INSULIN RESISTANCE IN HORSES

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Insulin is a hormone produced and stored in the pancreas and is the key modulator for the glucose homeostasis, ensuring no elevated blood glucose concentration for elongated periods.
Insulin is secreted when the glucose concentration in the blood rises. It binds to insulin receptors especially on skeletal muscle, fat and liver cells. Through this binding the cells activate a cascade of events and eventually allow glucose to stream in where it is used for energy storage and utilisation, the cells are thus insulin sensitive. The uptake of glucose in the cells allows the glucose concentration in the blood to drop to its basal level again and with this the secretion of insulin decreases as well. Even though the blood glucose concentration is the major stimulus for the secretion of insulin other physical or sensory stimuli, such as stress and with this the production of cortisol, stimulate the secretion of insulin as well. Besides the regulative function of the blood glucose concentration insulin also plays a vital role in other metabolic responses, such as the fat, protein and mineral metabolism.

Insulin Resistance

Insulin resistance is generally defined as insulin not being able to induce an adequate response in the target tissue under normal concentrations or as diminished ability of cells responding appropriately to the insulin signalling (Kahn, 1978). Cells can become insulin insensitive/resistant on the cell surface, a diminished transport capability of glucose into the cell, and/or may become ineffective, a disrupted glucose metabolism inside the cell (Kronfeld et al., 2005b). Especially liver, skeletal and adipose tissues are prone to become insulin resistant. It has been investigated that within a given tissue different degrees of insulin resistance can exist (Cusi et al., 2000).

As shown in figure 1 does a glucose challenge result in a short term increase of the blood glucose concentration, which is regulated through increased secretion of insulin, binding to cell receptors, activating glucose transporters and enabling glucose to enter the cells. The insulin will adjust to the blood glucose supply, so that glucose homeostasis in ensured. With the down regulation of glucose also secretion of insulin diminishes and clearance is promoted. In insulin resistant horses the same peak of glucose will appear. However, more insulin is secreted to induce the same regulative effect. (Sillence et al., 2007)
In the beginning phase of IR the horse compensates for this developing resistance to avoid a long term increase of the blood glucose concentration through producing and secreting more insulin, leading to pathological hyperinsulinaemia. Compensated IR thus means that the insulin level is (chronically) highly elevated, but still sufficient glucose is transported into the cells keeping the blood glucose on a normal level, often towards the higher end of the reference range (reviewed by Frank, 2009; Frank, 2010).
However, in affected horses it will take more time to lower the glucose concentration. Both high insulin and elevated glucose concentrations will thus be present for an elongated period (Eiler et al., 2005). Another factor contributing to this situation can be a reduced clearance of insulin through a compromised liver function (Frank et al, 2009).

In such a situation a horse having received a glucose challenge and being affected with IR, might even reach a state of hypoglycaemia; this because even though glucose homeostasis would be achieved, insulin would still be too high allowing too much glucose entering the cells.

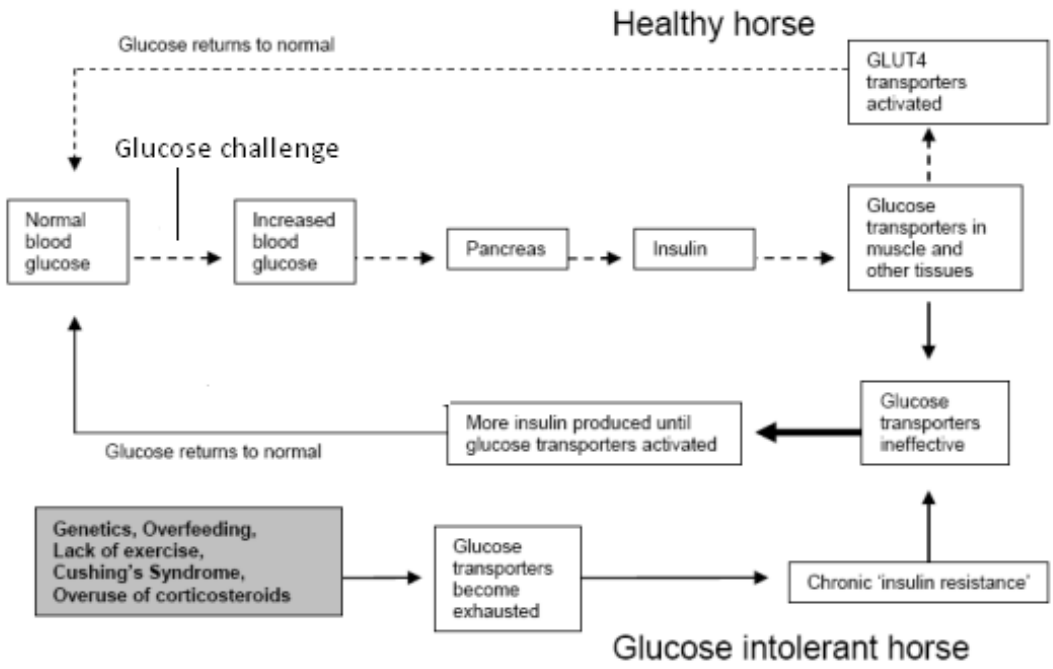

Figure 1: Course of events for healthy and glucose intolerant horses when receiving a glucose challenge. Dashed arrows represent the response of a healthy horse to an increase in blood glucose. Solid arrows represent the response of a horse or pony that is insulin resistant. (derived and adapted from Sillence et al., 2007)

On the long term however, insulin resistance may, if conditions stay unchanged, become uncompensated. This than implies that the cells become even more insensitive and insulin cannot compensate for this situation anymore and the pancreas loses its ability to produce sufficient insulin. The insulin mediated glucose cannot enter the cells and is not converted into energy anymore, leading to an elevated blood glucose and a variable insulin concentration (Frank, 2009). In this state the pancreatic function might decrease and less insulin is produced and secreted and the glucose level will increase further (Treiber et al., 2005b).

Continuous hyperglycaemia from reduced insulin secretion and/or insulin resistance is referred to as diabetes mellitus (Menzies-Gow, 2009). A considerable decrease of the pancreatic function and a highly elevated glucose level has been assumed to rarely occur in horses (Johnson et al., 2009), but diabetes type II might actually be more present in horses than previously thought (Menzies-Gow, 2009). In view of the fact that different cells might display different degrees of resistance, it is likely that while in some cells insulin still can compensate for this resistance and enabling the glucose to stream into the cells, where other cells might for the same have reached the state that insulin cannot compensate for the resistance and with that not being able to regulate the glucose metabolism anymore.

Since skeletal muscle cells make up about 80% of the stimulated glucose uptake, they are most prone of becoming insulin resistant and on the long term not being able to take up and convert glucose anymore (reviewed by Schmidt et al., 2009). An impaired uptake of glucose results in energy deficiency what than might lead to muscle tension, "unwillingness" to work lethargy and eventually to muscle mass waist. General disruption of cellular processes, intracellular disorders, and related health problems and diseases could be associated with altered glucose metabolism and thus IR (Kronfeld, 2005a). Further critical investigation is needed, but it seems to be complicated to discover the whole range of possible related effects in which IR may be involved in.
Until now the specific mechanisms of the development of insulin resistance are not fully investigated and understood. However, several factors are likely to be involved in the development of IR, such as a density reduction of insulin receptors or a malfunction of these receptors. Also internal signal pathways and a disturbed cell function in general can lead to a reduced binding of insulin and to a defective activation of glucose transporters. (Kitamura et al, 2004)
Molecular biology sciences often observe that a malfunction of receptors and especially the reduction of those receptors may build a protection of the body's system not to overload the cells with in this case glucose and run danger of cell poisoning and general damage on the short term. However, pathological hyperinsulinaemia will on the long term result in tissue and organ damage as well and might bring other indirectly related problems to the horse, often due to production of counter-regulatory hormones (reviewed by Wilcox, 2005).
When reaching the state that insulin cannot compensate for glucose intolerance anymore in the first instance both the glucose as well as the insulin level will rise leading to capillary damage as well as possible consequences for the cardiovascular system, the kidneys and damage on neurological level (reviewed by Valberg et al., 2009).

The actual onset of insulin resistance is not fully understood yet, but as Kronfeld reviewed in 2005 it is commonly agreed on that factors such as diet, activity, chronic stress, general body condition and sepsis, but also breed and genetic disposition can contribute to the development of insulin resistance. Especially modern feeding regimes, being rich in soluble carbohydrates, and too little movement/exercise often collide with the physiology of the horse, which is most likely one of the major reasons for the development of insulin resistance.
Obesity in general (Hoffman et al., 2003; Frank et al., 2006b; Vick et al., 2007; Carter et al. 2010) and local accumulation of adipose tissue especially in the neck, shoulder and tail regions (Johnson, 2002; Treiber et al., 2006) have been associated with insulin resistance. However, although obesity is a major indicator and factor for the horse becoming and being insulin resistant, also lean horses can become insulin resistant (Bailey et al., 2007). Obese horses do have considerably higher numbers of fat cells than non-obese horses. Higher numbers of adipocytes imply elevated free fatty acid (FFA) concentrations as well as elevated cytokine levels; therefore obesity nowadays is also classified as mild, but chronic inflammatory state (Das, 2001). It has been shown that high concentrations of FFA's and cytokines have a direct influence on insulin and suggestively could set of IR (Vick et al., 2007). Furthermore, Wilcox reviewed in 2005 that insulin promotes fat synthesis (lipogenesis) in adipose tissue. Besides this, it has been shown that adipocytes can become resistant to the anti-lipolytic effects of insulin and thus secreting high concentrations of FFA's into the bloodstream (DeFronzo, 2004). This thus means that in conditions of pathological hyperinsulinaemia fat synthesis is increased, FFA and cytokine concentrations become elevated and the horse will most likely gain even more weight, which both in turn increase IR and with that insulin secretion. A viscous circle has developed. On top of that comes that affected fat cells have a diminished fat storage capacity which

means that at a certain point fat will be stored visceral around the organs, exacerbating insulin resistance even more (DeFronzo, 2004).

A major focus of medical equine research currently is the relation of high insulin concentrations and pasture associated laminitis (Asplin et al., 2007; De Laat et al., 2010). In 2005 Treiber et al. described horses diagnosed being insulin resistant and with that being, under specific pasture conditions, at high risk of developing laminitis as having the pre-laminitic metabolic syndrome.
Hypertension, hypertriglyceridemia and hyperleptinemia (Bailey et al., 2008; Forhead et al., 1994; Frank et al., 2006b), but also more obvious signs such as chronic lethargy, muscle stiffness and cramping and altered reproductive cycling with a prolonged interovulatory period in mares (Vick et al. 2006) are all suggestively associated with and linked to IR. The Equine Metabolic Syndrome (EMS) (Johnson, 2002) as well as the Equine Cushing Syndrome (ECS) both are strongly related to insulin resistance.

The risk factors, short and long term consequences and symptoms of insulin resistance are thus highly diverse and very individual per affected horse, laminitis being one of the most concerning developing diseases. Since insulin is not only a fundamental hormone in the energy metabolism, but in other metabolic processes as well, pathological hyperinsulinaemia will have consequences on other processes such as the protein and mineral metabolism. On top of that are the exact mechanisms behind the onset of IR and its related symptoms still not fully understood yet.

Diagnosis

Insulin resistance in horses and the related health issues is a rather modern problem, but is becoming of increasing interest and concern for equine health (Geor, 2008). Since there is tremendous diversity of clinical signs and symptoms this health problem is until now often not very well recognized neither by veterinarians nor by horse owners and a sound and reliable diagnosis is still very complicated and complex

Clinical Signs

In advanced stages of this health problem often a visual diagnosis based on clinical signs may be sufficient. Below the most typically linked signs to insulin resistance are presented:

Body Condition Score

Since obesity is associated with insulin resistance, a general tool to assess the horses' condition is the body condition scoring (BCS) developed by Henneke et al. (1983). This scoring system can be a helpful tool to estimate the degree of general obesity, but it misses the assessment of local fat accumulation (Carter et al. 2009). It is advisable to divide the horse in several sections, assess these individually and calculating the mean of the different sections. With this division more focus can be put on local fat accumulations and more detailed body condition score can be established. Although this system is often regarded as an objective tool, in fact it is rather a subjective tool and the evaluation may strongly depend on the observers' skills and experience handling this tool. It has been suggested that when horses get scored with >6 (from a scale of 1 till 9) it can be indicated that the horse belongs to the risk group of being insulin resistant and an increased risk for laminitis (Treiber et al., 2005a).

Cresty Neck Score

Since local fat accumulations especially in the neck region are strongly associated with insulin resistance and the increased risk of laminitis (Johnson, 2002; Treiber et al., 2006, Carter et al., 2007) a more specific scoring system has currently been developed (Carter et al. 2009). This system is called cresty neck scoring (CNS). Scores have been determined from a range from 0 till 5, 0 showing no signs of fat accumulation on the neck and 5 showing obvious signs of severe fat accumulation on the neck. A score of >3 is within this scoring system described as "cresty neck" (Carter et al. 2009). In 2007 a CNS >/=3 has been associated with increased risk of laminitis and insulin resistance (Carter et al. 2007). The CNS may thus be a valuable tool to estimate local fat accumulation and could give a more substantiated estimation on local adiposity than the BCS does. However, also this scoring system is a subjective tool and the outcome strongly depends on the observers' skills and experience with this tool.

Laminitis

Hyperinsulinaemia and along going glucose intolerance have been suggested to be strongly related to pasture associated laminitis. It has been shown that high concentrations of insulin can directly cause laminitis in horses, although the hoof tissue itself is not depended on glucose uptake mediated through insulin. It is suggested that insulin toxicity is the major causative factor for this kind of laminitis. (Aspilin et al., 2007, De Laat et al., 2010)

In 2005 Treiber et al. suggested the labelling of the pre-laminitic metabolic syndrome for horses being at risk developing laminitis during specific pasture conditions. For clinical examination of horses being insulin resistant the diagnosis of pasture associated laminitis is thus a suggestive tool for horses having elevated insulin concentrations in the blood. Typical examination of laminitis will include walking on different grounds, sensitivity tests and examination of the general hoof condition (founder rings, convex sole, seedy toe, bruising).

Blood Pressure

Blood pressure measurements are not a commonly applied diagnostic tool in general in horses. However, since hypertension is associated with laminitis and IR (Bailey et al. 2008) it could be another helpful indicative measurement for the diagnosis of horses being insulin resistant or belonging to a risk group. References values are from considerable importance here, however until now only very few studies have dealt with assessing the blood pressure in horses.

Since measuring the blood pressure is a non specific tool, it could rather be supportive for clinical studies when wanting to observe and assess the effect of management adjustments such as change of diet, exercise and the application of a dietary supplement or drug.

Endocrinological Diagnosis

There are several ways to test a horse for insulin resistance, which however are until now either technically challenging and cost expensive, or not highly accurate and reliable (Firshman et al., 2007). The four most commonly applied tests are described in more detail in the following paragraphs.

For all tests applies that when testing for insulin resistance both the insulin and the glucose level need to be measured to derive accurate data (Firshman et al., 2007), measuring only one value may lead to inaccurate findings and misinterpretations.
The two most reliable, but most challenging tests are the euglycemic hyperinsulinemic clamp (EHC) test and the frequently sampled IV glucose tolerance test (FSIGT).

Euglycemic Hyperinsulinemic Clamp (EHC) test

The EHC is one of the two applied glucose clamp techniques and is accepted as the gold standard in human and equine science. The second technique is the hyperglycaemic clamp test and measures pancreatic insulin production. These glucose clamp techniques have first been developed by Andres et al. in 1966 and the EHC test has firstly been applied on horses by Elmahdi in 1998. The EHC's principle is to maintain euglycemic concentrations, to clamp glucose on a fixed level, while inducing a steady hyperinsulinemic state and observing the glucose rate required maintaining the euglycemic state. The average glucose disposal rate is calculated in the last 60 minutes of the test (DeFronzo et al., 1979). The EHC serves as a measure for insulin sensitivity of skeletal and adipose tissue. Horses being insulin resistant will thus require less glucose to maintain their euglycemic state and thus have a lower disposal rate, than horse being insulin sensitive.

For the EHC both insulin and glucose are injected intravenously and regular blood samples are drawn to administer insulin and glucose levels. This test requires special equipment, skills and staff and is therefore not commonly used in equine science yet (Kim et al., 2003). Furthermore, horses are required to retain in a clinic for at least two days. During the investigation the horses are attached to catheters for 120-180 minutes and they are fasted the night before and during the test, increasing chances of stress and with possible disturbances on the outcomes. These are all factors aggravating the application of these techniques. Since this test is not applied on a large scale, reference values are also not yet obtained in an extensive way (Kim et al., 2003; Kronfeld et al., 2005) indicating the need for further procedure standardisation to be able to apply this method more frequently in equine science (Kronfeld et al, 2005). Lacking references values is detrimental for a proper diagnosis, but for clinical studies comparing the effect of a management adjustment or a drug the EHC, even with lacking reference values, is a very valuable tool. Until now it seems that the EHC is the most accurate and reproducible test with regards to testing for insulin sensitivity (Kim et al., 2003; Pratt et al., 2005; Firshman et al., 2007). A study of Powell et al. in 2002 reviewed that an increase of the glucose disposal rate after short term exercise could very well be investigated with the EHC, but the increase was not evident in plasma glucose and insulin measurements.

Although this test is the most reliable test for testing horses for insulin resistance it is rather difficult to be used for either private horse owners or for (large scale) clinical studies yet.

Frequently Sampled IV Glucose Tolerance Test (FSIGT) - Minimal model analysis

The FSIGT and the minimal model analysis were primarily developed by Bergman et al. 1979. The FSIGT is another endocrinological test applied to test for both insulin sensitivity and pancreatic β-cell response. Being able to test for both factors gives the opportunity to differentiate between compensated and uncompensated insulin resistance.

The data obtained from the FSIGT are inserted into a software program and values for insulin sensitivity and pancreatic function are calculated. However, these calculations are partly based on assumptions of insulin and glucose kinematics and might therefore result in estimation errors (reviewed by Pratt et al., 2005). The FSIGT and minimal model analysis have successfully been applied in horses in several studies, from which Treiber et al. (2005) tried to obtain reference values for this test, but also this test requires more practical application to obtain more reliable values of healthy and affected horses (Firshman et al., 2007).

The principle of the FSIGT is that the horse is attached to a catheter and glucose is injected intravenously. After twenty minutes a small dose of insulin is injected intravenously. The glucose and insulin levels are administered via blood samples for 180 minutes in regular frequencies. The data obtained is than inserted in a specific software, which is very complex and can only be handled and interpreted by experts, making the test complicated to execute (Treiber et al., 2005b; Kronfeld et al., 2005c).

The FSIGT is technically less challenging than the EHC and has the advantage of being able to differentiate between compensated and uncompensated IR (Kronfeld et al., 2005c). However, this approach requires specific software and is based on several assumptions. Both tests lack frequent application and thus comparable data and reliable reference values. It has been shown that the outcomes of the minimal model approach are less repeatable than the EHC which makes this approach even less applicable for clinical studies (Pratt et al., 2005). No specific cost calculations have been found, but since costs are often highly related to the blood samples and the effort required it can be assumed that the costs of this diagnostic approach will be close to the costs of the EHC. Factors which make this approach rather unpractical are similar to the ones of the EHC, namely required retention in the clinic for one to two days and frequent blood sampling and eventually related stress for the horse. An advantage of the FSGIT is that no fasting is needed the night before (Firshman at al., 2007).

The two previously mentioned tests are technically challenging and not applicable for the individual horse owner. For practical reasons two common tests are often advised to be used from veterinarians to indirectly diagnose insulin resistance, namely the iv combined glucose-insulin test (CGIT) or the measurement of resting serum insulin and glucose concentrations. (Frank, 2006a)

Intravenous Combined Glucose-Insulin Test (CGIT)

The CGIT is a combination of two traditionally applied tests, the intravenous glucose tolerance test (IV GTT) and the insulin sensitivity test (IST). The combination provides the possibility to simultaneously inject glucose and insulin at the very beginning of the test and thus testing for insulin sensitivity and glucose tolerance. The CGIT has been developed by Eiler et al. in 2005.

The principle of the CGIT is that both glucose and insulin are provided intravenously at the very beginning of the test. On beforehand basal glucose and insulin samples are taken. During a timeframe of 150 minutes blood is drawn in regular frequencies, with in total 14 blood samples. In healthy horses the blood glucose, measured with a glucometer, will be below the baseline value after 45 minutes. Horses with insulin levels of >100mU/mL at 45 minutes have higher concentrations than healthy horses, showing that insulin sensitivity is compromised and/or insulin clearance is slowed down. The longer the glucose concentration stays above the baseline value concentration the more compromised the cells are for insulin sensitivity and/or compromised clearance and thus the higher the degree of insulin resistance (Eiler et al., 2005; Frank, 2006b; Frank et al., 2010).

Compared to previously named tests, the CGIT is relatively easy to perform and shows high repeatability (Eiler et al., 2005), this since it is not technically challenging and in principle executable by every veterinarian. However, also this test requires retention in a clinic and the horse is fasted during the night before. The CGIT is same as all endocrinological tests susceptible to stress and pain. Besides, also here reference values for factors such as breed and age would be beneficial. Horses might be at risk of developing hypoglycaemia during the test. This needs careful supervision, but is a relatively small risk factor. (Eiler at al., 2005)

Resting Serum Insulin and Glucose Measurements

Taking samples of both resting serum insulin and glucose concentrations to detect the possibility of IR in horses has initially been applied in the field by Kronfeld et al. (2005a) and Treiber et al. (2006a). These measurements are commonly described as a screening test (Frank, 2006a). For this test blood will be drawn after the horse has fasted for about 12 hours. Sampling the resting serum insulin and glucose concentrations turns out to be a very practicable and most commonly applied test. This because it is easy to execute (can be done at home), it is with around 100-150€ relatively cheap, it is rather stress less, easy to understand and executable by each veterinarian.

However, it is mentioned that the accuracy of this test is rather questionable (Powell et al., 2002, Treiber, 2005, 2006; Pratt et al. 2009) and that such nonspecific indicators may be non conclusive (Kronfeld et al., 2005c); this mainly because the individual basal levels can vary widely within a short period of time, glucose up to about 15% and insulin even up to 70%. Furthermore, glucose and insulin concentrations strongly depend on external factors as well, such as the time of the day, the stress level and the feeding time. In table 1 commonly applied reference values to determine IR in horses are presented.

Table 1: Reference values for insulin and glucose levels and the interpretation of the results. (GD Deventer, 2011)

Glucose level	Insulin level	Result interpretation
<5,5 mmol/L	< 10 mU/L	Insulin sensitive
	10 - 20 mU/L	Slightly elevated, possibly because of recent feeding. Repeat test.
	20 mU/L >	Compensated insulin resistance, adapting feeding regime. Repeat test after 4 weeks.
>5,5 mmol/L	< 10 of 10 - 20 mU/L	Investigating time of sampling in relation to feeding, possibly the sample has not been chilled properly
	20 mU/L >	Insulin resistance with diminished compensation

A resting insulin concentration of >20 mU/L is considered to be suggestive for IR (Frank, 2008c). However, when being in the reference values of below 20mU/L this screening test may not be appropriate for a profound diagnosis (Frank, 2006a). A horse might have IR in a mild stage and still might not show a significantly elevated resting insulin concentration, but only under a glucose challenge a disproportional increase of insulin could be observed. Besides, since the serum concentrations show a large variability it could mean that one measurement would identify the horses as being insulin resistant, whereas on another day under same circumstances the horse might fall in the reference values. A negative diagnosis with this test might thus give a wrong impression. However, if executed properly a positive test is strongly suggestive that the horse is being insulin resistant indeed. Another factor which might enhance this misinterpretation of reference values is that currently no differentiation between factors such as breed, age, nutrition and general body condition are made (Firshman et al., 2007). It has however been shown that ponies seem to be less insulin sensitive than horses and still for both the same reference values are used (Jeffcott et al., 1986, Kim et al, 2003).

Taking basal insulin and glucose measurements should thus be seen as a screening test, but not as proper diagnostic testing. However, even when using it as screening tests the testing procedure needs to be standardized to guarantee as little influence as possible. In practise however, it seems that application of this procedure is still rather diverse among veterinarians. Although certain factors can be standardized, the large variations and (unknown) factors having an influence on the outcomes make this test rather inappropriate for clinical studies, but still it is a commonly applied test. An important factor to consider is that already in 2002 in has been investigated by Powell et al. that an increase in insulin sensitivity could be detected with the EHC, but not with basal glucose and insulin measurements, which makes this method even more unattractive for clinical studies (Kronfeld et al., 2005).

It has been suggested that the mean value of three samples on three following days under the same circumstances might be comparable in its accurateness with that of the EHC (Pratt et al., 2009). However, the practicability and cost factor than become comparable with that of the EHC as well. Also so called proxies or ratios have been developed for the resting levels of glucose and insulin, although they are still applied, they might not represent high accuracy and an increasing number of veterinarians disclaims the application of such proxies/rations (Frank et al., 2008c).

So far it seems that until now there is no ideal test existing meeting both accurateness and practicability, which challenges veterinarians and practitioners in their diagnosis for insulin resistance (Valberg et al., 2009). Especially for clinical studies it is a real challenge, since very accurate, but yet practical methods are necessary.
A perfect test would need to be easy to execute and performed with a single blood sample. Besides insulin and glucose concentrations, also adipocyte, lipid and cytokine levels and liver values should be added in the diagnosis as well (Frank et al., 2010).

Treatment

Once diagnosed as being insulin resistant it becomes necessary to apply an individually balanced treatment. For so far this mainly includes adjustments of feeding and exercising regimes. The current stage of medical treatment is that until now no registered medication exists and often medical treatment for humans is applied on horses (Durham et al., 2008; Frank et al., 2008b).

Insulin Resistance and Nutrition

Since IR is strongly associated with obesity, the major goal of treating obesity related insulin resistant horses is avoidance of gaining weight, promoting losing weight and the reduction of glycaemic and insulinaemic responses to meals. The avoidance strategy includes the reduction/avoidance of feedstuff with a high glycaemic index and thus a high percentage of non-structural carbohydrates, which also includes (young) grasses (reviewed by Geor, 2010). It has been investigated that horses fed with a diet high in soluble carbohydrates, (compared to horses fed a diet supplemented with fat), show a decrease in insulin sensitivity and horses chronically adapted top sweet feed have a decreased insulin sensitivity as well. (Hoffman et al., 2003; Treiber et al. 2005a; Pratt et al. 2006; Carter et al., 2010; Stewart-Hunt et al., 2010). In general obese horses do not require any concentrated feed and should be kept on a simple, low-carbohydrate based roughage diet and eventual vitamin/mineral supplementation and thus lower the risk of becoming or exacerbating insulin resistance (Hoffman et al., 2003, Pratt et al., 2006).

Losing weight is the other important factor and it has been shown that intensive weight loss of 1% body mass per week improves insulin sensitivity (van Weyenberg et al., 2008). However, in studies investigating weight loss and the relation to insulin sensitivity the horses/ponies are fasted rather extreme, from 1% dry matter intake of the body mass down to 35% of the recommended requirements of about 1.5-2% dry matter of the horses body weight (Van Weyenberg et al., 2008, Dugdale et al., 2010). Such extreme diets have shown to be beneficial for IR horses with regards to weight loss and insulin sensitivity, but other metabolic and behavioural problems might develop through this. Furthermore, horses being deprived of feed for long periods of the day might show changes of behaviour and stress, possibly even worsening insulin resistance. Geor (2010) therefore recommends a modest diet of losing 0.7-0.8% of the initial bodyweight per week over a period of three to four months.

To be able to promote weight loss, but still fulfil the horses' physiological needs several actions are recommendable:
- restrict pasture accessthrough strip grazing or hourly grazing per day
- letting grasses flower first before the horse is allowed to graze
- use a grazing muzzle for the horse to restrict intake
- use slow feeders to slow down roughage intake
- soak hay for about 30-60 minutes in water to reduce soluble carbohydrate content
- provide roughage low in energy (NSC<10%)
- mix hay with straw to reduce and slow down intake
- provide twigs for time consumption and chewing

Insulin Resistance and Physical Activity

Besides feeding adjustments it is important to review the physical activity and whether it needs to be adjusted as well. Unfortunately until now results on the effect of physical activity on insulin sensitivity in horses are controversial (Geor, 2010). Studies in humans have shown that moderate training, for 150-200 minutes per week, significantly increases insulin sensitivity and decreases other risk factors related to IR. These studies state that through regular exercise the intracellular glucose pathways in the skeletal muscles are stimulated enabling better and more glucose uptake as well as the lipid metabolism is increased, having a direct influence on insulin resistance. (Goodyear et al., 1998, Havley, 2004; Bonen et al., 2006; Crandall et al., 2008)

In equine studies Powell et al. (2002) found that after already seven days of light training insulin sensitivity could be increased in obese horses. Steward-Hunt et al. (2010) found that during a seven week moderate training insulin sensitivity increased. However, De Graaf-Roelfsema et al. (2006) found no long term effect on insulin sensitivity after a long term trainings unit (18 weeks). In 2010 Carter et al. showed in their study that during eight weeks of moderate training no difference in insulin sensitivity between the trained and untrained horses could be found. These results thus show that it is not clear yet especially how intense a trainings regime needs to be in order to have an effect on insulin sensitivity. Differences in the research set up, use of tests, sample sizes and differently applied trainings and feeding regimes are most likely the factors for the controversial outcomes.

However, since clear positive effects have been found in humans the physiological principle stays the same. Same as for humans it is proposed that the combination of diet and activity will show the largest effects on weight loss and insulin sensitivity and more pronounced weight loss might show a more obvious effect on the training (Freestone et al., 1992; Geor, 2010; Frank et al., 2010; Carter et al., 2010). So far it is not clear what the perfect training regime would look like, especially since every horse is affected in another way and needs individual treatment. However, for now it is commonly recommended to start with 2-3 trainings sessions per week for 20-30 minutes per session. On the long term the duration and intensity should be increased. (Frank et al., 2010)

Insulin Resistance and Dietary Supplementation and Medication

Management adjustments with regards to nutrition and physical activity are certainly two important measurements to treat and control insulin resistance. However, dietary supplementation and medication might be beneficial and necessary as well. In the following paragraphs a brief overview of currently applied or potentially interesting substances is presented:

Metformin

Metformin is a medical drug originating from the French Lilac (Galega offincialis) and is used in humans for type-2 diabetes (Salpeter et al., 2006) to increase insulin sensitivity. The benefit for horses is still in discussion and contradictory results are obtained. Durnham et al. (2008) indicated in their study with 18 insulin resistant horses that insulin sensitivity increased and pancreatic β-cell secretion decreased significantly. However, Tinworth et al. (2011) did a similar study to test the effect of oral metformin application on the insulin and glucose response of six insulin resistant horses. In this study no effect on insulin sensitivity could be found. Recent studies also indicate that the bioavailability of metformin in horses is poor (Hustace et al., 2009; Tinworth et al., 2010a). It is suggested that metformin might only have an effect on obese insulin related horses for losing weight and for horses with hyperglycaemia (Tinworth et al, 2011).

Levothyroxine

Researches have shown that insulin sensitivity and disposal increase, blood lipid concentrations decrease and weight loss is promoted when healthy horses get supplied with levothyroxine (Frank et al., 2005; 2008a; 2008b). It has also been suggested that levothyroxine may have a protective effect on insulin sensitivity (Tóth et al., 2010). Although in the executed studies no adverse health effects could be detected, it is not yet scientifically proven what the long term, low dosage effects of levothyroxine on horses could be (Frank, 2009; Frank et al., 2010).

Chromium

Chromium is a widely applied element in humans with diabetes (Anderson, 1997) and is more commonly used in horses as well. It is assumed that chromium promotes increased insulin binding and receptor activation (reviewed by Firshman et al., 2007).

However, it needs to be mentioned that the European food regulation prohibits the use of isolated chromium in food and with this also in dietary supplements for horses. Still a promising pilot study in Germany has come up with indicative results that chromium might indeed have a positive effect on insulin and glucose levels in horses (Vervuert et al., 2010). Nevertheless, this study has been criticized for its set up and repetitive studies would be needed to confirm the outcomes (Geor, 2010).

Psyllium

Psyllium, which is the seed husk of *Plantago ovata*, has been proven in human studies to have a positive effect on the glucose metabolism (Sierra et al., 2001; 2002) after meals. It is suggested that the psyllium fibres slow down the nutrient absorption and have a positive effect on the micro flora and might therefore have a beneficial effect on the glucose metabolism and insulin sensitivity (Sierra et al., 2001; 2002; Ellis et al., 2005; Robertson, 2007). Moreaux et al. (2011) were able to indicate with their study similar effects on healthy, non-obese horses when fed 90-270g of psyllium on a daily basis (for 60 days). The horses showed lower glucose and insulin concentrations after the meals and lower glucose peaks during the meals as well.

Psyllium thus could indeed be from beneficial potential for insulin resistant horses, but further research is required in this field with larger sample sizes and especially with affected horses (Moreaux et al., 2011)

Short-chain Fructo-Oligosaccharides (scFOS)

Short-chain fructo-oligosaccharides are so called prebiotics from which studies have shown that they beneficially change or activate a change of composition and activity in the intestinal micro flora of horses (Respondek et al., 2007, 2008a). Due to this modulating effect it has been proposed that scFOS might have a positive effect on insulin sensitivity (Robertson, 2007, Respondek, 2008b). In 2011 Respondek et al., investigated the effect of scFOS on eight obese horses. The study indicated that moderate increase of insulin sensitivity and a reduction of an acute insulin response to glucose as well as a lowering of plasma insulin concentrations could be observed through the supplementation of scFOS. However, mechanisms behind the improvement of insulin sensitivity have not been clear and more knowledge is needed to more specifically investigate the mechanisms (Respondek et al., 2011). More extensive research is necessary to further investigate and confirm the potential positive of scFOS on obese, insulin resistant horses.

Herbal Agents

In 2010 a number of herbs being from potential benefit for horses with insulin resistance have been identified and classified into six sub groups in relation to their effect (see table 2). These identified agents now need to be applied in scientific research to be able to measure the potential clinical effects and safety. (Tinworth et al., 2010)

Table 2: Summary of herbal agents as candidates for research to address insulin resistance in the horse (Tinworth et al., 2010)

Activators of the peroxisome proliferator-activated receptors	-Panax (ginseng, japoncicus, quinquefolius, eleutherococcus, Asian ginseng, Radix ginseng) -Linum usitatissimum (Flaxseed)
Anti-obesity compounds	-Glycine max (Soy Protein) -Citrus paradisi (Grapefruit) -Beta vulgaris (Beet or Beetroot) -Garcinia cambogia (Brindleberry, Brindall Berry or Malabar Tamarind)
Anti-oxidants	-Vitex agnus-castus (Chaste tree, Chasteberry, Monks Pepper) -Silibum marianum (Milk Thistle, St. Mary's Thistle) -Ipomoea batatas (Caiapo) -Curcumin
Compounds that slow carbohydrate absorption	-Trigonella foenum-graecum (Fenugreek) -Aloe vera (Aloes, Aloe vera Leaf Gel, Aloe Juice, Aloe Sap) -Amorphophallus konjac (Konjak, Konnyaku, Konjaku, Devil's Tongue, Voodoo Lily, Snake Palm or Elephant Yam) -Opuntia fuliginosa and streptacantha (Prickly Pear Cactus; Nopal)
Insulin receptor activators	-Cinnamomum cassia (Chinese Cinnamon or Cinnamomum aromaticum) -Grifola frondosa (Maitake, Sheep's Head, Ram's Head or Hen of the Woods)
Stimulators of glucose uptake	-Berberine -Mormordica charantia (Bitter Melon, Bitter Gourd) -Corosolic Acid (Glucosol, Banaba) -Pterocarpus marsupium (Indian Kino Tree)

Since the symptoms of horses being insulin resistant are very diverse and individual also the treatment needs to be very individual and what works out for one horse might not at all work out for another horse. Therefore whether the insulin resistant horse is treated with the help of management adjustments or certain drugs or supplements, or a combination of this, it is important to administer the horses' condition to be able to see whether the specific treatment actually has a positive effect on the individual horse nor not.

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