Altered Cell-surface Receptor Levels Result from Fructose Advanced Glycation End Product-Induced Inflammation

Matthew Stryker  
*St. John Fisher College, mds05927@students.sjfc.edu*

Regina Blackley  
*St. John Fisher College, rcb00745@students.sjfc.edu*

Melinda E. Lull  
*St. John Fisher College, mlull@sjfc.edu*

Follow this and additional works at: [https://fisherpub.sjfc.edu/doctoral_ext_pub](https://fisherpub.sjfc.edu/doctoral_ext_pub)

Part of the Pharmacy and Pharmaceutical Sciences Commons

How has open access to Fisher Digital Publications benefited you?

Publication Information

[https://fisherpub.sjfc.edu/doctoral_ext_pub/3](https://fisherpub.sjfc.edu/doctoral_ext_pub/3)  
Please note that the Publication Information provides general citation information and may not be appropriate for your discipline. To receive help in creating a citation based on your discipline, please visit [http://libguides.sjfc.edu/citations](http://libguides.sjfc.edu/citations).

This document is posted at [https://fisherpub.sjfc.edu/doctoral_ext_pub/3](https://fisherpub.sjfc.edu/doctoral_ext_pub/3) and is brought to you for free and open access by Fisher Digital Publications at St. John Fisher College. For more information, please contact [fisherpub@sjfc.edu](mailto:fisherpub@sjfc.edu).
Altered Cell-surface Receptor Levels Result from Fructose Advanced Glycation End Product-Induced Inflammation

Abstract
Objective: As a result of the heightened reactivity fructose demonstrates compared to glucose and our current knowledge of glucose advanced glycation end-products, the aim of this research was to further elucidate the proinflammatory pathways involved in the response to fru-AGE exposure, including the effects of fru-AGEs on cell-surface receptor expression. We hypothesized that once microglia were activated in response to fru-AGE exposure, there would be an increase in the expression of RAGE and TLR4 to facilitate the proinflammatory cascade.

Disciplines
Pharmacy and Pharmaceutical Sciences

Comments
Poster presented at at American Society of Health Systems Pharmacy Midyear Clinical Meeting in Anaheim, California, in December 2014.

This poster presentation is available at Fisher Digital Publications: https://fisherpub.sjfc.edu/doctoral_ext_pub/3
Introduction

Fructose, a naturally occurring simple sugar, is also an industrial sweetener that has become a mainstay in the American diet, notably in sugar drinks. A consequence of excess fructose consumption is the non-enzymatic generation of fructose advanced glycation end-products (fru-AGEs). The non-enzymatic glycation with fructose is ten times greater than compared to glucose. Within the central nervous system, microglia, resident macrophages surveying their microenvironment, become activated when exposed to fru-AGEs. The activation of microglia initiates a cascade of proinflammatory processes. Some of these signals are mediated by TLR4, tumor necrosis factor (TNFα), and cytokines, which have been implicated in the development of diabetic retinopathy, nephropathy) and age-related diseases, such as Alzheimer's disease.

Methods

FrU-AGEs were generated by incubating fructose with bovine serum albumin (BSA) at 37°C for 8 weeks. An immortalized rat microglial cell line (HAPI) was treated with control media or fru-AGEs in vitro for 3 or 24 hours in the following concentrations: 0.1, 0.2, 0.4 μg/mL. Gene expression of pro-inflammatory markers and cell-surface receptors was measured using quantitative real-time polymerase chain reaction (qRT-PCR). Gene inflammation included the following complement 5 (C5), interleukin-1β (IL-1β), tumor necrosis factor α (TNFα), receptor for AGE (RAGE), and toll-like receptor 4 (TLR4). Levels of RAGE protein were measured after 24 hours of exposure to fru-AGEs via Western Blot. To further characterize the proinflammatory response, extracellular hydrogen peroxide (H₂O₂) was quantified using the ROS-Glo H₂O₂ chemiluminescent assay (Promega) following a 3 hour incubation with the fru-AGE treatments listed above. Statistically significant changes for each measure were determined using a one-way ANOVA with a Tukey post-hoc test; a p-value < 0.05 was considered significant. All data are expressed as the mean ± SEM.

Results

**Proinflammatory Signals**

**Receptor Expression Changes**

**Non-protein Inflammatory Signals**

**Conclusions**

- This evidence suggests that exposure to fru-AGEs increases the expression of known mediators of inflammation, including the following C5, IL-1β, TNFα (statistically significant, dose-dependent effect: acute and chronic effects) and extracellular H₂O₂ (statistically significant dose-dependent effect).
- Cell-surface receptors including RAGE and TLR4 also demonstrate changes in their gene expression when exposed to fru-AGEs. RAGE expression was acute and chronically suppressed after prolonged fru-AGE exposure. After 3 hours, TLR4 was also suppressed but more replicates are needed.
- Analysis of protein levels support the gene expression trend observed with both RAGE and TLR4 suggest that fru-AGEs lead to a diminished level of mature RAGE protein.
- The decrease in receptor expression observed with both RAGE and TLR4 suggests that microglia can become desensitized to pro-inflammatory stimuli. This observation is concerning because immune cells need to remain sensitized to noxious stimuli to help protect and defend the host.
- This research continues to illustrate and support the hypothesis that exposure to fru-AGEs induces an inflammatory state mediated by microglia within the brain and alters cell-surface receptors.
- In addition to their neurodegenerative effects in disease states such as Alzheimer’s disease, further investigation about the endogenous effects of fru-AGEs should be considered, especially as a result of its accessibility from its use as an industrial sweetener.
- Further areas of research include additional replicates of C5, IL-1β and TLR4 gene expression and extracellular H₂O₂ production to further validate this hypothesis.

**References**


**Disclosure**

The authors of this presentation have no personal or financial interest in the subject matter of this presentation.

Matthew Stryker: Nothing to disclose
Regina Blackley: Nothing to disclose
Melinda Lull: Nothing to disclose