Maddy Ford

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Hereditary Fructose Intolerance (HFI) is a metabolic disorder that causes affected individuals to improperly process the simple sugar, fructose [1]. The cause of this hereditary disorder is a mutation to the aldolase B gene. Aldolase B is a liver protein involved in glycolysis, the body’s process for breaking down sugars to make energy in the form of ATP [2,3]. It is important for cleaving fructose-1,6-bisphosphate, an intermediate in this process, into other intermediates, Glyceraldehyde-3-phosphate (G3P) and Dihydroxyacetone phosphate (DHAP) (see diagram at right) [1-3]. When aldolase B cannot do this, fructose builds up in the liver, causing the patient to experience nausea, vomiting, hypoglycemia, and liver damage [1,2]. *HFI affects approximately 1 in 23,000 people worldwide and there is no cure or treatment available [2]. HFI patients can avoid symptoms through dietary restriction, but this can be frustrating and inconvenient.*

Image courtesy of <http://david-bender.co.uk>, “Experiments on glucose metabolism.”

Symptoms of disorders such as lactose intolerance can be alleviated through supplementation [4]. No such supplements are available for HFI, but a substitute for dysfunctional aldolase B could alleviate symptoms induced by fructose consumption. I hypothesize that by identifying chemicals that mimic aldolase B and the genes these chemicals affect, progress toward an HFI supplement could be made. Additionally, I hypothesize that by researching the role of specific portions of homolog aldolase B, more insight on human aldolase B could be gained.

**The primary goal of this study is to identify drugs that mimic aldolase B and the genes they affect. The secondary goal of this study is to determine the importance of certain segments of the aldolase B gene.**

**Specific Aim 1:** To identify chemicals that mimic aldolase B using a chemical genetic screen with a focused library in Drosophila.

**Approach:** Use morpholinos to knock out aldolase β in Drosophila, Perform a chemical genetic screen with a directed chemical library on knockout and wild-type Drosophila. A chemical can be subject to further testing if it is seen to rescue the ability to process fructose in flies.

**Hypothesis**: Drugs most similar in enzymatic function to aldolase B will rescue the ability to process fructose in knockout flies.

**Specific Aim 2:** To determine the importance of the C-terminus region and the low complexity region (LCR) in fructose metabolism.

**Approach:** Use RNAi to knock out the C-terminus protein segment in fruit fly aldolase β and feed the knockout flies fructose. Use the same technique for the LCR. Knockouts will be unable to process fructose if the C-terminus region or the LCR are important for fructose metabolism.

**Hypothesis:**  C-terminus region knockout flies will be unable to process fructose and die because the C-terminus contains commonly mutated sites in human HFI cases. Thus, it is likely these sites are important in homologs. LCR knockout flies will die because the LCR is important for proper enzymatic folding.

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