**Review**

**The Effects of BCAAs on Insulin Resistance in Athletes**

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(Received March 19, 2019)

**Summary** The toxic catabolic intermediates of branched chain amino acids can cause insulin resistance, and are involved in different mechanisms in different metabolic tissues. In skeletal muscle, 3-hydroxy-isobutyrate produced by valine promotes skeletal muscle fatty acid uptake, resulting in the accumulation of incompletely oxidized lipids in skeletal muscle, causing skeletal muscle insulin resistance. In the liver, branched-chain α-keto acids decompose in large amounts, promote hepatic gluconeogenesis, and lead to the accumulation of multiple acylcarnitines, which damages the mitochondrial tricarboxylic acid cycle, resulting in the accumulation of incomplete oxidation products, oxidative stress in mitochondria, and hepatic insulin resistance. In adipose tissue, the expression of branched-chain amino acid catabolic enzymes (branched-chain amino acid transaminase, branched-chain α-keto acid dehydrogenase) is reduced, resulting in an increased level of plasma branched-chain amino acids, thereby causing massive decomposition of branched-chain amino acids in tissues such as skeletal muscle and liver, and inducing insulin resistance. However, branched-chain amino acids, as a common nutritional supplement for athletes, do not induce insulin resistance. A possible explanation for this phenomenon is that exercise can enhance the mitochondrial oxidative potential of branched-chain amino acids, alleviate or even eliminate the accumulation of branched-chain amino acid catabolic intermediates, and promotes branched-chain amino acids catabolism into beta-aminoisobutyric acid, increasing plasma beta-aminoisobutyric acid concentration, improving insulin resistance. This article reveals the mechanism of BCAA-induced insulin resistance and the relationship between exercise and BCAAs metabolism, adds a guarantee for the use of BCAAs, and provides a new explanation for the occurrence of diabetes and how exercise improves diabetes.

**Key Words** exercise, athletes metabolism, liver, skeletal muscle, adipose, beta-aminoisobutyric acid

Branched-chain amino acids (BCAAs) include leucine, isoleucine, and valine. BCAAs are important for maintaining body function. They promote glucose uptake and skeletal muscle protein synthesis (1) and can also be oxidized to provide energy (2). In addition, BCAAs are essential amino acids, so people need to obtain BCAAs from food to meet the needs of the body. Type 2 diabetes (T2D), with its high morbidity and mortality, is developing rapidly worldwide and is becoming a significant health problem (3). However, recent studies have noted that there is a close relationship between BCAAs and insulin resistance, and increased levels of BCAAs may cause insulin resistance (4). However, the mechanism is not clearly defined.

Because BCAAs can promote glucose uptake, skeletal muscle protein synthesis, and provide energy, BCAAs have become a very important nutritional supplement for athletes and are widely used, but there have been no reports of BCAAs increasing athletes’ risk of insulin resistance. BCAAs induce insulin resistance, but long-term use of BCAAs by athletes does not increase the risk of insulin resistance. Why is this happening? We have conducted in-depth research on this topic. This article reveals the mechanism of BCAA-induced insulin resistance and the relationship between exercise and BCAAs metabolism, adds a guarantee for the use of BCAAs, and provides a new explanation for the occurrence of diabetes and how exercise improves diabetes.

1. **The Catabolic Pathway of BCAAs**

The catabolism of BCAAs involves two important steps (5). The first step is the transamination of BCAAs with α-ketoglutaric acid by the branched-chain amino acid transaminase (BCAT) encoded by the BCAT2 gene, thereby causing the BCAAs to lose their amino groups to form the corresponding branched-chain α-keto acids (BCKAs) (5), while α-ketoglutaric acid binds to the amino groups to form glutamic acid. Due to the high activity in skeletal muscle (6), this step is mainly carried out in skeletal muscle, which can produce a large number of BCKAs. The BCKAs can enter the following catabolism. Studies have shown that the absence of BCAT can inhibit the production of BCAA catabolic products in peripheral tissues (5).

In the second step, BCKAs are decomposed by a
branched-chain α-ketoacid dehydrogenase complex (BCKDC) to form a variety of branched acyl-CoAs (CoA), such as acetocetyl-CoA, acetyl-CoA, and propionyl-CoA. Due to the high activity of BCKDC in the liver (6), this step is mainly carried out in the liver, which decomposes a large number of BCKAs. The acyl-CoA can be further metabolized by a plurality of mitochondrial matrix enzymatic reactions to produce fatty acids and gluconeogenesis substrates in the liver or enter the tricarboxylic acid cycle for complete oxidative decomposition. In addition, acyl-CoA can also be converted to various acylcarnitines (5). When acyl-CoA is produced in large amounts and exceeds the mitochondrial oxidative potential, it results in the accumulation of acylcarnitines.

2. BCAAs and Insulin Resistance

BCAAs are closely related to insulin resistance. Plasma levels of BCAAs are positively correlated with insulin resistance (7). Increased plasma BCAA levels can lead to insulin resistance and type 2 diabetes (4). Moreover, diabetic animals also have high plasma levels of BCAAs (5). In addition, insulin resistance was also observed in some peripheral tissues. Studies have shown that the skeletal muscle insulin signaling pathway is inhibited in BCAA-fed obese rats, and skeletal muscle insulin resistance is also enhanced (8). After adding BCAAs to muscle cells, Akt phosphorylation levels were also reduced, and glucose uptake was reduced (9), causing skeletal muscle insulin resistance. Moreover, elevated plasma BCAA levels can also inhibit hepatic insulin signaling pathways and induce hepatic insulin resistance (8, 10). These data indicate that BCAAs promote insulin resistance.

However, studies have shown that supplementation with BCAAs enhances glucose metabolism in skeletal muscle, adipose tissue, and liver. Insulin sensitivity was improved in mice treated with leucine and isoleucine on a high-fat diet (11). In addition, oral BCAA supplements can also reduce blood glucose in patients with chronic liver disease (12) and improve insulin resistance (13). The above effects of BCAAs appear to be contradictory, but they are not, related to plasma BCAA concentration. Studies have shown that an increase in plasma leucine concentration of approximately 30% (14) can enhance glucose metabolism in skeletal muscle, adipose tissue, and liver (1). However, when the plasma leucine/isoleucine concentration is increased by 80–150%, it can inhibit tissue glucose uptake and induce insulin resistance (15). The reason for this phenomenon needs to be explained in terms of the mechanism by which BCAAs induce insulin resistance.

3. Mechanisms by Which BCAAs Promote Insulin Resistance

There are currently two model mechanisms that explain how BCAAs induce insulin resistance (5). One is the mTORC1 signaling pathway model: it is thought that BCAAs can cause insulin resistance by activating the mTORC1 complex. However, many recent studies have shown that BCAAs-activated mTORC1 may not be sufficient to trigger insulin resistance (5).

The second mechanism is the metabolic disorder model: it postulates that BCAAs are not the direct cause of insulin resistance but that insulin resistance is caused by toxic metabolic intermediates produced by BCAA catabolic disorders, which can impair cell function and induce insulin resistance. This model is currently highly accepted. Studies have shown that toxic intermediates produced by BCAA catabolic disorders (especially isoleucine and valine) promote atherosclerosis and induce type 2 diabetes (16). BCKAs are the product of the first catabolism of BCAAs, which can lead to mitochondrial dysfunction and induce insulin resistance (5). The addition of BCKAs to glial cells or the cerebral cortex can lead to mitochondrial oxidative stress and mitochondrial dysfunction, and induce insulin resistance (17). Although the plasma BCAA levels of BCAT knockout mice (inhibiting BCKA production) were elevated, their blood glucose levels and insulin sensitivity were significantly improved (18). These data suggest that BCAAs do not directly induce insulin resistance but that insulin resistance is caused by their catabolic products. However, it does not indicate that BCKAs are the direct cause of insulin resistance, as there are further levels of catabolism in BCKAs. In addition, in the metabolic disorder model of BCAAs, BCAAs exhibit different mechanisms in different peripheral tissues.

3.1. Skeletal muscle

As mentioned above, although skeletal muscle can decompose BCAAs, the expression of BCKDH in skeletal muscle is very low, so it is difficult for skeletal muscle to decompose BCKAs as the liver dose. This does not mean that increased BCAA catabolism in skeletal muscle does not cause mitochondrial lipid overload (10). Studies have demonstrated increased skeletal muscle acylcarnitine levels in BCAA-induced insulin resistant individuals (19), which means that skeletal muscle has a mechanism different from that in the liver. However, insulin resistance induced by BCAAs in skeletal muscle is still caused by metabolic intermediates.

Recent studies have shown that PGC-1α promotes the decomposition of valine into an intermediate, 3-hydroxy-isobutyrate (3-HIB), which can promote skeletal muscle uptake of fatty acids from plasma by regulating fatty acid transporter 3 and fatty acid transporter 4 (FATP3 and FATP4) (15). The intermediate 3-HIB is produced by 3-hydroxyisobutyryl-CoA (HIBC) hydrolysis of HIBC hydrolase (HIBCH), and 3-HIB dehydrogenase (HIBADH) can further decompose 3-HIB into propionyl-CoA (15). Studies have shown that cellular fatty acid uptake increases after adding valine to C2C12 cells. After knocking out the myotube HIBCH, fatty acid uptake by the cells was almost completely diminished. In contrast, inhibition of myotube HIBADH expression enhances cellular fatty acid uptake. Inhibition of mouse skeletal muscle HIBADH expression also increased intracellular triglyceride levels (15). In addition, after marking valine with 13C, almost all of the 3-HIB found in the cells had 13C markers, demonstrating that 3-HIB in the cells was indeed derived from valine (15). These data
The Effects of BCAAs on Insulin Resistance in Athletes

Indicate that the valine catabolite 3-HIB promotes skeletal muscle fatty acid uptake. Moreover, 3-HIB plays an important role in the induction of skeletal muscle insulin resistance by BCAAs. Studies have shown that 3-HIB levels in the skeletal muscle of db/db mice and diabetic patients were significantly elevated (15, 20). Two weeks after adding 3-HIB to the drinking water of mice, the levels of 3-HIB in skeletal muscle increased, resulting in a large amount of fatty acids entering the skeletal muscle, leading to the accumulation of the incomplete lipid oxidation products diacylglycerol (DAG) and ceramide (CER). Additionally, impaired insulin signaling induces skeletal muscle insulin resistance (15). It has been shown that 3-HIB can cause skeletal muscle insulin resistance, which may be due to the accumulation of intramuscular lipids. In addition, there was no significant change in gluconeogenesis gene expression or glucose output in the liver, indicating that 3-HIB had little effect on liver function (15). That is, the mechanism by which BCAAs induce insulin resistance is different in skeletal muscle and the liver.

In summary, these data indicate that 3-HIB produced by BCAA decomposition promotes skeletal muscle fatty acid uptake, resulting in accumulation of incompletely oxidized lipids, impaired insulin signaling and skeletal muscle insulin resistance (Fig. 1).

3.2 Liver

BCAAs induce insulin resistance in the liver. When plasma levels of BCAAs are elevated as a result of dietary intake or other means, the amount of BCAAs entering the peripheral tissue and subsequent catabolism will increase (10). The BCKAs produced by skeletal muscle decomposition of BCAAs are transported via the circulatory system to the liver for further catabolism (6). In type 2 diabetic individuals, BCKAs are decomposed by branched-chain α-keto acid dehydrogenase (BCKDH) to produce a large amount of acyl-CoA (21), which then enters the liver tricarboxylic acid (TCA) cycle for further oxidation (22). If the production of acyl-CoA exceeds the oxidative potential of the mitochondria, the acyl-CoA produces acylcarnitine (5) and impairs the mitochondrial TCA cycle (23). Therefore reducing the potential of the liver to oxidize fatty acids and glucose causes the products of incomplete oxidation to accumulate, leading to mitochondrial oxidative stress and impaired insulin signaling, ultimately impairing glucose homeostasis and inducing liver insulin resistance (10). In addition, excessive acyl-CoA produced by BCKA decomposition can also increase the rate of lipogenesis and gluconeogenesis (10), further promoting liver insulin resistance.

Therefore, liver insulin resistance is not directly caused by BCKAs, but the decomposition of BCKAs promotes liver gluconeogenesis and leads to the accumulation of acylcarnitines and impairment of the mitochondrial TCA cycle, resulting in the accumulation of incomplete oxidation products, leading to mitochondrial oxidative...
stress and inducing liver insulin resistance (Fig. 1).

3.3. Adipose tissue

Adipose tissue can also decompose BCAAs into BCKAs (23). In addition, adipose tissue can decompose BCKAs into various acyl-coenzymes and acylcarnitines. This indicates that adipose tissue expresses both BCAT and BCKDH (24), but the activity and expression of BCKDH in adipose tissue is lower than that in liver (25). It is not difficult to speculate that there is a close relationship among the catabolism of BCAAs, the expression of catabolic genes in adipose tissue and insulin sensitivity (26). Unexpectedly, inhibiting BCAA decomposition in adipose tissue may promote insulin resistance. Studies have shown that Zucker obese rats and ob/ob mice have decreased BCKDH activity and decreased BCAT and BCKDH gene expression, indicating that BCAA decomposition in adipose tissue is inhibited. In addition, the level of circulating BCAAs was increased (27). Moreover, the expression or activity of BCAT and BCKDH in these animal skeletal muscles did not decrease or increase (10). These data indicate that the relationship between BCAAs and insulin resistance in adipose tissue is different from that in skeletal muscle or the liver. Inhibiting BCAA decomposition in adipose tissue may promote insulin resistance.

The mechanism is currently inconclusive, but there have been many important findings. Mild changes in BCAT and BCKDH expression in adipose tissue can have a significant effect on circulating BCAA levels (10). Studies have shown that circulating BCAA levels are significantly increased after decreasing the expression of BCAA catabolic enzymes in mouse adipose tissue (28). In addition, after humans undergo bariatric surgery, the level of circulating BCAAs is significantly increased (19). This allows other tissues, such as in skeletal muscle or the liver, to decompose and utilize BCAAs in large amounts, thereby inducing insulin resistance. Therefore, inhibiting the decomposition of BCAAs in adipose tissue can lead to plasma BCAA levels increasing, which causes skeletal muscle, liver and other tissues to decompose BCAAs in large amounts and induce insulin resistance (Fig. 1).

4. The Effects of BCAAs on Insulin Resistance in Athletes

4.1. BCAAs are commonly used in nutritional supplements for athletes

4.1.1. BCAAs promote glucose uptake

BCAAs are a very important nutritional supplement for athletes. In skeletal muscle, BCAAs activate phosphatidylinositol 3-kinase (PI3K) and Akt, which promote the expression of glucose transporter 4 (GLUT4), thereby promoting skeletal muscle glucose uptake (29, 30). In adipose tissue, leucine increases the phosphorylation level of Akt on Ser473 and Thr308 and the phosphorylation level of mTOR on Ser2448, thereby promoting adipose tissue glucose uptake (31). In the liver, BCAAs activate the liver X receptor α (LXRα)/regulatory element binding protein-1c (SREBP1c) pathway, thereby promoting GLUT2 expression and enhancing liver glucose uptake (32). The ability of BCAAs to promote tissue glucose uptake plays a very important role in both exercise and postexercise recovery. However, when the plasma BCAA concentration is too high, it can inhibit tissue glucose uptake and induce insulin resistance (15). It is further indicated that BCAAs are beneficial and only promote insulin resistance when BCAA intake is excessive, causing the accumulation of toxic metabolic intermediates.

4.1.2. BCAAs promote skeletal muscle protein synthesis after exercise

BCAAs play an important role in skeletal muscle protein synthesis after exercise (33). In particular, leucine (34) can serve as a substrate for skeletal muscle protein synthesis and as a signal to activate skeletal muscle protein synthesis pathways (35). Studies have shown that leucine promotes protein synthesis in muscle cells (36), rodent skeletal muscle (37), and human skeletal muscle (38). The underlying mechanism is that BCAAs can activate the skeletal muscle Akt/mTORC1 signal pathway (39), thereby promoting skeletal muscle protein synthesis. In addition, leucine is not the only BCAA that can promote skeletal muscle protein synthesis (34). Studies have shown that although valine and isoleucine cannot directly activate the Akt/mTORC1 pathway, they can enhance the activation effect of leucine on mTORC1 (40), thereby further promoting skeletal muscle protein synthesis.

In general, BCAAs promote glucose uptake and skeletal muscle protein synthesis. They are essential amino acids, so they are important for athletes participating in any sport and have been widely used by athletes.

4.2. Athletes using BCAAs do not increase their risk of insulin resistance

As we mentioned earlier, BCAAs promote insulin resistance and excessive intake of BCAAs should be avoided. BCAAs are a very beneficial nutritional supplement for athletes and have been widely used by athletes, but there have been no reports of athletes inducing insulin resistance due to the use of BCAAs supplements. Athletes using BCAAs inhibit the side effects of BCAA-induced insulin resistance, which can be explained by the effects of exercise on BCAA metabolism.

4.3. Exercise can inhibit BCAA-induced insulin resistance

As mentioned above, through the action of BCAT, BCAAs can produce BCKAs and alanine by transamination. In skeletal muscle, exercise promotes the transamination of BCAAs. Studies have shown that skeletal muscle alanine output and plasma alanine levels increase during exercise (2), and the plasma BCAA levels of rats from exercise group decreased significantly as compared with the rats from the sedentary group (41). This explain show exercise can promote the decomposition of BCAAs. In addition, a lot of energy is consumed during exercise (42). The BCKAs are further decomposed into acyl-coenzymes, which can enter the TCA cycle for oxidative decomposition and to provide energy (2), which can supplement the energy consumption during exercise.

Exercise increases muscle and plasma beta-aminoisobutyric acid (BAIBA) concentrations (43). BAIBA is
The Effects of BCAAs on Insulin Resistance in Athletes

BAIBA, a non-protein β-amino acid that can be generated by catabolism of the branched-chain amino acid valine (43). Studies have shown that BAIBA can enhance liver oxidize ability, promoting WAT browning, enhancing heat production, and thus improving insulin sensitivity (43). BAIBA levels were inversely correlated with fasting glucose, insulin, the homeostatic model assessment-insulin resistance (HOMA-IR), triglycerides, and total cholesterol (43). The BAIBA concentration in the plasma of exercised mice and humans was significantly increased compared to the sedentary group (43). Therefore, exercise can promote the catabolism of valine into BAIBA, thereby inhibiting BCAA-induced insulin resistance.

In addition (27), exercise can enhance the ability of skeletal muscle to oxidize BCAAs, especially leucine. Studies have shown that leucine oxidation provides a large amount of energy during exercise in rats (2). In addition, trained rat skeletal muscle has higher leucine oxidizing ability than untrained rat skeletal muscle (2). This indicates that exercise can promote the complete oxidative decomposition of acyl-coenzymes produced by BCAA decomposition, thereby reducing the accumulation of skeletal muscle acylcarnitines. This complete oxidative decomposition also reduce the burden on the liver to decompose BCKAs, thereby reducing the accumulation of acylcarnitine in the liver, improving insulin resistance. Therefore, these data suggest that exercise can enhance the ability of skeletal muscle to oxidize BCAAs and alleviate or even eliminate the accumulation of acylcarnitines in various tissues caused by BCAA catabolism, and promotes BCAAs catabolism into BAIBA, increasing plasma BAIBA concentrations, thereby improving BCAA-induced insulin resistance. This seems to be an explanation for the widespread use of BCAA supplements by athletes without inducing insulin resistance (Fig. 2).

5. Conclusion
Elevated levels of BCAAs promote insulin resistance, but BCAAs are not a direct cause of insulin resistance. Insulin resistance is caused by the toxic catabolic intermediates of BCAAs. The mechanism varies indifferent metabolic tissues. In skeletal muscle, 3-HIB produced by valine promotes skeletal muscle fatty acid uptake, resulting in the accumulation of incompletely oxidized lipids in skeletal muscle, causing skeletal muscle insulin resistance. In the liver, BCKAs decompose in large amounts, promote hepatic gluconeogenesis, and lead to the accumulation of multiple acylcarnitines, which damages the mitochondrial TCA cycle, causing the accumulation of incomplete oxidation products, oxidative stress in mitochondria, and liver insulin resistance. In adipose tissue, the expression of BCAAs catabolic enzymes (BCAT, BCKDH) is reduced, resulting in an increased level of...
plasma BCAA, thereby causing massive decomposition of BCAAs in tissues such as skeletal muscle and liver, and inducing insulin resistance. Therefore, BCAAs alone do not induce insulin resistance. Insulin resistance is only promoted when BCAAs are excessive, causing the accumulation of toxic metabolic intermediates.

In addition, BCAAs alone can promote glucose uptake in various tissues and skeletal muscle protein synthesis after exercise, as well as oxidative decomposition to provide energy. Therefore, BCAAs are a common nutritional supplement for athletes, but they do not induce insulin resistance. The reason may be that exercise can enhance the ability of mitochondria to oxidize BCAAs, alleviating or even eliminating the accumulation of BCAA catabolic intermediates, thereby eliminating the potential factors that induce insulin resistance, and promotes BCAAs catabolism into BAIBA, increasing plasma BAIBA concentrations, so that BCAAs only exert beneficial effects without inducing insulin resistance. This article reveals the mechanism of BCAA-induced insulin resistance and the relationship between exercise and BCAAs metabolism, adds a guarantee for the use of BCAAs, and provides a new explanation for the occurrence of diabetes and how exercise improves diabetes, but the role of exercise in promoting complete oxidative decomposition of BCAAs, thereby avoiding insulin resistance, requires further investigation.

Disclosure of state of COI
No conflicts of interest to be declared.

Authorship
Jian Shou is the first author.

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The Effects of BCAAs on Insulin Resistance in Athletes

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