

Adding intestinal enzyme to diets of mice appears to prevent, treat metabolic syndrome

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Feeding an intestinal enzyme to mice kept on a high-fat diet appears to prevent the development of metabolic syndrome – a group of symptoms associated with type 2 diabetes, cardiovascular disease and fatty liver – and to reduce symptoms in mice that already had the condition. In their report published online in *PNAS* Early Edition, Massachusetts General Hospital (MGH) investigators describe how dietary supplementation with intestinal alkaline phosphatase (IAP) reduced the inflammation believed to underlie metabolic syndrome by blocking a toxic molecule found on the surface of many bacteria.

"For the first time we are targeting production of inflammatory factors in the intestinal tract to prevent the systemic problem of the metabolic syndrome," says Richard Hodin, MD, of the MGH Department of Surgery, the study's senior author. "Animal studies have shown the gut to be the likely source of these factors, and we have previously shown in laboratory studies that IAP can block their activity. There are human studies that correlate low-grade systemic inflammation with the metabolic syndrome, so we expect that IAP's ability to interfere with the process will apply to humans as well."

Encompassing symptoms including obesity, glucose intolerance, [insulin resistance](#), hypertension and lipid abnormalities, metabolic syndrome affects more than one-third of the U.S. population and significantly increases the risk for cardiovascular disease and [type 2 diabetes](#). A possible contributor to metabolic syndrome is increased blood levels of [lipopolysaccharide](#) (LPS), a molecule found on the surface of many [gut](#)

[bacteria](#) and responsible for their toxic effects when it passes through the intestinal wall into the systemic circulation. A persistent increase in circulating LPS, a condition called endotoxemia, causes low-grade inflammation – a primary aspect of metabolic syndrome – throughout the body. LPS is known to bind to fat, and several studies have shown that a high-fat diet raises systemic LPS levels in animals and humans, increasing both intestinal inflammation and the permeability of the intestinal wall, allowing additional LPS to pass into the bloodstream.

Previous work in Hodin's lab showed that IAP, which is produced by cells lining the small intestine, can block the action of LPS, leading to the hypothesis that the enzyme could help prevent the [systemic inflammation](#) associated with a high-fat diet. In a series of experiments described in the current study, the investigators showed the following:

- mice in which IAP expression was either knocked out or suppressed developed endotoxemia, overexpression of inflammatory factors and symptoms of metabolic syndrome;
- feeding IAP to mice on a high-fat diet prevented weight gain and fat accumulation and reduced development of metabolic syndrome;
- feeding IAP to mice that had developed metabolic syndrome as a result of a high-fat diet, reduced endotoxemia, inflammatory factors and symptoms such as [glucose intolerance](#);
- feeding IAP to mice on a low-fat diet slightly improved glucose metabolism but significantly improved lipid metabolism.

The researchers note that IAP is naturally found in an environment containing many bacterial factors that induce inflammation – suggesting that it may suppress the activity of additional factors – and that several related enzymes should be investigated for shared protective abilities.

"While our findings clearly predict that IAP supplementation could have the same effect in human patients, future studies are required to test this directly," explains Hodin, a professor of Surgery at Harvard Medical School (HMS). "We need a formulation of the enzyme that can be safely given to humans – something we are working to develop – which we then can test as a prevention or treatment for [metabolic syndrome](#), a contributor to the number one cause of patient death in this country."

Provided by Massachusetts General Hospital

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