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Effects of insulin on glucolipid metabolism in fish

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Abstract:Carbohydrate is an important and cheap energy substance in fish feed. Adding a proper amount of carbohydrate into the feed can reduce the consumption of protein by fish and generate the "protein saving effect".However, due to the limited utilization ability of sugars in fish, fish are "born with diabetes constitution". Inappropriate intake of sugars will disturb the normal glucolipid metabolism of fish and affect the growth and development of fish.In this background, this review to integrate the current research about fish glucolipid metabolic response to carbohydrates , by studying the effects of carbohydrates to insulin to explain the regulation of glucolipid metabolism pathways from the perspective of molecular mechanism.

Key word:fish;glucolipid metabolism;Carbohydrate insulin

1.Introduction

It is well known that fish than mammals need more energy to break down protein and lipid [1], because of its rich protein metabolism ability, but for sugars and other carbohydrates limited digestion and the decomposition ability, fish have high degree of dependence on a high-protein diet [2], however as the global protein is in short supply, the price is rising, besides, protein diet also caused environmental pollution, aquaculture therefore has to explore the possibilities of carbohydrates diet in fish [3].

Carbohydrate is an important and cheap energy substance in fish feed. Adding a proper amount of carbohydrate into the feed can reduce the consumption of protein in fish.Studies have shown that In rohu (Labeo rohita)[4],Hybrid tilapia(Oreochromis niloticus)[5],carbohydrate has a significant effect on protein conservation.Moreover, compared with the fish lacking carbohydrate in the feed, the feed utilization rate and protein retention rate of rainbow trout (Oncorhynchus mykiss), eels (Anguilla anguilla)[6]were improved after carbohydrate addition in the feed.In addition, proper addition of carbohydrate can also reduce nitrogen excretion in fish to a certain extent, which is of positive significance for pollution prevention and control of aquaculture water and environmental protection.

But there are also studies show that fish intake of carbohydrate, usually causes fatty deposits in the fish liver, mesenteric arteries, and muscles [7], these can lead to fatty toxicity and liver damage, with high oxidative stress and inflammation, and alter the normal glucolipid metabolism in fish.Studies have shown that high levels of dietary carbohydrates lead to enlarged livers and increased levels of glycogen in rainbow trout[8-11]、 Furuichi and Yone et al. have also shown that the growth and feed efficiency of red sea bream, Xenocypris davidi and carp are inhibited when fed with high-carbohydrate diets [12].In general, herbivorous and omnivorous fish have higher carbohydrate tolerance than carnivorous fish.Thus, although carbohydrates have partially replaced expensive proteins in aquaculture, the metabolic disorders they cause should not be overlooked.Under such conditions, it is of scientific research and practical significance to integrate the current studies on the response of fish glycolipids metabolism to carbohydrate and explain the relevant regulatory issues from the perspective of molecular mechanism, so as to enrich the theoretical study of fish

glycolipids metabolism and improve the practical application of fish nutritional requirements.

2. glucolipid metabolic pathways

Glucose and other carbohydrate consumed by fish produce ATP through the glycolytic pathway, the tricarboxylic acid cycle and respiratory chain metabolism under aerobic conditions, or decompose through the pentose phosphate pathway to produce NADPH for lipid biosynthesis.

Excess carbohydrate can be stored as glycogen or converted into lipids [13].

In the metabolism of fat, triglycerides produce acetyl-COA through catabolism. Acetyl-coa can enter the Krebs cycle for energy metabolism, and can also be synthesized into ketones in the liver and used in the brain and other tissues.Glycolysis and lipid metabolism are closely linked by glycolysis and lipid synthesis and are correlated with acetyl-COA and NADPH.

Dietary supplementation with high carbohydrate content may cause fat accumulation, insulin resistance, and the increased expression of lipogenesis，gluconeogenesis，β-oxidation and other related genesis[14].Studies have shown that carbohydrate can be transformed into fat cells in the livers of fish such as rainbow trout [15-16] ,and the activity of glucose 6 phosphate dehydrogenase (G6P-DH) in fish liver was increased after feeding with high carbohydrate,content,feed conversion rate is more than 100% fat [17-19], besides,the liver G6P-DH and PK activity of carnivorous fish such as perch and rainbow trout increased after high carbohydrate intake [20],these all suggest fish feeding high carbohydrate feed may enhance lipid synthesis activity[21].And it was found that fish with high fat synthesis ability made better use of carbohydrates [15].However, some researchers believe that fish bodies have a poor ability to synthesize fat by using carbohydrates [22]， studies on Atlantic cod （Gadus Morhua） [23] found that only 0.3% of glucose was converted into liver fat after injection.

Glucose metabolism and lipid metabolism are closely linked through glycolysis and lipid synthesis, and glucolipid metabolic pathways are regulated by hormones such as insulin .

The structure of insulin gene mainly includes 3 exons and 2 introns.At present, insulin genes have been found in a variety of fish, most of which, such as rainbow trout, have two insulin genes [28], while only one exists in largemouth bass （Micropterus Salmoides)[24].There are only two insulin receptor subtypes in most fish [25], while there are four IR subtypes (IR1, IR2, IR3 and IR4) in rainbow trout [26].

Insulin has long been recognized as a major inducer of glycolysis and lipogenic gene transcription [23]. When glucose levels in fish plasma are elevated, beta cells in the pancreas secrete insulin to maintain homeostasis of carbohydrates and lipids.After liver cells absorb glucose, they convert it into glycogen. When liver glycogen content reaches saturation (generally 5% of liver weight), the excess glucose is converted into fatty acids and further esterified to produce triglyceride (TG), which is transported to adipose tissue in the form of very low density lipoprotein (VLDL).

In liver tissue,insulin lowers glucose levels by reducing liver gluconeogenesis and glycogen decomposition, accelerates glucose uptake in adipose tissue and skeletal muscle tissue, regulates glucose homeostasis, and prevents excess glucose from being converted into lipid deposition [27].

Mammalian studies have shown that insulin can stimulate the synthesis of fatty acids and triglycerides, improve the deposition of liver triglycerides, and inhibit fatty acid β-oxidation [28].However, there is still a lack of research on the effect of insulin on glucolipid metabolism in fish,limited research pointed out that similar to mammals, the pancreas is also the main production and secretion site of insulin in fish. In addition, insulin is produced in other sites including brain and adipose tissue[29].In general, fish plasma insulin concentrations of 1 ~ 30 ng/mL, , the insulin level in fish is comparable to or even higher than that of mammals [30].

Insulin is a key hormone in the dynamic balance of blood glucose. Intraperitoneal injection of insulin upregulates the liver activity of glycogen synthase (GSase) and glycogen phosphorylase (GPase), leading to glycolysis and glycogen deposition enhancement in rainbow trout[31].In addition to rainbow trout, exogenous insulin also significantly affected the glucose metabolism of megalobrama amblycephala. Insulin injection significantly reduced blood glucose levels,

but activated AMPK, thereby promoting glucose transport, glucose and fat generation, and inhibiting gluconeogenesis and fatty acid oxidation [32].Some studies have added that insulin stimulates the rate of fat generation in fish, mainly in salmon [33].

In addition,Insulin-like Growth factor 1 (IGF-1), is a kind of polypeptide protein molecular structure similar to insulin, fish IGF - I and insulin in promoting growth and enhance the capability of metabolic role than mammals have more overlapping [23,25], studies have found rainbow trout after feeding high carbohydrate feed, in addition to increased insulin and insulin receptor, IGF - I receptor number increases.In experiments [30], (Dicentrarchus Labrax were fed with feeds with different sugar levels. With the increase of feed carbohydrate level, the plasma insulin content increased, while the IGF-1 content did not change significantly.

3.Insulin responds to carbohydrate

The absorption of carbohydrates in the feed lead to a change in glucose concentration, but it is also accompanied by a change in insulin concentration.Studies have found that the plasma insulin level of fish can be regulated by exogenous nutrients, and the carbohydrate in the diet, including glucose, fructose and starch, can promote the secretion of insulin by the pancreas of fish, thereby causing the increase of plasma insulin level [7].

Glucose itself does not stimulate insulin secretion and must be metabolized to produce ATP to function.The glucose transporter 2(GLUT2) transports glucose into islet B cells, where it produces ATP through glycolysis or the tricarboxylic acid cycle in mitochondria.The increase of ATP, especially the ATP/ADP ratio, can cause the closure of ATP-sensitive potassium channels on The B cell membrane, the decrease of potassium outflow, and the hyperpolarization of the B cell membrane, leading to the activation of all L-type calcium channels controlled by the voltage gate, the influx of calcium ions, and the increase of intracellular calcium ion concentration, which can induce the release of insulin [33].

Compared with mammals, fish have a lower tolerance to glucose, insulin secretion response to blood carbohydrate is slower than mammals.The plasma insulin level of fish reaches its highest level 2 ~ 3 h after glucose uptake [27-28].

Integrating the current studies on the response of insulin to glucose, it is found that there are still differences in the rules of insulin secretion in fish: some reports have reported that the plasma insulin content of fish increases after oral glucose [34].Research has shown that a diet rich in carbohydrate can induce insulin secretion in fish such as rainbow trout, insulin secretion and insulin receptor number after the feed intake of glucose were increased [30-31], studies on pompanos （Trachinotus ovatus）, Cobia（Rachycentron canadum）, and Nile tilapia（Oreochromis niloticus）also showed that with the increase of feed glucose level, insulin secretion could be promoted to some extent [35].However it has been reported that the insulin content of fish decreased in the first few hours after glucose intake. For example, some studies found that the insulin secretion of fish rainbow trout was not related to the sugar content in the feed [32], and the insulin content of rainbow trout was not increased but decreased after feeding high carbohydrate level feed [33]， It has also been reported that insulin content increased but secretion lagged after glucose intake in fish [36].Other studies have suggested that plasma glucose concentration has a weak induction effect on insulin secretion in fish [37].When glucose tolerance test was conducted on Chinook salmon(Oncorhynchus tshawytscha）, it was found that there was no significant relationship between glucose tolerance curve and insulin level [38].

In addition to the above conditions, it was also found in the experiment of Wuchang bream（Megalobrama amblycephala Yih）hat the transcription levels of insulin and insulin receptor increased after high-carbohydrate feeding, but the transcription levels of insulin receptor substrates decreased [35].Moreover, Cai found that high-carbohydrate diets also significantly increased the expression of insulin receptor IR2 in the liver of grass carp. Ablett et al. [36] also found that high-carbohydrate diets could cause an increase in the number of insulin receptors in liver cells of rainbow trout fed with different carbohydrate content diets.

In terms of glucose injection in vitro, studies have shown that insulin in fish plasma is induced by intraperitoneal and intravenous glucose injection [37]. For example, after glucose injection in Red seabream（Pagrus major）， Chinook salmon(Oncorhynchus tshawytscha)[38]， Tilapia, plasma insulin levels gradually increased.Interestingly, plasma

insulin levels were found to be in direct proportion to dietary lipid content when fed to Chinook salmon namely lipid components in the diet could positively affect plasma insulin levels [39].However, Hemre et al. suggested that amino acids such as arginine could stimulate insulin secretion more effectively [40].Therefore, the relationship between plasma insulin level and fish blood glucose needs further study.

In addition to glucose, fructose disrupts insulin sensitivity by interfering with gluconeogenesis and glycogenolysis [41].Fructose metabolism enters the liver without insulin regulation, and is converted into free fatty acid (FFA), triglyceride (TG), and increases the content of very low density lipoprotein (VLDL).Although fructose itself does not increase blood glucose, it has a certain effect on fat metabolism. If too much fructose is eaten, it will also reduce insulin sensitivity, thus causing metabolic disorders.High fructose in the feed can lead to hypertriglyceridemia and insulin resistance, and in zebrafish, fructose can cause lipid accumulation, inflammation and oxidative stress in the liver of the juvenile fish.

Fructose is partially converted to glucose in the liver, which enters the blood and causes a slight increase in blood glucose and insulin levels [41].Recent studies have shown that high-fructose diet is an important risk factor for insulin resistance [42].A study found that after long-term intake of a large amount of fructose, insulin resistance was caused by transhipment inhibiting the expression of response factors TIR2 and T1R3.In vitro experiments showed that high dose of fructose could stimulate insulin secretion of islet B cells and enhance the effect of glucose on insulin secretion , but adding fructose into rainbow trout feed could not improve the utilization rate of glucose in the feed.Besides, KUHRE et al. [43] reported that fructose may affect the secretion of insulin by stimulating the secretion of glucagon-like peptide-1 (GLP-1) in the small intestine.

In addition, compared with mammals, galactose has been found to have a stronger stimulation effect on insulin secretion than glucose in studies on Channel catfish（Ictalurus punctatus）, but this kind of carbohydrate has a very weak effect on mice [44].Moreover , nonmetabolic glucose analogue 2- deoxyribose is effective in promoting insulin secretion in catfish, but completely ineffective in mammals [45].Unfortunately, this huge difference in insulin response between fish and mammals has not been properly explained.

4.Conclusion

So far, there have been many studies on the response of lipid metabolism to sugars in mammals, while the relevant studies in fish are relatively limited.The explanation for the low utilization capacity of carbohydrate in fish has not been unified, and the relevant regulatory mechanism is still unclear.Therefore, to deepen the research on the response of fish glycolipid metabolism to carbohydrate is the key to making better use of carbohydrate to address the protein shortage, and will therefore be the focus of further research.

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