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Carbohydrate metabolism and metabolic disorders in horses

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ABSTRACT - Horses evolved consuming primarily fermentable forage carbohydrates, but forage diets have been traditionally supplemented with grain meals rich in starch and sugar in order to provide additional calories, protein and micronutrients. Starch and sugar are important for performance horses, but the consumption starch-rich meals may cause equine digestive and metabolic disorders. The critical capacity for preileal starch digestibility appears to be 0.35 to 0.4% but may be as little, depending on the source of starch. Small intestinal absorption of simple sugars is limited by the activity and expression of two classes of glucose carrier proteins, which are affected by chronic intake of hydrolyzable carbohydrate but may be sluggish to respond to abrupt changes in diet, further exacerbating the risk of overload. The most rapid fermentation occurs during starch overload or in the presence of fructans. Rapid fermentation perturbs the microbial and pH balance of the cecum and colon, favoring proliferation of *Lactobacillus spp* and acid production and increasing the risk of colic and laminitis. In addition to digestive disturbances, feeding grain concentrates rich in hydrolyzable carbohydrate may increase the risk of insulin resistance, which has been associated with obesity, laminitis and chronic founder, developmental orthopedic disease, and Cushing's disease in horses. This threshold concentration of starch intake may be a starting point for horse owners, feed manufacturers and veterinarians that may be claimed to be "low" enough to reduce risk in insulin resistant horses sensitive to grain-associated disorders.

Key Words: carbohydrate metabolism, glucose, horse, insulin resistance

Metabolismo de carboidratos e disfunções metabólicas em equinos

RESUMO - Equinos desenvolvem-se consumindo primordialmente os carboidratos fermentáveis das forragens, porém as dietas a base de forragens vem sendo suplementadas com dietas a base de grãos, ricas em amido e açúcar, visando fornecer adicionais calorias, proteínas e micronutrientes. Amido e açucares são importantes para os equinos atletas, porém o consumo de dietas ricas em amido pode causar problemas digestivos e metabólicos aos equinos. A capacidade critica da digestão pré-ileal do amido varia entre 0,35 a 0,4%, podendo ser inferior, dependendo da fonte de amido. A absorção de açucares simples, no intestino delgado, depende da expressão de suas proteínas carreadoras de glicose, as quais são afetadas pela ingestão continua de carboidratos solúveis, porém podem ser mais vagarosas a responder a mudanças abruptas na dieta prevenindo o risco da sobrecarga. A fermentação mais rápida ocorre quando amido não digerido no intestino delgado adentra o intestino grosso e na presença de frutanas. A rápida fermentação perturba o equilíbrio da microbial e do pH de ceco e colon, favorecendo a proliferação de *Lactobacillus spp* e produção de ácido lático, aumentando o risco de cólicas e laminite. Adicionalmente aos distúrbios digestivos, dietas a base de grãos com alta concentração de carboidratos hidrolisáveis, pode aumentar o risco de resistência a insulina, a qual vem sendo associada com obesidade, laminite, distúrbios crônicos e desenvolvimento de problemas ortopédicos. O valor mínimo de ingestão de amido pode ser um ponto inicial na dieta de cavalos vencedores, processamento de alimentos e veterinários que podem estar recomendado a ser baixo o suficiente para reduzir o risco de resistência e insulina em equinos sensíveis a distúrbios associados a grãos.

Palavras-chave: equinos, glicose, metabolismo de carboidrtatos, resistência a insulina

Introduction

The horse evolved primarily as a grazing and browsing, hind-gut fermenting herbivore, with a wide range of forage carbohydrates—hydrolyzable to fermentable—as its main source of energy. Pastures provide the main habitat and nutrition for most horses, and the remaining stall-confined horses have at least one-half of their nutrition supplied by conserved pasture. Horse owners supplement a diet of pasture and hay with grain concentrates in order to meet energy demands of performance and to provide a carrier for micronutrients that are marginal or deficient in forages. Common experience has been supported by epidemiological and experimental studies that associate grain concentrates

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with several digestive and metabolic disorders, including colic (Clarke et al., 1990; Hudson et al., 2001), laminitis (Pass et al., 1998), gastric ulcers (Murray, 1994), developmental orthopedic disease (Kronfeld et al., 1990; Ralston, 1996), insulin resistance (Hoffman et al., 2003a; Treiber et al., 2005) and some forms of exertional rhabdomyolysis (Valentine et al., 2001). The abundant starch in grain concentrates has been implicated as the culprit, leading to development and marketing of "low starch" concentrates for horses. Corresponding trends in human nutrition towards "low carb diets" have fed wide consumer support of low starch feeds for horses, perhaps to excess.

While low starch grain concentrates provide an alternative energy source that is critical for horses with a history of digestive and metabolic disorders that are sensitive to starch, these concentrates are not a "one fits all" solution. Specifically, exercising horses require some dietary starch in order to appropriately fuel performance. Horses have an opportunity for small intestinal metabolism of starch and simple carbohydrates to glucose, which is more metabolically efficient than hindgut fermentation of fibers to volatile fatty acids. Compared to fatty acids, glucose (or its stored form, glycogen) is aerobically metabolized nearly twice as fast to generate ATP for muscle contraction. As speed and exertion increase to the point of anaerobic work, glycogen is metabolically favored over fatty acids.

Carbohydrate digestion

Carbohydrates may be hydrolyzed or fermented in horses, depending on the linkage of their sugar molecules: carbohydrates with a-1,4 linked molecules are subject to enzymatic hydrolysis, whileb-1,4 linked molecules must be fermented. Hydrolyzable carbohydrates include hexoses, disaccharides, some oligosaccharides (e.g. maltotriose) and starches not resistant to enzymatic hydrolysis. Fermentable carbohydrates include soluble fibers (e.g. gums, mucilages, pectins), some oligosaccharides (e.g. fructans, galactans), starches resistant to enzymatic hydrolysis, hemicellulose, cellulose, and lignocellulose.

Hydrolytic digestion

Enzymes secreted in the small intestine specific to carbohydrate hydrolysis include a-amylase,a-glucosidases (sucrase, glucoamylase, maltase), and b-galactosidase (lactase). Relatively little a-amylase is present in equine saliva, so limited hydrolysis occurs prior to arrival of carbohydrates in the stomach. In the stomach, gastric acid hydrolyzes carbohydrates to an extent, independent of enzymes.

In the small intestine, hydrolysis of carbohydrates is initiated primarily by pancreatic a-amylase. In the lumenal phase, a-amylase cleaves a-1,4 linkages but not a-1,6 or terminal a-1,4 linkages of starch molecules. Amylopectinase cleaves a-1,6 linkages. The end products of the luminal phase are disaccharides and oligosaccharides—no free sugars are yielded. Sucrase, lactase and maltase are expressed along the length of the equine small intestine at the brush border mucosal cells (Dyer et al., 2002). Sucrase activity was higher in the duocenum and jejunum than the ileum, while maltase activity was similar in duodenum, jejunum and ileum (Dyer et al., 2002). Functional lactase was present in all portions of the small intestine of mature horses, higher in the duodenum and jejunum than the ileum. Although its activity was lower in mature than weaned horses, the presence of functional lactase suggests that mature horses can digest lactose (Dyer et al., 2002). The action of these disaccharidases at the brush border mucosal cells completes hydrolysis to yield free sugars, glucose, galactoseand fructose, providing relatively high energy yield.

Fermentation

Fermentation occurs predominantly in the hind gut of horses but may occur in any area of the digestive tract where microorganism populations are sufficiently established as a result of favorable conditions, such as adequate retention time and pH greater than 5 (Van Soest, 1994). The presence of viable anaerobic bacteria as well as acetate, propionate, butyrate and lactate suggests that limited fermentation occurs in the equine stomach, particularly in the fundic region and favors lactic acid (Argenzio et al., 1974; Kern et al., 1974). The brief retention time in the stomach and the dorsal to ventral pH gradient of the gastric mucosa likely supports only nominal fermentation (Murray & Grodinsky, 1989). Some fermentation occurs in the small intestine of horses (Zentek et al., 1992; Moore-Colyer et al., 2002), but it is not well known if small intestinal fermentation occurs independent of large bowel fermentation or is merely due to reflux of large bowel contents. Fermentative gases in breath exhalation indicate that microbial fermentation in the stomach and small intestine partially degrades starch and fructans, but not pectin and cellulose (Coenen et al., 2006).

Carbohydrates fermented by intestinal microflora yield volatile fatty acids, mainly acetate, propionate, butyrate, and to a lesser extent, lactate and valerate. The relative proportions of volatile fatty acids produced are dependent on substrates, i.e. the proportions of dietary forage and

concentrate (Longland et al., 1997; de Fombelle et al., 2001; Hoffman et al., 2001). Increasing proportions of grain favored production of propionate and lactate at the expense of acetate (Hintz et al., 1971; Willard et al., 1977; de Fombelle et al., 2001). Feeding higher percentages of grain depressed the efficiency of fiber utilization by altering the microbial ecosystem in the equine cecum and colon (de Fombelle et al., 2001). Rapid fermentation favors proliferation of *Lactobacilli* spp and production of lactate, which is poorly absorbed (Argenzio et al., 1974; Garner et al., 1978).

Carbohydrate absorption

Two classes of glucose carrier proteins have been identified in mammalian cells (Shirazi-Beechey, 1995): the high affinity, low capacity, Na^+/glucose cotransporter type I (SGLT1) and facilitative glucose transporters (GLUT). The SGLT1 is present on the intestinal lumenal membrane and in kidney proximal tubule absorptive epiethelial cells. It transports primarily D-glucose and D-galactose across the brush border membrane against the concentration gradient by active transport of Na^+ and the Na^+/K^+-ATPase (Dyer et al., 2002). The sugars accumulate within the enterocytes and are transported down gradient into systemic circulation via GLUT (Joost & Thorens, 2001). The major site of glucose absorption in horses is the proximal small intestine, with glucose transport highest in the duodenum, followed by jejunum and ileum (Dyer et al., 2002).

The lag time between an abrupt change in dietary hydrolyzable carbohydrate and the appearance of enhanced SGLT1 was 12 to 24 h in mice (Ferraris and Diamond, 1993). Equine SGLT1 has 85% homology with mouse SGLT1 and 92% similarity at the amino acid level (Dyer et al., 2002). In mice, dietary regulation of glucose transport involves increased transcription of SGLT1, mainly in crypt cells (Ferraris and Diamond, 1993). Comparatively in horses, expression of SGLT1 is regulated at the level of mRNA abundance (Dyer et al., 2002). The differences in length and function of horse and mouse digestive tracts may play a role in appearance of SGLT1 after changes in dietary hydrolyzable carbohydrate, so direct comparisons should be considered with caution. If a similar lag time for SGLT1 exists in horse, then in the event of an abrupt change in diet, sugar transport would be inadequate, thus exacerbating hydrolyzable carbohydrate overload to the hind gut.

Metabolic disorders in horses associated with carbohydrates

Carbohydrate overload

Sugars and starches are hydrolyzed in the equine small intestine up to the point at which the enzymatic capacity becomes overloaded, and the excess is rapidly fermented in the hind gut. The critical capacity for starch overload appears to be in the range of 0.35 to 0.4% of body weight per feeding (Potter et al., 1992), but may be as little as 0.2%, depending on the source of starch (Radicke et al., 1991; Kienzle et al., 1992). Prececal digestion of corn starch increased from an intake of 0.1% to peak at approximately 0.35% of body weight, then decreased at starch intakes above 0.4% of body weight (Potter et al., 1992). Similarly, the presence of ileal starch remained at a plateau from intakes of 0.1% to approximately 0.25% of body weight then increased exponentially at intakes above 0.25% of body weight. Compared to oat starch, feeding corn starch resulted in lower cecal pH at all levels of starch intake (from 0.1% to 0.4%), and differences in cecal pH between the starch sources increased in proportion to starch intake (Radicke et al., 1991). Accumulation of lactic acid may overpower the buffering mechanism of the hind gut and lower pH, normally at 6.4 to 6.7 in grazing horses. A cecal pH of 6 was considered to represent sub-clinical acidosis (Radicke et al., 1991). A pH less than 6 favors production of lactic acid (Garner et al., 1978; Van Soest, 1994) and was associated with clinical conditions such as osmotic diarrhea, overgrowth of undesired bacterial populations and lysis of desired bacterial populations, thus increasing the risk of endotoxemia and laminitis (Sprouse et al., 1987; Bailey et al., 2002).

Aside from the rapid fermentation of excess hydrolyzable carbohydrates, other rapidly fermentable carbohydrates include resistant starches and oligosaccharides, especially fructans, which may comprise 5 to 50% of the dry matter in cool season grasses (Longland et al., 1999; Cuddeford, 2001). The b-2,6 glycocidic bonds in fructans are not hydrolyzed in mammalian small intestine but may be partially degraded by small intestinal microbes (Coenen et al., 2006). Fructans were used to initiate equine carbohydrate overload and laminitis (Pollitt et al., 2003; van Eps and Pollitt, 2006) and produced a more rapid fall in cecal pH than an equal amount of corn starch (Bailey et al., 2002).

Insulin resistance

Insulin resistance has been generally defined as a abnormal metabolic state when normal concentrations of circulating insulin fail to elicit a normal physiologic response in target tissues (Kahn, 1978). More specifically, cells in muscle, adipose tissue and liver that become insulin resistant require larger concentrations of circulating insulin to stimulate glucose uptake. In humans, insulin resistance is

fundamental in the pathology of type II diabetes and is a risk factor in obesity (Frayn, 2001), cardiovascular disease and hypertension (Reaven, 1988), polycystic ovaries (Legro et al., 1998; Legro, 2002), pregnancy loss (Craig et al., 2002) and colorectal cancer (Kim, 1998; Sturmer et al., 2006).

Diets rich in simple sugars have been associated with insulin resistance in several animal and human studies (Storlien et al., 2000; Bessesen, 2001), and the common practice feeding starch-rich cereal grains with high glycemic indices may promote insulin resistance in horses (Hoffman et al., 2003a; Treiber et al., 2005). Insulin resistance has been observed in obese (Hoffman et al., 2003a, Frank et al., 2006) and sedentary (Powell et al., 2002) horses. Similar to humans, mares became insulin resistant during late pregnancy and recovered to normal sensitivity during early lactation (Hoffman et al., 2003b; George et al., 2007). Insulin resistance may be a risk factor in horses with hyperlipaemia (Jeffcott & Field, 1985; Jeffcott et al., 1986), osteochondrosis (Ralston, 1996), Cushing's disease (Garcia & Beech, 1986; Johnson, 2003), colic (Hudson et al., 2001), and laminitis (Pass et al., 1998; Treiber et al., 2006; Hoffman et al., 2007), especially chronic grass founder (Hoffman et al., 2007). Dietary therapy alone may not be sufficient to reverse insulin resistance (Hoffman et al., 2003; Frank et al., 2005). Exercise is beneficial, as both obese and lean mares had improved insulin sensitivity after seven days of moderate exercise training (Powell et al., 2002).

Carbohydrates in horse forages and feeds

Forages

During photosynthesis, green plants produce glucose and other simple sugars, with oxygen as a by-product, from water and atmospheric carbon dioxide in the presence of light:

$$6\,CO_2 + 12\,H_2O + \text{light energy} \rightarrow C_6H_{12}O_6 + 6\,O_2 + 6\,H_2O$$

When the production of sugars exceeds the energy requirements of the plant, they are converted to storage carbohydrates, most commonly starch or fructans. Cool season pasture grasses accumulate fructans, while warm season grasses and legumes accumulate starch. The accumulation of storage carbohydrates in plants is affected by temperature, light intensity and plant growth rate (Longland et al., 1999; Hoffman et al., 2001). While plants that accumulate starch are limited to maximum storage when their chloroplasts are saturated, plants that accumulate fructans have no self-limiting mechanism, so high concentrations may accumulate.

Abrupt changes in fructan concentrations were observed from day to day in rapidly growing pastures and diurnally as plant composition changed from night to day or from shade to sunlight (Longland et al., 1999; Longland & Byrd, 2006; McIntosh et al., 2007). Fructan concentrations usually rose during the morning, peaked in the afternoon, and declined to a low overnight until the early morning hours. Horses grazing in the afternoon, as compared to morning, may ingest between two to four times as much fructans (Longland et al., 1999).

An association between an abrupt increase in pasture plant fructans and the incidence of laminitis has been suggested. Laminitis has been clinically induced with 3.75 kg of fructan (Pollit et al., 2003; van Eps & Pollit, 2006), thus establishing a link between pasture fructans and laminitis. Considering pasture intake and cool season pasture fructan concetrations, a horse grazing in the summer potentially could ingest 5 kg or more of fructans per day (Longland et al., 1999; Longland & Byrd, 2006). Although the amount of fructans ingested while grazing can be as much as that used to clinically induce laminitis, it is relevant to consider that the gradual dose encountered over time during grazing likely has a far different impact than the entire dose in a single bolus during clinical induction of laminitis. Circadian and seasonal patterns in plasma glucose and insulin in grazing horses have been noted, however, to correspond with changes in pasture forage sugars, starches and fructan content (McIntosh et al., 2007a,b). These changes during periods of pasture growth may increase the risk of laminitis by exacerbating insulin resistance in affected horses.

Glycemic index

The glycemic index is a reflection of plasma glucose and insulin responses to a meal, an *in vivo* estimate, rather than a chemical analysis of the hydrolyzable carbohydrates in a feed. The glycemic index provides information about the food but not necessarily the animal. It has been applied primarily in human nutrition for diabetics in order to formulate diets with a low glycemic impact, with glycemic index calculated as a percentage of the response to a standardized reference: an oral glucose dose or white bread (Jenkins et al., 1981; Englyst et al., 1996; Wolever and Mehling, 2002). In horse nutrition, meal-related responses of blood glucose and insulin to different diets have been quantified in several reports (Stull & Rodiek, 1988; Rodiek et al., 1991; Pagan et al., 1999; Williams et al., 2001). Most studies compared ingestion of different feeds as either equal-weight or isocaloric meals and did not calculate glycemic index as a

percentage of a standardized reference. More recently, glycemic indices were quantified in a series of studies by Rodiek (2003) and reported using whole oats as a standardized reference feed, with the calculated area under the curve for oats set to a standard value of 100. The range of feeds tested and their glycemic indices included beet pulp, 1, alfalfa hay, 26, timothy hay, 32, carrots, 51, oats, 100, barley, 101, and corn, 117 (Rodiek, 2003). Several factors may affect glycemic response including meal size, amount of hydrolyzable carbohydrates in the meals, fiber and fat content of the feed, processing, intake time, gastric emptying, digestibility and rate of absorption (Pagan et al., 1999; Hoekstra et al., 1999).

In human nutrition, the glycemic index provides a physiological classification of foods useful in developing nutritional programs for patients with insulin resistance or non-insulin dependent diabetes. Similarly, glycemic indices of horse feeds may be useful in developing nutritional programs for horses with metabolic problems associated with carbohydrate intake. There is currently a trend in the horse feed industry to manufacture low or controlled starch feeds, with claims of reducing the risk of grain-associated metabolic disorders; however, lack of reports elucidating the effect of various starch intakes on blood glucose response leave questions regarding exact concentrations of dietary starch for horses that may be considered "low." A study in this laboratory examined glucose responses in equal-weight meals that provided intakes of nonstructural carbohydrate ranging from 0.6 to 2.0 g/kg bodyweight (Hoffman et al., in press). The magnitude of each glucose response was calculated as the incremental area under the curve (AUC) by graphical approximation. The threshold of glycemic sensitivity, i.e. the inflection point, or knot, after which higher nonstructural carbohydrate intakes produced less of a slope in AUC changes, was determined using nonstructural carbohydrate intake as the independent variable and blood glucose AUC as the dependent variable. The results indicated that glucose AUC data have a positive slope (37.9, $r^2 = 0.76$) at low nonstructural carbohydrate intakes, and become more flat (slope = 4.3, $r^2 = 0.31$) at higher nonstructural carbohydrate intakes. Thus, dietary changes in intake at lower nonstructural carbohydrate concentrations have a greater influence on blood glucose response compared to dietary changes at higher NSC intakes. The segmented regression indicated an inflection point at nonstructural carbohydrate intake equal to 0.3 g/kg BW (Hoffman et al., in press). These data provide a concentration of nonstructural carbohydrate intake for horse owners, feed manufacturers and veterinarians that may be low enough to be below a threshold at which a glycemic impact may be noted, and perhaps low enough to thus reduce risk in horses sensitive to grain-associated disorders.

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