



## **PROTEIN PHOSPHATASE 2A INHIBITION PRESERVES ARTERIAL FUNCTION IN OBESE MICE**

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Cardiovascular diseases (CVD) are more prevalent in individuals with diet-induced obesity (DIO) and type two diabetes (T2DM). Examples of CVD include blood vessel dysfunction and systemic hypertension. Both of these pathologies are associated with a reduced ability of the inner lining of the blood vessel (the endothelium) to release a substance (nitric oxide) that causes the blood vessel to dilate. At present the mechanism whereby T2DM and DIO decrease the function of the enzyme (nitric oxide synthase; NOS) responsible for nitric oxide synthesis and release is unknown. Determining this mechanism is the current focus of our laboratory. Earlier we reported that the sphingolipid ceramide is elevated in cell models of lipotoxicity and in mice with DIO. Most recently in endothelial cells we showed that ceramide causes protein phosphatase 2A (PP2A) to bind directly with NOS which disrupts the interactions among proteins that are necessary for optimal NOS function. My overall project was concerned with determining whether this mechanism is operational in mice with DIO. Specifically, we tested the hypothesis that PP2A inhibition would preserve vascular protein-protein interactions required for optimal NOS enzyme function to an extent that arterial dysfunction and hypertension would not occur. Mice consumed a control (CON) or high fat (HF) diet for 12 weeks. During the last 2 weeks, cohorts of mice from each group were injected (IP) with saline (vehicle control) or the PP2A inhibitor LB1 (1.0 mg/kg/day). We observed that interactions among proteins required for optimal NOS enzyme function were disrupted in arteries from mice with DIO treated with saline but not with LB1. Furthermore, arterial dysfunction and hypertension existed in mice with DIO that received saline but not LB1. These results strongly suggest that PP2A activation contributes importantly to arterial dysfunction that exists in a preclinical model of DIO.

