Fructose-Induced Insulin Resistance and Hypertension in the Sprague-Dawley Rat Model

A two-week study designed to screen for risk factors associated with the onset of metablic disease

Overview

The introduction of high-fructose corn syrup in many sweetened processed foods has been brought to the attention of both researchers and the public because the health implications are not well characterized. Multiple studies in both humans and laboratory animals have suggested that the addition of fructose to the diet of an otherwise "healthy" individual may substantially increase the risk for metabolic disease (4-5).

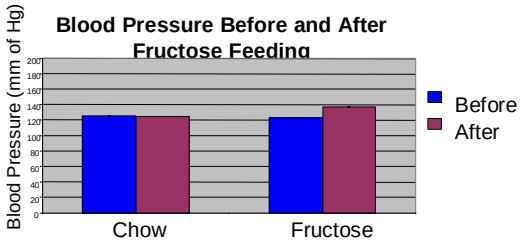
A study conducted in Sprague-Dawley rats was able to show the development of several conditions that are known risk factors for metabolic disease in only 2-weeks of fructose feeding. These include hypertension, insulin resistance, and increases in blood triglyceride levels (1; see data on right). Similar findings have been documented in humans, making this a very attractive model for the onset of these conditions in humans (2-3). Other studies have demonstrated the ability of a fructose-based diet to induce these and other metabolic symptoms; however this study is unique because symptoms were observed after a substantially shorter feeding period (2 vs. 8-weeks).

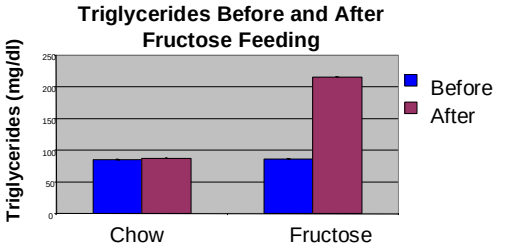
Model Development

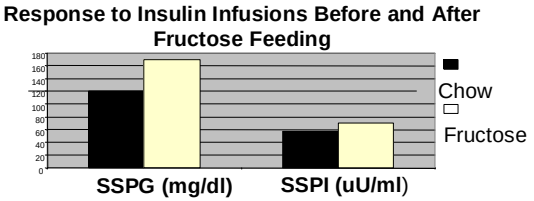
MuriGenics is developing a Sprague-Dawley rat model of fructose-induced insulin resistance and hypertension that will consist of fructose-feeding for a two-week period. The Sprague-Dawley rat model is of particular interest because this strain is not spontaneously hypertensive nor predisposed to hypertension or insulin resistance under normal feeding conditions, thus, serving as an appropriate model for the development of this condition in otherwise "healthy" humans under similar feeding conditions.

Additionally, the construction of this model is being undertaken to reduce the time needed to assess the development of certain metabolic risk factors that may develop under fructose-feeding conditions and provide the client a less costly option for assessing initial disease susceptibility. This model can then be used to examine the effectiveness of test compounds to combat the effects of fructose feeding and thus aid in drug discovery, and/or to investigate genetic factors that contribute to this disease through the comparison of genetically distinct inbred strains.

Data







Experimental Design

Groups and Variables

Group	Treatment	Total Animals	Strain	Sex	Therapeutic Agent
1 (Control)	Standard Chow	10	Sprague-Dawley	Male	TBD
2	High-Fructose Chow	10	Sprague-Dawley	Male	TBD
3**	TBD	TBD	TBD	TBD	TBD

Testing Paradigm

Group	Week 1 (Acclimation)			Weeks 2-3 (diet testing)				Week 4	Add. Weeks
1 Control	2 day accl. with Chow diet	4 day accl to BP chamber baseline BP on final day	2 day stress recov. from BP measure	4 hour fast Baseline blood and body weight	Chow	Post-test BP	2 day recov.	Post-test blood and BW	Assess In Vivo Insulin Action*	Additional measures to be determined
2 Fructose					Fructose diet begins	Post-test BP	2 day recov.	Post-test blood and BW		
3 TBD**					TBD	Post-test BP	2 day recov.	Post-test blood and BW		

*Piloting a Minimal Assay for collection of this measure see below in "Additional Measures"

**Gray denotes variables or measures that will be determined based upon the design of future studies and the needs of the client.

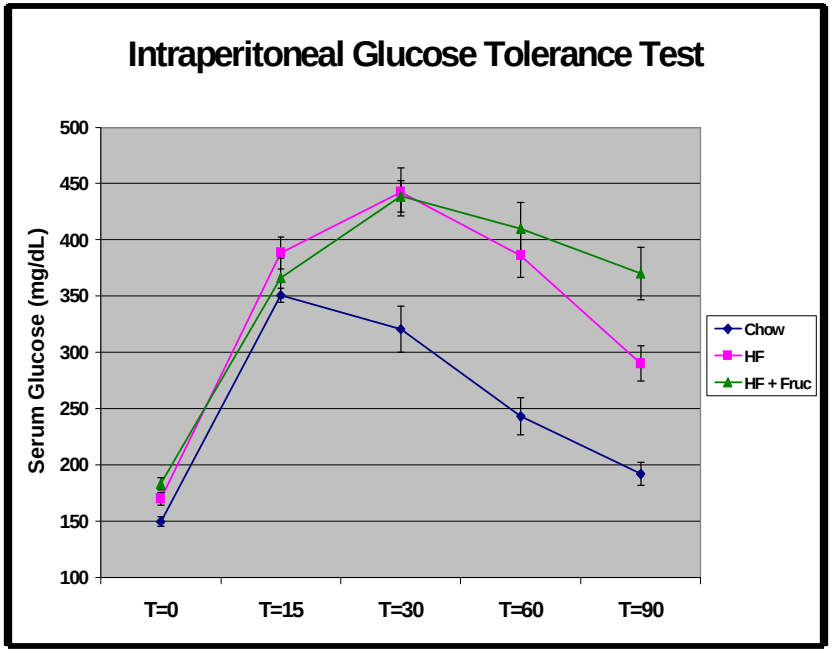
Additional Measures and Pilots

In addition to the previously mentioned measures, MuriGenics will be validating additional assays and therapeutic agents:

Minimal Assay for Assessing Insulin Action and Resistance: The standard assay for assessing the action of insulin on available glucose is the Euglycemic Clamp, however two limitations exist: (1) stabilizing glucose levels is difficult, (2) infusions last several hours and require the cannulation of animals. However, the minimal assay combines simple tail vein injections with advanced algorithms to determine insulin action.

Rosiglitazone for Increasing Insulin Sensitivity: Rosiglitazone is a drug used to treat diabetics. By attaching itself to insulin receptors and making them more responsive to glucose, this drug increases the sensitivity of diabetic individuals to insulin. Murigenics plans to assess laboratory animals in pilot studies to assess it's effectiveness in reducing diet-induced increases in glucose and for increasing sensitivity to insulin.

Client Requested Experimental Measures: In addition to the measures above, additional measures can be added to the model including, but not limited to: measurement of fat depots and organs, additional blood panels, examination of additional therapeutic compounds and their effectiveness, and the examination of any of the above in varying strains of laboratory rats.



4 weeks Bars