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LITERATURE REVIEW

Development of insulin resistance in horses (*Equus caballus*): etiologic and molecular aspects

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Abstract

M. Gandarillas, J.T. Matus, R.I. Márquez-Hernández, and E. Vargas-Bello-Pérez. 2015. Development of insulin resistance in horses (*Equus caballus*): etiologic and molecular aspects Cien. Inv. Agr. 42(2): 125-137. In horses, insulin resistance is associated with several comorbidities such as obesity, laminitis, colic and osteochondrosis. The multifactorial causes of insulin resistance in horses have been addressed, which include genetic and environmental factors. As a consequence of these factors, the cellular signaling pathways responsible for insulin synthesis, the glucose intake in target cells of peripheral tissues and other related processes (e.g., adipocytokine signaling pathways) are affected. In response to insulin, changes in gene expression occur, which are required for the integration of an entire network of metabolic and physiological responses in different organs. The peroxisome proliferator-activated receptors (PPARs) were the particular focus of studies in recent years, mostly in humans. The PPARs are the primary transcriptional regulators of adipocyte differentiation and lipid metabolism. They have a direct effect on the expression of the genes involved in glucid homeostasis and were recently associated with type-2 diabetes. A molecular framework to define the insulin-related pathologies has not been developed for horses. Additionally, the establishment of a proper diagnosis of insulin resistance is fundamental in this species. The aims of this review were to discuss the etiology to identify the primary causes of insulin resistance and to examine the current progress in understanding this pathology in horses. Future research should study how nutrients modulate the expression of genes related to energy metabolism under the physiopathological condition of insulin resistance.

Key words: Equine nutrition, insulin resistance, PPAR-gamma.

Introduction

Horses are a species that have a relatively long life, with a mean life span of 25 years (equivalent

to 71 years of human age) and a maximum life span that approaches 40 years (McFarlane *et al.*, 2001). Classified by the manner of feeding, horses are nonruminant herbivores that evolved a fermentation chamber to digest fiber and forage in the hindgut (cecum and colon) (Hintz and

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Cymbaluk, 1994). According to Hofmann (1973), the horses are further divided into a subclass of “bulk and roughage eaters” with an extra subclass as a “roughage grazer”, as are the elephants, white and Indian rhinos and zebras (Van Soest, 1994).

Based on endocrinology, horses and humans regulate glycemia and insulinemia with the induction of similar adaptive mechanisms. Influenced by inefficient nutritional programs, these responses may result in further metabolic disorders, with the consequent increase of inflammatory responses that are common in obesity and insulin resistance. As an example, the diets that are rich in simple sugars are associated with insulin resistance in several animal and human studies (Storlien *et al.*, 2000; Bessesen, 2001; Hoffman, 2009). Similar to the condition in humans, insulin resistance in horses is associated with obesity and a lack of exercise (Hoffman, 2009). In many of these cases, the common factor among the horses was the starch and sugar-rich meal that was used to feed the horses during long periods of inactivity. The other comorbidities in horses include colic (Hudson *et al.*, 2001) and osteochondrosis (Ralston, 1996). Several molecular links that associate cellular signaling responses, gene expression networks and the establishment of insulin resistance and other copathologies have been found in humans and animal models. However, a molecular framework for these pathologies in horses has not been developed yet. Additionally, the establishment of a proper diagnosis of insulin resistance in horses is fundamental. The aims of this review are to discuss the etiology to identify the primary causes of insulin resistance and to examine the current progress in the gathering of evidence to understand this pathology in horses.

Digestive physiology in horses

Effects of modified feeds on glycemia and metabolism

Before digestion begins, incisors nip and tear off plant components in the mouth. The molars

(cheek teeth) are used to grind feeds to increase the surface area for subsequent exposure to enzymatic and microbial digestion (Lawrence, 2002). The saliva is produced and mixed with the feed only during chewing, and horses produce between 40 and 90 ml of saliva per minute. The saliva of horses contains enzymes and significant amounts of minerals and sodium bicarbonate (50 mmol L^{-1}), which are used to neutralize the acids formed in the initial portion of the stomach, and moisturizes the food to ease the passage through the entire digestive tract (Brandi and Furtado, 2009).

The stomach has only 8% of the capacity of the total digestive tract compared with the small intestine (30%), the cecum (16%) and the colon (46%) (Stevens, 1977). The hindgut of a horse has several distinguishing characteristics compared with that of other domestic animals; the hindgut is much larger than that of cattle, sheep or swine (relative to the size of the whole organism) and contributes much more relatively to the capacity of the equine tract. The enzymatic digestion of starches, proteins and lipids occurs in the small intestine. However, if an excessive amount of cereal grain or other high-starch feed is consumed, the capacity of the small intestine to digest and absorb these nutrients will be exceeded and the nutrients will reach the large intestine/colon (Lawrence, 2002).

The colon has sacculations with narrow and broad compartments that are delimited by discrete bands of smooth muscle and connective tissue (Burns, 1992). The primary function of the microbial flora found in these areas is to digest the fiber found in common horse feeds such as pasture and hay. Although the microbial digestion in the horse is not as efficient as in the ruminants, this digestion remains extremely important in equine nutrition. As in the rumen, the fermentation in the hindgut produces carbon dioxide, methane, and most importantly, the volatile fatty acids: acetate, propionate, and butyrate. The total methane production (between 2.0% and 3.5%

of the total energy intake) in horses is small in comparison with ruminants and therefore, the methane from horses has little effect on global warming (Vermorel *et al.*, 1997).

The domestication of horses resulted in an increased demand for equine performance, which required additional sources of energy. To provide these sources, domesticated horse feeds are supplemented with highly concentrated energy and rapidly metabolized nutrients, typically in the forms of sugars and starch (Treiber, 2003). In over 90% of modern equine activities (e.g., racing, playing polo, displaying endurance, and jumping), the horse feeds are supplemented, with almost 60% of the supplements based on molasses and grain concentrates with high glucose equivalents (USDA, 1998). The reliance upon this type of nutrition results in several complications. The majority of the supplemented starch and sugar is further digested in the small intestine and is absorbed as glucose, fructose and galactose monosaccharides (Hintz *et al.*, 1971), which generate a rapid increase in glycemia.

Carbohydrates in equine nutrition and the glycemic index

The cereal grains (e.g., oats, corn and barley) are common supplements for horses that work hard (e.g., racing, polo, jumping, endurance and rodeo). These supplements are often in a mix ratio with sweet molasses and are therefore rich in starch and sucrose. These carbohydrates are digested and hydrolyzed in the small intestine by amylases and invertases, and the products glucose, fructose and galactose are absorbed through an enterocyte, which induces a sudden increase in the concentrations of these monosaccharides in the bloodstream (Fransson and Spurgeon, 1995). This hyperglycemia triggers a chain reaction of fluxes in the regulatory and counter-regulatory hormones associated with glucose-energy allocation [e.g., insulin, growth

hormone and Insulin Growth Factor-1 (IGF-1)]. As described in several studies on animals and humans, those diets rich in starch are associated with insulin resistance when maintained for prolonged periods of time (Storlien *et al.*, 2000; Bessesen, 2001).

The nature of the starch granules, the type of carbohydrates, the physical form of the food and the level of processing influence the glycemic effects of food in humans (Wolever, 1990). A glycemic value for a particular food is determined by a comparison of the area under the curve for the plasma response food test with that of a standard food (originally glucose and recently white bread). The glycemic index (GI) of a food is then calculated and is expressed as a percentage of the glucose response to the standard food (Wolever *et al.*, 1991). The GI of the horse feed is relevant because the digestion of starch and sugar and the metabolism of glucose in horses are similar to those in humans, which allows for comparisons in the fluctuations in blood glucose and insulin concentrations. Additionally, horses also suffer at least some of the health maladies that are associated with high concentrations of glucose. However, less research has been conducted to show similar relationships between high glycemic diets and equine conditions that are comparable with those in humans; although some research, together with unpublished evidence, indicates that horses experience obesity, insulin resistance and other problems associated with high starch and sugar intake. Rodiek and Stull (2007) determined the GI values for ten common horse feedstuffs (i.e., oats, alfalfa, corn, barley, sweet feed, jockey oats, wheat bran, rice bran, beet pulp, and soybean hulls), and these feeds had GI values that ranged from 7 to 129. The sweet feed, corn, jockey oats, and oats had significantly higher GI values than those of the beet pulp, alfalfa, rice bran, and soybean hulls.

Glycemic and insulinemic control in horses and the relation to metabolic disorders and physiological pathologies associated with insulin resistance

The anabolic and catabolic pathways of glucose and lipids involve integrative homeostatic regulation at different molecular levels, and the sum of one or more abnormal homeostatic episodes can lead to a metabolic disorder. For example, the sudden increase in simple sugars may ignite a flux of chain reactions in the regulatory and counter-regulatory hormones associated with glucose-energy allocation, which disrupt the normal functioning of the system. The diets that cause large postprandial fluctuations in the plasma levels of glucose and insulin could decrease insulin sensitivity in horses. However, numerous factors influence the digestion and the absorption of glucose from starches and sugars; therefore, the contents of starch and sugars are not the sole indicator of a glycemic response to a feed (Englyst *et al.*, 2003).

Insulin regulates energy homeostasis by coordinating the storage, mobilization, and utilization of free fatty acids and glucose in adipose tissue, liver, and muscle (Ruan and Lodish, 2003). The reduced insulin sensitivity (also known as insulin resistance) is defined as the suppressed ability of insulin to induce glucose uptake into cells (Xu *et al.*, 2003). Insulin resistance in horses was previously documented, and some equine studies associated the obesity with this condition as a cause of abnormal reproductive function (Vick *et al.*, 2006) and debilitating laminitis (Coffman and Colles, 1983; Field and Jeffcott, 1989).

The specific factors that contribute to the development of insulin resistance in horses remain unknown. However, studies with humans provide several lines of evidence to suggest that high circulating concentrations of inflammatory cytokines such as IL-1 (He *et al.*, 2006), IL-6, and tumor necrosis factor alpha (TNF-alpha) play direct roles in the development of obesity-associated insulin

resistance (Dandona *et al.*, 2004; Krogh-Madsen *et al.*, 2006).

Laminitis is a worldwide problem in horses and ponies (Geor, 2008) and has major implications for animal welfare. Laminitis is a systemic disease and manifests as a noninfectious condition of the foot of the animal. The high carbohydrate diets that may exacerbate insulin resistance (Treiber *et al.*, 2005; Miller and Colaguirui, 1994) and predispose humans to type-2 diabetes mellitus (WHO, 1999) and coronary heart disease (Adult Treatment Panel III, 2002) may cause laminitis in equines (Kahn, 1978; Jeffcott and Field, 1985). The Equine Metabolic Syndrome is a predisposition for the development of laminitis and is characterized by obesity, insulin resistance, hypertension and dyslipidemia (Winkelsett and Vervuert, 2008).

Assessment of insulin sensitivity

To document insulin insensitivity in horses, various types of evidence are used. The analogy to human metabolic syndrome provides a tempting scenario of possible disease associations, mechanisms, and interventions, but unsupported assumptions should be considered carefully. Similarly, the associations with risk factors, such as obesity or equine Cushing's disease, suggest that insulin resistance is insufficient upon which to base a diagnosis of a genuine metabolic disorder (Treiber *et al.*, 2006a).

Several techniques are used in humans (Ferranini and Mari, 1988) and horses (Treiber *et al.*, 2006a) to determine glucose tolerance and insulin sensitivity, which include the ratio of basal glucose to insulin; the glucose tolerance test; clamping and the Minimal model of insulin and glucose dynamics (Firshman and Valberg, 2007); the euglycemic-hyperinsulinemic clamp; and the insulin suppression test (Vigil *et al.*, 2007), which is highly correlated ($r = 0.93$) with the euglycemic-hyperinsulinemic clamp (Greenfield *et al.*, 1981).

Adipose tissue and the role in energy homeostasis: the role of adipocytokines in inflammation and insulin resistance

Vick *et al.* (2007) provided the first evidence to associate obesity with elevations in inflammatory cytokines in horses and to show that insulin resistance in horses may develop following systemic inflammation, and these authors suggested that adipose tissue might contribute to this inflammatory response.

The adipose tissue, previously considered simply a fat storage organ, is now recognized to have a critical role in energy homeostasis (Yang *et al.*, 2001). As the developing pre-adipocytes differentiate to become mature adipocytes, these cells acquire the ability to synthesize hundreds of proteins, many of which are released as the enzymes, cytokines, growth factors, and hormones involved in the overall energy homeostasis (Ahima and Flier, 2000). Moreover, mature adipocytes are active endocrine and paracrine organs that secrete a number of mediators, which increase in number with further research, that participate in diverse metabolic processes (Van Gaal *et al.*, 2006). Recently, adipose tissue was recognized as a rich source of pro-inflammatory mediators that might contribute directly to vascular injury, insulin resistance, and atherogenesis (Lau *et al.*, 2005).

The adipocytes secrete biologically active molecules, the adipocytokines or adipokines (any protein that is synthesized and secreted by adipocytes). In humans, these molecules may influence insulin resistance and play critical roles in energy homeostasis. The adipocyte production is altered in obesity, type-2 diabetes, metabolic syndrome and cardiovascular disease (Gandhi *et al.*, 2010). The pro-inflammatory adipocytokines include TNF-alpha (TNF-a), IL-6, leptin, plasminogen activator inhibitor-1 (PAI-1), angiotensinogen, resistin, and C-reactive protein (Lau *et al.*, 2005; Bastard *et al.*, 2006).

Two important adipocytokines are leptin and adiponectin, which are two potential insulin-

sensitizing agents (Havel, 2002). The leptin apparently modulates feeding behavior and energy expenditure and therefore plays an important role in the regulation of body weight (Matsubara *et al.*, 2002). Moreover, elevated levels of leptin are a potential laminitis risk factor (Pleasant *et al.*, 2013). In horses, the body condition score is positively correlated with the plasma concentration of leptin (Diez *et al.*, 2012). In humans, the secretion of leptin increases with insulin resistance (Matsubara *et al.*, 2002). Additionally, because leptin is associated with oxidative stress in endothelial cells, it may promote atherogenesis (Bouloumie *et al.*, 1999).

By contrast, the concentration of adiponectin is inversely proportional to adiposity in humans (Arita *et al.*, 1999; Weyer *et al.*, 2001; Yang *et al.*, 2001), decreased diabetes mellitus (Hotta *et al.*, 2000) and insulin resistance (Hotta *et al.*, 2000; Weyer *et al.*, 2001). The adiponectin was proposed to have anti-atherogenic and anti-inflammatory properties because it accumulates in injured vessel walls and inhibits the TNF-alpha (Arita *et al.*, 1999; Ouchi *et al.*, 1999).

The inflammatory cytokines may be a key link between obesity and insulin resistance in horses. The accretion of intra-abdominal adiposity by equines is associated with the development of insulin insensitivity (hyperinsulinemia), glucose intolerance, dyslipidemia, hypertension, and insidious-onset laminitis in this species. The omental adipocytes are metabolically active and secrete free fatty acids and hormonally active mediators including cortisol, leptin, and resistin, which might contribute to the persistence and worsening of insulin refractoriness (Treiber, 2006b). Some evidence was found in horses that the insulin sensibility (IS) increased as the body condition score (BCS) and the percentage body fat (%FAT) decreased. Moreover, a decrease in the IS is associated with increased levels of IL-1, IL-6 and TNF-alpha (Vick *et al.*, 2007).

The molecular mechanisms involved in the physiopathology of type-2 diabetes are not

clearly understood. It was suggested that the pro-inflammatory effects of not only cytokines but also the reactive oxygen species and the free fatty acids in obesity are mediated through specific intracellular signaling pathways that involve the nuclear factor (NF)- κ B, I κ B kinase (IKK), Activating Protein-1 (AP-1) and c-Jun NH₂-terminal kinase (JNK) signaling molecules (Bastard *et al.*, 2006).

The adiponectin has insulin sensitizing properties (Berg *et al.*, 2001) that are activated by the peroxisome proliferator activated receptor gamma (PPAR-gamma), which is a transcription factor involved in the adjustment of the organism to metabolic changes. Among these responses, the PPARs affect fatty acid oxidation, ketone body synthesis, and glucose sparing. Thus, these mechanisms under which the PPAR factors affect metabolism and the relation to metabolic disorders are an interesting focus for research on insulin resistance diagnosis and treatment.

Gene expression regulation

Regulation of gene expression in response to insulin and the role of PPARs in insulin resistance

The PPARs are the primary transcriptional regulators of adipocyte differentiation and lipid metabolism (Tontonoz *et al.*, 1994), but the PPARs are also proposed to have a direct effect on the expression of the genes involved in carbohydrate homeostasis (Picard and Auwerx, 2002). Studies that related the resistance to insulin to the PPARs were derived from the analysis of thiazolidinediones (TZD); compounds that are used as hypoglycemic, muscle insulin-sensitizing agents in type-2 diabetes (these molecules activate the of PPARs).

The PPARs are a subgroup member of the nuclear hormone receptor superfamily of ligand-dependent transcription factors, which modulate the expression of the genes involved in insulin

signaling and lipid metabolism (Evans *et al.*, 2004). The modular structure is similar to that of all nuclear receptors. The less conserved NH₂-terminal region has a ligand-independent activation domain. The DNA binding domain is extremely well conserved, which the PPARs use to bind to DNA as heterodimers with the retinoid X receptor (RXR). This complex then recognizes the PPAR response elements (PPRE), which have direct repeats of two hexamers that are closely related to the sequence AGGTCA and that are separated by one nucleotide (DR-1 sequence). The five nucleotides that flank the 5'-end of this core sequence are also important for the efficiency of the PPAR:RXR binding (Desvergne *et al.*, 2006).

Several target genes were identified for the PPAR:RXR complex, many of which are activated in specific tissues. For humans and several types of animals, three isoforms (alpha, beta/delta and gamma) were described. The PPAR-alpha (PPAR- α) is highly expressed in organs with high activity levels of lipid catabolism (e.g., liver, brown adipose tissue, and skeletal and heart muscle). The PPAR-beta or delta (PPAR-b/d) is ubiquitously expressed in tissues. The PPAR-gamma (PPAR- γ) has two splicing variants in which the second variant has a different NH₃ terminal sequence. The PPAR- γ 1 is primarily expressed in adipose tissues (Loviscach *et al.*, 2000) but is also detected in the colon, spleen, retina, hematopoietic cells, and skeletal muscle. The PPAR- γ 2 is found primarily in the brown and the white adipose tissues. Although the skeletal muscle is the primary organ for the clearance of insulin-stimulated glucose (Saltiel and Olefsky, 1996), the expression of the PPAR- γ is very low in skeletal muscle cells and accounts for as little as 5–10% of the expression in human fat cells (Loviscach *et al.*, 2000).

The PPAR- γ is required for the sufficient differentiation of the adipocytes. In the adipocytes, the PPAR- γ regulates the expression of numerous genes involved in lipid metabolism, including *PHOESPHOENOL PIRUVATE CARBOXIKI-*

NASE (PEPCK) (Tontonoz, *et al.*, 1995), *ACYL-COA SYNTHASE* (Schoonjans *et al.*, 1995) and *LIPOPROTEIN LIPASE (LPL)* (Schoonjans *et al.*, 1996). Additionally, the PPAR- γ is associated with several genes that affect the action of insulin. The TNF- α (the cytokine expressed in adipocytes) is associated with insulin resistance and decreases insulin signal transduction (Nieto-Vasquez *et al.*, 2008). Because the loss-of-function mutations of the PPAR- γ were associated with severe insulin resistance and type-2 diabetes mellitus in humans (Barroso *et al.*, 1999), the PPAR- γ had a specific role in the etiology of insulin resistance. Additionally, and in relation to many other pathologies (e.g., cancer, inflammatory responses, and vascular cell proliferation, among others), an increase in PPAR- γ signaling (caused by a mutation that increased the intrinsic activity) was also associated with human obesity (Balasubramanyam and Mohan, 2010). Although disease-causing mutations of the PPAR- γ are rare, the changes in PPAR- γ expression or in the expression of the target genes in response to an altered nutritional or feeding program (in the case of animals) may also be associated with insulin resistance in the absence of any mutation. As previously mentioned, Vick *et al.* (2007) found links among inflammatory responses, insulin sensitivity and the adipocytes. The PPAR might be the missing link among these responses and therefore requires further examination to determine the relation to insulin resistance. Thus, the assessment of the changes in the expressions of the PPAR- γ target genes that control the different metabolic pathways under such metabolic disorders becomes very important.

Future considerations

Horses (*Equus caballus*) suffer similar metabolic disorders as humans, possibly because of the similar high starch and sugar food diets and sedentary behaviors (in the case of humans, exceeding energy expenditure and fat mass accumulation is a product of modern living). Notably, these

metabolic disorders occur particularly in older subjects of both species. Therefore, the present feeding programs based on starch and sugars, which result in high carbohydrate intake in horses, must be reconsidered.

A proper diagnosis of insulin resistance in horses is essential, particularly for those horses used for reproduction, and it is important to recognize that insulin resistance is the tip-of-the-iceberg for multiple associated morbidities.

For the purposes of future diagnoses and treatments in horses, several regulation points of metabolic and cell signaling pathways should be studied. The integrative “nutrigenetic” and “nutrigenomic” analyses will help to comprehend the changes in gene expression of key enzymes related to metabolic disorders, together with the analyses of nutrients and signal molecules in different organs. Different molecular platforms and approaches are now available to study the transcriptome and the metabolome of the horse. Microarrays can be used to identify the networks that are affected under insulin resistance and may also help to determine whether particular treatments (e.g., changes in nutrition) can change these effects in the long-term. Finally, the genomic resources of the horse (*Equus caballus*) are available at the National Center for Biotechnology Information (NCBI; <http://www.ncbi.nlm.nih.gov/>), with the full genome sequence, cDNA libraries and the isolated genes. Many of the PPAR genes and the sequences of the target genes are available as annotated gene models in the horse genome, and we suggest studies of the expression of some of the genes that are listed in Table 1. These genes were identified or were predicted as gene models in genomic horse resources (the NCBI Nucleotide, Entrez Gene or Unigene databases). Additionally, the homologous genes in humans show expression in the adipocytes (based on the Genevestigator human microarray data—data not shown). Future research should focus on the expression behaviors and the contributions of these genes in establishing or responding to metabolic disorders.

Table 1. List of genes with expression quantified by real-time PCR. This list of genes was selected based upon different criteria: 1) Genes expressed in adipocytes (based on Genevestigator microarray data); 2) Genes that shared one or two KEGG pathways (PPAR, Insulin and PPAR signaling); and 3) Genes with sequences or predicted gene models that were available in genomic horse resources (the NCBI Nucleotide, Entrez Gene or Unigene databases-db).

| Gene | Name | <i>Equus caballus</i> | | KEGG Signaling Pathway (PPAR) | Function |
|-----------|---|-------------------------------|-----------------------|-------------------------------|---------------------------|
| | | mRNA or Gene model (LOC1000#) | Unigene EST db. Eca.# | | |
| PPAR-a | PPAR alpha | 49840 | - | | Transcription factor |
| PPAR-b | PPAR beta/delta | 53404 | - | | Transcription factor |
| PPAR-y | PPAR gamma | 51258 | - | | Transcription factor |
| RXR-a | Retinoid X receptor alpha | 60371 | - | a-b-y | PPAR interaction |
| SCD-1 | Stearoyl-CoA desaturase | 60485 | - | a-y | Lipogenesis |
| LXR-a | Nuclear receptor subfamily 1 (NR1H3) | 51253 | - | a-y | Cholesterol metabolism |
| ACBP | Diazepam binding factor (DBI) | 49822 | - | a-b-y | Fatty acid transport |
| LPL | Lipoprotein lipase | AB278557 | - | a-b-y | Fatty acid transport |
| ACS | Acyl-CoA synthetase | 54459 | 13574 | a-b-y | Fatty acid transport |
| CPT-2 | Carnitine palmitoyltransferase II | 61061 | 15130 | a-b-y | Fatty acid oxidation |
| ACAA1 | Acetyl-CoA acyltransferase (thiolase B) | 50082 | 11757 | a-b-y | Fatty acid oxidation |
| MCAD | Acyl-CoA dehydrogenase | 67343 | | a-b-y | Fatty acid oxidation |
| ACOX1 | Acyl-CoA oxidase (ACO) | 51466 | 14267 | a-b-y | Fatty acid oxidation |
| ADIPO | Adiponectin (ADIPOQ) | - | - | a-b-y | Adipocyte differentiation |
| Perilipin | Perilipin | - | - | a-b-y | Adipocyte differentiation |
| aP2 | Fatty acid binding protein 4 | - | - | a-b-y | Adipocyte differentiation |
| UCP-1 | Uncoupling protein 1 | 63105 | | a-b-y | Thermogenesis |
| ILK | Integrin-lined kinase | 70066 | 14605 | b | Cell survival |
| PEPCK | Phosphoenolpyruvate carboxykinase | 54903 | - | y | Gluconeogenesis |
| C/EBP | CCAAT/enhancer binding prot. | - | - | a-b-y | Transcription factor |
| E2F | E2 transcription factor 1 | 52248 | - | a-b-y | C/EBP target |
| INSR | Insulin receptor | 66248 | 15354 | | Cell signaling |
| IRS1 | Insulin receptor substrate 1 | 61987 | - | | Cell signaling |
| AKT3 | V-akt murine viral oncogene homolog3 | 54961 | - | | Cell signaling |
| FOX-O1 | Forkhead box O1 | 50481 | 7913 | | Gluconeogenesis |
| SREBF1 | Sterol regulatory element binding protein | 52283 | 16602 | y | Gluconeogenesis |
| PFK | Phosphofructokinase (PKLL) | AB088683 | 8957 | | Gluconeogenesis |
| AMPKK | Ca/calmodulin dep prot kin kinase | 55913 | - | | Cell signaling |
| AMPK | Protein kinase AMP activated | DQ318135 | 12514 | | Lipogenesis inhibition |
| ACC2 | Acetyl-CoA carboxylase alpha | 66740 | - | | Lipogenesis |
| FASN | Fatty acid synthase | 57311 | - | | Lipogenesis |
| JNK | MAP kinase 8 | 51978 | - | | Cell signaling |
| SLC2A4 | GLUT4 transporter | - | - | y | Glucose uptake |
| LEP | Leptin | AF179275 (partial) | - | a-y | Lipid homeostasis |
| TNFR1 | TNF receptor-1a | 59548 | 16374 | | Inflammatory response |
| TRAF2 | TNF receptor-associated factor 2 | 68006 | - | | Inflammatory response |

Resumen

M. Gandarillas, J.T. Matus, R. I. Márquez-Hernández y E. Vargas-Bello-Pérez. 2015. Desarrollo de resistencia a la insulina en caballos (*Equus caballus*): aspectos etiológicos y moleculares. Cien. Inv. Agr. 42(2): 125-137. La resistencia a la insulina en caballos se ha asociado con diversas comorbilidades, tales como obesidad, laminitis, cólicos y osteocondrosis. Se han descrito múltiples factores causantes de la resistencia a la insulina especialmente los genéticos y ambientales. Los cuales pueden afectar las vías de señalización celular responsable de la síntesis de insulina en las células pancreáticas, la ingesta de glucosa en las células diana de los tejidos periféricos y otros procesos relacionados (por ej., las vías de señalización de adipocitocinas). En respuesta a la insulina, se producen cambios en la expresión génica que son necesarios para la integración de toda una red de respuestas metabólicas y fisiológicas en diferentes órganos. Los receptores activados por proliferadores peroxisomales (PPARs, por sus siglas en inglés) se han estudiado particularmente en los últimos años, principalmente en los seres humanos. Los PPARs son importantes reguladores de la transcripción en la diferenciación de adipocitos y el metabolismo de lípidos. Estos tienen un efecto directo sobre la expresión de genes implicados en la homeostasis de los glúcidos y han sido recientemente relacionados con la diabetes tipo 2. Sin embargo, no se ha desarrollado un marco de trabajo a nivel molecular que permita identificar patologías relacionados con la insulina. Además, el establecimiento de un diagnóstico adecuado para la resistencia a la insulina es fundamental en esta especie. El objetivo de esta revisión es ilustrar las principales causas y etiología de la resistencia a la insulina así como examinar el progreso actual que demuestra esta patología en caballos. Investigaciones futuras deben estudiar el efecto de nutrientes sobre la expresión de genes relacionados con el metabolismo de energía bajo esta condición fisiopatológica.

Palabras clave: Nutrición equina, PPAR-gamma, resistencia a la insulina.

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