandial responses of glucose and insulin to a MR meal strongly increase after weaning.
Key words: veal calf, weaned calf, insulin sensitivity, glucose homeostasis, fructo-oligosaccharide

INTRODUCTION

Veal calves are fed milk replacer (**MR**) and solid feed (**SF**; consisting of concentrates and roughages). The vast majority of ingested MR is directed into the abomasum through closure of the esophageal groove upon MR ingestion. Despite the tendency to increase the amounts of roughage and concentrates in veal calf diets, approximately 60 to 70% of the digestible nutrient intake originates from MR.

Milk replacer contains high amounts of lactose (~45%) and fat (~20%) on a DM basis. It has been shown that a prolonged intake of high levels of MR (hence large amounts of lactose and fat) may induce problems with glucose homeostasis and insulin sensitivity in heavy veal calves (>4 mo old), as characterized by high incidences of hyperglycemia and hyperinsulinemia (Hostettler-Allen et al., 1994; Hugi et al., 1997). These problems may ultimately result in (pro)inflammatory stress and metabolic diseases, as evident from human studies (Hotamisligil, 2006; Shoelson et al., 2006), and

Received February 24, 2016.
Accepted May 7, 2016.
[1]Corresponding author: a.j.pantophlet@umcg.nl

hepatic steatosis (Gerrits et al., 2008). A previous study showed that replacing 33% of the lactose in the MR by fructose or glycerol improved postprandial glucose homeostasis (i.e., lower glucose and insulin peaks), but not insulin sensitivity in calves (Pantophlet et al., 2016). More interestingly, that study also showed that calves at ~14 wk of age are already relatively insensitive to insulin, compared with healthy nonruminants (Caumo et al., 2000; Stefanovski et al., 2011). Another study revealed that insulin sensitivity in neonatal dairy calves (<6 wk of age) decreases from wk 3 to 6, when calves are gradually weaned (Stanley et al., 2002). Moreover, Bach et al. (2013) reported that a greater level of MR allowance (8 vs. 4 L/d) had a negative effect on the development of insulin sensitivity in young calves (1–8 wk of age) with ad libitum access to starter feed. Yet, it remains unclear whether the decrease in insulin sensitivity in young calves can be influenced by feeding strategy (prolonged MR feeding vs. progressive weaning), or is explained by the ontogenetic development of calves. In contrast to dairy calves, veal calves are commonly maintained at diets containing large amounts of MR. Preventing the decrease in insulin sensitivity in veal calves during early life may augment the efficiency of energy utilization for growth and possibly also metabolic health in later life. This requires more insight in the changes in insulin sensitivity in young calves and underlying mechanisms (age- or diet-related).

In addition, the reduction in insulin sensitivity in young calves may—to some extent—be prevented by supplementation of short-chain fructo-oligosaccharides (**FOS**). Studies in various animal species have shown that dietary short-chain FOS affect whole body insulin sensitivity. In dogs and horses with obesity, for example, an increase in insulin sensitivity was measured after feeding FOS for a period of 6 wk (Respondek et al., 2008, 2011). The mechanisms behind the effects of short-chain FOS are poorly understood, but it has been hypothesized that short-chain FOS alters the intestinal microbiota composition, which directly or indirectly increases insulin sensitivity. In veal calves, oral short-chain FOS supplementation to a high-lactose MR decreased postprandial levels of plasma glucose and lactate, whereas insulin levels increased (Kaufhold et al., 2000). Whether this is due to changes in insulin sensitivity is not known, but if similar mechanisms operate in young calves then short-chain FOS supplementation may improve insulin sensitivity.

Therefore, the objective of this study was to assess age-related and diet-induced (i.e., MR only vs. MR+FOS vs. progressive weaning) changes in whole-body glucose homeostasis and insulin sensitivity in veal calves during the first 3 mo of life.

MATERIALS AND METHODS

Animals and Housing

Thirty male Holstein-Friesian calves were housed at experimental facility "De Haar" of VanDrie Group, the Netherlands. At start of the trial, calves were 18 ± 0.7 d of age and weighed 44 ± 0.3 kg (both mean ± SEM).

During the whole trial calves were housed individually, in 1.50 × 1.10 m pens fitted with a wooden slatted floor and galvanized fencings. Ventilation occurred by ceiling fans, and illumination by natural light and artificial (fluorescent lamps) light between 0600 and 1800 h. The average temperature and humidity were 18.2 ± 0.1°C and 75.3 ± 0.1%, respectively (both mean ± SEM).

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 randomly assigned to 1 of 3 treatment groups: the control group (**CON**, n = 10), fructo-oligosaccharide group (**FOS**, n = 10), or solid feed group (**SF**, n = 10).

Calves were fed amounts of MR (see Table 1 for MR composition) according to practical feeding schemes (Table 2), which were based on the expected BW. Body weight was measured weekly to monitor for any major deviations from the expected BW gain. The CON and FOS calves received similar amounts of MR, which increased from 400 g/d at the start to 1,400 g/d at the end of the trial. In addition, FOS calves received short-chain FOS supplementation (Profeed P95, Beghin-Meiji, Marckolsheim, France), which increased gradually from 0.8 g/d on d 5 to 2.2 g/d at the end of trial (d 71), and was equally divided over the 2 daily feedings and provided with the MR. For SF calves, the amount of MR increased from 400 g/d at the start of trial to 850 g/d at d 39 of the trial. Subsequently, the amount of MR gradually decreased to 250 g/d at d 60. From d 63 these calves were completely weaned to only SF.

In addition to MR, all calves received SF, which consisted of 70.9% concentrate, 14.5% wheat straw, and 14.6% alfalfa (based on DM). For CON and FOS calves, the amount of SF increased from 0 to 376 g/d during the trial (Table 2), whereas this amount increased from 0 to 2,158 g/d for SF calves.

Milk was fed at a concentration of 125 g of MR/L reconstituted MR and supplied at a temperature of