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Experimental hyperlipidemia induces insulin resistance in sheep

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ABSTRACT

This study aimed to evaluate the effects of intravenous infusion of a soybean-based lipid emulsion on some blood energy–related metabolites and insulin sensitivity indexes in sheep. Four clinically healthy ewes were assigned into a 2-treatment, 2-period cross-over design. Either normal saline (NS) or lipid emulsion (LE) was intravenously introduced at a rate of 0.025 mL·kg^{-1} min^{-1} for 6 h. The concentrations of blood nonesterified fatty acid (NEFA), beta-hydroxybutyrate, triglyceride, cholesterol, urea, creatinine, cortisol, glucose, and insulin were measured at different time points. After 6 h, intravenous glucose tolerance test was performed. Lipid infusion elicited an increase ($P < 0.05$) in the NEFA, beta-hydroxybutyrate, and triglyceride concentrations compared with the baseline value and NS infusion. Infusion of NS did not influence blood glucose concentration; however, LE infusion increased plasma glucose concentration ($P < 0.05$). At time point 12 h, serum insulin concentrations were increased ($P < 0.05$) in NS treatment; however, such an increase was not observed in the LE treatment. Insulin sensitivity index for the LE infusion was lower ($P < 0.05$) than that for the NS treatment. The glucose effectiveness was not ($P > 0.05$) different among treatments. In the LE treatment, acute-phase insulin responses increased ($P < 0.05$) and disposition index decreased ($P < 0.001$) compared with NS treatment. The results showed that experimentally induced NEFA in blood could cause insulin resistance in sheep. The current model could be used to evaluate the pathogenesis of conditions associated with increased lipid mobilization and insulin resistance.
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1. Introduction

Insulin resistance (IR) is regarded as a decrease in insulin-mediated uptake of glucose in insulin-sensitive tissues [1]. It is an important risk factor in many disorders in horses, particularly local or/and general obesity, equine hyperlipemia syndrome [2], equine laminitis [3], and equine metabolic syndrome [4]. In addition, important disorders in ruminants such as bovine ketosis, fat cow syndrome [5], displaced abomasum [6], and pregnancy toxemia of sheep [7] are all associated with alteration in insulin metabolism. Intense lipid mobilization and associated excessive increase in blood NEFA occurs around parturition in sheep suffering from disorders like pregnancy toxemia. However, the exact pathogenesis of such conditions has not been elucidated. Experimental induction of increased plasma NEFA concentrations and its effects on IR can be used as a reliable method to mimic events occurring in excessive adipose tissue lipolysis. A factor playing a role in the pathogenesis of IR is hypertriglyceridemia or hyperlipidemia. It is well known that the elevation of plasma NEFA concentrations causes IR in the muscle and liver [8]. In addition, the raise of NEFA has a negative impact on insulin secretion from pancreatic beta cells [9]. Increased plasma NEFA seen after intravenous (IV) infusion of a lipid emulsion (LE) can be used to induce IR. In

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many studies, experimental hyperlipemic models have been used to evaluate the relationship between hyperlipidemia and IR. Pires et al [10] showed that the elevation of circulating NEFAs caused by IV administration of a tallow infusion led to severe hyperlipidemia and IR in nonpregnant and nonlactating dairy cow. Nishi et al [11] demonstrated that IV infusion of an LE (intralipid, 20%) induced significant IR in healthy cats. In a study, experimental hyperlipidemia in dogs significantly lowered insulin sensitivity measured by glucose infusion rate and reduced access of insulin into skeletal muscles [12]. The composition of LEs, which have been used to induce hyperlipidemia is medium-to-long-chain triglycerides (TGs) originated from various plant oils (eg, soybean), egg phosphatides, and glycerin [13]. To build on these studies, we hypothesized that IV infusion of an LE could also induce hyperlipidemia and IR in sheep. The aim of this study was to evaluate whether experimental hyperlipidemia through IV infusion of a soybean based LE (Lipovenoes 10% PLR, Fresenius Kabi Deutschland GmbH) could induce IR in sheep. In addition, the effects of hyperlipidemia on blood NEFA, beta-hydroxybutyrate (BHB), TG, cholesterol, urea, creatinine, cortisol, insulin, and plasma glucose concentrations were evaluated.

2. Materials and methods

2.1. Study design

The study protocol was evaluated and approved by the Research Council of Urmia University, and the animals were handled and cared for according to the guidelines approved by this Committee. Four nonpregnant and nonlactating clinically healthy ewes (average body weight [BW], 54.1 $\pm$ 2.3 kg; average age, 17.2 $\pm$ 2.1 mo) were randomly assigned into treatments in a 2 $\times$ 2 Latin Square design as a 2-treatment 2-period cross-over trial. To prevent sex hormone interference, the study was performed between early spring and early autumn when sheep are usually anestrous. However, to verify their anestrous status, serum estradiol (E2) and progesterone (P4) were measured immediately before, during, and at the end of each period.

The sheep were housed individually in indoor pens and fed according to National Research Council to maintain BW. The animals had ad libitum access to trace mineral blocks and water. The overall health of the sheep was monitored before and during the study. The animals were allowed 3 wk to adjust to the diet and handling.

One day before the initiation of experiments, catheters (16G, 8.25-cm) were inserted into the right and left jugular vein. The left catheter was used for infusion of treatments and the right one for blood sampling. Patency of catheters was maintained using heparinized saline (100 IU of heparin/mL of saline) flushed at 3-h intervals. The sheep were given procaine penicillin G at a rate of 10,000 IU$\cdot$d^{-1} kg^{-1} BW (Nasr Pharmaceutical Co) after the insertion of catheters as a prophylactic procedure. The sheep were fasted overnight before each period, but were allowed water ad libitum. All treatments were started at 7:00 AM throughout the study.

Treatments consisted of 6-h infusion of the Lipovenoes (Lipovenoes 10% PLR, Fresenius Kabi Deutschland GmbH) at the rate of 1.1 g/kg BW [10] (LE treatment) or the same volume of normal saline (NS treatment) as the control, so that each sheep received either NS or the LE in each period with a 4-wk washout interval between periods (to avoid carryover effects) before switching to the other treatment. Treatments were infused at a rate of 0.025 mL.kg^{-1} min^{-1} for 6 h using a 2-channel infusion pump (model AP22, Ascore SA). The dose and the rate of LE infusion were adopted from previous studies [10]. The fatty acid contents of the Lipovenoes are linoleic acid (54%), oleic acid (24%), palmitic acid (10%), α-linoleic acid (8%), and stearic acid (4%) [14].

2.2. Blood sampling and analytical procedures

Serum E2 and P4 were measured immediately before, during, and at the end of each period by commercial chemiluminescence kits (Liaison Estradiol and progesterone, Diasorin, Saluggia) using a Liaison analyzer (Liaison analyzer; Diasorin, Saluggia).

To measure NEFA, BHB, TG, cholesterol, urea, creatinine, cortisol, insulin, and glucose, blood was obtained from "jugular vein catheters" using disposable 10-mL syringes immediately before (0 or baseline), and 2, 4, 6, 12, 24, and 48 h after starting the infusions. The samples were transferred to vacutainer tubes (Hebei Xinle Sci & Tech Co, Ltd) to separate plasma (tubes contained potassium oxalate and sodium fluoride as a glycolytic inhibitor) and serum (additive-free tubes). Tubes for collection of blood plasma were kept on ice until centrifugation at 1,600*g* at 4°C, for 15 min. The tubes for serum collection were allowed to clot at room temperature and were centrifuged at 2,500*g* at 20°C for 15 min and stored at −20°C until analysis.

The samples were analyzed for NEFA (NEFA nonesterified fatty acids assay; Randox Laboratories Limited, United Kingdom), BHB (UV method using commercial kit, RANBUT; Randox Laboratories Limited, United Kingdom), TG (Glycerol-3-phosphate oxidase method; Pars Azmoon Inc, Tehran, Iran), cholesterol (cholesterol oxidase method; Pars Azmoon Inc, Tehran, Iran), urea (UV-Test; Pars Azmoon Inc, Tehran, Iran), creatinine (Jaffe method; Pars Azmoon Inc, Tehran, Iran), and cortisol (Cortisol AccuBind ELISA; Monobind Inc Lake Forest, USA). Interassay and intra-assay coefficients of variations (CVs) were 3.5% for NEFA and 3.7% for BHB. Interassay and intra-assay CVs were 1.6% and 0.6% for TG, 2% and 0.5% for cholesterol, 3.5% and 1.7% for urea, 3.7% and 1.2% for creatinine, and 7% and 6.4% for cortisol. The plasma samples were analyzed for glucose (enzymatic colorimetric method using glucose oxidase kit; Pars Azmoon Inc, Tehran, Iran), and the serum samples were examined for insulin (Insulin AccuBind ELISA; Monobind Inc). Interassay and intra-assay CVs were less than 2.2% for glucose and 4.3% and 7.2% for insulin, respectively. All biochemical tests were measured by using a BT-3000 auto analyzer (Biotechnica, Rome, Italy).

2.3. Intravenous glucose tolerance test (IVGTT) protocol

After 6 h of IV infusion, IVGTT was started. Baseline blood samples were taken at −15 min and immediately before IV glucose injection (0.25 g/kg BW, 50% dextrose, Glucojet; Zoopha, Parnian Pars). Blood samples were taken at 2, 4, 6, 8, 10, 12, 14, 16, and 18 min after glucose injection. Twenty

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