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beauty and diabetes are increasingly of concern worldwide, with diabetes estimated to affect over 200 million people. A causal factor of diabetes is hyperglycaemia (high blood sugar) and this is well known to be linked with high sugar diets. Dr Hoffmann is focused on evaluating how hyperglycaemia influences health during the onset and progression of diabetes.

Through a project funded by the United States National Institutes of Health (NIH), the team is investigating the effects of glycosylation (sugar modification of a protein) on the cardiovascular system as a result of increasing concentrations of high glucose. In normal cellular function, glycosylation plays an important role in the management of protein structure, function and location; along with other post-translational modifications like phosphorylation. The disruption of this fine balance in individuals with high blood sugar contributes to many of the health problems associated with diabetes, such as cardiovascular disease or other systemic diseases.

By influencing the populations of these glycosylated and phosphorylated proteins in cellular and animal models through exposure to varying concentrations of high glucose, Dr Hoffmann and his colleagues are able to probe the resulting changes in cell signalling and function. The lab uses highly sensitive mass spectrometry technologies to analyse the molecular make up of cell fractions and performs functional tests on isolated endothelials (cells that line the blood vessels) to identify alterations in the balance of protein populations and subsequent impairments of homeostatic signalling. Through complex bioinformatic analyses of the data they are then able to understand the impact of these changes on cardiovascular function.

IDENTIFY, ANALYSE, REPEAT

The first aim of their current project is to identify cell surface glycoproteins in blood vessels that are altered during states of hyperglycaemia, particularly those related to the regulation of blood pressure through vasodilation and constriction, among other cardiovascular effects.

The second aim of the project is to analyse the downstream effects on these pathways related to the disturbances in the receptor populations. By enriching for glycosylated and phosphorylated proteins in the cell and testing their expression in the cells to get a better idea of the synergistic balance between different modifications, are then compared to gene expression in the cells to get a better idea of the changes occurring. Dr Hoffmann’s laboratory is using these experiments to robustly test the hypothesis that exposure of endothelial cells to high glucose will alter the downstream effects on these pathways.

Dr Hoffmann from the joint Department of Biomedical Engineering at the Medical College of Wisconsin and Marquette University studies the effect of high sugar and non-caloric artificial sweetener diets on the progression of diabetes. His laboratory is particularly interested in the contribution of these food additives to factors associated with diabetes, such as obesity and cardiovascular disease. He has found evidence showing that both glucose and non-caloric substitutes alter the cardiovascular system, albeit through different mechanisms.

The laboratory hypothesises that glycosylation is driving alterations of important homeostatic vascular endothelial pathways during states of hyperglycaemia.
researchers such as Dr. Hoffmann, the negative health effects of a high sugar diet are well documented and known amongst the general population. This has resulted in a significant market for non-caloric artificial sweeteners to replace sugar in many foods, which have now become one of the most used food additives worldwide. Due to limited research into the use and action in the body, it is only recently that the negative impact of consuming artificial sweeteners in the place of sugar has become recognised.

Dr. Hoffmann is now turning the focus of his laboratory to include research aimed at better understanding how artificial sweeteners might contribute to the onset of diabetes, as the rise in the disease has dramatically increased despite the addition of these sweeteners in everyday diets. Using a combination of cell, tissue, and animal models, Dr. Hoffmann’s laboratory has seen very interesting changes in lipid and energy metabolism following acute exposure to various non-caloric artificial sweeteners, which they believe may be a big contributing factor to the progress of the disease. The laboratory also has gene expression data showing that various artificial sweeteners cause global downregulation of signalling pathways important to the cardiovascular system. At the same time, glucose had little changes as the gut bacteria of this acute study, supporting the glycoalyx hypothesis and showing that the two types of signalling pathways have different roles in the disease through very different routes.

Dr. Hoffmann’s laboratory is performing more research to further elucidate just how these effects are caused, but one interesting strand of his investigations focuses on the microbiome or the gut bacteria. These populations of commensal organisms are vital for your body’s proper function and imbalances can lead to a rise of pathogenic microbes in the digestive system that can cause severe illness. Dr. Hoffmann and his collaborators have an evidence-based hypothesis that alterations in the diet, such as an increase in sugar or non-caloric artificial sweeteners, will change the composition of the microbiome, in turn negatively altering the body’s homeostatic metabolic functions. It is their belief that subsequent processing of these food additives by the gut bacteria could ultimately be contributing to impaired glycoalyx control and other negative physiological health outcomes.

**DEVELOPING SCIENCE, DEVELOPING SCIENTISTS**

There is much more work to do to fully understand the complex processes which underlie the effects seen in the preliminary tests. Dr. Hoffmann, like other researchers, will need talented young scientists to take forward their ideas and assist in uncovering the web of interactions. Perhaps this is why he is driving forward the SUPREMES (Students Understanding Principles of Research Education Through Medicine, Engineering, and Science) Program at the Medical College of Wisconsin in collaboration with Tim Sobotta, his department’s Education Outreach Manager. This programme aims to equip high school students to be the ground-breaking researchers of the future by providing them with year-long experience in biomedical research and technology development in laboratories at the Medical College of Wisconsin, Marquette University, and the Children’s Hospital of Wisconsin. Research brings students from local schools into the funded laboratories at the partnering institutions, providing an experience where the students can apply what they learn in the classroom. The broad open-access application process allows for a diversity of students, who might otherwise miss out on the opportunity, to participate in scientific research first-hand. Dr. Hoffmann is rightly proud of this exciting initiative, one which pioneers the development of our future health care professionals.

**What immediate effects of a high sugar diet have you observed in your studies?**

The key to dietary sugar is moderation. Our studies show that if your body has the machinery to process sugar and in moderation it can be cleaned quite effectively. However when it is consumed in excess your body’s machinery gets stressed and breaks down, allowing glucose accumulation. Our current studies have demonstrated that following an acute two-week exposure to high glucose in a healthy cardiovascular model system you start to see glycoalyx-dependent dysfunction, among other changes. As diabetes progresses, hyperglycaemia becomes more persistent, allowing these modifications to build up and cause significant impairment of numerous systems within the body.

**What are the metabolic effects of a diet rich in non-caloric artificial sweeteners?**

Non-caloric artificial sweeteners are foreign chemicals that your body does not have the machinery to deal with. Even those marketed as “natural” because they are from a plant are foreign and it does not make it any easier for your body to process them. There are a lot of poisons from plants that are “natural”. In our studies examining the rat metabolome following acute non-caloric artificial sweetener diet supplementation we have observed alterations in lipid (fat) and energy processing. We observed accumulation of lipids and indicators of muscle breakdown, possibly as a compensatory energy source. Your body needs some glucose for energy and if not available it will find energy through other sources that may be detrimental to your health.

**How do high sugar and artificial sweetener diets contribute to the onset of diabetes and related health problems such as obesity and cardiovascular disease?**

Our studies show that in a healthy model exposed to high glucose continuously for two weeks you start to see vascular impairment. As sugar concentrations increase this catalyses spontaneous glycosylation of proteins (Maillard reactions) which can alter cardiovascular function. As this high blood glucose persists you start to develop insulin resistance so glucose cannot be cleared and you get further accumulation of glycosylation altering homeostatic functions. Non-caloric artificial sweeteners were introduced to alleviate such problems, but recent research suggests there are a variety of metabolic alterations that result, including lipid and energy processing, and thus potentially contribute to the increase in obesity and diabetes.

**How will your research impact on treatment options?**

We have evidence that removing glycosylations from proteins during states of hyperglycaemia partially restores endothelial function and this may be an approach that can be taken improve cardiovascular health among diabetic patients. We also want to bring awareness to the public that glucose is okay in moderation and your body requires some for normal function. Additionally, just because something is marketed as non-caloric does not mean it is healthy for you, there are big changes happening to your body altering the gut bacteria that may be able to impact the effects seen with numerous food additives to improve overall health.

**Why is the SUPREMES program important to you?**

In my laboratory we look to develop future research scientists at all levels, from high school students all the way up to the postdoctoral level. Our lab consists of high school students, undergraduates, graduate, and medical students, along with postdoctoral fellows. This mix of researchers at various levels brings unique perspectives to the laboratory and enriches the learning process. It is also important to get youth involved in various scientific fields early on to ensure that we have a continued influx of high quality researchers in the future to further improve worldwide health.

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**BIO**

Dr. Brian Hoffmann is an Assistant Professor in the joint Department of Biomedical Engineering at the Medical College of Wisconsin and Marquette University at Milwaukee, WI. He received his PhD in Molecular and Cellular Pharmacology from the University of Wisconsin-Madison and his Bachelor and Chemistry from St. Norbert College.

**RESEARCH OBJECTIVES**

Dr. Hoffmann’s research explores the causative mechanisms leading to the onset and progression of diabetes. In particular, his interests lie in the effects of protein glycosylation on the cardiovascular system and alterations in lipid and energy metabolism during the disease.

**FUNDING**

National Institutes of Health (NIH)

**COLLABORATORS**

- Professor Martin J. Hessner, PhD, Medical College of Wisconsin and Children’s Hospital of Wisconsin
- Professor Andrew S. Greene, PhD, Medical College of Wisconsin (NIH NIDDK K01 Mentor)
- Michael E. Widlansky, MD, MPH, Medical College of Wisconsin (NIH NIDDK K01 Co-Mentor)
- Tim Sobotta, SUPREMES Co-Director, Education Outreach Manager, Clinical and Translational Science Institute, Medical College of Wisconsin

**SUPREMES**

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