“Why is Eating **Too Much Sugar So Toxic?**”

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Americans consume about **140 lbs. of sugar annually** (57 gallons of soda!).

One hundred years ago we consumed ~**10 lbs.**

Mostly **sucrose, glucose and fructose.**

**Fructose**, is particularly toxic - especially High Fructose Corn Syrup – **cheap and sweet!**

ubiquitous in almost all **processed foods**: soda, fruit juices, cereals, ketchup, jellies, graham crackers, breads, most chocolate milk, and **many** others – kids eat a LOT of fructose!

**Eating Sugar Makes Us Hungry** - it interferes with three hormones—**ghrelin, leptin** and dopamine—all of which signal our brain that we have had enough to eat.

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Glucose Stimulates Insulin Signaling to
Up-Regulate Leptin
Which Tells you to Stop Eating.

Fructose is
metabolized
In the Liver mostly to
Fat And it **Does NOT**
stimulate Insulin
Signaling to Stop Eating.

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http://www.eatchicchicago.com/blog/2014/01/21/is-fat-or-sugar-making-us-fat/
http://www.joearrigo.com/2012/09/11/the-toxin-that-is-sugar/
Sugar Toxicity: Chronic High Blood Sugar

- Nephropathy
- Retinopathy
- Neuropathy
- Cardiovascular disease
- Hepatic and skeletal muscle insulin resistance

Why is Prolonged High Blood Sugar So Toxic?
Properties of O-GlcNAc.

- Highly Dynamic **Enzymatic** Modification of Ser and Thr residues by β-N-acetylglucosamine
- Localized to the **cytoplasm and nucleus** on cell’s regulatory proteins.
- Highly abundant PTM (>4000 identified proteins) & Often Reciprocal (Competitive) with phosphorylation - Abundance = pancreas islets>>brain>>other tissues>liver.
- Dynamically **cycling** on Ser/Thr residues - **Time scale similar to phosphate.**

O-GlcNAc is Abundant on Nuclear & Cytosolic Proteins

2-5% Glucose To Hexosamine Biosynthesis

UDP-GlcNAc

Ser/Thr

OGT

UDP

Naked protein

Glycoprotein

UDP-GlcNAcase

(Hart *et al.*, Nature, April 2007)

Pan >O-GlcNAc Antibody Western Blot - HeLa
O-GlcNAc Has Extensive Crosstalk with Phosphorylation to Serve As A Nutrient Sensor that Regulates Many Cellular Processes


UDP-GlcNAc Is a Major Node of Metabolism.
High Glucose Increases O-GlcNAcylation on Many Proteins

Jurkat Lymphocytes Grown in Media With 5mM or 30mM Glucose

(Coomassie not different)

WB with Pan >O-GlcNAc Antibody:
Steady-State O-GlcNAc Increases on Many Proteins.
High Glucose Increased O-GlcNAc is a Major Mechanism of “Glucose Toxicity”

- Hyperglycemia, hyperlipidemia and hyperinsulinemia all increase O-GlcNAcylation of many proteins.

**Mechanisms:**

- Signaling Molecules & Kinases – Balance with Phosphorylation is Disrupted.

- Some Examples:
Elevation of O-GlcNAc Blocks Insulin Signaling:

- Blocks AKT phos. at T308 and S9 on GSK3β
- Inhib. OGase greatly increases OG on β-catenin and IRS1.

Transgenic Mice with Overexpressed OGT in Muscle or Adipose - Become Diabetic. (McClain & Hanover)

**Blocks Pathway At Many Points!!**
Over one-half of all human protein kinases are dynamically modified by the sugar O-GlcNAc.

The sugar, O-GlcNAc Regulates Kinases Key to Signaling:

- AKT is regulated by O-GlcNAcylation (*Am J Physiol Endocrinol Metab.* 295:E974-80)
- All PKCs: O-GlcNAc Negatively Regulates (*Biochim Biophys Acta.* 1783:695-712)
- O-GlcNAc Inhibits PFK1 & Glycolysis in Cancer - Increases Flux Through Pentose phosphate pathway. (*Science* 337:975-80)

Cardiac Myocytes: CAMKII Becomes Constitutively Active Due to Hyper-O-GlcNAcylation in Diabetes

Contributes to Arrhythmias and Cardiac Problems in Diabetes

Key to Diabetic Cardiomyopathy

Collaboration with Donald M. Bers Ph.D. UC Davis

Nephrin & Podocin Proteins Are Key to Kidney Function: Podocyte Filtration Barrier
Increased O-GlcNAc Due to High Glucose Blocks the Transcription of Podicin and Nephrin

Inhibition of the O-GlcNAc Transferase, Even in High Glucose Restores Podicin and Nephrin Expression.
At Least 88 Mitochondria proteins are O-GlcNAcylated:

**Normal Mitochondria:**
Elevating O-GlcNAc Improves Mitochondrial Function.

O-GlcNAcylated proteins in complex I (in red color)

Overview of mitochondrial O-GlcNAcome.
(in ★ )

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Junfeng Ma

O-GlcNAc Transferase is Mislocalized in Cardiac Mitochondria From Diabetic Rats:

**a** BN PAGE of mito samples with anti-OGT

**b** WB: AL03

**c** OGT activity assay on complex IV IP with antibody conjugated beads

Dramatic reduction in OGT Activity in Complex IV

Partha Banerjee

PNAS 112, 6050-6055 (2015)
Mitochondrial proteins are O-GlcNAcylated differentially (control vs diabetic rat heart).

Directly Results in Mitochondrial Dysfunction.

PNAS 112, 6050-6055 (2015)
What Happens When You Knock-Out the Enzyme that Adds O-GlcNAc to Proteins In the Region of the Brain in Adult Mice that Controls Feeding and Satiety?

OGT-expressing neurons as nutrient sensors in hypothalamus and brainstem

Paraventricular nucleus (PVN): controls feeding and satiety
Arcuate nucleus (ARC): controls adipose metabolism

Gary J. Schwartz Science 2016;351:1268-1269
~2-3 Weeks Targeted KO is Morbidly Obese & Hyperactive

Mice Missing O-GlcNAc in the PVN Brain Region Can’t Stop Eating!

Conclusions – O-GlcNAc:

♥ O-GlcNAc is a Major **Nutrient** Regulatory Post-Translational Modification in all multicellular eukaryotes - Plants & Animals & Viruses (some bacteria).

♥ O-GlcNAc is **Required for Life at All Levels in Mammals and Plants.**

♥ **Crosstalk** or Interplay Between O-GlcNAcylation & Phosphorylation is Extensive and Involved in Many Cellular Processes.

♥ O-GlcNAc is **Important to Transcription**: is Part of the Histone Code where Most Sites are at Contact Regions with the DNA of the Nucleosome.

♥ Many Toxic Affects of Hyperglycemia Result From **Dysregulation of the Balance Between O-GlcNAc and Phosphorylation & Dysregulated Transcription** = Glucose Toxicity.

♥ **Future Drug Targets for Treating Obesity & Diabetes**: 1) Lower O-GlcNAcylation Globally; 2) Lower it Selectively by Targeting the Over 800 specific proteins that Target the O-GlcNAc Transferase to its Substrates.

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Department of Biological Chemistry
The biology of order, the chemistry of life