Fat and Diabetes: Bad Press, Good Paper, and the Reemergence of Our Good Friend Glutathione

AUGUST 30, 2011 BY CHRISTOPHER MASTERJOHN
(HTTPS://WWW.WESTONAPRICE.ORG/AUTHOR/CMASTERJO/)

Print post

A number of people have asked for my comments on the recent headlines claiming that "high-fat diets cause diabetes," based on a recent paper published in *Nature Medicine* (1 (http://www.ncbi.nlm.nih.gov/pubmed/21841783)):

> *Oshtsubo K, Chen MZ, Olefsky JM, Marth JD. Pathway to diabetes through attenuation of pancreatic beta cell glycoslyation and glucose transport. Nat Med. 2011; Aug 14 [Epub ahead of print]. (http://www.ncbi.nlm.nih.gov/pubmed/21841783)*

Robb Wolf (http://robbwolf.com/2011/08/18/of-mice-and-morons/?utm_source=feedburner&utm_medium=feed&utm_campaign=Feed%3A+RobbWolfThePaleoSolution+%28Robb+Wolf+|+The+Paleo+Solution+book+and+podcast+|+Paleolithic+nutrition%2C+intermittent+fasting%2C+and+fitness%29) and Denise Minger (http://www.marksdailyapple.com/does-a-high-fat-diet-cause-type-2-diabetes/) have already critiqued this study, but I have a few things to add about the potential for our good friend glutathione (http://www.westonaprice.org/blogs/cmasterjohn/2010/09/11/the-biochemical-magic-of-raw-milk-and-other-raw-foods-glutathione/) to protect us from diabetes.

It's Not About the Diet

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For those who are concerned that this paper might indicate that traditional, nutrient-dense fatty foods are bad for us, I would echo what Denise has already written. "When it comes to studies like this one," our approach should always be to "white out the headline" and "read with an open but critical mind." In this case, we can safely ignore the media headlines and observe that even the title of the paper says nothing about high-fat diets. The authors plant a few token sentences in the paper about the ability of a "high-fat or Western-style diet" to cause obesity and thus predispose someone to diabetes, but the paper is fundamentally about mechanism, not diet.

The investigators fed mice either a "high-fat" or "standard" diet. Both diets contained about 12 percent of calories as maltodextrin, which is a string of an average of ten glucose molecules hitched together like links on a chain, and is recommended for use (http://blog.cholesterol-and-health.com/2010/11/they-did-same-thing-to-lab-rats-that.html) in these diets to aid in pelleting and to reduce heat damage during the pelleting process. Both diets used casein for protein, a small amount of soybean oil to provide essential fatty acids, and a collection of purified vitamins and minerals. Both of the diets contained hydrogenated coconut oil and sucrose. The only difference between the two diets is that the "high-fat" diet contained an extra 47 percent of calories from hydrogenated coconut oil and the "standard" diet contained an extra 47 percent of calories from sucrose. Since fat packs in more calories per gram than sucrose, the high-fat diet was also 37 percent richer in calories.

It should be evident by now that **neither of these diets contains any food**.

In "They Did the Same Things to the Lab Rats That They Did to Us," (http://blog.cholesterol-and-health.com/2010/11/they-did-same-thing-to-lab-rats-that.html) I discussed the emergence of these purified diets in the 1970s, when they first began to replace the cereal-based (i.e., "food"-based) rodent diets of yesteryear. The animals consuming the new diets developed fatty liver, excessive bleeding, kidney calcification, and greater vulnerability to stress, toxins, and carcinogens. Leading scientists have revised and improved the diets to curb their worst effects, but they still don't contain any food.

Purified diets are advantageous to scientists because they make it easy to control for

single variables and to make comparisons between different studies using the same diets. At the same time, the studies become irrelevant to the dietary choices faced every day by human beings. When we decide whether to choose a fat-rich egg yolk or a sugar-rich orange, for example, our choice has a profound impact on our intake of choline, vitamin C, and dozens or hundreds of other chemicals. Rodents consuming purified diets don't face these effects because the diets contain a standardized amount of each vitamin and mineral and lack hundreds of other substances found in natural foods.

Even if this were not the case — that is, even if we humans were to eat nothing but casein, sugar, refined fats, and multivitamins — we would still be faced with the fact that we are not and never will be mice.

Quite often we find that certain disease processes exhibit remarkable similarities across species but that the dietary factors that can induce those diseases do not. For example, hypercholesterolemia produces atherosclerosis in baboons, monkeys, cats, mice, chickens, parrots, chimpanzees, pigs, dogs, pigeons, goats, rats, guinea pigs, and hamsters, but some of these animals such as rats and dogs are remarkably resistant to the effects of *dietary* cholesterol. This would suggest that there might be something universal about hypercholesterolemia that is worth studying, but also that it would be profoundly foolish to generalize dietary factors from rabbits to humans if we can't generalize them to rats or dogs.

As Denise Minger already pointed out (http://www.marksdailyapple.com/does-a-high-fat-diet-cause-type-2-diabetes), and as we will see in more detail below, the effect of high-fat refined diets on obesity is difficult to generalize even from one strain of mice to another; it would be all the more profoundly foolish, then, to generalize the effects from mice to humans.

This study provided no evidence that diets made from casein, sugar, and hydrogenated coconut oil cause diabetes in humans, but it did show that **some of the mechanisms they observed in mice were active in human cells,** so let's take a

look and see if we can learn anything that might be of interest to those of us who walk on two feet.

. . . It's About the Mechanism

The authors concluded from their work that the following scenario is likely to be involved in the development of diabetes:

- Dietary and genetic factors lead to obesity and insulin resistance.
- These conditions elevate concentrations of free fatty acids, which in turn cause insulin resistance to worsen.
- In the pancreas, elevated free fatty acids decrease the ability of two proteins called FOXA2 and HNF1A to travel to the nucleus and bind to DNA.
- When these proteins fail to bind to DNA, the cell fails to make an enzyme involved in processing glucose transporters and stabilizing them at the cell surface.
- The loss of glucose transporters at the cell surface impairs the ability of the pancreas to sense glucose levels in the blood and adequately stabilize these levels. As a result, we lose glucose tolerance and type 2 diabetes begins to emerge.

The investigators obtained pancreatic cells from a very small sample of humans (six healthy donors and two diabetics) and found some evidence to support the belief that this basic mechanism is active in humans just as it is in mice: the cells taken from diabetics had lower binding of the same proteins to DNA, lower production of the same enzyme, and 80-90 percent loss of glucose transporters at the cell surface. Moreover, the researchers were able to reproduce this mechanism in healthy human cells by incubating them with palmitic acid, a free fatty acid.

These results suggest that **we may be able to learn something useful to our understanding of human diabetes from these mouse experiments.**

What's With Those Funny Mice?

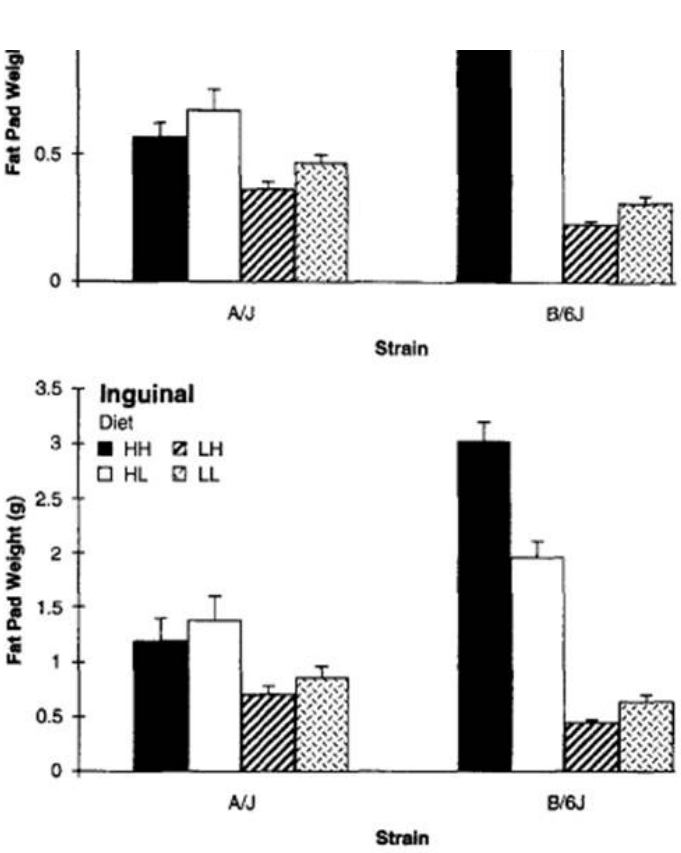
The authors of this study uncovered a little hint that oxidative stress is critically involved in the aspects of the disease process they studied and that the master cellular antioxidant, glutathione, may offer complete protection against the loss of

glucose tolerance.

First, let's consider the strain of mice they used, C57BL/6J. This strain is often called "B6" and the "J" indicates these particular mice are a substrain from Jackson Labs, so I'll call them "B6/J" from hereon out.

The diets these researchers used were named "Surwit diets" after Professor Richard Surwit of Duke University, who had helped Research Diets formulate the diets in 1992. Surwit had shown in the 1990s that B6/J mice are uniquely vulnerable to obesity and diabetes when fed high-fat diets, and that the inclusion of sugar in these diets has little or no effect.

Surwit's team published several papers comparing the effects of different diets in B6/J mice to the effects of the same diet in A/J mice, which are highly vulnerable to hearing loss and cancer but resistant to obesity, diabetes, and atherosclerosis. I've blogged about these studies before (http://blog.cholesterol-and-health.com/2011/04/let-us-honor-ancel-keys-our-patron-as.html). Here is what happened when the team fed these mice high-fat or low-fat diets with or without sugar for four months (2 (http://www.ncbi.nlm.nih.gov/pubmed/7752914)):



HL= High-Fat, No Sugar (58% Fat, 13% Starch)

LH = Low-Fat, High-Sugar (11% Fat, 60% Sucrose)

LL = Low-Fat, No Sugar (11% Fat, 13% Starch)

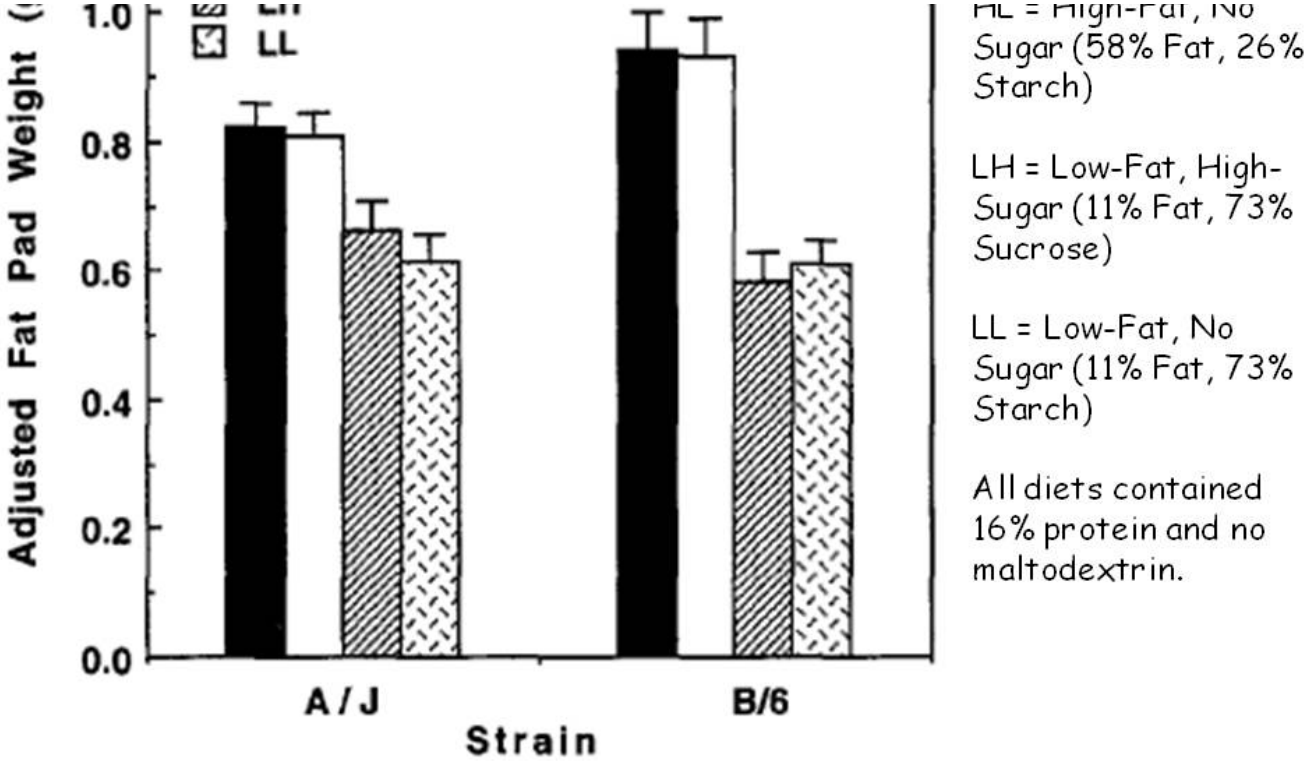
All diets contained 17% protein and 12% maltodextrin.

If you need to enlarge this or any of the subsequent pictures, you can do so by clicking on it.

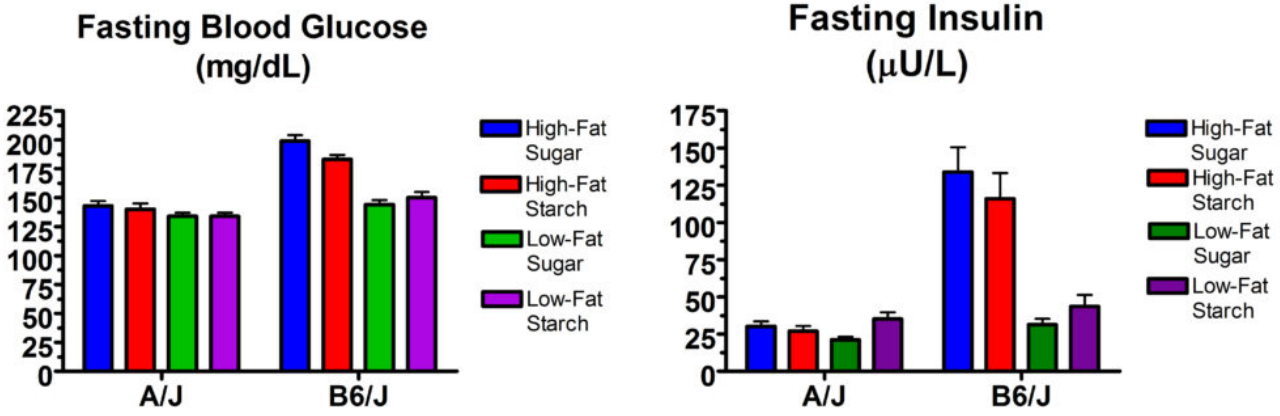
The fat in this study was hydrogenated coconut oil. We can see that the high-fat diet increased fat mass in B6/J mice to a much greater degree than it did in A/J mice. Sugar increased adipose mass even further in B6/J mice fed high-fat diets, but reduced adipose mass in B6/J mice fed low-fat diets. It had no effect in A/J mice at all. We should keep in mind that this is absolute fat mass, and not fat mass as a percent of body weight.

The Surwit team repeated the study a few years later, but excluded maltodextrin from the diet and expressed fat mass as a percent of body weight. Here we see similar effects of fat, but no effect of sugar at all (3 (http://www.ncbi.nlm.nih.gov/pubmed/9826212)):

HH = High-Fat, High-Sugar (58% Fat, 26% Sucrose)



In the earlier study (2 (http://www.ncbi.nlm.nih.gov/pubmed/7752914)), Surwit's team also measured glucose and insulin levels. The vulnerability of B6/J mice to diabetes was even more apparent than their vulnerability to obesity:



Here we see that a high-fat diet increased fasting glucose and dramatically increased fasting insulin in B6/J mice, while sugar had no effect in these mice. At the same time, neither fat nor sugar had any effect on either variable in A/J mice at all.

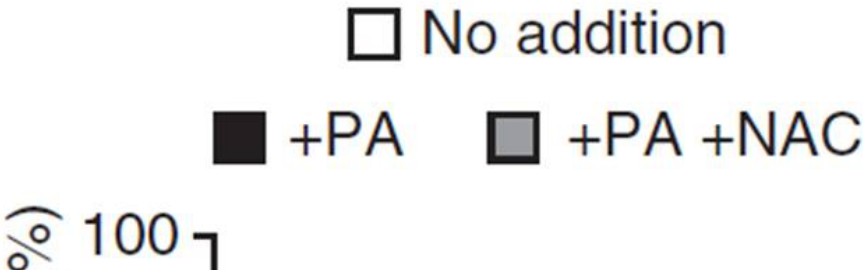
Why would B6/J mice be so vulnerable to the effects of a high-fat diet? Well, it turns

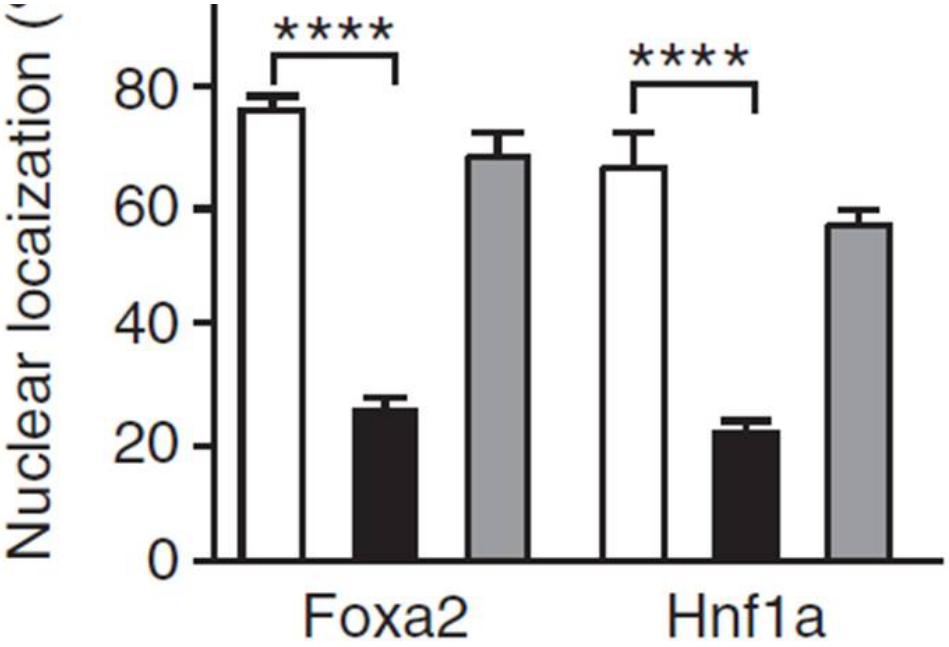
out that **both strains of mice have a higher caloric intake on this diet**, so it's not that.

There are likely numerous genetic differences between these strains of mice, but one particularly interesting difference was discovered in 2006 (4 (http://www.ncbi.nlm.nih.gov/pubmed/16497723)). **It turns out that B6/J mice — but not other sub-strains B6 mice or non-B6 mice — have a deletion in the gene that codes for a critical enzyme in glutathione metabolism.** As a result of the deletion, the mitochondria of these mice are unable to regenerate a particular form of the B vitamin niacin, and thus have a seriously impaired ability to recycle the master cellular antioxidant glutathione under conditions of oxidative stress.

Glutathione To the Rescue?

Now, how might this relate to the fat-and-diabetes study we're trying to pick apart at the moment? Well, these researchers also used B6/J mice. And when they induced the disease process in healthy cells by incubating them with palmitate, they showed they could block the effect entirely if they also incubated the cells with N-acetylcysteine (NAC):





The black bars show that palmitate reduced the ability of these two critical proteins to bind to DNA, while the gray bars show that palmitate no longer had this effect if the cells were simultaneously given NAC.

NAC is best known as a precursor to glutathione, and is used for this purpose not only in experimental science but even in clinical practice. Depletion of glutathione is essential to the mechanism of acetaminophen (Tylenol) toxicity, for example, which accounts for half of all cases of acute liver failure in the United States and Great Britain. Administration of NAC is a highly effective remedy in the first ten hours of overdose, and it is believed to act at least in part by restoring glutathione levels (5 (http://www.ncbi.nlm.nih.gov/pubmed/20020268)).

The authors of this study did not measure glutathione levels, but the hypothesis that glutathione is protective is consistent with a study I wrote about in a post back in January, "Eating Fat and Diabetes." (http://blog.cholesterol-and-health.com/2011/01/eating-fat-and-diabetes-response-to-bix.html) In that study (6 (http://www.jci.org/articles/view/37048)), high-fat diets depleted glutathione and impaired insulin sensitivity and glucose tolerance in rats and mice, but treating the rats with a mitochondrial antioxidant and genetically engineering the mice to make lots of the antioxidant enzyme catalase both reversed these effects. Catalase is an enzyme that converts hydrogen peroxide to water.

How Does This All Fit Together?

When mitochondria are overloaded with more energy than they can handle, they begin making increasing amounts of the free radical superoxide. Superoxide carries out important signaling roles. Among them, it directs excess energy into fat synthesis. But it can also wreak havoc on the cell by forming oxidants that can damage vulnerable proteins, lipids, and other important molecules. Thus, a manganese-dependent enzyme called superoxide dismutase converts it into hydrogen peroxide. Hydrogen peroxide can also damage important molecules, but increasing evidence suggests it also regulates the activity of hundreds of proteins by controlling several "redox switches," including glutathione.

An interesting picture begins to emerge as a working hypothesis:

- When the mitochondria's capacity to burn lipids and fats in order to make ATP is overloaded, it makes signals such as superoxide that will redirect incoming energy to be stored as fat.
- Superoxide also generates hydrogen peroxide, which oxidizes glutathione and thereby flips a "redox switch" controlling a multitude of proteins. These proteins may then help the cell stop responding to insulin in order to minimize energy overload.
- This is a desperate attempt of the cell to protect itself from oxidants that would otherwise destroy its basic machinery, and has the unfortunate consequence of increasing glucose and other forms of energy in the blood, and thus contributing to the metabolic abnormalities we associate with diabetes.
- Supporting the cell's antioxidant defense network helps it to handle more energy and thereby protects against this entire process. Thus, providing NAC to cells, synthetic mitochondrial antioxidants to rats, or extra catalase to mice all seem protect against the development of diabetes-like features in the face of energy overload.

In my view, the major causative factor in this pathogenic process is energy overload. This, however, does not simply mean "excess calories." It means that calories are supplied in excess of our body's capacity to burn them. This capacity is increased by exercise, optimal thyroid status, lack of infection and inflammation, and a variety of

vitamins and minerals involved in energy metabolism and antioxidant defense.

If this is correct, does a "high-fat diet" cause diabetes? The obvious question that must follow is "which high-fat diet?" An anti-inflammatory, invigorating, nutrient-dense diet likely protects against diabetes regardless of whether it is low or high in fat.

For more on glutathione, see "The Biochemical Magic of Raw Milk and Other Raw Foods: Glutathione." (http://www.westonaprice.org/blogs/cmasterjohn/2010/09/11/the-biochemical-magic-of-raw-milk-and-other-raw-foods-glutathione/)

Read more about the author, Chris Masterjohn, PhD, here (http://www.cholesterol-and-health.com/about-cholesterol-and-health.html).

Print post

About Christopher Masterjohn

Chris Masterjohn, PhD, is creator and maintainer of www.chrismasterjohnphd.com. Chris is a frequent contributor to Wise Traditions, the quarterly journal of the Weston A. Price Foundation, and is a perennial speaker at the annual Wise Traditions conference. He has written five peer-reviewed publications, and has submitted two additional experimental papers for peer review, one of which has been accepted for publication. Chris has a PhD in Nutritional Sciences from the University of Connecticut and has worked as a Postdoctoral Research Associate at the University of Illinois where he studied interactions between vitamins A, D, and K. The contents of this blog represents his independent work and does not necessarily represent the positions of the University of Illinois.