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EFFECTS OF FEEDING WITH NON-AUTOCLAVED AND AUTOCLAVED FRUCTOSE-ARGININE MIXTURE ON STRESS RESISTANCE OF DROSOPHILA MELANOGASTER

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Abstract. The diet of modern people includes fast food that leads to the development of obesity and related diseases. One of the reasons for the negative impact of such a diet is advanced glycation end products (AGEs), substances formed as a result of the interaction of amino acids with carbohydrates, especially under the influence of high temperature (the Maillard reaction). Once in the body, these substances lead to oxidative stress and inflammation, which in turn can accelerate aging process. Also, AGEs are involved in the development of metabolic syndrome, diabetes, cardiovascular disease, and cancer. However, mild oxidative stress can activate cellular defense systems and make cells more resistant to a stronger oxidative stress or other types of stress that is called hormesis or cross-tolerance. Our study shows an effect of non-autoclaved (FAMn) and autoclaved (FAMa) fructose-arginine mixtures on the body of fruit flies. In our study, we used the *Drosophila melanogaster* line w^{1118}. Flies were grown on nutrient medium with the addition of different amounts of FAMn or FAMa to the final concentrations of reagents in a mixture of 10, 20 and 100 mM and maintained on the respective media until the second day of age. The flies were then used to determine physiological and biochemical parameters. The increase in absorbance at 294 nm and 420 nm and a decrease in fructose concentration in FAMa indicated that autoclaving of the fructose-arginine mixture led to caramelization of fructose and formation of Maillard products. The study showed that FAM in both forms did not affect lipid peroxide level, a marker of oxidative stress. Also, FAM in both forms did not affect the resistance of flies to hydrogen peroxide. However, FAMn, but not FAMa, increased the resistance of flies to sodium nitroprusside (SNP). This effect is likely caused by the presence of arginine, a substrate for NO-synthase, which may pre-adapt flies to $^{\bullet}$NO released from SNP. FAMn and FAMa at the concentration of 100 mM increased content of storage lipids, but decreased resistance of flies to starvation.

Keywords: fructose, arginine, advanced glycation end-products, oxidative stress, triacylglycerides, fruit fly.

1. INTRODUCTION

Western diet is one of the modern human nutrition schemes characterized by the consumption of large amounts of fried foods, sugary drinks and sweets (so-called fast food). Fast food is associated with the development of metabolic syndrome, cardiovascular disease and cancer (Van

Nguyen, 2006b). The health threat of fast food is the high calorie content and high amounts of so-called Maillard reaction products that are formed during baking and roasting.

The Maillard reaction is a chemical reaction between amino acids and carbohydrates that occurs at temperatures 140 to 165 °C. Chemicals compounds formed in the Maillard reaction during food processing confer special taste and smell on food. Hundreds of different compounds can be formed via this reaction, depending on which amino acids and carbohydrates react, on the time and temperature at which the reaction takes place (Semchyshyn, 2013; Van Nguyen, 2006a). Maillard products can be characterized by specific properties. In particular, it was shown they may absorb light with maxima at wavelengths at 294 nm and 420 nm (Zhou et al., 2016).

The Maillard reaction occurs in several steps. The intermediates of this process are Schiff bases or Amadori products, which are chemically interconvertible molecules. If these products undergo certain modifications and thereby stabilize, they are converted into advanced glycation end-products (AGEs) (Semchyshyn, 2013). Both Maillard products and AGEs are capable of inducing oxidative stress (Hegele et al., 2009; Nitti et al., 2022; Schmitt et al., 2006; Van Nguyen, 2006b). Oxidative stress results in tissue damage and accelerates aging (Liguori et al., 2018). However, a mild oxidative stress may activate defense systems of cells and make cells more resistant to a stronger oxidative stress or other types of stress, that is called hormesis or cross-tolerance (Nitti et al., 2022; Schirrmacher, 2021).

Hormesis is studied in different model organisms and the fruit fly, *Drosophila melanogaster*, allows to apply power of contemporary genetics' toolkit to study the mechanisms of hormesis (Le Bourg, 2020). However, the ability of Maillard products to exhibit toxicity or hormesis is poorly investigated in this model organism. A recent study conducted showed that Maillard products obtained from crocodile meat peptide hydrolysates and xylose may increase *D. melanogaster* resistance to hydrogen peroxide and redox-cycling agent paraquat (Li et al., 2021).

The aim of our study was evaluating the effects of food enriched with Maillard products formed via heating of arginine with fructose on resistance of *D. melanogaster* to hydrogen peroxide, sodium nitroprusside (a donor of reactive nitrogen species, nitric oxide), and starvation, as well as on indices of oxidative stress, such as lipid peroxides, and markers of obesity, triacylglycerides.

2. MATERIALS AND METHODS

2.1. Preparation of fructose-arginine mixture

We prepared Maillard products by autoclaving solution of fructose and arginine. Fructose-arginine mixture (FAM) was prepared by mixing 1 M fructose and 1 M L-arginine solutions at the ratio 1:1 (Hwang et al., 2011). The resulting FAM contained 0.5 M fructose and 0.5 M L-arginine. This mix was divided into two parts. One part of FAM denoted as FAMa was autoclaving by heating for 30 min at 120 ℃. The formation of Maillard reaction products during FAM autoclaving was confirmed by measurement of free fructose level, UV-absorbance at 294 nm and browning at 420 nm. Another part of FAM was not autoclaved and denoted as FAMn.

2.2. Flies and rearing conditions

Drosophila melanogaster line w^{1118} was used in the experiments. The stock culture was obtained from the Bloomington Drosophila Stock Center (NIH P40OD018537, Indiana University, USA). The parental culture of flies was reared on food containing 5% sucrose, 5% dry yeast (PJSC Enzym, Lviv), 1% agar and 0.18% methyl parahydroxybenzoic acid and this group was used as a control. The experimental groups of flies were reared on the same food but with the addition of different amounts of FAMn or FAMa to final concentrations of reagents in the mix of 10, 20 and 100 mM. All fly cultures were maintained at 25 °C, 55-60% humidity and 12:12-hour light cycle. Newly hatched

flies were transferred to bottles with fresh food of the same composition for two days before the measurements. Two-day-old flies were anesthetized with carbon dioxide (CO_2), separated by sex and then used for physiological tests or quickly frozen in liquid nitrogen for biochemical analyses. Before physiological testing, flies were given 120 minutes to recover at 25 °C to avoid exposure to CO_2 (Bayliak et al., 2019).

2.3. Determination of resistance to starvation, hydrogen peroxide and sodium nitroprusside

Ten flies of each sex were placed in empty glass tubes (males and females separately) for 2 h to recover from CO_2 exposure. The flies were then transferred to tubes containing a folded and compacted strip (2.4 × 12 cm) of four-layer cellulose tissue soaked with 0.75 ml of 5% sucrose solution supplemented by either 10 mM sodium nitroprusside (SNP) or 5% hydrogen peroxide. To determine resistance to starvation, flies were placed on 1% agar. The number of dead flies was counted at regular intervals for 72 h. The results are presented as percentage of flies that survived (Bayliak et al., 2020).

2.4. Determination of lipid peroxides content

For determination of lipid peroxides, a method with xylenol orange was used (Bayliak et al., 2020). The method is based on oxidation of Fe^{2+} ions by lipid peroxides to Fe^{3+} ions. Further Fe^{3+} ions form a complex with xylenol orange, which absorbs light with a maximum at the wavelength of 580 nm at low pH values. Cumene hydroperoxide is also capable of oxidizing iron in an acidic environment. If cumene hydroperoxide is added in known concentrations, it can be used as an internal standard. In this method, the lipid peroxide content is expressed in cumene hydroperoxide equivalents (Bayliak et al., 2020). For extraction of lipid peroxides from frozen flies, cold 96% ethanol was used.

2.5. Determination of triacylglycerides

For triacylglyceride (TAG) assay, frozen flies were homogenized in phosphate-buffered saline with 0.1% triton x-100 (PBST) followed heat inactivation of endogenous enzymes at 70 °C for 10 min. Heated homogenates were then centrifuged and the resulting supernatants were used for TAG assay. TAG levels were measured by a commercial diagnostic kit (“Reagent”, Dnipro, Ukraine) according to manufacturer’s recommendations. The method is based on the enzymatic cleavage of TAG to free fatty acids and glycerol, followed by phosphorylation of glycerol formed and subsequent oxidation of glycerol 3-phosphate. The latter results in the formation of hydrogen peroxide as a product. Hydrogen peroxide oxidizes colorless 4-aminoantipyrine to crimson-red quinonimine derivative with an absorbance maximum at λ = 540 nm. The color intensity is directly proportional to the concentration of triacylglycerides. Standard TAG solutions were used for calibration curve.

2.6. Statistical analysis

For statistical processing of the results, the program "Microsoft Excel" and "GraphPad Prism 8" were used. The arithmetic mean and standard error of the mean (SEM) were calculated for each set of data. Comparison of groups and determination of statistical significance of difference between them was carried out using the Student's *t*-test. Survival curves were compared using the Gehan-Breslow-Wilcoxon test. P values < 0.05 were considered as a criterion for significant difference between the experimental groups.

3. RESULTS AND DISCUSSION

3.1. UV absorbance, browning and free fructose content in FAMa and FAMn solutions

To confirm formation of Maillard reaction products, we determined some parameters in the FAM before and after sterilization of the solution. Figure 1A shows that FAMa had significantly higher absorbance at 294 nm and 420 nm that FAMn. Also, the fructose level was 72% lower in the FAMa solution compared with the FAMn solution (Fig. 1B). These results indicate that fructose may undergo reaction with arginine during autoclaving with formation of brown-colored products of caramelization, intermediate Maillard products with maximal absorbance at 294 nm, and, therefore, levels of free fructose decreased in FAMa after sterilization.

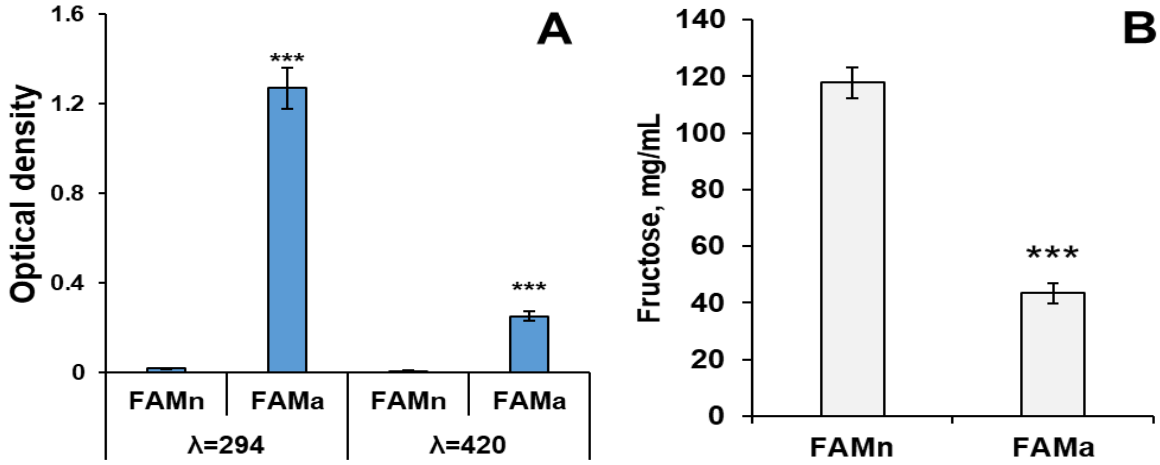

*Fig. 1. Physical and chemical properties of FAMn and FAMa: A) absorbance at wavelengths 294 nm and 420 nm and B) free fructose level in FAMn and FAMas, n=3. ***significantly different from FAMn with P < 0.001. For absorbance determination, solutions of FAMn and FAMa were diluted by 410 times*

3.2. Resistance of *D. melanogaster* flies fed with FAMn and FAMa to hydrogen peroxide

As mentioned earlier, products of Maillard reaction may cause the development of oxidative stress, participating in reactions of lipid peroxidation (Semchyshyn, 2013). On one hand, this may damage flies' tissues and make it vulnerable to toxicants. On the other hand, a possible induction of oxidative stress by Maillard products may activate defense systems of the flies and precondition them to other stressors (i.e. hormesis or cross-adaptation).

Resistance of *D. melanogaster* to hydrogen peroxide indicates power of antioxidant system and allows us to judge whether Maillard products activate it and act as hormetins or compromise it, acting as a sensitizer. Therefore, we measured resistance to hydrogen peroxide in two-day-old female flies reared on foods supplemented with FAMn or FAMa at different concentrations. Feeding with FAMn or FAMa did not significantly change survival of flies upon treatment with hydrogen peroxide (Fig. 2). But, flies reared on FAMa showed a tendency to die faster when exposed to hydrogen peroxide.

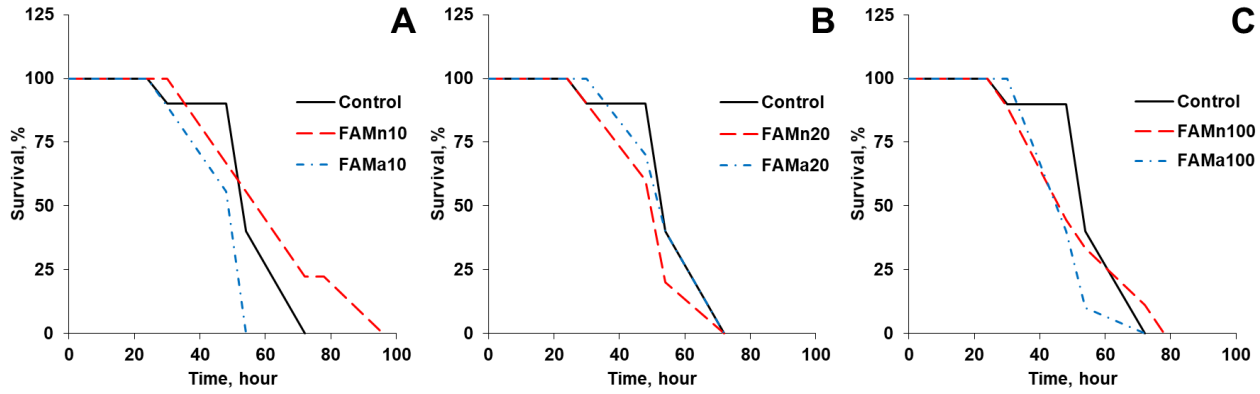

Fig. 2. Survival of D. melanogaster females w^{1118} treated with 5% H_2O_2, n = 9-10 flies. Flies were reared on standard food supplemented with non-autoclaved or autoclaved fructose-arginine mixture at different concentrations – 10, 20 and 100 mM.

3.3. Resistance of adult flies fed with FAMn and FAMa to sodium nitroprusside

Another compound which is toxic to flies is sodium nitroprusside (SNP) (Lozinsky et al., 2012). Sodium nitroprusside is used in medicine as a vasodilator, but it is toxic at high concentrations (Bayliak et al., 2022). Female flies reared on FAMn-containing medium were more resistant to the 10 mM SNP than the control ones (Fig. 3).

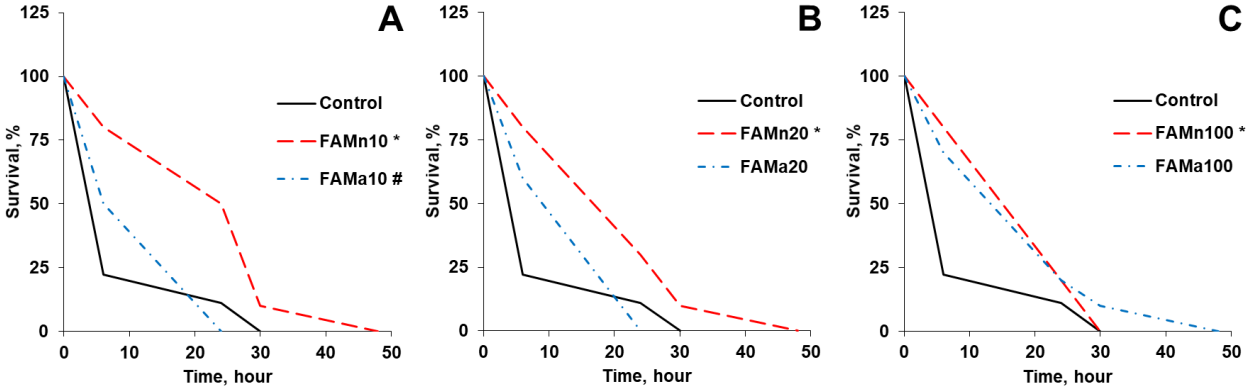

Fig. 3. Time dynamics of survival D. melanogaster females w^{1118} treated with sodium nitroprusside (SNP), n = 9-10 flies. Flies were reared on standard food supplemented with non-autoclaved and autoclaved fructose-arginine mixture at different concentrations – 10, 20 and 100 mM.
**significantly different from the control with P < 0.05.*
#significantly different from the FAMn with P < 0.05.

It can be assumed that this effect was caused by arginine in FAMn. Recently, we found, that supplementation food with L-arginine increased resistance of *D. melanogaster* flies to SNP due to inducing mild nitrosative stress (Bayliak et al., 2022). Arginine is a substrate for the enzyme NO-synthase that produces nitric oxide (•NO). Feeding with arginine can makes flies more resistant to •NO due to possible activation of mechanisms related to arginine metabolism, including those involved in detoxification of excess •NO. Since SNP is also a donor of •NO, flies reared on arginine-rich food may become more resistant to sodium nitroprusside as we observed in our experiments. There was no statistical difference between control flies and those on food with FAM. The absence of the statistically significant effect was likely due to decrease in arginine amount in food via non-enzymatic reaction with fructose.

3.4. Levels of lipid peroxides in flies reared on FAMn and FAMa

Lipid peroxidation causes biomembrane damage. The main targets of peroxidation are unsaturated fatty acids (Lushchak, 2014). Feeding of flies with FAMn and FAMa at different concentrations did not affect the levels of lipid peroxides in female w1118 flies (Fig. 4).

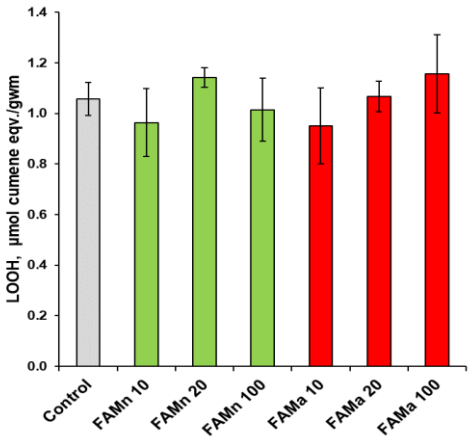

Fig. 4. Levels of lipid peroxides in two-day-old D. melanogaster females w^{1118} reared on standard food supplemented with non-autoclaved and autoclaved fructose-arginine mixtures at different concentrations – 10, 20 and 100 mM, n = 4

3.5. TAG content in flies reared on FAMn and FAMa

The levels of triacylglycerides (TAG) in w^{1118} female flies reared on foods supplemented with 10 mM and 20 mM FAMn and FAMa did not differ from the values in the control group (Fig. 5). At the same time, flies fed with food supplemented with 100 mM FAM, both autoclaved and non-autoclaved, contained 2.1-fold and 1.7-fold more TAG, as compared with the control flies. The difference is likely conferred by high concentration of fructose in the mixture. In addition, FAMa-fed flies had slightly higher TAG levels than FAMa-fed ones. These results suggest, that Maillard products formed during autoclaving of FAM might stimulate accumulation of triacylglycerides in fruit flies.

3.6. Resistance to starvation in flies reared on FAMn and FAMa

Resistance to starvation is an indicator of stress resistance and the levels of reserve metabolites. Larger amounts of reserve fats and carbohydrates allow flies to survive longer without food (Lee & Jang, 2014). The starvation resistance of female flies consumed food supplemented with FAMn and FAMa at concentrations 10 mM and 20 mM did not differ from the control ones (Fig. 6). At the same time, flies consumed 100 mM FAMn and 100 mM FAMa were more sensitive to starvation than the control group. Organisms that have activated autophagy in cells are often more resistant to starvation than counterparts with an average levels of autophagy (Lőrincz et al., 2017).

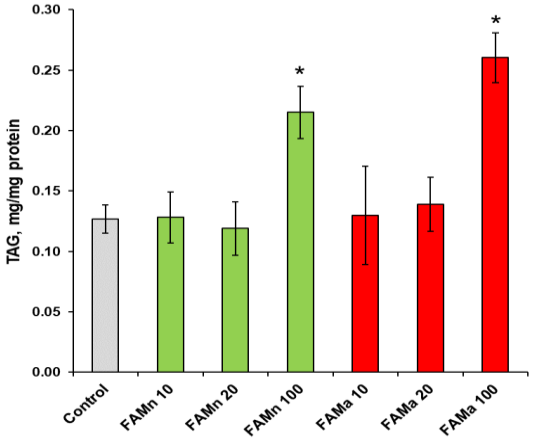

Fig. 5. Levels of TAG in two-day-old D. melanogaster females w^{1118} reared on standard food supplemented with non- autoclaved or autoclaved fructose-arginine mixture at different concentrations – 10, 20 and 100 mM, n=4
**significantly different from the control with P < 0.05*

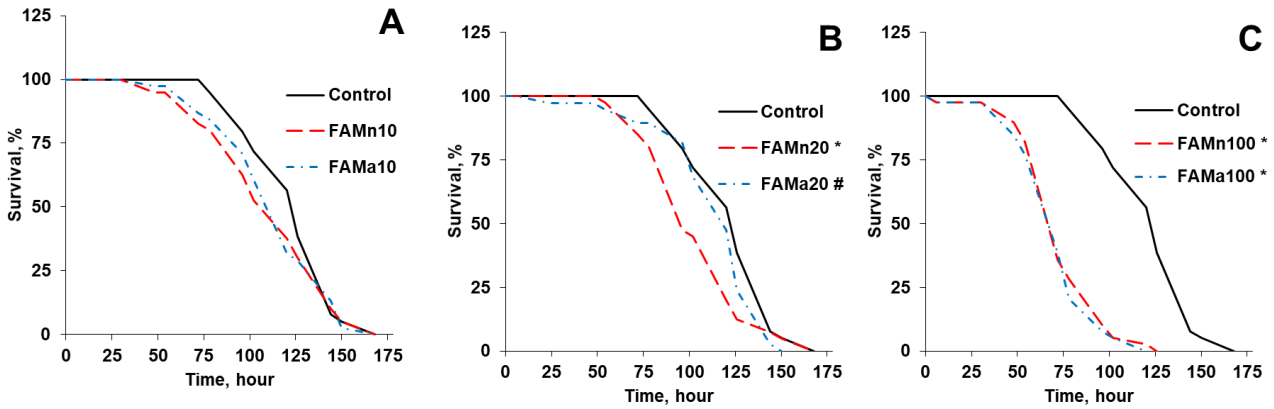

Fig. 6. Starvation survival of D. melanogaster females w^{1118} reared on standard food supplemented with non-autoclaved and autoclaved fructose-arginine mixture at different concentrations – 10, 20 and 100 mM , n=4 with 9-10 flies per repeat
**significantly different from the control with P < 0.05.*
#significantly different from the FAMn with P < 0.05.

Arginine is an inducer of mechanistic target-of-rapamycin, a protein kinase that suppresses autophagy (Liu et al., 2021; Saxton et al., 2016). Resistance to starvation is an indicator of stress resistance and the levels of reserve metabolites. Larger amounts of reserve fats and carbohydrates allow flies to survive longer without food (Lee & Jang, 2014). The starvation resistance of female flies consumed food supplemented with FAMn and FAMa at concentrations 10 mM and 20 mM did not differ from the control ones (Fig. 6). At the same time, flies consumed 100 mM FAMn and 100 mM FAMa were more sensitive to starvation than the control group. Organisms that have activated autophagy in cells are often more resistant to starvation than counterparts with an average levels of autophagy (Lőrincz et al., 2017). Arginine is an inducer of mechanistic target-of-rapamycin, a protein kinase that suppresses autophagy (Liu et al., 2021; Saxton et al., 2016). Also, fatty acids derived from TAG may inhibit autophagy (Guo et al., 2021; Mei et al., 2011). As we show, 100 mM FAM results in increase in TAG levels. Despite TAG may provide flies with energy during starvation, their gain on food at 100 mM is not sufficient to counteract starvation. Moreover, 100 mM FAM sensitize flies to starvation, likely via combined influence of fructose and arginine on autophagy.

4. CONCLUSIONS

Autoclaving of fructose-arginine mixture (FAM) led to caramelization and formation of Maillard products. The rearing of *D. melanogaster* flies on foods supplemented with both non-autoclaved or autoclaved FAMa at different concentrations had no effects on fly resistance to hydrogen peroxide and lipid peroxide levels in the body of female fruit flies. However, food with non-autoclaved, FAMa, increased the resistance of female flies to sodium nitroprusside (SNP), an NO-donor. This effect is probably caused by consumption of arginine, a substrate for NO-synthase, that might pre-adapt flies to •NO released from SNP. At the concentration 100 mM FAMn and 100 mM FAMa increased the levels of reserve fats in fly bodies but at the same time reduced resistance of flies to starvation. These results require further investigation. In particular, it would be interesting to evaluate the levels of autophagy in flies consumed food with 100 mM FAM, as well as to measure whether gut microbiota is able to decompose Maillard products. It is also important to know whether consumption of FAM leads to an increase in the levels of fructose or free arginine in fruit fly hemolymph.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

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Дем'янчук Олег, Бутенко Наталя, Господарьов Дмитро, Байляк Марія. Вплив неавтоклавованої та автоклавованої фруктозо-аргінінової суміші на стійкість *Drosophila melanogaster* до стресу. *Журнал Прикарпатського університету імені Василя Стефаника*, **9** (4) (2022), 15–24.

Дієта сучасної людини включає фаст-фуд, який призводить до розвитку ожиріння та пов'язаних з ним хвороб. Однією з причин негативних ефектів цієї дієти є кінцеві продукти прискореної глікації (КПГ) – речовини, які утворюються внаслідок взаємодії між амінокислотами та вуглеводами, зокрема, під дією високої температури (реакція Маяра). Потрапляючи в організм, ці речовини призводять до оксидативного стресу і розвитку запалення, що, в свою чергу, може прискорити процеси старіння. Також КПГ беруть участь у розвитку метаболічного синдрому, діабету, серцево-судинних захворювань та раку. Проте, легкий оксидативний стрес може активувати захисні системи клітин і робити клітини більш стійкими до сильнішого оксидативного стресу або інших видів стресу, що називається гормезисом або перехресною толерантністю. У нашому дослідженні було вивчено вплив фруктозо-аргінінової суміші (ФАС), неавтоклавованої (ФАСн) та автоклавованої (ФАСа), на організм плодових мушок. У нашому досліджені ми використовували *Drosophila melanogaster* лінії w^{1118}. Мушок вирощували на поживному середовищі із додаванням різної кількості ФАСн або ФАСа до кінцевих концентрацій реагентів у суміші 10, 20 і 100 мМ та утримували на відповідних середовищах до дводенного віку. Далі мух використовували для визначення фізіологічних та біохімічних показників. Збільшене поглинання світла при довжинах хвиль 294 нм та 420 нм та нижча концентрація фруктози у ФАСа свідчать про те, що автоклавування ФАС призводить до карамелізації фруктози та утворення продуктів Майяра. Дослідження показало, що ФАС в обох формах не впливає на маркер оксидативного стресу пероксиди ліпідів. Також ФАС в обох формах не впливає на стійкість мушок до пероксиду водню. Проте, ФАСн, але не ФАСа, підвищує стійкість мух до нітропрусиду натрію (НПН). Цей ефект, ймовірно, спричинений наявністю аргініну, субстрату для NO-синтази, який може попередньо адаптувати мух до •NO, який вивільняється з НПН. ФАСн і ФАСа в концентраціях 100 мМ збільшували вміст запасних ліпідів, але знижували стійкість мух до голодування.

Ключові слова: фруктоза, аргінін, кінцеві продукти прискореної глікації, оксидативний стрес, триацилгліцериди, плодова мушка.