

Insulin Resistance, and What May Contribute to It



By *Lila Abassi* — March 14, 2016



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Insulin resistance is an abnormal response to insulin produced either by the pancreas or given as an injection, as evidenced by blood glucose levels in relation to serum insulin. Previous evidence supports the connection between branched-chain amino acids (BCAA) and the development of insulin resistance.

In a [study](#) [2] published in *Nature Medicine*, scientists have discovered that 3-hydroxyisobutyrate (3-HIB), one of the intermediate products in the breakdown of the BCAA valine, plays a role in the transport of fatty acids into skeletal muscle cells, which creates fatty muscles — a contributor to insulin resistance.

[Amino acids](#) [3] are the building blocks of proteins – there are 20 of them all together. There are nine essential amino acids which cannot be made by the body — [three of them](#) [4] are BCAAs, leucine, isoleucine, and valine – which account for 35 percent of the essential amino acids in muscle proteins and 40 percent of the preformed amino acids required by mammals.

When proteins are [digested](#) [3] or broken down, amino acids result. The human body uses amino acids to make proteins to help the body:

- Break down food
- Grow
- Repair body tissue
- Perform many other body functions

Amino acids can also be used as a source of energy — but that's not typical.

BCAA have profoundly altered metabolism in insulin resistant conditions or situations where there is insulin deficiency – and it is only recently that their role has been so closely associated with insulin resistance.

Insulin resistance is a major pathological feature in individuals with Type-2 diabetes (T2DM) or part of what is known as the [metabolic syndrome](#) [5] — an association between abdominal obesity,

insulin resistance, cardiovascular disease (T2DM is considered a cardiovascular disease equivalent), high blood pressure, elevated cholesterol and heart disease.

Thus far, it has been a relative mystery as to how BCAA play a role in insulin resistance. Skeletal muscles display resistance to insulin when there is excess fat inside their cells.

Some of the questions that the senior author, [Zoltan Arany](#) [6], MD, PhD, an associate professor of cardiovascular medicine at the Perelman School of Medicine at the University of Pennsylvania, asked was, "How does fat get into skeletal muscle? And how is the elevation of certain amino acids in people with diabetes related to insulin resistance?"

"We have appreciated for over ten years that diabetes is accompanied by elevations in the blood of branched-chain amino acids, which humans can only obtain in their diet," Dr. Arany said.

"However, we didn't understand how this could cause insulin resistance and diabetes. How is elevated blood sugar related to these amino acids?"

What the researchers found was that 3-HIB acted as a shuttle in muscle cells, allowing blood vessels in skeletal muscle tissue to move fat into skeletal muscle. The more 3-HIB, the more fat was transported — and conversely, when scientists blocked 3-HIB from being made, there was less uptake of fat into skeletal muscle.

In mouse models of diabetes 3-HIB was also noted to be elevated in individuals with T2DM.

"In this study we showed a new mechanism to explain how 3-HIB, by regulating the transport of fatty acids in and out of muscle, links the breakdown of branch-chained amino acids with fatty acid accumulation, showing how increased amino acid flux can cause diabetes," according to Dr. Arany.

Hopefully, this research will pave the road to elucidating the etiology of insulin resistance and developing medications to help combat it.

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