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### The differential effects of fructose and glucose on advanced glycation end-product formation and cellular damage in vitro

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## The differential effects of fructose and glucose on advanced glycation end-product formation and cellular damage in vitro

### Abstract

The protective mechanisms of microglia cells help to maintain central nervous system (CNS) homeostasis and function.1 Microglia are innate immune cells that constantly survey their surrounding CNS microenvironment for pathogens, damaged cells, and inflammatory molecules. Sugars from our diet, including glucose and fructose, combine with endogenous proteins non-enzymatically and form advanced glycation-end products (AGEs).2 AGEs are shown to produce reactive oxygen species, leading to inflammation and cellular damage that may be mediated by microglia.3 Fructose consumption has become increasingly prevalent within the American diet, as it is a lower cost sweetener.4 Microglia become activated and phagocytic in the presence of high levels of glucose, but the effects of fructose are not yet fully understood.3 The reactivity of fructose within the body and its long-term health implications remain unclear.

### Disciplines

Pharmacy and Pharmaceutical Sciences

### Comments

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

# The differential effects of fructose and glucose on advanced glycation

## end-product formation and cellular damage *in vitro*

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### Introduction

The protective mechanisms of microglia cells help to maintain central nervous system (CNS) homeostasis and function.<sup>1</sup> Microglia are innate immune cells that constantly survey their surrounding CNS microenvironment for pathogens, damaged cells, and inflammatory molecules. Sugars from our diet, including glucose and fructose, combine with endogenous proteins non-enzymatically and form advanced glycation-end products (AGEs).<sup>2</sup> AGEs are shown to produce reactive oxygen species, leading to inflammation and cellular damage that may be mediated by microglia.<sup>3</sup> Fructose consumption has become increasingly prevalent within the American diet, as it is a lower cost sweetener.<sup>4</sup> Microglia become activated and phagocytic in the presence of high levels of glucose, but the effects of fructose are not yet fully understood.<sup>3</sup> The reactivity of fructose within the body and its long-term health implications remain unclear.

### Objective

Fructose has been shown to produce a faster rate of glycation, or AGE formation, compared to glucose.<sup>2</sup> The accumulation of AGEs in the body causes damage and negatively impacts health. AGE formation occurs as part of the natural aging process, but is also associated with diabetes and neurodegenerative diseases, such as Alzheimer's and multiple sclerosis.<sup>3</sup> The goal of this research was to compare the reactivity of fructose and glucose as well as the viability of microglia treated with each sugar.

### Methods

To measure AGE production in a non-cellular environment, 1M glucose or fructose was incubated at 37°C with 1mM bovine serum albumin for eight weeks. Weekly fluorescence readings of each sample were made to measure the amount of glucose-AGE (Glu-AGE) and fructose-AGE (Fru-AGE) production. *In vitro* effects of glucose and fructose were observed by measuring microglia viability and AGE production after treatment with glucose or fructose. An immortalized microglial cell line (HAPI) was treated with control media and fructose 100, 50, 25 and 10mM or the equivalent concentrations of glucose. Cell survival was measured following a 24 hour incubation using an MTT assay. *In vitro* AGE production was measured using an anti-AGE antibody via Western Blot. AGE production was quantified after a 24 hour incubation, in the presence of fructose 100, 50, 25 and 10mM, glucose 50mM, or control. Statistical analysis included a one-way ANOVA with a Tukey post-hoc test; p-values less than 0.05 were considered significant.

### Results

#### Glu-AGE and Fru-AGE Production and Weekly Fluorescence

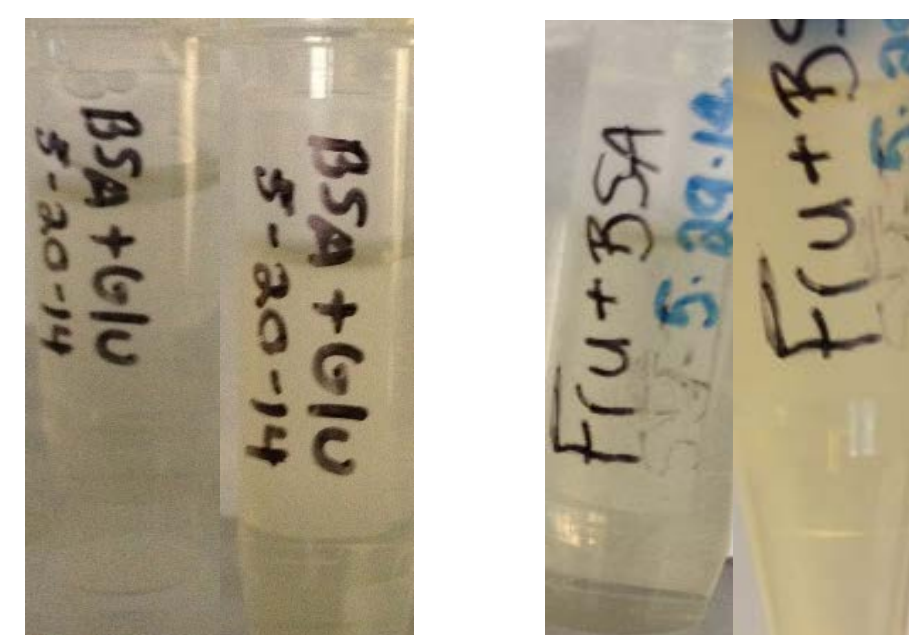


Figure 1. Glu-AGE and Fru-AGE production. Left: Change in Glu-AGE production from week 1 to week 4. Right: Change in Fru-AGE production from week 1 to week 4. Change in color signifies AGE production.

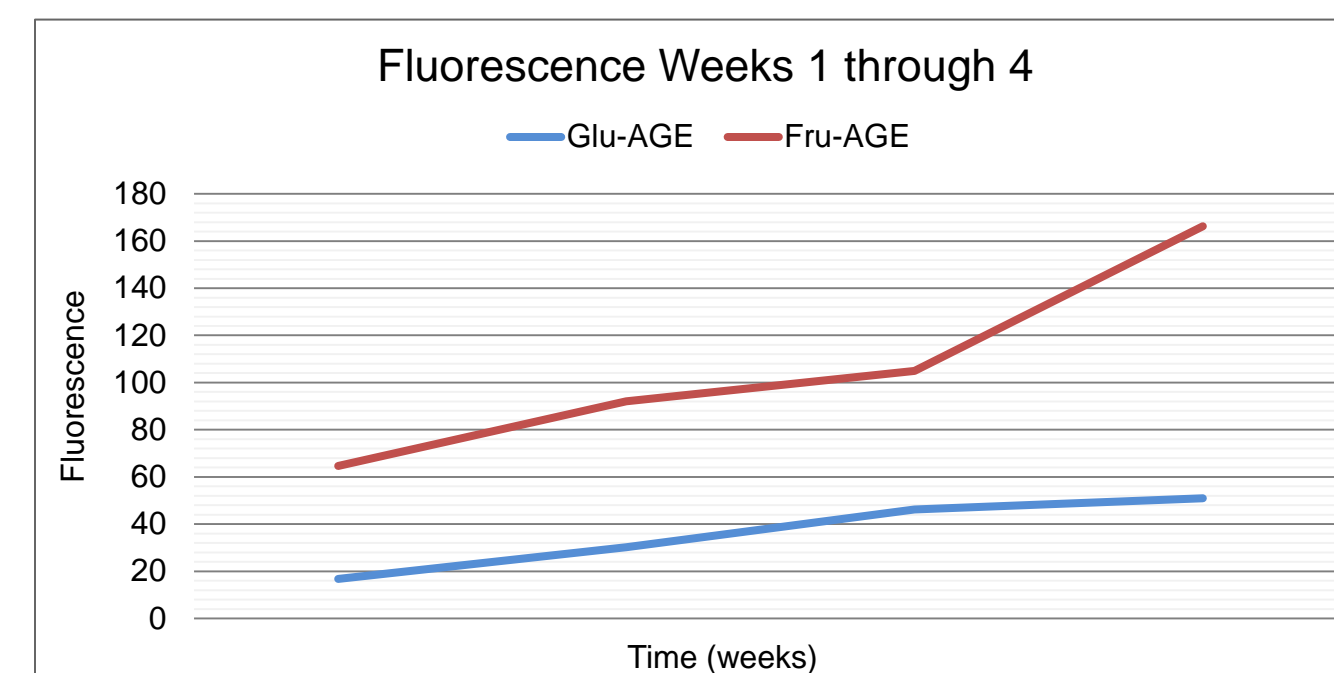


Figure 2. Weekly fluorescence readings of Glu- and Fru-AGEs. Increases in fluorescence each week indicates the reaction between sugars and bovine serum albumin (BSA). Fructose has a faster rate of glycation than glucose.

#### Microglia Cell Survival

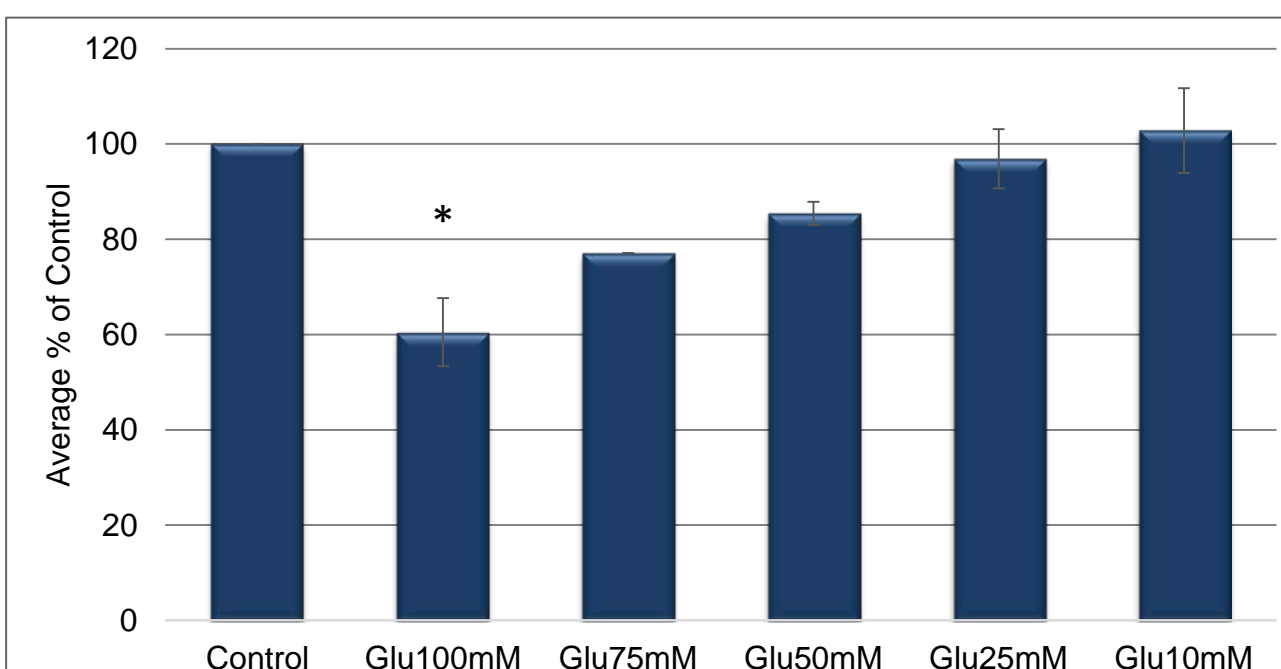


Figure 3. Effect of glucose on microglia survival. Glucose 100mM was the only treatment to significantly decrease cell survival compared to control. Cell survival increased proportionately as glucose concentration decreased. \*p<0.05

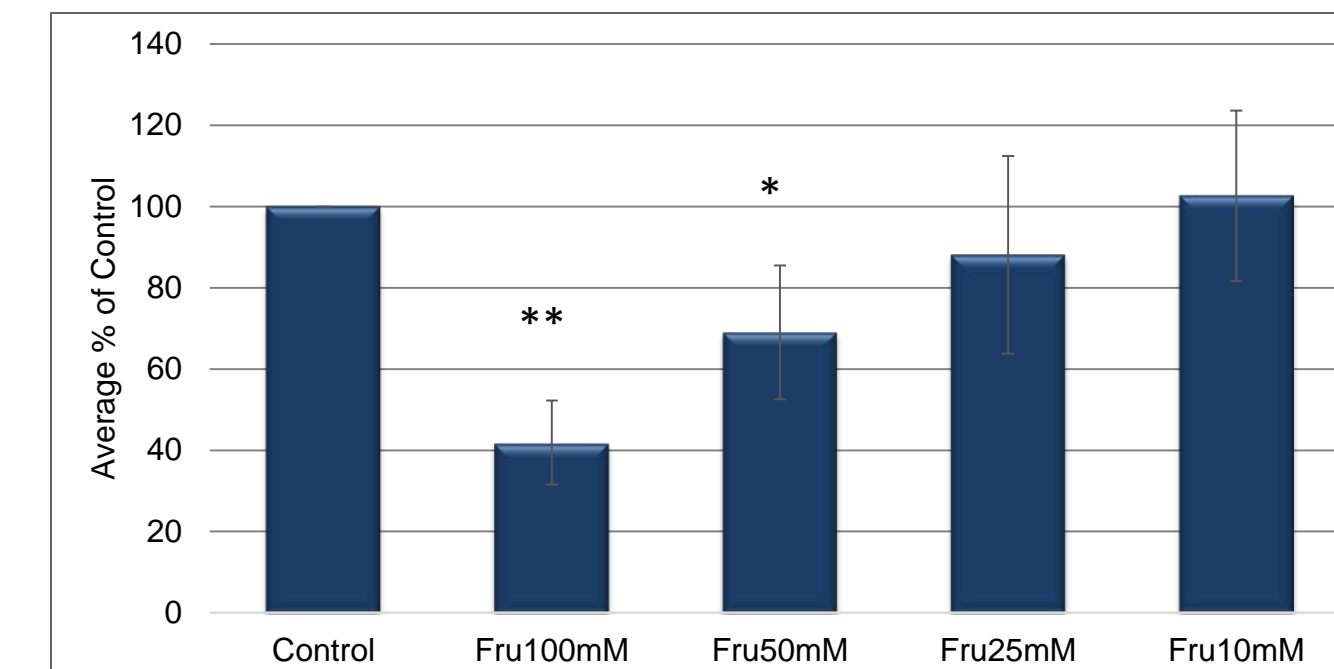
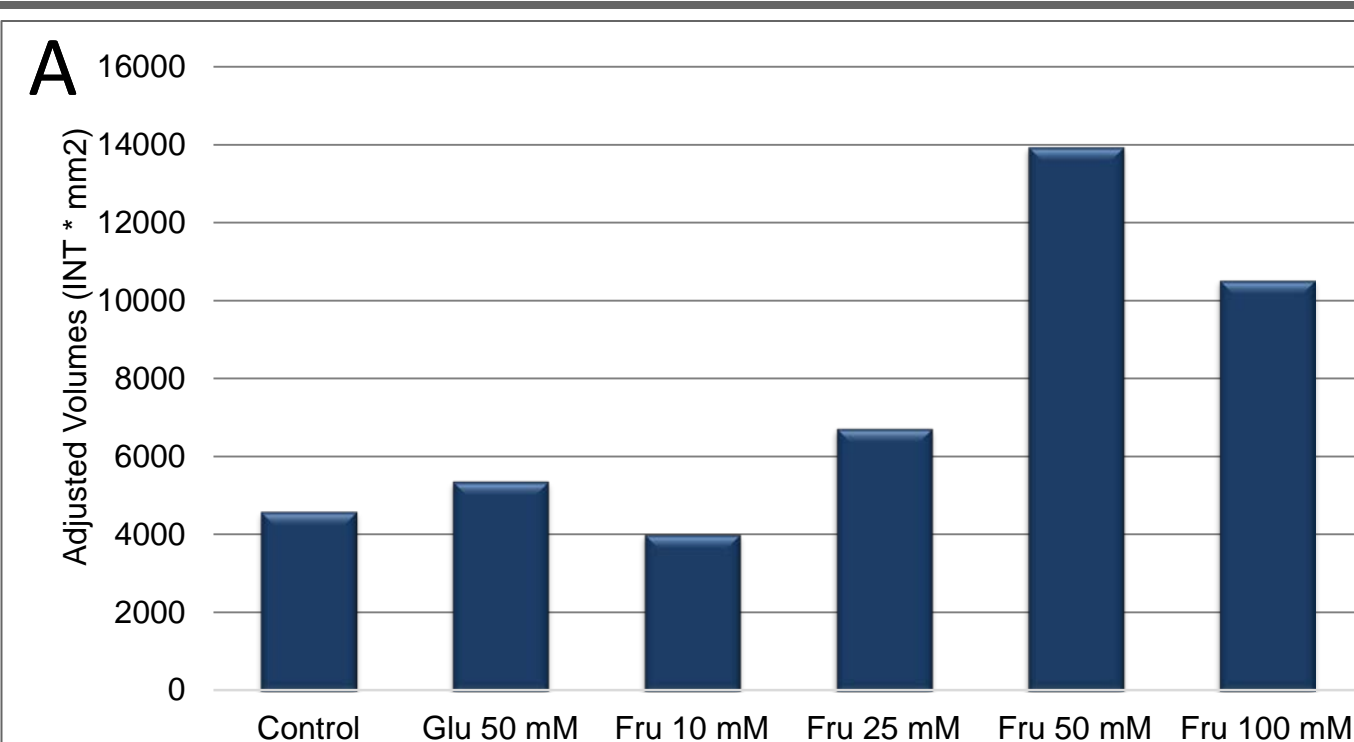


Figure 4. Effect of fructose on microglia survival. Fructose 100 and 50mM significantly decreased cell survival compared to control. Cell survival increased proportionately as concentrations decreased. \*\*p<0.001, \*p<0.05



#### Quantification of Glu-AGE vs Fru-AGE Production

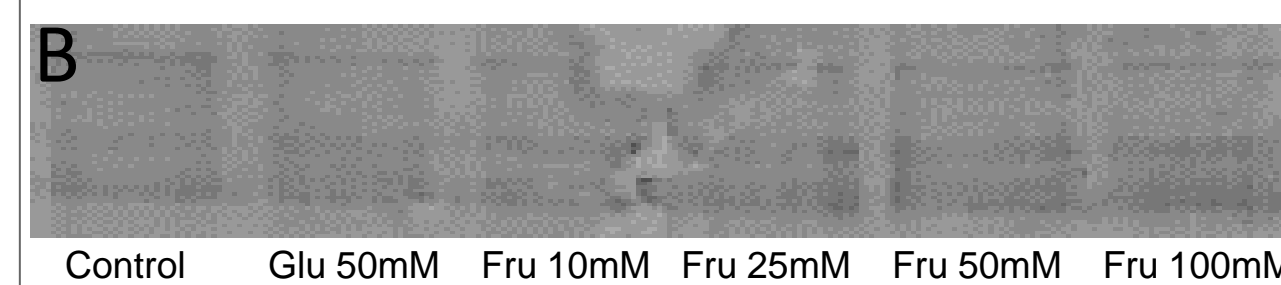


Figure 5. AGE-protein production in HAPI cells. An anti-AGE antibody was used to quantify the amount of AGEs produced in HAPI cells when treated with glucose or fructose. AGE protein production increased as fructose concentration increased, with the exception of Fructose 100mM. The quantity of Fructose 50mM was greater than twice that of Glucose 50mM. (5A) A representative western blot image is shown in 5B.

### Conclusions

- Both fructose and glucose are shown to be reactive and detrimental to cells in cellular and non-cellular environments.
- At higher concentrations, both sugars resulted in AGE formation and cellular death.
- Fructose glycation occurs at a higher rate than glucose glycation in a non-cellular environment (Figures 1 and 2).
- The highest sugar concentrations tested, glucose 100mM and fructose 100mM, both significantly decreased microglia cell survival. Fructose 50mM also significantly reduce cell survival (Figures 3 and 4).
- Cell viability is reduced at a higher level in fructose-treated cells compared to treatment with equivalent concentrations of glucose (Figures 3 and 4).
- A higher rate and amount of Fru-AGE production was seen in cells treated with 100mM and 50mM fructose eluding that fructose may have more potent deleterious effects than glucose (Figure 5).
- Our data suggests that fructose may be more reactive and produce more deleterious effects than glucose, but more data are needed to determine if higher Fru-AGE production causes greater cellular damage and inflammation *in vitro* and *in vivo*.

### References

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### Disclosures

Authors of this presentation have personal or financial interest in the subject matter of this presentation.

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