Genetic variants in glucocorticoid and mineralocorticoid receptors are associated with concentrations of plasma cortisol, muscle glycogen content, and meat quality traits in male Nellore cattle

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ARTICLE INFO

ABSTRACT

The glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) are key components in the regulation of the hypothalamic-pituitary-adrenal neuroendocrine axis and coordinate the physiological response to stress agents to reestablish homeostasis. Genetic variations of GR (NR3C1) and MR (NR3C2) genes could explain the alterations in animals to adapt to challenges, and therefore, their influence on production traits. The present study aimed to identify single-nucleotide polymorphisms (SNPs) in the bovine NR3C1 and NR3C2 genes and explore their associations to relevant traits of beef cattle production. Genotypes and phenotypes were collected from 241 male Nellore cattle (119 noncastrated and 122 castrated surgically) with an average of 24 ± 1.2 mo of age and live weight of 508 ± 39 kg. The traits evaluated were concentrations of plasma adrenocorticotropic hormone (ACTH) and cortisol, muscle glycogen and lactate content, and pH, color, cooking loss, and shear force of longissimus thoracis measured on the 1st, 7th, and 14th days postmortem. Five SNPs were identified, 2 in the NR3C1 gene and 3 in the NR3C2 gene. There was an associative relationship between the SNP NR3C1_1 g.3293A>G and postmortem plasma concentration of cortisol ($P = 0.0008$). The SNPs NR3C2_1 g.115T>C and NR3C2_2 g.570T>C were associated with muscle glycogen content ($P = 0.0306$ and $P = 0.0158$), postmortem plasma concentration of ACTH ($P = 0.0118$ and $P = 0.0095$), and cooking loss of the steak aged 1 d ($P = 0.0398$ and $P = 0.0423$). Haplotype analysis showed associations of GR haplotypes with postmortem plasma concentrations of cortisol and MR haplotypes with meat color, cooking losses, muscle glycogen content, and plasma concentrations of ACTH.

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The associations observed in the present study show that SNPs in GR and MR genes are related with changes of hypothalamic-pituitary-adrenal axis activity and metabolic profile in cattle, leading to individual variation in meat quality traits.

1. Introduction

Glucocorticoids are related to metabolic homeostasis and participate in regulating concentrations of plasma glucose. In addition, during stress, these hormones are secreted at higher concentrations to promote adaptive coping. High concentrations of glucocorticoids affect metabolism, immune system, reproduction, inflammatory processes, and brain function [1–4]. The hypothalamic-pituitary-adrenal (HPA) axis releases pulses of adrenocorticotropic hormone (ACTH) into the circulation, which stimulates the cortex of the adrenal gland to produce and secrete cortisol, the major glucocorticoid. Cortisol acts on various cells and tissues via its interaction with 2 nuclear receptors: the glucocorticoid receptor (GR), encoded by the NR3C1 gene and the mineralocorticoid receptor (MR), encoded by the NR3C2 gene [5,6].

The MR and GR are corticosteroid receptors in which the MR is characterized as high affinity and the GR as low affinity. These receptors are located in the cytoplasm, but on binding with a hormone, the receptors translocate into the nucleus and bind to hormone-responsive elements in the DNA, thus, increasing or decreasing the expression of a large number of genes in many tissues [7]. Cortisol results in metabolic effects stimulating hepatic gluconeogenesis, muscle tissue catabolism, and lipogenesis [4,8,9]. Furthermore, increased secretion of cortisol amplifies the mobilization of energy by lipolysis, glycogenolysis in the muscle, and gluconeogenesis induced by the catecholamines to supply the "fight or flight" response of the body to environmental challenges [10].

Previous studies have reported that significant depletion of muscle energy stored before slaughter, such as glycogen and impacts on several meat quality attributes such as ultimate pH, tenderness, color, and water-holding capacity [11,12]. In case of chronic stress, muscle glycogen reserves are depleted, producing carcasses with a high pH at 24 h postmortem. This favors the appearance of dark, firm, and dry meat, which has low consumer acceptability [12].

Genetic polymorphisms in candidate genes related to stress response, including the NR3C1 and NR3C2 genes, and their functional consequences in production traits and stress hormones have been investigated in pigs. Significant associations between stress reactivity and aggressive behavior with single-nucleotide polymorphisms (SNPs) in 10 HPA axis–related genes were demonstrated, included SNP in the NR3C1 gene with plasma cortisol concentration and adrenal gland weight [13]. SNPs in the NR3C1 gene were associated with carcass weight, drip loss, slaughter plasma lactate level, and weight of the adrenal gland in 2 divergent breeds of pigs, the Large White and the Meishan. The SNP of the NR3C2 gene was associated with basal level of total urinary glucocorticoid [14].

In humans, SNPs in both the NR3C1 and NR3C2 genes modulate basal nonstress as well as stress-induced concentrations of ACTH and cortisol [15–17]. Four NR3C1 gene SNP (ER22/23EK, N363S, BclI C/G, and A3669G) and 2 NR3C2 gene SNP (−2 G/C and MR I180V) have been described to influence the transactivation ability of their receptors, resulting in changes in sensitivity to glucocorticoids, including cortisol [18,19]. Importantly, the same genetic variants in the NR3C1 gene were associated with bone mineral density, body mass index, abdominal obesity, and total cholesterol under nonstress conditions [16]. Remarkably, MR I180V SNP also was associated with metabolic variables such as body mass index and circulating concentrations of low-density lipoprotein cholesterol [20].

Individual variation in cortisol secretion has a considerable genetic influence [21]. Changes in cortisol signaling due to variations in the MR or GR gene could explain why individual organisms respond differently to the same stressor and help understand the influence of these changes in important traits of animal production. Little is known about the genetic variants in these genes in cattle. Therefore, this study aimed to identify SNPs in the MR and GR genes of male Nellore cattle and assess their associations with antemortem and postmortem endocrine and metabolic traits demonstrating that these variations can be a determinant of meat quality.

2. Materials and methods

2.1. Animals and samples

This study was approved by the Animal Care and Use Committee from the College of Animal Science and Food Engineering, University of São Paulo. In the experiment, 241 males of the Nellore breed (119 noncastrated and 122 castrated surgically) were used in 3 different experiments between 2009 and 2011, 76 animals in 2009, 79 in 2010, and 86 in 2011, sired by 22 different bulls. The animals were raised on pasture until approximately 21 ± 1 mo of age and were finished in a feedlot. A diet, composed of 74.8% of total digestible nutrients, 14.4% of crude protein, sugarcane bagasse (15%, dry basis), ground corn (50%), soybean meal (5.6%), corn gluten feed (28%), mineral premix (1%), and urea (0.4%), was fed to the animals.

The cattle were weighed every 28 d during the feedlot phase. At the end of each feeding period (70, 91, 115, and 129 d on feed) in each year, after a 24-h fast, 2 groups of approximately 10 animals per sexual condition (total = 20 animals) were loaded onto a vehicle and transported to the abattoir. Castrated and noncastrated groups of animals were transported separately for approximately 200 m to the experimental abattoir of the College of Animal Science and Food Engineering the morning before slaughter. On arrival, the animals were unloaded and each sublot of animals of the same sex was kept in collective pens with water access. The animals were slaughtered between 7 AM and 12 PM in compliance with humane slaughter guidelines, as required by Brazilian legislation. The animals were