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Review

Glucose homeostasis and the enteroinsular axis in the horse: A possible role in equine metabolic syndrome

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ABSTRACT

One of the principal components of equine metabolic syndrome (EMS) is hyperinsulinaemia combined with insulin resistance. It has long been known that hyperinsulinaemia occurs after the development of insulin resistance. But it is also known that hyperinsulinaemia itself can induce insulin resistance and obesity and might play a key role in the development of metabolic syndrome. This review focuses on the physiology of glucose and insulin metabolism and the pathophysiological mechanisms in glucose homeostasis in the horse (compared with what is already known in humans) in order to gain insight into the pathophysiological principles underlying EMS. The review summarizes new insights on the oral uptake of glucose by the gut and the enteroinsular axis, the role of diet in incretin hormone and postprandial insulin responses, the handling of glucose by the liver, muscle and fat tissue, and the production and secretion of insulin by the pancreas under healthy and disrupted glucose homeostatic conditions in horses.

Introduction

The three principal components of the equine metabolic syndrome (EMS) are obesity, hyperinsulinaemia and insulin resistance (IR), which together increase the risk of laminitis in horses (Frank et al., 2010). Evaluation of glucose homeostasis and insulin sensitivity is an essential aid in diagnosing EMS (Frank et al., 2010), while reducing glucose intolerance and IR is an important therapeutic goal to prevent the development of laminitis. Hyperinsulinaemia is widely viewed as representing compensation for systemic IR, but there is evidence that hyperinsulinaemia itself may cause obesity and IR (Mehran et al., 2012). Both relationships should be further studied in horses with EMS.

Several reviews exist on the available tests for measuring glucose homeostasis in horses and humans (Ralston, 2002; Kronfeld et al., 2005; Firshman and Valberg, 2007; Muniyappa et al., 2008). New tests are under development to find more appropriate or more practical tests (Eiler et al., 2005; Bertin and Sojka-Kritchevsky, 2013), and research towards good therapeutic interventions is growing (Chameroy et al., 2011; Respondek et al., 2011; McGowan et al., 2013). Interpretation of tests and therapeutics is based on knowledge of glucose homeostasis in the species studied. This review focuses on glucose homeostasis in the horse compared with what is already known in humans. It also discusses possible directions for future research into the pathophysiological mechanisms and possibilities for therapeutic interventions in horses with EMS.

Glucose homeostasis

Plasma glucose concentration is normally tightly controlled between 3.3 and 5 mmol/L in horses (Ralston, 2002). Following glucose absorption, plasma glucose levels increase and stimulate insulin secretion by the pancreas. Both hyperglycaemia and hyperinsulinaemia suppress hepatic glucose production and stimulate glucose uptake in the liver, fat and muscle to restore normoglycaemia. The route of entry into the body determines tissue distribution of glucose. For instance, oral intake of glucose in humans leads to 30–40% uptake by the liver while intravenous (IV) administration leads to only 10–15% uptake (Abdul-Ghani et al., 2006). In the post-absorptive state or after fasting, insulin levels are low and most glucose uptake occurs in insulin-insensitive tissues; this uptake is matched mainly by endogenous glucose production by the liver and to a smaller extent by the kidney (Stumvoll et al., 1997).

Oral glucose uptake

Absorption of D-glucose in the small intestine in the horse occurs via two types of insulin-independent glucose carriers, namely, SGLT1 (Na^+/glucose cotransporter 1) on the luminal membrane and the facilitated glucose transporter (GLUT)2 on the basolateral

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membrane (Dyer et al., 2009; Shirazi-Beechey et al., 2011). Sodium must be available in the intestinal lumen for enteral glucose absorption via SGLT1.

The major site of glucose absorption in horses maintained on conventional pasture forage diets is in the proximal to mid small intestine (Dyer et al., 2002; Shirazi-Beechey, 2008). Equine intestinal SGLT1 expression is enhanced with time in response to increased dietary hydrolysable carbohydrate in first the proximal and then the distal small intestine. (Shirazi-Beechey, 2008; Dyer et al., 2009). A similar increased expression occurs for GLUT2 on the basolateral membrane in the intestine of horses maintained on concentrate diets (Salmon et al., 2002; Dyer et al., 2009) indicating a coordinated enhancement of rate of glucose transport in equine intestine from lumen into the blood in response to increase in carbohydrates in the diet (Dyer et al., 2009).

Oral glucose absorption is partly regulated by the enteroinsular axis which consists of neuronal as well as hormonal factors (Marks et al., 1991). Lumenal glucose above a threshold triggers a signalling pathway in endocrine cells involving activation of the gut sweet receptor (a heteromeric combination of taste receptor 1 family subunits: T1R2 + T1R3). This receptor functions in association with α-gustducin and other signalling elements to cause secretion of gastrointestinal hormones, so-called incretins (INtestine seCRETion INsulin; Zunz and La Barre, 1929), which are synthesized in endocrine cells of the gastrointestinal tract and released upon the stimulus of food absorption (Shirazi-Beechey et al., 2011; Daly et al., 2012).

Incretins promote the release of insulin under hyperglycaemic conditions (Marks et al., 1991) and explain why insulin secretion after oral glucose intake is higher than after an isoglycaemic IV glucose load (Dühlmeier et al., 2001). Only two gut hormones, glucose-dependent insulinotropic polypeptide (GIP) (formerly known as gastric inhibitory polypeptide) and glucagon-like peptide (GLP)-1, have been shown to act as physiological incretins in humans (Yabe and Seino, 2011). Another glucagon-like peptide, GLP-2, does not increase insulin secretion but modulates intestinal growth, blood flow and expression of SGLT1 in several species (Shirazi-Beechey et al., 2011).

The receptor for GLP-2 resides in enteric neurons and not in any surface epithelial cells, suggesting that the enteric nervous system is involved in SGLT1 up-regulation. In neurons in horse intestine, GIP as well as GLP-2, T1R2 and T1R3 mRNA and protein are expressed (Shirazi-Beechey et al., 2011; Daly et al., 2012). The presence of these hormones and receptors in the horse intestine suggests the presence of an enteroinsular axis. Schmidt et al. (2001) and Dühlmeier et al. (2001) confirmed functionality of the enteroinsular axis by measuring GIP concentrations in ponies under different circumstances during oral glucose tolerance tests (GTTs). To the author's knowledge no studies are available on GLP-1 in horses.

Incretins in humans

In humans, GIP is secreted by K cells of the upper small intestine (Inagaki et al., 1989) while GLP-1 is produced from proglucagon and secreted by L cells mostly of the lower small intestine and colon (Bell et al., 1983). Secreted incretins undergo rapid degradation catalysed by dipeptidyl peptidase-4 and are thereby inactivated and excreted by the kidney (Yabe and Seino, 2011). Half-lives of approximately 5 and 2 min have been reported for intact GIP and intact GLP-1, respectively, in humans (Deacon et al., 1995; Meier et al., 2004; Vilsbøll et al., 2006).

Human GLP-1 and GIP account for approximately 50–60% of insulin secretion during a meal (Nauck et al., 1986). The insulinotropic effects of GLP-1 and GIP are exerted via receptors expressed on pancreatic α- and β-cells. Activation of incretin receptors increases c-AMP levels and insulin secretion in a glucose-dependent manner (Kazakos, 2011). The incretins, GIP and GLP-1 also exert non-insulinotropic actions on the pancreas such as controlling β-cell proliferation and survival (Schou et al., 2005; Yabe and Seino, 2011) and GIP also plays an important role in fat metabolism. It has been postulated that GIP might function as an obesity-promoting hormone (Marks, 1988; Vilsbøll et al., 2003), an hypothesis supported by obese healthy subjects showing increased fasting levels of GIP and increased early phase GIP response towards a meal compared with lean healthy subjects (Vilsbøll et al., 2003). Additionally, GIP-receptor knock-out mice gained less weight on a high-fat diet than normal mice (Miyawaki et al., 2002).

Several studies in type 2 diabetes mellitus (DM) patients have shown that impaired function of the enteroinsular axis contributes to the inadequate insulin secretion. These include defects in the secretion and action of GLP-1 and GIP (Nauck et al., 1986; Miyawaki et al., 1999; Toft-Nielsen et al., 2001; Vilsbøll et al., 2001; Schou et al., 2005). Administration of pure GLP-1 to type 2 DM patients lowers glucose levels (fasting and postprandial; Nauck et al., 1993) which has led to GLP-1-based anti-diabetic medications such as GLP-1R agonists and DPP-4 inhibitors with beneficial effects (Rizzo et al., 2009; Kazakos, 2011).

Incretins in horses

Only a few publications exist on the enteroinsular axis in equines. The incretin, GIP has been reported to be involved in glucose as well as fat absorption in horses (Dühlmeier et al., 2001; Schmidt et al., 2001). Dühlmeier et al. (2001) showed increased plasma concentrations of GIP in ponies and horses during an oral GTT but an IV GTT did not increase GIP levels. Peak GIP concentration was found 150 min after oral glucose administration together with the plasma glucose peak (Dühlmeier et al., 2001). One pony showed exaggerated responses during the IV GTT and oral GTT indicative of IR. GIP levels in this pony were almost three times higher compared with the other ponies and horses (Dühlmeier et al., 2001).

Adaptation to a fat-enriched diet seems to be a potent inducer of GIP secretion in ponies, rats and humans (Morgan et al., 1988; Gniuli et al., 2010). In rats, a high-fat diet for 60 days induced proliferation of K cells and overexpression of GIP and insulin after oral GTT at several time points (Gniuli et al., 2010). Feeding Shetland ponies an energetically adequate fat-based diet for 5 weeks induced higher plasma GIP concentrations after oral glucose administration than the respective carbohydrate-based diet for 5 weeks (Schmidt et al., 2001). Feeding the same ponies a hypercaloric fat diet for 5 weeks significantly increased insulin response, combined with decreased glucose tolerance, and showed a trend towards an increase in GIP levels after oral GTT compared with a hypercaloric carbohydrate diet. This increase of GIP might represent a stimulus for insulin hypersecretion and IR, ultimately resulting in a derangement of glucose metabolism and diabetes development associated with obesity and fatty diets (Gniuli et al., 2010).

Horses appear to adapt to a diet rich in starch and sugar by increasing first phase insulin response and consequently produce a moderated glucose response to an oral GTT (Nielsen et al., 2010). Hoffman et al. (2003b) found a lower glucose response combined with more rapid glucose clearance during an oral GTT in horses accustomed to twice daily grain meals rich in sugar and starch compared with mares adapted to a diet high in fibre and fat that resembles the more natural diet of wild horses. The insulin peak after glucose loading in the mares fed sugar and starch was earlier (30 vs. 60 min), suggesting a more developed enteroinsulin