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Fuel for Felines: Cats and Carbohydrates

Margarethe Hoenig, Dr.med.vet., PhD
University of Illinois
College of Veterinary Medicine
Department of Veterinary Clinical Medicine
Urbana, IL
Email: mhoenig@illinois.edu

Introduction

The physiology of cats regarding the metabolism of carbohydrates is similar in many respects to that of other mammals, but with key differences. Cats are obligatory carnivores and, as such, their natural diet consists primarily of fat and protein, and a small amount of carbohydrate. A bird or a mouse consists of approximately equal amounts of fat and protein and <5% carbohydrates. Commercial diets, however, contain on average 33% carbohydrates in dry food and 15% carbohydrates in canned food (Forrester D, et al. Consensus Statement. ACVIM. 2011). Cats have alterations in their metabolism that may lead one to conclude that they are ill-equipped to deal with dietary carbohydrates. It is for those reasons that it has long been discussed in the lay and scientific literature that carbohydrates cause obesity and diabetes mellitus. The premise is that high-carbohydrate intake drives overproduction of insulin resulting in excess fat deposition and obesity. High-carbohydrate intake has also been blamed for inducing chronic hyperglycemia, which increases demand on the beta cells to secrete insulin and leads to beta cell failure and diabetes. In this review, we will examine the validity of those statements in cats by focusing on physiologic mechanisms involved in carbohydrate use.

Glossary of Abbreviations

GK: Glucokinase
GLUT5: Glucose Transporter 5
IVGTT: Intravenous Glucose Tolerance Test
SGLT1: Sodium-Glucose Transporter 1

1. Physiology of Tasting, Digestion and Absorption of Carbohydrates

Sweet taste receptors in most mammals are heteromers consisting of T1R2 and T1R3 proteins. In cats, T1R3 is an expressed and likely functional receptor, whereas T1R2 is an unexpressed pseudogene. Because cats lack functional sweet receptors, they are neither attracted to nor show avoidance to the taste of sweet carbohydrates and high-intensity sweeteners, such as saccharin and cyclamate, and they avoid stimuli that taste bitter or sour to humans.[1]

Cats also lack salivary amylase, the enzyme involved in the initial digestion of starch. However, the effect of this is not known because amylase is also found in feline pancreas and chyme.[2] Compared to dogs, the activity of intestinal disaccharidases, such as sucrose and maltase, is lower in cats, whereas lactase activity is lower in some parts of the feline small intestine and much higher than in dogs in others.[3] Despite these differences, cats are capable of digesting cooked starch and various carbohydrates with an apparent digestibility of >94% in one study[4] and 89 to 100% in another.[5]

In the intestine, the sugars glucose and galactose, products of dissaccharidase digestion, are absorbed into enterocytes by Na+/Glucose Co-Transporter 1 (SGLT1) against an electrochemical gradient, whereas fructose is absorbed by facilitated diffusion by glucose transporter 5 (GLUT5). All are extruded into blood by GLUT2, a high-Km, low-affinity glucose transporter with characteristics similar to the GLUT2 in liver, pancreas and kidney. Many species can upregulate the capacity of the intestine to absorb glucose in response to high concentrations of dietary carbohydrate.[3,6-9]

It was shown in a study by Buddington and co-workers[6] that cats are unable to upregulate intestinal sugar absorption. However, these studies need to be evaluated with caution because the number of animals used was small (two and three per group on a high-protein and high-carbohydrate diet, respectively) and the cats were only 3 months old. Batchelor and co-workers showed that cats express SGLT1, and they suggested that the level of SGLT1 was sufficient for absorbing the carbohydrate content of their natural diet.[3] They also showed that the sweet receptor subunit T1R2 was not expressed in the feline intestine, limiting the capacity to upregulate the transport of sugars with increased intake.

While they concluded that this inability to upregulate the intestinal capacity to transport glucose suggests that high-carbohydrate diets are unsuitable for cats, they did not document that cats cannot upregulate glucose transport. What they did show is that the V_{max} of cats is about 50% that of dogs. However, the affinity for glucose is higher. It is impossible to deduce from this or other studies which concentration of sugars must be present in the lumen of the small intestine after the ingestion of carbohydrate-containing diets to exceed V_{max}, and whether such concentration would be reached with commercially available diets. Currently, there is no information on this topic, to my knowledge.

2. Physiology of Glucose Phosphorylation: Cats Lack Glucokinase

Glucokinase, the high-capacity, low-affinity glucose-phosphorylating enzyme, which has a Km for glucose of approximately 10 mmol/L, is present in brain, liver, beta cells, and the intestinal tract in humans and most other vertebrates. This enzyme is also called the glucosensor in beta cells and the brain because it is the rate-limiting enzyme for insulin and neurotransmitter release.[10,11] Cats do not have glucokinase, however, the activity of other hexokinases, which have a higher affinity for glucose than glucokinase, and other enzymes within the glycolytic pathway is upregulated.[12-14]

Regarding insulin secretion, a lack of beta cell glucokinase would be similar to maturity onset diabetes of the young type 2 (MODY2) in people, which is characterized by mild to severe hyperglycemia, depending on the mutation of the GK gene.[15] Healthy cats, however, do not show persistent hyperglycemia. In fact, cats have fasting glucose concentrations that are not different from those of humans or other mammals, and they are able to respond very rapidly to an IV or oral glucose bolus with insulin release.[16,17]

Phenotypically, there is great similarity in the insulin response of cats compared to other species, including the insulin secretion pattern. It has been suggested that glucose clearance seems to be delayed in cats compared to dogs,[18] based on two studies where a high dose of glucose (1 g/kg body weight) was administered during an intravenous glucose tolerance test (IVGTT) and a return to baseline was seen at 60 minutes in dogs[19] and at 90 minutes in cats.[16] The response to lower glucose dosages, however, appears similar among cats, dogs and humans,[16,20,21] although it has been shown in one study using a glucose dose of 500 mg/kg that baseline levels were not reached at 60 minutes. The variation in glucose values in that study were large during the last hour of testing and ranged from severe hypo- (12 mg/dl) to hyperglycemic values (223 mg/dl).[22] It is quite possible that in cats the high-dose IVGTT leads to attenuation of insulin-receptor kinase activity and signaling pathways involved in insulin-mediated glucose uptake leading to a delay in glucose clearance.[23,24] However, because glucose disposal is not only a function of insulin secretion and insulin-dependent glucose uptake but also includes glucose uptake by insulin-independent means and elimination through the kidney, other mechanisms may contribute to the slower clearance at high-glucose concentrations.

Insulin concentrations should not be compared among cats and other species in a quantitative way because of the lack of a feline-specific insulin assay. Based on the qualitative insulin response pattern to a glucose stimulus, it appears that cats compensate well for the lack of glucokinase. We also can assume that the lack of hepatic glucokinase is compensated by the upregulation of other hexokinases, as it has been shown that hyperglycemia is also the clinical sign for animals with isolated hepatic glucokinase deficiency,[25] and is, in part, due to impaired hepatic glycogen synthesis.[26] It has been documented that liver glycogen content in cats is similar to that of humans[27] and except for glucokinase, a deficiency of the other hexokinases that are responsible for the bulk of peripheral glucose uptake, has not been described.

The study by Curry and co-workers[28] is frequently cited as documentation that the beta cell response of cats differs from that of other species and that insulin release is higher with amino acids than with glucose. However, results from that study show that following a low dose of glucose, insulin secretion is higher during the first phase, whereas the second phase is equally stimulated by amino acids or low-dose glucose. Although the authors concluded that amino acids are more potent insulin secretagogues in the cat compared to other species, such a conclusion is confounded by the use of different concentrations and the nonuse of amino acids without glucose in the perfusion medium. Furthermore, no attempt was made to establish a dose-response relationship for the amino acid or glucose effect.

3. Physiology of Glucose Metabolism: Cats Can Adapt to Different Macronutrients

The notion that cats are unable to adjust their metabolism and are always gluconeogenic is based primarily on the results from a study by Rogers, et al. (1977) in which three cats fed a low- or high-protein diet lacked the ability to adapt levels of enzymes regulating amino acid catabolism, gluconeogenesis and ureagenesis.[29] Another study also showed that the gluconeogenic capacity of cats on a high-protein diet was already high in the fed state and no further increase was seen during fasting; however, in the same study, it was shown that cats have metabolic flexibility, because similar to omnivorous animals when fed a diet with higher carbohydrate content, they increased gluconeogenesis when fasted.

A further indication that cats can adjust their metabolic fluxes was the fact that cats on a high-carbohydrate diet have higher glycogen deposits and lower phosphoenolpyruvate kinase activity than those on a high-protein diet.[30] Results from other studies also support the notion that cats can adapt to variations in macronutrients in the diet. In several studies, it was shown that cats can adapt to increased protein by increasing amino acid oxidation and the activation of related enzymes;[31-33] other investigators have shown that cats can adapt to varying dietary fat concentrations.[34]

In our laboratory, we also have documented that cats show metabolic flexibility and increase glucose oxidation, glycogenesis and lipogenesis.[35] In lean male cats, the respiratory exchange ratio increased to >1 during a euglycemic hyperinsulinemic clamp indicating that these cats can replete their glycogen and lipid stores in response to insulin. In a recent study from our laboratory, we showed a difference between hepatic glucose fluxes when measured in the fasted and postprandial states, although little

effect of different diets was seen, likely because their differences in macronutrient composition were not large.[27] We also showed that the magnitude of postprandial gluconeogenesis and glycogenolysis in cats is not different from that seen in people. Six hours after food intake, glycogenolysis in cats contributed about 45% to total glucose production and about 55% to gluconeogenesis; in people, after intake of a 1000 Kcal meal, almost identical values were seen at approximately the same postprandial period,[36] demonstrating the importance of gluconeogenesis even in the postprandial state of omnivorous humans.

4. Physiology Meets Pathology?

Few studies of insulin and glucose concentrations after a meal have been conducted. Unfortunately, the majority have not been performed in a blinded fashion and may therefore be subject to bias. For obvious reasons, including differences in ingredients and manufacturing, as well as amounts of Kcal (i.e., the percentage of the daily food requirement), it is difficult to compare dietary studies. In one study, different amounts of starch led to dose-dependent increases in glucose levels, yet even with the highest amount of starch (34% dry matter) glucose concentrations remained well within the normal glucose concentrations range of cats.[37] Similarly, when different carbohydrate sources were examined, glucose concentrations remained in the low range of normal.[5] Even with extremely high levels of dietary carbohydrates, the majority of the glucose concentrations during a 24-hour observation period were well within the normal glucose range in lean cats.[38]

A recent publication showed that cats stay well within the normal glucose range during a 24-hour period.[39] Unfortunately, many times, any increase in postprandial glucose is incorrectly called hyperglycemia even when glucose concentrations never exceed the normal range. It appears unlikely and has not been shown that such normal glucose concentrations would have detrimental effects even long term. It is known that even in MODY2 patients with mild hyperglycemia, long-term glucose control remains stable for many years. Deteriorations were only seen when those patients gained excessive weight.[40]

Feeding studies often require animals to eat a calculated amount of food, which frequently is different than their maintenance requirement, within a short period of time and after a long fasting period. This is dissimilar from the normal eating behavior of a cat, and, therefore, results may not reflect what might be seen naturally. To overcome this potential pitfall, cats were monitored for several days with a continuous glucose monitoring system. It was documented that there was little daily variation in glucose concentration and that lean as well as obese cats, except for one obese diabetic cat, stayed well within the lower half of the normal glucose range after intake of a dry commercial diet with a carbohydrate content of 47% dry matter.[39]

Studies examining whether increasing dietary carbohydrate leads to higher postprandial insulin secretion have not shown consistent results. It has been speculated that a higher, long-term insulin secretion rate would lead to insulin resistance. It is questionable whether insulin concentrations elicited by glucose concentrations within the normal range would have long-term detrimental effects. It also has not been documented that diets with higher carbohydrate content lead to a change in insulin sensitivity.[27, 41]

Learning Points

The major culprit of the development of obesity and diabetes is likely not the carbohydrate content of the diet but rather the amount that the cats are fed. In a recent unpublished study, we found that the large majority of already obese and even diabetic cats still had unlimited access to food. This implies that the greatest need is for improved client education. This is especially important in view of the findings, which indicate that initially, with increasing obesity, cats increase their metabolic rate, but the rate becomes slower when body weight gain is >60% and/or obesity exists longer term.[42]

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