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Insulin resistance in horses; causes, development and prevention

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Sammanfattning

Syftet med denna litteraturstudie var att utreda vilka faktorer som spelar in vid utveckling av insulinresistens. Evolutionärt sett är hästen ett betande djur och övergången till att bli domesticerat har bland annat inneburit en delvis ändrad diet. Uppstallade hästar får ofta ren spannmål eller spannmålsbaserade koncentrat som komplement till grovfodret vilket beroende på utfodrad mängd kan leda till foderrelaterade sjukdomar som insulinresistens. Vissa hästar har sämre förmåga än andra att stå emot stora mängder stärkelse och socker och faktorer som kan spela in vid utveckling av insulinresistens är utfodring, ålder, kön och ras. Insulinresistens är i sin tur kopplat till sjukdomar som fetma, osteokondros, fång och korsförlamning, men kan förebyggas genom daglig träning och genom en balanserad foderstat där intaget täcker hästens behov av näringsämnen.

Abstract

The aim of this review was to investigate the possible causes and factors related to insulin resistance. The horse is a grazing animal but domestic horses are today sometimes fed large amounts of grains and concentrates rich in starch and sugars, which leads to an increased risk of developing insulin resistance. Some horses seem more prone to develop insulin resistance than others and factors affecting the susceptibility are age, sex, breed, and diet. In addition to insulin resistance, related diseases like obesity, laminitis, osteochondrosis and exertional rhabdomyolosis as well as the impact of training, starch digestion and preventive measures are discussed. In summary, a balanced energy intake is the most important preventive measure when it comes to insulin resistance. Effort should also be placed on improving the animals' body condition through exercise.

Introduction

Horses have gone from being wild grazing animals to being domesticated animals in the service of humans. The way we keep and feed our horses today might not be optimal given their evolutionary history of solely grazing and in order to prevent disease, finding knowledge about how the diseases develop should be the first approach. As many horses suffer from dietary illnesses it is interesting to investigate the causes and possible solutions to the problem.

Due to that horses are grazing animals and in a wild state spend approximately 65 % of a 24-hour period eating grass, their physiology is adapted to small frequent meals consisting mostly of fibers (Richards *et al.*, 2006). Many stabled horses are in addition to hay fed concentrates, often primarily consisting of different grains. In some cases, for example race horses with a high energy requirement, complementary feeding might be justified. Regardless of the work performed, grains may however not be a comparable feed to grass and their impact on the gastro intestinal tract of the horse is related to diseases including insulin resistance, which will be discussed in this review.

Amongst other components, grains contain large amounts of starch (Hoffman *et al.*, 2003; Richards *et al.*, 2006). Starches are a group of glucans built up by varying proportions of the two polysaccharides amylose and amylopectin and have the role of reserve carbohydrate in for example grains, seeds and roots (Mc Donald *et al.*, 2002). For stabled horses, the foremost source of starch comes from oats, corn and barley. Since the gastro intestinal tract of the horse is adapted to small meals, the small intestine's capability of degrading all the starch presumably decreases with increasing amount of fed grains (Richards *et al.*, 2006).

As a response to feed intake the body's insulin secretion enhances. Insulin is an anabolic pancreatic produced hormone important in regulation of fat metabolism, circulation and growth (Trieber *et al*., 2005a). Secretion of insulin is triggered by elevated glucose concentrations in the blood and by hormones produced in the intestinal tract as a response to feed intake (Sjaastad *et al*., 2003). A meal containing great amounts of sugars and starches induces and elevates the body's insulin response in order to maintain a normal blood glucose level (Trieber *et al*., 2005a) and prevent hyperglycemia (Sjaastad *et al*., 2003). Horses frequently fed meals rich in sugar and starch may have an increased risk of developing insulin resistance (Hoffman *et al*., 2003) which is considered a risk factor in several diseases, including laminitis, osteochondrosis (Trieber *et al*., 2005a), obesity (King *et al*., 2004), and exertional rhabdomyolosis (Trieber *et al*., 2006).

The diet has a great impact on an animal's wellbeing and it is therefore necessary to investigate its potential role in metabolic diseases. The main focus of this review will be placed on insulin resistance and its obvious relation to high intakes of starch and sugar, i.e. only diet- related insulin resistance will be discussed. Considering healthy horses as starting-point the risks associated with a high grain intake will be discussed, as well as the impact of training on insulin resistance. An apparently healthy and non-obese horse may also be at risk of developing insulin resistance if unnecessarily fed high amounts of grains.

Insulin resistance

Insulin resistance is a probable risk factor in metabolic diseases including obesity and laminitis, exertional rhabdomyolosis (Trieber *et al*., 2006) and osteochondrosis (Trieber *et al*., 2005a). Insulin resistance was defined by Kahn (1978) as a condition where no normal biological response follows a normal secretion of insulin. According to Kahn insulin resistance can occur at three different locations; before, after or at the cell's insulin receptor. Alterations of the insulin concentration prior to the cell receptor may be due to an increased binding of insulin to anti-insulin antibodies or, leading to lower amounts of circulating free insulin. Errors at the insulin receptor or signaling failure across the cell membrane are other possibilities (Kronfeld *et al*., 2005). A decreased response in insulin sensitive cells, i. e cells in liver, muscle and adipose tissue (Trieber *et al*., 2005a), gives an altered signaling in normally unaffected tissues leading to hyperinsulinemia (Trieber *et al*., 2006).

The glycaemic index (GI) of a carbohydrate explains what kind of an influence a specific amount of the carbohydrate has on the postprandial blood glucose value, in comparison to a standard amount of either glucose or white bread (Willet *et al*., 1981). According to Foster-Powell *et al*. (2002) food with high GI gives a greater rise in blood glucose levels and results in a greater glucose response than food with low GI. Feeds rich in non-structural carbohydrates i. e simple sugars, starch and fructan (Longland and Byrd, 2006) might therefore induce a greater insulin secretion in the horse. In a study carried out by Trieber *et al.* (2005a) Thoroughbred weanlings given feed rich in non-structural carbohydrates secreted more insulin in compensation for decreased insulin sensitivity. The insensitivity to insulin was probably a result of developing insulin resistance. Because grains due to large amounts of starch have a high GI they seem to induce a larger insulin response in the horse than do fiber-rich feed containing of smaller amounts of starch. Increased insulin responses could be the factor triggering insulin resistance.

Other feedstuffs might be able to lower the starch and sugar- induced glycaemic and insulinaemic response if fed in addition to the feed rich in starch and sugar. Unfortunately, the effect of feeding fibre in addition to a diet rich in starch had a low impact on the insulinaemic and glycaemic responses when examined on healthy horses by Vervuert *et al*. (2005). The responses registered after intake of fibre in addition to starch were not significantly lower than after a meal consisting of only starch. Further studies are needed to demonstrate if other feeds have positive impacts on the insulinaemic and glycaemic responses when fed in addition to sugar- and starch-rich meals.

Model used for determination of insulin sensitivity

Several methods, both specific and unspecific, are used to determine the sensitivity to insulin in horses. The Minimal Model is used in several studies to estimate the dynamics of insulin and glucose and to determine the acute insulin response to glucose, the insulin sensitivity, and glucose effectiveness (Trieber *et al*., 2005a; Hoffman *et al*., 2003). Using a computer program called MinMod and samples from an intravenous glucose tolerance a pattern of the plasma insulin is achieved. The Minimal Model can therefore estimate the insulin sensitivity of an individual (Bergman *et al*., 1987). With the Minimal Model it is also possible to identify insulin insensitive animals in need of specific treatment (Trieber *et al*., 2005b) which makes it a suitable model considering insulin resistance.

The impact of training on insulin resistance

Exercise probably has a favorable impact on the sensitivity to insulin (Hoffman *et al*., 2003). Hypothetically, exercise improves the sensitivity to insulin in several ways including increased glucose uptake in muscle cells and depletion of glucose stored as glycogen in liver and muscle. An increase in insulin binding to the insulin receptor on the cell surface may also be an explanation to improved sensitivity induced by exercise (Powell *et al*., 2002).

Geor *et al*. (2002) examined the effects of moderate-intensity exercise in Standardbred and Thoroughbred horses. The results of the study indicate that 6 weeks of training decreases the glucose flow during sub-maximal exercise. According to the authors, the decreased glucose flux may be explained by altered concentrations of glucoregulatory hormones including insulin, glucagon, norepinephrine and epinephrine. The lowered glucose flow during exercise could have a small positive impact when trying to reduce the development of insulin resistance. The results are supported by another study performed by Powell *et al*. (2002). A 48 % increase in insulin sensitivity was demonstrated in lean mares of various breeds exposed to short-term low intensity exercise. In the same study, obese insulin resistant mares improved their insulin sensitivity with 60 % performing the same work. The impact of training on insulin resistance is according to the study substantial, but important to note is that the favorable effects of exercise were no longer apparent 9 days after the training was completed. In summary, exercise on daily basis is (in addition to a balanced diet) probably the most efficient way to reduce the risk of developing insulin resistance in healthy horses and to improve insulin sensitivity in obese and insulin resistant horses.

Starch digestion

Grains contain large amounts of starch (Hoffman *et al*., 2003; Richards *et al*., 2006) and the ability of the horse to digest starches in the small intestine is limited (Jose-Cunilleras *et al*., 2005).

Excess intakes of grain may not only give rise to insulin resistance. In a study carried out by Richards *et al.*, (2006) large intakes of cereal grains affect the rest of the gastro intestinal tract negatively and alter the environment in the hindgut. The small intestine may not enzymatically degrade all the starch which therefore is fermented in the hindgut. The rapid fermentation of starch in the large intestine leads to a lower pH, and in some cases acidosis, due to an increased production of volatile fatty acids by the micro-organisms. An upset gut has been considered a predisposition to laminitis (Trieber *et al.*, 2006).

A greater usage of processed grains may reduce the risk of rapid fermentation of starch in the hindgut because it increases the absorbing capacity of the small intestine (Richards *et al.*, 2006). Regardless of botanical origin, the digestion of the starch in the small intestine is increased if processed with thermal or hydrothermal methods. Water in combination with heat biochemically modifies starch leading to a crystallization of the starch granules. The reaction is irreversible and results in a gel more susceptible to enzymes in the gastro intestinal tract (Juilland *et al.*, 2006).

Diseases related to insulin resistance

Insulin resistance is associated with several diseases; obesity, laminitis, osteochondrosis and exertional rhabdomyolosis being the most prominent (Trieber *et al.*, 2006).

Obesity

According to a study at the Swedish University of Agriculture, 30 % of the Swedish riding horses might be obese (Personal communication, Jansson, Department of Animal Nutrition and Management). Since obesity is related to increased insulin insensitivity these horses may also have, or be in at risk of developing, insulin resistance. Obese horses with insulin resistance have to rely on higher glucose effectiveness for glucose disposal than do lean healthy horses (Hoffman *et al.*, 2003).

Glucose and insulin metabolism is altered by several factors, including obesity and fitness level. Depending on the diet to which an animal has adapted the insulin and glucose responses may differ (Ralston, 2002) and the sensitivity to insulin seems to decrease when feeding horses a diet rich in non-structural carbohydrates (Hoffman *et al.*, 2003). Obese and insulin resistant horses have higher concentrations of resting insulin than do lean horses (Frank *et al.*, 2006) and the higher concentrations might be due to an increased insulin secretion in order to compensate for the insulin insensitivity. Less calories and more exercise is an adequate way to prevent obesity and indirectly, insulin resistance (King *et al.*, 2004; Trieber *et al.*, 2006).

Laminitis

Insulin resistance is considered a predisposition to laminitis (Trieber *et al.*, 2006) because of the fact that healthy ponies are more sensitive to insulin than laminitic ponies or ponies with a history of laminitis (Coffman and Colles, 1983). Laminitis is a hoof failure caused by separation of the laminae from the inner hoof wall. Due to the separation of the laminae, the pedal bone detaches from the hoof wall sometimes leading to irreversible hoof damage (Trieber *et al.*, 2005b). Laminitis is in addition to large intakes of starch and sugar associated with horses eating lush pastures. The insulin resistance coupled laminitis might be elicited by a lack of energy in the hoof cells due to the insulin's inability to induce uptake of glucose normally providing the hoof with energy (Longland and Byrd, 2006).

Hypothetically, laminitis could possibly be prevented in several ways, for example soaking hay rich in excess water-soluble carbohydrates (Watts, 2004) or feeding forages low in rapidly fermentable materials (Harris *et al.*, 2006). It is recommended to do an analysis of the fed hay in order to determine the content of the starch, fructan and sugar (Longland and Byrd, 2006). Restricted grazing is also favorable at times when the pasture consists of higher amounts of fructans and sugars i.e. at times when the pasture is growing or is exposed to cold or draught stress (Watts, 2004).

Osteochondrisis

Osteochondrosis is a cartilage developmental disorder affecting young, rapidly growing horses. Altered levels of plasma insulin-like growth factor (IGF-1) seem to affect the processes related to the development of osteochondrosis (Wittwer *et al.*, 2006). Trieber *et al.* (2005a) registered higher concentrations of IGF-1 in Thoroughbred weanlings adapted to high glycaemic meals, which suggests that the risk of developing osteochondrosis is increased in young horses fed with excess amounts of grains. According to a study by Wittwer *et al.* (2006) mares were more prone to develop osteochondrosis but no significant interactions were found between sex and age.

Body weight is a factor probably influencing the development of osteochondrosis in horses that are bred to become tall and muscular, i. e big horses (Wittwer *et al.*, 2006). Because obesity and insulin resistance are interrelated (King *et al.*, 2004), smaller horses with high body weight due to obesity may also have an increased risk of developing osteochondrosis.

Breeds more prone to develop insulin resistance

Considering all different horse breeds it may be of interest to investigate if some breeds or animals at different ages are more prone to developing insulin resistance. There are also differences between ponies and horses that could matter.

Small differences between breeds could be the reason for some animals being more prone to developing insulin resistance. Trieber *et* al. (2005a) suggested that ponies might develop insulin resistance easier when adapting to feeds rich in starch because they have evolved in nutritionally penurious environments. That theory is however not supported by a study made by June *et al.* (1992), where glucose tolerance tests where performed on horses, ponies and donkeys. No differences in plasma glucose values were registered between horses and ponies 6 hours after an oral glucose administration, meaning both horses and ponies had reached the initial glucose values before 6 hours (the donkeys on the other hand still remained higher after six hours). Schmidt (1994) achieved the same results when comparing 5 Shetland ponies to 4 Standardbred horses; no significant differences were found between breeds. Interesting however is the fact that the ponies in the study had lower basal blood insulin concentration and also had lower blood glucose elimination than did the horses.

Ponies that have previously suffered from laminitis seem to be more intolerant to an oral glucose administration than healthy ponies and Standardbreds (Jeffcott *et al.*, 1986) and are in addition less sensitive to insulin (Coffman and Colles, 1983).

Effect of age on insulin resistance sensitivity

Regardless of breed, horses and ponies may not be equally sensitive in different stages of life. Besides obesity, age and diet are factors shown to have significant effects on plasma glucose concentrations. In a study by Murphy *et al*. (1997) foals (6-9 months) in comparison to mature individuals (6-13 years) were less capable of handling an oral glucose administration with higher blood glucose concentrations as a result.

When interpreting the results from tests performed on young horses it is important to take into account the amount of stress the animal is exposed to. Other factors affecting the results independently of age is previously fed rations, exercise condition and time of day (Ralston, 2005).

Preventive measures for insulin resistance

There are several ways of preventing insulin resistance but most important is to make sure the total energy intake meets the requirements of the horse. Because of the relation between obesity and insulin resistance (King *et al*., 2004) excess feeding and lack of exercise are two major risk factors (Hoffman *et al*., 2003). Exercise probably prevents insulin resistance because it reduces body fat and has other biological effects (Harris *et al*., 2006). Avoidance of grains containing large amounts of starch or feeds rich in rapidly fermentable material should also be taken into consideration (Hoffman *et al*., 2003). To prevent the development of starch related diseases in horses it is recommended not to feed more than 0.4 kg/100 kg body weight per ration of a starch-rich feed (Planck and Rundgren, 2003).

Considering insulin resistant horses, feeding a restricted amount of feeds rich in sugar and starch is an appropriate way of preventing sickness (Kronfeld *et al*., 2005; Vervuert *et al*., 2005). Thermal heating or physical processing of grains could possibly increase the digestibility of starch and prevent an upset hindgut and acidosis in horses free from insulin resistance (Richards *et al*., 2006).

Discussion

Several factors seem to contribute to the development of insulin resistance. Age (Murphy *et al*., 1997), obesity and diet (Hoffman *et al*., 2003) can induce insulin resistance and a combination of these factors probably increases the risk. The role of genetic influence and breed is only briefly discussed in the literature but should maybe also be taken into consideration when evaluating possible causes to the development of insulin resistance.

Because obesity is related to insulin resistance (Trieber *et al*., 2006) it is of interest to investigate whether insulin resistance is a predisposition to obesity or the other way around. A horse becoming fat is more noticeable than a horse developing insulin resistance and it would therefore be easier to detect insulin resistance if the obesity came first. Frequent body condition controls could in that case be a preventive action in order to decrease the risk of developing insulin resistance. Solely checking the horses' body condition is though not enough due to the fact that other factors than obesity can induce insulin resistance.

Ponies seem more prone to develop insulin resistance (Trieber *et al*., 2005a), which could be coupled either to a lowered sensitivity to insulin due to biological factors, different feeding strategies, or less exercise. Considering ponies afflicted by insulin resistance, their current and previous training conditions are rarely discussed in the literature. Limited exercise contributes to insulin resistance (Hoffman *et al*. (2003); Powell *et al*. (2002); Geor *et al*. (2002); King (2004)) and one can speculate if ponies in general are less active than horses. The favorable impact of training on insulin resistance may not only be due to biological effects, but also to the fact that it reduces the body fat (Harris *et al*., 2006). Another speculation following this assertion is whether ponies in general are more obese than horses. A combination of obesity and lack of training in ponies could probably be a risk factor considering insulin resistance. It also seems that ponies have lower basal blood insulin concentrations than horses (Schmidt, 1994); a factor that could contribute to the lower resistance to diets rich in sugar and starch. Ponies have evolved in more penurious environments than horses, which could be the reason for the biologically lower concentrations of resting insulin (Trieber *et al*., 2005a).

Some ponies and horses on pasture seem more susceptible to developing insulin resistance than others in the same herd or of the same breed. Due to a sometimes varying exposure to the sun etc, a pasture may not have equal contents of non-structural carbohydrates everywhere. Horses have individual preferences and some horses may choose to eat grass with higher contents of non-structural carbohydrates making them more susceptible of developing both laminitis and insulin resistance. Ethological factors could possibly also increase an animal's risk of developing insulin resistance. A highly ranked animal preferring pasture rich in non-structural carbohydrates may have the ability to hustle away other individuals, being the only one eating the grass highest in fructans and sugars.

High intakes of starch do not only induce insulin resistance, but also alter the environment of the intestinal tract. Acidosis and low hindgut pH can occur and it is unclear how much the animal's performance is reduced given these conditions. After adaptation to a diet rich in starch or sugar it is likely that the intestinal environment stabilizes, making the horse's body adjust to the new diet. When stabilization has occurred the animal can either be left unaffected or get ill over time if the new intestinal environment has an unfavorable impact on the animal's wellbeing. Maybe only horses and ponies more sensitive to greater transposition of diets are affected while others due to biological factors like for example higher resting insulin concentrations handle it better.

Although horses are different there could be a specific amount of grains always giving rise to insulin resistance. According to Planck and Rundgren (2003) horses should be fed a maximum of 0.4 kg dry matter of grains/100 kg BW and ration. This means a horse with a body weight of 500 kg can handle a bit over 2 kg of grains at one ration. Although many horse owners don't feed their horses grains or other concentrates more than a few times a day, the authors fail to mention an upper limit for the amount of rations per day. Richards *et al*. (2006) investigated hindgut starch fermentation in Thoroughbred horses fed grain concentrates. On average, the horses were fed 7.3 ± 0.23 kg of grain concentrates per day. Some horses in the study were fed up to 13,2 kg of grain concentrates per day and acidosis and hindgut starch fermentation was observed in 27 % of all the animals in the survey (the frequency of insulin resistance was however not investigated). This means there probably exists an upper limit for the amount of rations per day when discussing acidosis and hindgut starch fermentation and one can assume there is also an upper limit considering insulin resistance.

Most likely a combination of several factors contributes to the development of insulin resistance. Foals seem to have a harder time eliminating glucose (Murphy *et al*., 1997) and it is not impossible that older animals also are more sensitive to large intakes of glucose or starch. In addition, foals or old animals of specific pony breeds may easier develop insulin resistance, while horses of other breeds may only be more susceptible when fed high amounts of starch, independent of age.

Some horse owners frequently spend large amounts of money on curing ill animals and an alternative to visiting the veterinary with an already ill animal is to focus on preventive actions. Poorly adapted diets may not only lower the performance and welfare in horses and ponies, it can also be considered as one of the major reasons for unhealthy animals. Insufficient knowledge, tradition or lack of interest may be possible reasons for feeding incorrectly. Fortunately, diets can be adjusted but the information regarding preventative measures seems to have a hard time reaching the public. An improvement of the information flow to horse owners could probably reduce dietary illnesses in horses substantially. Owning an animal automatically gives a responsibility and effort must therefore be placed on the animal's wellbeing and welfare. More research is also needed to be able to identify the horses or breeds extra sensitive to high intakes of starches and sugars. In case some breeds at specific ages or of a specific sex are more prone to develop insulin resistance, diets can easily be adjusted before the animal gets ill. The Minimal Model is practical when estimating an animals' sensitivity to insulin (Trieber *et al.*, 2005b) and a greater usage of the model could probably assist in the identification of individuals in the risk zone of developing insulin resistance. However, the economical aspects need to be taken into consideration too.

Conclusions

To summarize this review, more effort should be placed on preventive measures regarding insulin resistance. Preventive work could possibly lower the frequency of horses and ponies developing insulin resistance and other insulin resistance related illnesses; laminitis, and obesity naming two. Most important is to make sure the feed intake of the horse doesn't exceed its requirements of energy. As exercise has a favorable impact on the insulin sensitivity of the horse, daily training and restricted intakes of feeds rich in starch, fructans and other soluble sugars can also prevent illness. Younger horses and horses predisposed to laminitis seem to be more sensitive to glucose than horses in general, why extra precautions can be justified when these horses for example eat lush pastures.

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