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Acetoacetate enhancement of glucose mediated DNA glycation

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ABSTRACT

Acetoacetate (AA) is a ketone body, which generates reactive oxygen species (ROS). ROS production is impacted by the formation of covalent bonds between amino groups of biomacromolecules and reducing sugars (glycation). Glycation can damage DNA by causing strand breaks, mutations, and changes in gene expression. DNA damage could contribute to the pathogenesis of various diseases, including neurological disorders, complications of diabetes, and aging. Here we studied the enhancement of glucose-mediated DNA glycation by AA for the first time. The effect of AA on the structural changes, Amadori and advanced glycation end products (AGEs) formation of DNA incubated with glucose for 4 weeks were investigated using various techniques. These included UV–Vis, circular dichroism (CD) and fluorescence spectroscopy, and agarose gel electrophoresis. The results of UV–Vis and fluorescence spectroscopy confirmed that AA increased the DNA-AGE formation. The NBT test showed that AA also increased Amadori product formation of glycated DNA. Based on the CD and agarose gel electrophoresis results, the structural changes of glycated DNA was increased in the presence of AA. The chemiluminescence results indicated that AA increased ROS formation. Thus AA has an activator role in DNA glycation, which could enhance the adverse effects of glycation under high glucose conditions.

1. Introduction

Reactive oxygen species (ROS) are free radicals derived from molecular oxygen, and are highly reactive. The recognition of their increased roles in pathogenesis of many diseases has led to significant areas of investigation [1]. A free radical is independent molecular specie having an orbital with only one unpaired electron [2]. Free radicals can be derived either from internal sources such as normal essential metabolic pathways or from external sources such as industrial chemicals and foods [3]. The most important oxygen-containing free radicals in the body, which cause diseases, are hydroxyl radical, superoxide anion radical, hydrogen peroxide, oxygen singlet, hypochlorite, and nitric oxide and peroxynitrite radicals [4]. One of the endogenous sources for free radical production is β-oxidation of free fatty acid in the liver, which leads to formation of ketone bodies [5]. There are three types of ketone bodies generated in the body, namely 3-β-hydroxybutyrate, acetone, and acetoacetate (AA) [6]. High levels of ketone bodies are produced in diabetes, childhood hypoglycemia, growth hormone deficiency, intoxication with alcohol or salicylates, several inborn metabolic disorders [7], fasting, and prolonged exercise [8]. However, among ketone bodies, only AA can generate ROS [5].

Glycation is a spontaneous process which occurs between the amino groups of biomacromolecules and carbonyl groups of reducing sugars [9]. During the first and second stage of this reaction, a reversible compound including Schiff base and Amadori is produced [10,11]. In the late stage, this compound produces “advanced glycation end products” (AGEs) via oxidation, dehydration, and cyclization, which is irreversible [12]. AGEs contribute to pathogenesis of many diseases including diabetes complications [13], Parkinson’s [14], Alzheimer’s [15], and aging [16].

The amino group of nucleic acids can be modified by reducing sugars to form DNA-AGEs [17], which affect DNA structure and function [18].

Abbreviations: AA, Acetoacetate; AGEs, Advanced glycation end products; DNA, Deoxyribonucleic Acid; CD, Circular Dichroism; NBT, Nitro blue Tetrazolium.

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Also, it can lead to strand breaks, mutations [19] and decreased gene expression [20]. N2-carboxyethyl-2′-deoxyguanosine (CEdG) is the most common advanced glycation of DNA [21,22]. DNA damage could contribute to pathogenesis of diseases like cancer, aging, inflammation and neurological disorders [23]. There are a number of compounds with inhibitory effects on glycation, such as Aminoguanidine [24], aspirin [25], vitamin B6 [26], quercetin [27], and 3-β-hydroxybutyrate [28]. Other compounds such as potassium sorbate [29] and sodium benzoate [30] promote glycation process.

We recently reported that AA can enhance human serum albumin AGEs formation [31]. With regards to the free radical production by AA, and its increased concentration in diabetes, the aims of these studies were: (i) to determine the effects of AA on DNA glycation in the presence of glucose, and (ii) to characterize the structural changes and Amadori products and DNA-AGEs formation using UV–vis, fluorescence and CD spectroscopy and agarose gel electrophoresis.

2. Materials and methods

2.1. Chemicals

DNA from Calf thymus, agarose, ethidium bromide, acetoacetate (AA), sodium dihydrogen orthophosphate, disodium hydrogen phosphate, EDTA, nitro-blue tetrazolium (NBT) sodium chloride and Tris–HCl, were obtained from Sigma-Aldrich (USA). β-D Glucose was purchased from Fluka. All reagents were of analytical grade and were used as received without further purification.

2.2. Preparation of AGE-DNA

For the preparation of glycated products, DNA (25 μg/mL) was added to D-glucose (130 mM) in a sodium phosphate buffer (200 mM; pH 7.4) in the presence or absence of AA with the concentration of 3.125 mM [32] under sterile conditions. After 4 weeks incubation, the mixtures were dialyzed over sodium phosphate buffer for 48 h to eliminate unbound particles. The samples were then kept at −30 °C. The control was DNA incubated without glucose and AA.

2.3. UV–vis analysis

The UV–Vis analyses of all samples were carried out according to the procedures described in the literature [33] by a Cary spectrophotometer (UV-2100, Rayleigh, China) in 200–600 nm spectral range with path length 10 mm in a quartz cuvette.

2.4. Circular dichroism (CD) analysis

Circular dichroism (CD) studies were performed using a spectropolarimeter (Jasco J-815, Japan) in 220–400 nm spectral range.

2.5. Amadori product measurements

The Amadori product measurements were determined based on colorimetric fructosamine assay using nitro-blue tetrazolium (NBT) reaction with ketoamines [26] as follows: 100 μL of sample (25 μg/mL) was added to 100 μL of NBT reagent (250 μM in 0.1 M carbonate, pH 10.8) and incubated at 37 °C for 45 min. The absorbance was recorded at 525 nm over a blank using a BioTek Power Wave XS2 plate reader (USA).

2.6. Fluorescence analysis

The fluorescence studies were carried on the spectrofluorophotometer (RF-5301-PC, Shimadzu, Japan) at 290 nm and 400 nm excitation wavelength. The fluorescence emission intensities were measured at 10 nm upper than the excitation up to 600 nm. The presence of AGEs in the samples was confirmed by AGE-specific fluorescence compared with control DNA [27].

2.7. Agarose gel electrophoresis

The electrophoresis analyses were performed using a 0.8% agarose gel at 30 mA for 2 h in TAE buffer (40 mM Tris–acetate, 2 mM EDTA, pH 8.0). The bands were detected under UV after staining with ethidium bromide [34].

2.8. ROS measurements

The samples ROS measurements were performed using a chemiluminescence technique [35] (Shourian, Tavakoli, Ghourchian, & Rafiee-Pour, 2010) as follows. Luminol (10 μl; 2×10^{-7}M, 100 mM carbonate buffer; pH 11) was mixed with 480 μl of samples in buffer (100 mM carbonate buffer; pH 11). Diperiodatocuprate (DPC) (10 μl; 2×10^{-5} M, 100 mM carbonate buffer; pH 11) was then added to the above solution. The chemiluminescence at 425 nm was immediately recorded during 3 s using a fluorescence spectrophotometer in the chemiluminescence mode (Eclipse; Varian Co, Australia). Experiments were performed at least in triplicates. The results were considered as the chemiluminescence of incubated DNA with Glc + AA, AA alone, and Glc alone, which were normalized with DNA control.

3. Results

3.1. UV–visible spectroscopy

The UV–Vis spectra of all samples including control-DNA, DNA + AA, DNA + Glc + AA and DNA + Glc are shown in Fig. 1. These results indicated that absorption of DNA + Glc + AA was higher than absorption of DNA + Glc, increasing by approximately 44.7%.

3.2. Circular dichroism (CD) profiles

The CD analyses of all samples are shown in Fig. 2. The control-DNA revealed a negative peak of −5.9 mdeg at 245 nm, and a positive peak of +16.4 mdeg at 275 nm. The DNA + Glc, DNA + AA, and DNA + Glc + AA had a negative pick of −3.9, −4.9 and −3.2 mdeg at 245 nm, and a positive peak of +12.7, +14.6 and + 10.5 at 275 nm, respectively.

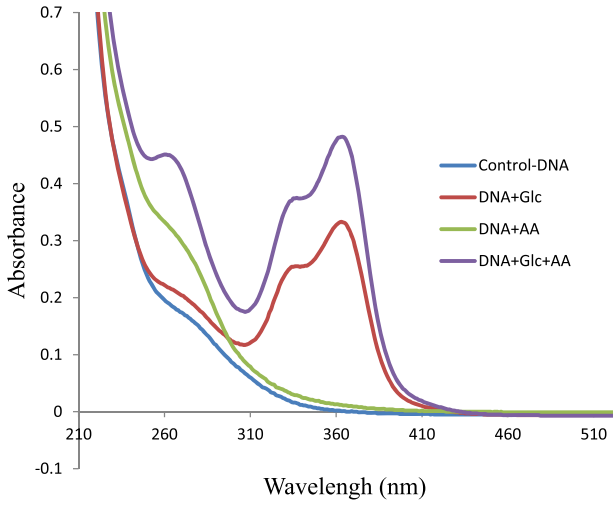


Fig. 1. UV spectra of control-DNA, DNA + AA, DNA + Glc + AA and DNA + Glc after 4 weeks of incubation at 37 °C in 200 mM phosphate buffer pH 7.4.

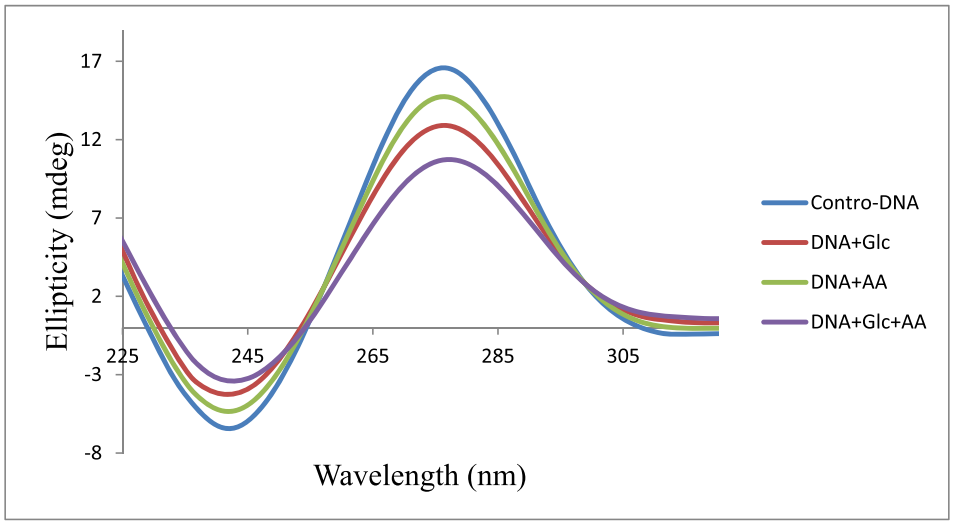


Fig. 2. CD profile of control-DNA, DNA + AA, DNA + Glc + AA and DNA + Glc after 4 weeks of incubation at 37 °C in 200 mM phosphate buffer pH 7.4.

3.3. Determination of DNA Amadori product

Fig. 3 demonstrates the amount of Amadori product for all samples. These results showed that the amount of Amadori product of DNA + Glc + AA was higher than other samples. The amount of Amadori product of DNA + Glc + AA was increased by approximately 42.5% compared with DNA + Glc.

3.4. Fluorescence spectroscopy

Fig. 4 shows the fluorescence spectra of all samples at 290 and 400 nm excitation wavelengths. These results showed the fluorescence emission intensity of DNA + Glc + AA is higher than other samples at 290 nm (Fig. 4a). The same results were also obtained at 400 nm excitation wavelength (Fig. 4b).

3.5. Agarose gel electrophoresis

The electrophoresis analyses of all samples are shown in Fig. 5. The DNA + Glc + AA had a higher mobility compared with other samples.

3.6. ROS measurements

Fig. 6 shows the amount of ROS formation based on a chemiluminescence procedure. The chemiluminescence intensity of DNA + Glc + AA was higher than DNA + Glc and DNA samples.

4. Discussion

Diabetes is a disease in which blood glucose levels remains high. High blood glucose levels increases glycation process and AGE formation [36]. The glycation process could mediate DNA structural changes, strand breaks, and mutations [37]. Some agents such as ROS (chemical compounds) could increase AGE formation causing further DNA damage. Thus, the study of glycation promoting agents will allow the identification of their harmful effects on health. Based on the UV–Vis results (Fig. 1), the absorbance of DNA + Glc + AA increased compared with DNA + Glc. UV–Vis absorbance of DNA + Glc rises because of the partial unfolding of double helix and exposure of chromophoric bases [32,33]. Thus, AA increases the partial unfolding of DNA incubated with glucose. Also, our findings indicated a new peak (300–400 nm) for DNA + Glc + AA that was higher than that of DNA + Glc. The peaks in the range of 300–400 nm confirm DNA-AGEs formation [38], which was further enhanced in the present of AA.

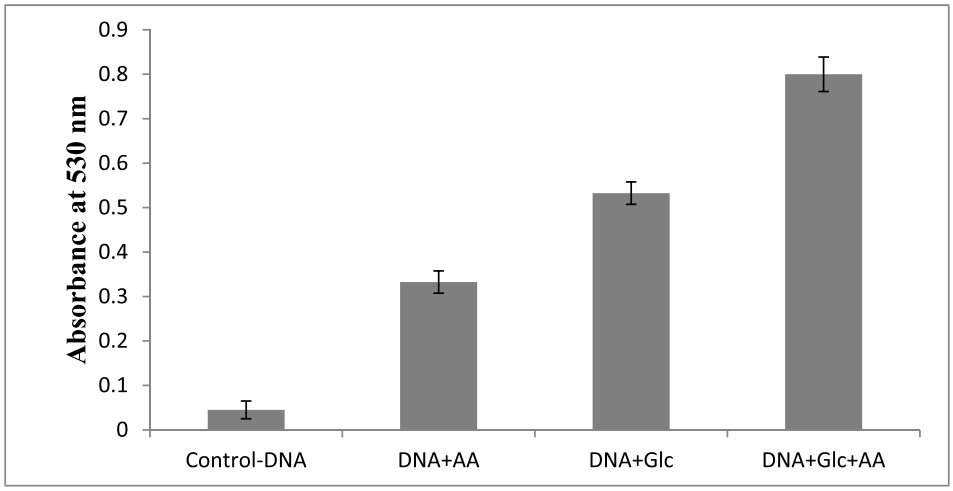
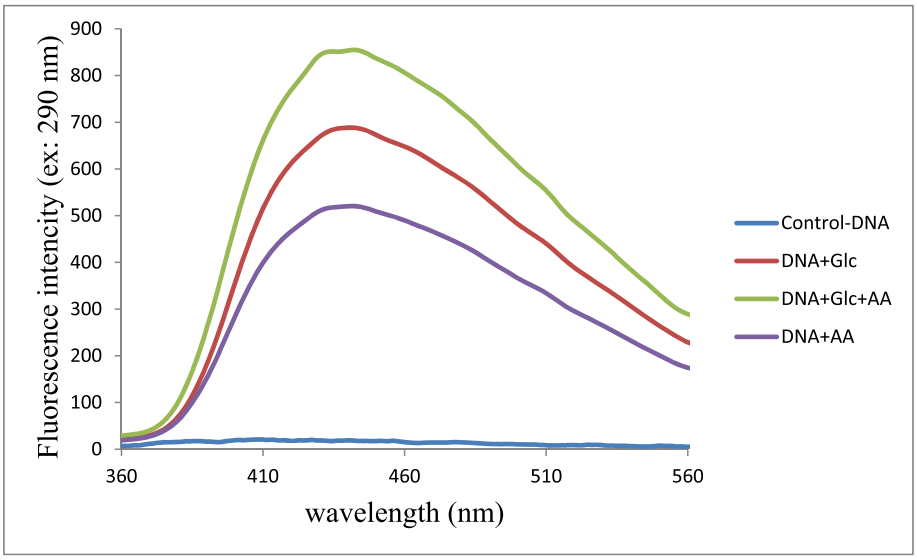


Fig. 3. Amount of Amadori products of control-DNA, DNA + AA, DNA + Glc, and DNA + Glc + AA after 4 weeks of incubation at 37 °C in 200 mM phosphate buffer pH 7.4.



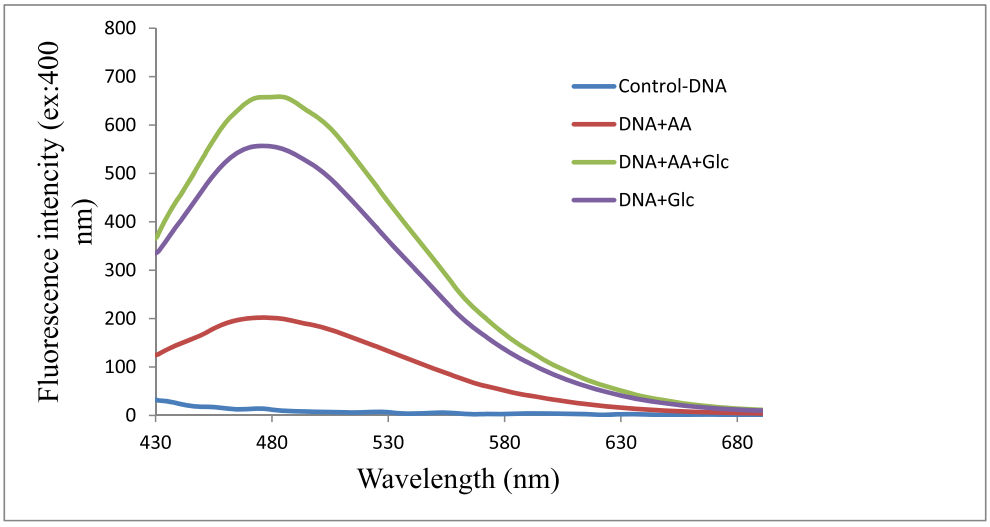


Fig. 4. Fluorescence intensities of control-DNA, DNA + AA, DNA + Glc + AA and DNA + Glc after 4 weeks of incubation at 37 °C in 200 mM phosphate buffer pH 7.4. Excitation at 290 nm (a) excitation 400 nm (b).

In comparison with CD spectra of control-DNA, the negative and positive parts of CD spectra of the DNA + Glc increased and decreased, respectively (Fig. 2). These were in agreement with the results reported by a similar study in the literature [38]. Moreover, based on CD results the structural changes of DNA in the presence of Glc + AA was higher than Glc alone. Thus, AA could cause enhanced structural changes and DNA-AGEs formation. These results are consistent with that of the UV–Visible results. According to the NBT test, the amount of Amadori product of DNA + Glc + AA was also increased compared with the DNA + Glc. These results were also consistent with the CD and UV–Vis findings.

The fluorescence results revealed that the emission of DNA + Glc + AA was increased compared with the DNA + Glc sample. As previously noted, the glycated DNA shows an excitation of 400 nm and an emission of 290 nm [20,39]. The presence of AA increased the fluorescence intensity, thus causing increased DNA structural changes. Based on electrophoresis results, the mobility of DNA + Glc was higher than native DNA, which is in agreement with a previous study [39]. The mobility of DNA + Glc + AA sample was higher than DNA + Glc. Thus, the presence of AA could cause more structural changes and damage in the DNA. According to the chemiluminescence results, the ROS formation was increased in DNA + Glc + AA samples, which was more than DNA + Glc samples (Fig. 6). These results are in agreement with those reported by a previous study, which showed the glycation process [40] and ROS formation by AA [5].

Collectively, our results demonstrate that the structural changes, Amadori products, ROS and AGEs formation of glycated DNA were increased in the presence of AA. We recently reported that 3BHB, as a ketone body, inhibited DNA glycation by glucose [41]. In contrast, the results of present study indicate that AA increases DNA glycation by glucose. These differences in behaviors of AA and 3BHB as ketone bodies are mainly attributed to their structural differences. While AA can generate ROS, 3BHB cannot [42]. Thus, AA can cause ROS formation and activation of DNA glycation process.

5. Conclusions

Acetoacetate is a ketone body, which increases during ketosis in diabetic patients. Our results establish that AA possesses an activating effect on glucose-mediated DNA glycation. According to our findings, AA shows a significant activation effect on DNA glycation because of its ROS production ability. ROS production induces DNA-glycation. Also, AA had a significant effect on the DNA structural changes and AGEs formation, as demonstrated by changes in UV–Vis and fluorescence

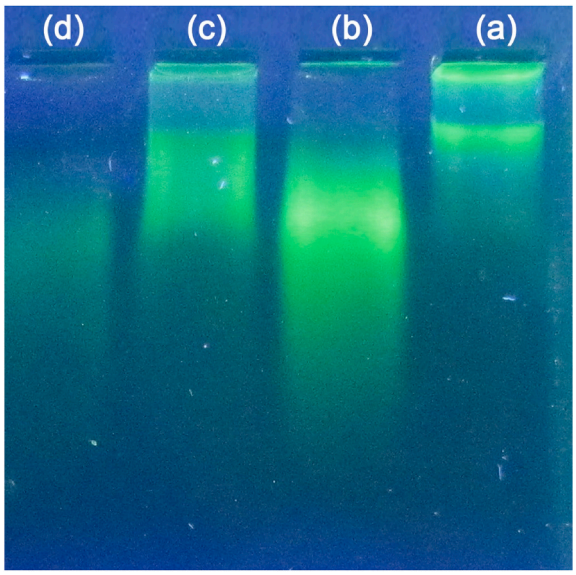


Fig. 5. Agarose gel electrophoresis of native and modified DNA after 4 weeks of incubation at 37 °C in 200 mM phosphate buffer pH 7.4: Lane (a), Native DNA; Lane (b), DNA + Glc; Lane (c), DNA + AA; Lane (d), DNA + Glc + AA.

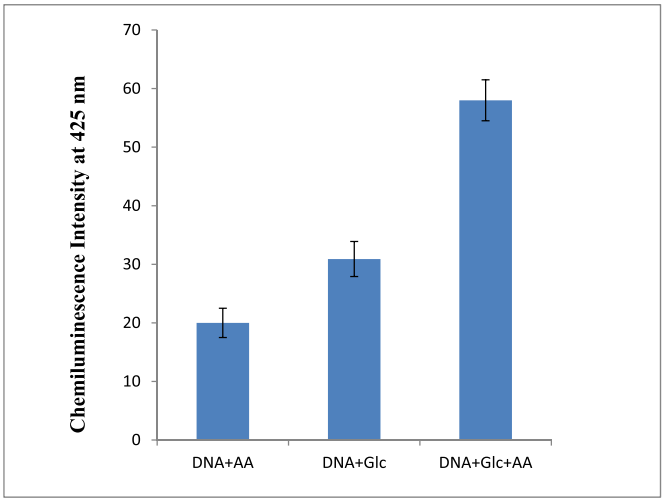


Fig. 6. Chemilumiescnce intensity of DNA + AA, DNA + Glc and DNA + Glc + AA at 425 nm after 4 weeks of incubation at 37 °C in 200 mM phosphate buffer pH 7.4.

spectrometry. The UV–Vis absorbance (at 363 nm), the fluorescence intensity (at 290/440 nm), the amount of Amadori products (at absorbance 525 nm) and the amount of ROS decreased by approximately 44.7%, 24.1%, 42.5% and 49.6%, respectively, when AA was incubated with glucose and DNA solution. Increased DNA AGEs formation and structural changes can lead to enhancement of diabetes mediated complications associated with hyperglycemia.

CRediT authorship contribution statement

M. Bagherzadeh-Yazdi: Investigation. **M. Bohlooli:** Conceptualization, Supervision, Writing - original draft. **M. Khajeh:** Methodology. **F. Ghamari:** Methodology, Validation. **M. Ghaffari-Moghaddam:** Writing - original draft. **N. Poormolaie:** Investigation. **A. Khatibi:** Resources. **P. Hasanein:** Writing - original draft. **N. Sheibani:** Writing - review & editing.

Declaration of competing interest

The authors declare no conflict of interest.

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