The Contribution from Ceramide to Vascular Dysfunction in Diet-induced Obesity

Milda Palionyte, Brandon McDonald, Bradlee Duncan, Judd Cahoon & J. David Symons
College of Health

This study focuses on the mechanisms responsible for arterial dysfunction (a cause of elevated blood pressure and impaired blood and oxygen delivery) that is observed in patients and experimental animal models of type 2 diabetes.

In preliminary studies, compared to mice that consumed standard chow (i.e., 10% fat; CON), mice that consumed high-fat chow (i.e., 45% fat, HF) showed characteristics of arterial dysfunction that were similar to patients with diet-induced obesity. This arterial dysfunction may be explained, at least in part, by the fact that the arteries of HF mice contained nearly no activated endothelial nitric oxide synthase (eNOS), an enzyme that produces nitric oxide (NO) and causes blood vessels to vasodilate.

Obesity initiates a variety of cellular stresses that leads to the formation of the sphingolipid ceramide. Though studies have suggested ceramide contributes to arterial dysfunction, none has directly investigated this hypothesis. Our rationale for testing this hypothesis originates from cell culture studies showing that ceramide inhibits phosphorylation of Akt (an "upstream" modulator of eNOS). Thus, ceramide may decrease eNOS phosphorylation, and lead to vascular dysfunction.

We are using two methods that limit ceramide production to test our hypothesis. In the first, HF mice are given either myriocin (a drug that inhibits ceramide production) or vehicle (phosphate buffered saline; PBS). We hypothesize that HF mice treated with myriocin will have less severe vascular dysfunction than HF mice treated with PBS. In the second method, vascular function of wild type (WT) mice is compared to that of mice with a genetically altered disruption of the enzyme that catalyzes ceramide formation (cer short mice). We hypothesize that HF cer short mice will have less severe vascular dysfunction compared to HF WT mice. Both of these strategic interventions to limit ceramide synthesis will provide powerful evidence that ceramide contributes to vascular dysfunction in diet-induced obesity. Results from this study will aid in gaining further insight concerning the development of novel therapeutic interventions used to limit vascular dysfunction in patients with diabetes.

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