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Research progress of insulin resistance in alcoholic liver disease

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Abstract: Alcoholic liver disease (ALD) is a liver disease caused by long-term heavydrinking, but its pathogenesis is relatively complex, among which Insulin resistance(IR) is closely related to the formation of ALD. In this paper, the epidemiological status of ALD at home and abroad and the research progress of insulin resistance in alcoholic liver were reviewed from the relationship between ALD and IR.

Key words: Alcoholic fatty liver, Insulin resistance, insulin signaling pathway

1. Overview of alcoholic liver disease and insulin resistance

Ethyl alcohol (molecular formula CH3CH2) is the main component of ethyl alcohol. It is soluble with water in any proportion. After entering the human body, ethanol quickly enters the blood circulation through biofilm and is quickly metabolized and utilized by various tissues and organs, 90% of which is oxidized in the liver [1]. Some people who are long-term alcoholics have serious liver damage. The consumption of ethanol has a certain relationship with the severity of liver damage. Excessive drinking will lead to the occurrence of Alcoholic liver disease (ALD). In China, although viral hepatitis accounts for the majority of patients with liver diseases, the incidence of ALD is also increasing with the change of dietary structure [2], making the study on the prevention and treatment of ALD an important topic. In the process of ALD, starting from alcoholic fatty liver, due to adipocyte degeneration, it can gradually evolve into alcoholic hepatitis, liver fibrosis, cirrhosis, and hepatocellular carcinoma, which is difficult to reverse and has high morbidity and mortality [3].The pathogenesis of ALD is complex and not yet fully understood. Current studies have shown that after drinking, genetic factors, nutritional conditions, alcohol metabolism, oxidative stress, cytokines and other factors play a key role in the pathogenesis [4].Previous studies have shown that adipogenesis is a risk factor for the development of cirrhosis in the early stages of ALD.Intervention of early ALD with drugs or treatment has attracted extensive attention in the field of treatment and improvement of ALD.

Insulin resistance (IR), which is the pathological basis of a series of glucose and lipid metabolic diseases, refers to the decrease of Insulin utilization rate and sensitivity of the body to Insulin caused by various reasons. Current studies believe that the main cause of insulin resistance is the increase of inflammatory cytokines, which interfere with the phosphorylation of a series of receptors in insulin signal transduction and block a series of cascade amplification reactions activated by downstream signals, thus affecting physiological functions such as insulin generation and transport and causing IR[5].Several studies have shown that insulin signal activation may be positive antagonism ALD important endogenous protective mechanism of insulin signal regulation function obstacle is the most typical performance IR, IR can cause a variety of tissues and organs, including liver, a variety of REDOX metabolic abnormalities, it's in the occurrence and development of ALD has played an important role in [6, 7].By summarizing the mechanism of alcohol-mediated hepatic insulin resistance, this paper will discuss the role of impaired insulin signal transduction in the pathogenesis of ALD, and provide a reasonable reference for the prevention and treatment of alcohol-induced liver injury in the future.

2. The mechanism of insulin resistance in ALD

2.1 Alcohol and PI3K

Alcohol has multiple effects on hepatic insulin, and long-term alcohol feeding has been shown to reduce insulin receptor binding capacity. In De la Monte et al. ‘s experiment, using competitive saturation analysis, insulin receptor binding was reduced in rats fed an alcohol diet compared to a control group [8].Insulin acts on target tissues by binding to the insulin receptor and stimulating the phosphorylation of the receptor itself, thus recruiting and activating the insulin receptor substrate protein 1/2 (IRS1/2).IRS1/2 can activate phosphatidylinositol-3-kinase (PI3K) to convert phosphatidylinositol 4, 5-diphosphate (PIP2) into phosphatidylinositol 3,4, 5-triphosphate (PIP3), and continue to transmit signals downstream [9].Through experiments on the effects of alcohol on effectors PI3K, PIP2 and PIP3 [10], it was found that the data obtained were mixed, which may be related to the difference of animal model and alcohol concentration. Alcohol can not only upregulate phosphatase and tensin homologue (PTEN), but also inhibit the effect of PI3K.Low doses of alcohol can also increase the activity of PI3K by down-regulating the P55γ subunit post-transcriptional, thus increasing insulin sensitivity.PI3K is composed of two subunits, p85 and p110, of which p85 anchors and binds, while p110 plays a key regulatory role. Activated IRS-1 binds to p85 to activate the p110 subunit, and p110 phosphorylates phosphatidlinositol (PIP3) to transmit signals downwards.Akt is activated by 3-phosphate-dependent protein kinase (PDK) [11].Although it has been clear that alcohol can have a certain effect on PI3K, the role of its subunit is still not clear. Perhaps the regulation of its subunit on glucose and lipid metabolism can become a new target for the treatment of ALD.

2.2 Alcohol and Akt and their downstream targets

PIP3 is activated by phosphorylated protein kinase B (Akt) in muscle and adipose tissue and transmits signals downstream. Insulin-mediated Akt activation in the liver has several roles: Inactivation of transcription factor FoxO1 inhibits partial gluconeogenesis, activation of transcription factor sterol regulatory element binding protein-1 (SREBP-1) promotes the production of genes related to fatty acid synthesis, and phosphorylation of glycogen synthase kinase-3 (GSK-3) stimulates the production of glycogen [12].Phosphorylation of Akt is the center of typical insulin signal transduction. Long-term consumption of alcoholic diet resulted in decreased phosphorylation of Akt at Thr308, increased phosphorylation at Ser473, and increased cytoplasmic Akt content. The increase of TRB3, a negative regulator of Akt, was induced in the liver of alcohol-fed rats. Alcohol can induce TRB3 and Akt to bind to the original structure and organize its plasma membrane association, leading to the inhibitory effect of insulin signal [13].Alcohol also has effects on several target proteins of Akt, namely FoxO1, GSK and SREBP-1. Alcohol feeding can increase the FoxO1 mRNA and protein as well as its phosphorylation. Activation of FoxO1 promotes the transformation of hepatic stellate cells to collagenous myofiber cells and causes liver fibrosis, which has a certain connection with the development of ALD.GSK inhibits glycogen synthesis through phosphorylation, insulin inhibits GSK activation through phosphorylation of Akt to promote glycogen synthesis, and ethanol can increase GSK levels through reactive oxygen species and glucocorticoid receptor signaling pathways [14,15].SREBP-1 plays an important role in regulating the transcription of genes related to liver adipogenesis. As described in Liu’s article [16], ethanol directly up-regulates the expression of SREBP-1 through its metabolite acetaldehyde, and indirectly up-regulates the expression of SREBP-1 by activating the endoplasmal reticulum stress response, enteric lipopolysaccharide and downstream proteins of SREBP-1.Elevated expression levels increased triglyceride accumulation in the blood and fat production in the liver, leading to the progression of ALD.

2.3 Alcohol and adipokines

Adipokine is a hormone derived from white adipose tissue, regulating blood glucose, blood lipid and energy homeostasis. Leptin and adiponectin are two major adipokines, which can promote insulin sensitivity and are related to a variety of liver diseases [17], including the pathogenesis of ALD. Leptin levels were positively correlated to the fat

quality and regulate food intake and energy expenditure, long-term edible alcohol feed mice prone to lard type hepatitis, and reduces the quality of white adipose tissue and decrease the blood thin element level, if taking exogenous leptin can improve fatty hepatitis [18], prompt leptin levels may be associated with development of ALD. Adiponectin is an adipocytokine secreted by adipocytes, which is closely related to the regulation of lipid metabolism in the liver, and also has anti-inflammatory and insulin sensitivity functions. Studies have shown that the decrease of adiponectin in the circulatory system is closely related to insulin resistance. Insulin resistant animals can be reversed after a period of adiponectin treatment, and it also has the effect of inhibiting inflammation. The promotion of insulin sensitivity by adiponectin may be closely related to the enhancement of free fatty acid oxidation by adenylate activated protein kinase (AMPK) and peroxisome proliferator-activated receptor (PPARα) pathways. Adiponectin can also inhibit the production of tumor necrosis factor (TNF-α) by immune cells in the liver, and can directly antagonize TNF-α.More and more experiments have shown that during the pathological process of ALD, adiponectin production obstacle exists in adipose tissue and adiponectin receptor expression decrease in surrounding tissue [19].

2.4 Alcohol and other substances

Bioactive lipids may also play an important role in the IR of ALD. Diacylglycerol (DAG) and ceramide are two major lipid metabolites, among which DAG can induce IR by inhibiting the activation of IRS1/2 and Akt, while ethanol and metabolite acetaldehyde can increase DGA level [9,20], and ceramide can inhibit the transport and activation of Akt. Akt dephosphorylation was also significantly increased in alcohol-fed mice, and drug reduction improved steatosis, glucose intolerance, and insulin sensitivity [21].In addition, changes in circulatory cytokines and metabolites of intestinal dysregulation may be related to IR of ALD. Studies have shown that the intestinal permeability of patients with ALD is increased and the recovery rate is higher after oral polyethylene glycol [22].There is indirect evidence that long-term alcohol consumption can alter intestinal flora, and such changes may have systemic effects on glucose and fat homeostasis [23].Future studies can be combined with in vivo metabolic phenotypes, metabolomics and microbiome studies to clarify the specific relationship between intestinal flora and glucose and lipid metabolism in patients with ALD.

3.Summary and outlook

ALD is a disease with high morbidity and mortality. At present, little is known about the factors that promote the disease progression.IR is common in patients with ALD and increases the risk of advanced disease. In ALD patients, there are a variety of IR mechanisms that may lead to accelerated progression of the disease, including insulin signal transduction pathway and indirect influence on target protein, adipokines and fat mediators, thereby damaging signal transduction. Many experiments have shown that targeted insulin signal pathway can improve the disease pharmacologically. Therefore, the clinical application of insulin sensitizer and ALD is of great significance. In the current studies, a number of experiments have been conducted to regulate IR in ALD from the microRNA level, such as miR-378, miR-192, and miR27a, etc. [24]. In future studies, glycolipid metabolism and the biological and environmental factors that play a role in ALD can be further discussed. To find new therapeutic targets and provide a new basis for therapeutic methods and drug interventions.

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