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Short Communication

Comparison of surrogate indices for insulin sensitivity with parameters of the intravenous glucose tolerance test in early lactation dairy cattle

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ABSTRACT

The aim of this study was to investigate the correlation between different surrogate indices and parameters of the intravenous glucose tolerance test (IVGTT) in dairy cows at the start of their lactation. Ten dairy cows underwent IVGTT on Days 3 to 7 after calving. Areas under the curve during the 90 min after infusion, peak and nadir concentrations, elimination rates, and times to reach half-maximal and basal concentrations for glucose, insulin, nonesterified fatty acids, and β-hydroxybutyrate were calculated. Surrogate indices were computed using the average of the IVGTT basal samples, and their correlation with the IVGTT parameters studied through the Spearman's rank test. No statistically significant or strong correlation coefficients ($P > 0.05$; $|\rho| < 0.50$) were observed between the insulin sensitivity measures derived from the IVGTT and any of the surrogate indices. Therefore, these results support that the assessment of insulin sensitivity in early lactation cattle cannot rely on the calculation of surrogate indices in just a blood sample, and the more laborious tests (ie, hyperinsulinemic euglycemic clamp test or IVGTT) should be employed to predict the sensitivity of the peripheral tissues to insulin accurately.

1. Introduction

Insulin plays a key role in the nutrient partitioning processes that take place to support lactation in dairy cattle. Cows undergo a period of decreased insulin sensitivity (IS) before and after calving to support fetal glucose needs and to prioritize the insulin-independent uptake of glucose by the mammary gland [1,2]. A dysregulated insulin function during the transition period has been related to several pathological processes in cattle [3,4].

Previous studies investigated the effect of various nutritional strategies [5,6] or the administration of different substances [7–11] on IS of the peripheral tissues in dairy cattle. However, the results of those studies are difficult to compare due to the different methods employed to assess IS. The gold standard method for assessing peripheral IS is the hyperinsulinemic euglycemic clamp test [12]. This test is laborious and expensive and, therefore, the intravenous glucose tolerance test (IVGTT) is frequently used to assess IS given its good agreement with the gold standard test [13,14]. Both these tests, however, are time consuming and invasive procedures and therefore are not

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suitable for use under field conditions or on a larger scale in epidemiological investigations [15]. In human medicine, simple and cheap surrogate indices have been developed to assess IS in patients with diabetes that can also be used in large-scale studies. Their intended purpose is to predict IS in the peripheral tissues based on a single blood sample after an overnight fast. Some of these indices have already been applied in studies on dairy cows [4,16–19], but their use has not yet been fully validated. Some studies reported these indices as useful tools to identify lactating cows with disturbed insulin function [17]. Others, however, showed no correlation between different surrogate indices and results from the hyperinsulinemic euglycemic clamp test or IVGTT at the various stages of the transition period [6,13]. Hence, the aim of the present study was to compare IS in dairy cows at the onset of lactation as measured by the IVGTT or through the calculated surrogate indices for IS.

2. Materials and methods

The protocols of this study were approved by the Bioethical Committee of the University of Santiago de Compostela (Spain), and the animals were enrolled with owner consent.

2.1. Animals

Data from the 10 cows of a previous study [7] were used. Selection criteria included: parity (entering their second to fifth lactation), milk production in the preceding lactation (9,000–9,500 kg), body condition score (3–3.5, on a 1 [lean] to 5 [obese] scale as previously described [20]), and proximity in their expected calving date. Animals were kept in a free-stall barn with concrete stalls and fed a total mixed ration (Supplementary Table 1), delivered once daily at 9:00 AM.

2.2. Intravenous glucose tolerance test

A detailed description of the IVGTT protocol is presented in the previous study by Abuelo et al [7]. Briefly, animals were subjected to IVGTT at 3:00 PM between Days 3 to 7 after calving. Cows were restrained in feedbunk headlocks, and feed was removed from their access. Subsequently, a 14-gauge catheter was inserted in one of the jugular veins, and cows were allowed to rest for 15 min before blood sampling started. Blood samples were collected at −10, −5, 5, 10, 20, 30, 45, 60, and 90 min after the infusion of 0.25 g/kg BW of glucose (GlucosaVet 40 g/100 mL, B. Braun VetCare SA, Barcelona, Spain). The infusion of glucose was completed in 3 to 4 min. After infusion, the catheters were flushed with 10 mL of sterile saline (FisioVet solucion para perfusion, B. Braun VetCare SA, Barcelona, Spain) and the first 5 mL of blood discarded from the first collection. Samples were collected into tubes without anticoagulant (BD Vacutainer; Becton, Dickinson and Company, Plymouth, UK) and tubes containing fluoride heparin (2 mL Glucose Fluoride, Sarsted AG & Co, Nuremberg, Germany).

Values from both baseline samples (−10 and −5 min samples) of each IVGTT were averaged to generate a single baseline value, as previously described [6,9]. The areas under the curve (AUCs) of glucose, insulin, nonesterified fatty acids (NEFA), and β-hydroxybutyrate (BHB) were computed with the trapezoid method [21] during the 90 min following infusion. Peak and nadir concentrations of these analytes were also determined. Elimination rates and times to reach half-maximal ($T_{1/2}$) and basal (T_{basal}) concentrations for glucose, insulin, NEFA, and BHB were computed with the following formulas, as previously described by Pires et al [22]:

$$Elimination\ rate = \left[(\ln[t_a] - \ln[t_b])/(t_b - t_a)\right] \times 100$$

$$T_{1/2} = \left[\ln(2)/Elimination\ rate\right] \times 100$$

$$T_{basal} = \left[(\ln[t_a] - \ln[t_b])/Elimination\ rate\right] \times 100$$

In these formulas, $[t_a]$ is the concentration of the metabolite at time a (t_a) and $[t_b]$ is the concentration of metabolite at time b (t_b).

2.3. Laboratory analysis

Samples were placed on crushed ice and transported to the laboratory, where they were centrifuged at 2,000 × *g* for 20 min within 2 h of collection and the supernatant serum or plasma was collected, aliquoted and stored at −80°C pending analysis within 3 mo of collection. Plasma was analyzed for glucose concentration (Glucose-Hexokinase Gernon, RAL Tecnica para el Laboratorio, Barcelona, Spain), whereas serum was used to measure the concentration of nonesterified fatty acids (NEFA H(2) R1+R2 Set, Wako Chemicals GmbH, Neuss, Germany) and β-hydroxybutyrate (BHB, Biochemical enterprise, Milan, Italy). These analytical determinations were performed in duplicate on a biochemistry autoanalyzer (CST-240, DIRUI Industrial Co, Ltd, Changchun, China).

Duplicated serum samples also were analyzed for insulin using a bovine-specific ELISA kit (Bovine Insulin ELISA, Catalog Num. 10–1201-01, Mercodia, Uppsala, Sweden). Conversion of insulin concentration from gravimetric units to international units was done as described by Abuelo et al [23]. The intra-assay coefficients of variation for all the determinations were below 4.8%, and all samples were analyzed in the same run.

2.4. Surrogate indices for insulin sensitivity

The surrogate indices were calculated using the average of the concentrations of glucose, insulin, NEFA, and BHB in the IVGTT basal samples (−10 and −5 min). The homeostatic model assessment (HOMA), its logarithmic ($\log_{10}$HOMA) and reciprocal score ($HOMA^{-1}$), the quantitative insulin sensitivity check index (QUICKI), the revised quantitative insulin sensitivity check index (RQUICKI), and the revised quantitative insulin sensitivity check index