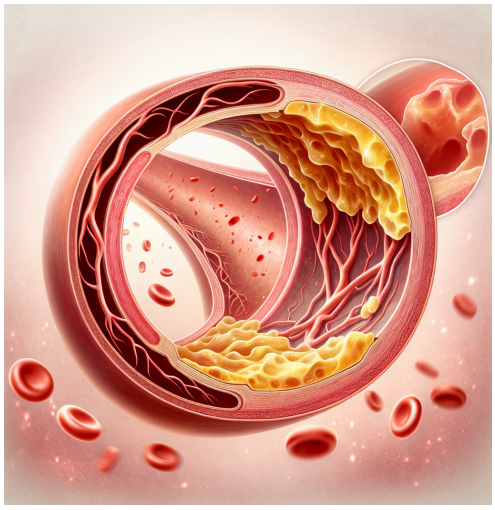
Artificial sweetener linked to atherosclerosis.

New research has found a potential link between the artificial sweetener aspartame and an increased risk of atherosclerosis (1). Researchers in China have shown that the popular non-nutritive sugar substitute increases insulin levels in the body, independently of glucose. What's more, they identified a mechanism by which the multifactorial disease can develop.

by Cliff Dominy, PhD

The study is the first direct evidence of a mechanism by which aspartame aggravates atherosclerosis. The scientists identified a signalling molecule in the chemokine family and showed its direct activation in the arterial wall by the hormone insulin. The chemokine, named CX3CL1, has been associated with coronary artery disease, but now they have determined the exact role it plays in disease progression (2,3).



Researchers fed aspartame to atheroma-prone (*ApoE*$^{-/-}$) mice for 12 weeks and monitored their clinical markers of health. Postmortem examination of the animals showed an aspartame-based dose-dependent acceleration of coronary plaque development over this period.

The data was clear. Under these conditions, aspartame significantly increased atheroma volume, fibrous cap size, plaque instability, inflammatory signals, and lipid content in the coronary arteries of the mice. Sucrose-fed controls did not exhibit the same degree of pathology.

Insulin is key

The bloodwork contained an unexpected result. The aspartame group showed chronically elevated plasma insulin levels. Corresponding plasma glucose levels, usually highly correlated with insulin, remained low. Researchers confirmed these results in *Cynomolgus* monkeys suggesting the data might apply in humans too.

The role of the gut-brain axis

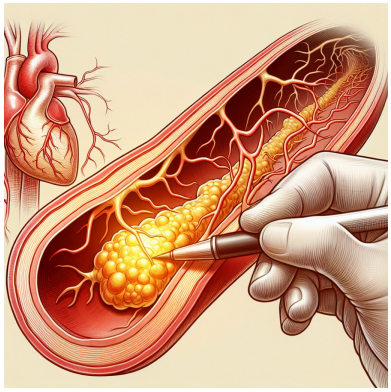
The vagus nerve helps regulate insulin production in mammals. It is part of the gut-brain axis which is central to several metabolic and immunological pathways. To investigate the role of this neural regulation in atherosclerosis, *ApoE*$^{-/-}$ mice underwent a bilateral vagotomy to examine the influence of the vagus nerve on these results.

The researchers observed a loss of the insulin response to aspartame, and the inhibition of atheroma formation in these animals. The experiment neatly demonstrated aspartame's para-sympathetically regulated insulin response in atherosclerosis.

Next, they explored the role of exogenous insulin infused into mice that had not consumed aspartame. Modest insulin levels (equivalent to 25 μIU/ml in humans) significantly increased atheroma development and plaque instability over a 12-week period.

Shoot the messenger!

To investigate the mechanism by which insulin can trigger plaque development, the researcher performed mRNA sequencing analysis on aortic epithelial cells incubated with insulin.



Metabolomic profiling revealed CX3CL1 to be the predominant upregulated gene in the insulin-treated arterial cells. The researchers created knock-out mice for the CX3CL1 receptor to look at its role in plaque development. They noted that even in the presence of insulin, the knockouts no longer exhibited an inflammatory profile, nor did they develop coronary plaques.

CX3CL1 functions as a proinflammatory cell signaling molecule. It has two forms, a free-form that functions as a chemoattractant to the cells that produce it. The second membrane-bound form serves as an adhesion molecule. CX3CL1 can summon macrophages and cause them to stick together in coronary arteries. This is the very definition of atherosclerosis.

Clinical implications

If these results are replicated in humans, this study will raise important considerations for managing chronic diseases such as obesity, atherosclerosis, and insulin-managed type 2 diabetes. For example, aspartame is used as a calorie reducing sweetener in people trying to lose body fat.

Atherosclerosis is a multifactorial disease. This study identified just one (insulin dependent) pathway by which cholesterol-laden plaque can form in the arterial wall. It explains why people with hyperinsulinemia (pre-diabetes, type 2 diabetes) are susceptible to coronary artery disease. These results suggest CX3CL1 may prove to be a useful clinical marker of atherosclerotic risk- and a possible therapeutic target in the fight against this significant global killer.

References

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