Mini Review

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Translational Biomedicine
2172-0479

2022
Vol. 13 No. 10: 257

A Review on Antiviral Property of Methylglyoxal: Possible Therapeutic Implications of the α-dicarbonyl Compound in the Treatment of Viral Infection

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Citation: Ghosh S, Banerjee S, Chakraborty B, Rahaman W, Chowdhury M, et al. (2022) A Review on Antiviral Property of Methylglyoxal: Possible Therapeutic Implications of the α-dicarbonyl Compound in the Treatment of Viral Infection. Transl Biomed, Vol. 13 No. 10: 257.

Abstract

Methylglyoxal (MG) is a highly reactive α-dicarbonyl compound which reacts with proteins to form advanced glycation end products (AGEs). Its level significantly increases in diabetic condition. MG primarily modifies arginine and lysine residues of proteins resulting in cross-linking and inactivation. Antiviral activity of methylglyoxal has been reported against several viruses including different strains of influenza, alpha herpes, varicella-zoster, etc. Recently, it has been suggested that SARS-CoV-2 proteome is susceptible to inactivation by MG. The studies in overall indicate a possible therapeutic potential of MG which may be explored in the treatment of wide range of viral diseases. The present article discusses and reviews on the probable mechanism of action of MG against viral infections including possible modification and inactivation of viral proteins. A scope to characterize MG-modified proteins by biophysical techniques including analysis of MG-derived AGE adducts by proteomic studies has also been discussed.

Keywords: Methylglyoxal; Advanced Glycation End Products; Antiviral; Hydroimidazolone; Antitumor Drugs

Received: 29-Sep-2022, Manuscript No. iptb-22-13101; **Editor assigned:** 03-Oct-2022, PreQC No. PQ- iptb-22-13101; **Reviewed:** 10-Oct-2022, QC No. iptb-22-13101; **Revised:** 17-Oct-2022, Manuscript No. iptb-22-13101 (R); **Published:** 27-Oct-2022, DOI: 10.21767/ 2172-0479.100251

Introduction

Important reactive metabolites that are known to induce significant modification of the proteome in physiological systems are: reactive oxygen species (ROS) and dicarbonyls (glyoxal, methylglyoxal) [1, 2]. The reactive α-dicarbonyl compound, methylglyoxal (MG), which is mainly formed by trace level degradation of triosephosphate glycolytic intermediates, glyceraldehyde-3-phosphate and dihydroxyacetonephosphate, is metabolised by glutathione-dependent glyoxalase 1 (Glo1) of the glyoxalase pathway [1]. Its blood level increases in both type 1 and type 2 diabetes [3-5]. MG has been reported to react with different proteins namely, insulin [6], human serum albumin [7], cytochrome c [8], α-synuclein [9], hemoglobin [10-12], myoglobin [13, 14] and hen egg white lysozyme (HEWL) [15]. MG forms argpyrimidine, hydroimidazolones and tetrahydropyrimidine adducts with arginine residues. On the other hand, carboxyethyllysine and MG-lysine dimer are formed with lysine residues. Proteins susceptible to MG modification with related functional impairment are called the ''dicarbonyl proteome'' [16], which are predominantly modified on arginine residues with formation of dominant arginine adduct hydroimidazolone (MG-H1). MG-mediated toxicity associated with free radical generation by its metabolism and modification of biological macromolecules has been discussed in an earlier report [17]. The structures of some of the MG-derived AGE adducts are shown in (**Figure 1**)

AGE adducts have been reported to cause oxidative stress [18], protein cross-linking [19] etc., and are known to be associated with pathological conditions, including diabetes, Alzheimer's disease, multiple sclerosis etc. [18, 20, 21]. MG-induced modification in several proteins has been associated with physiological

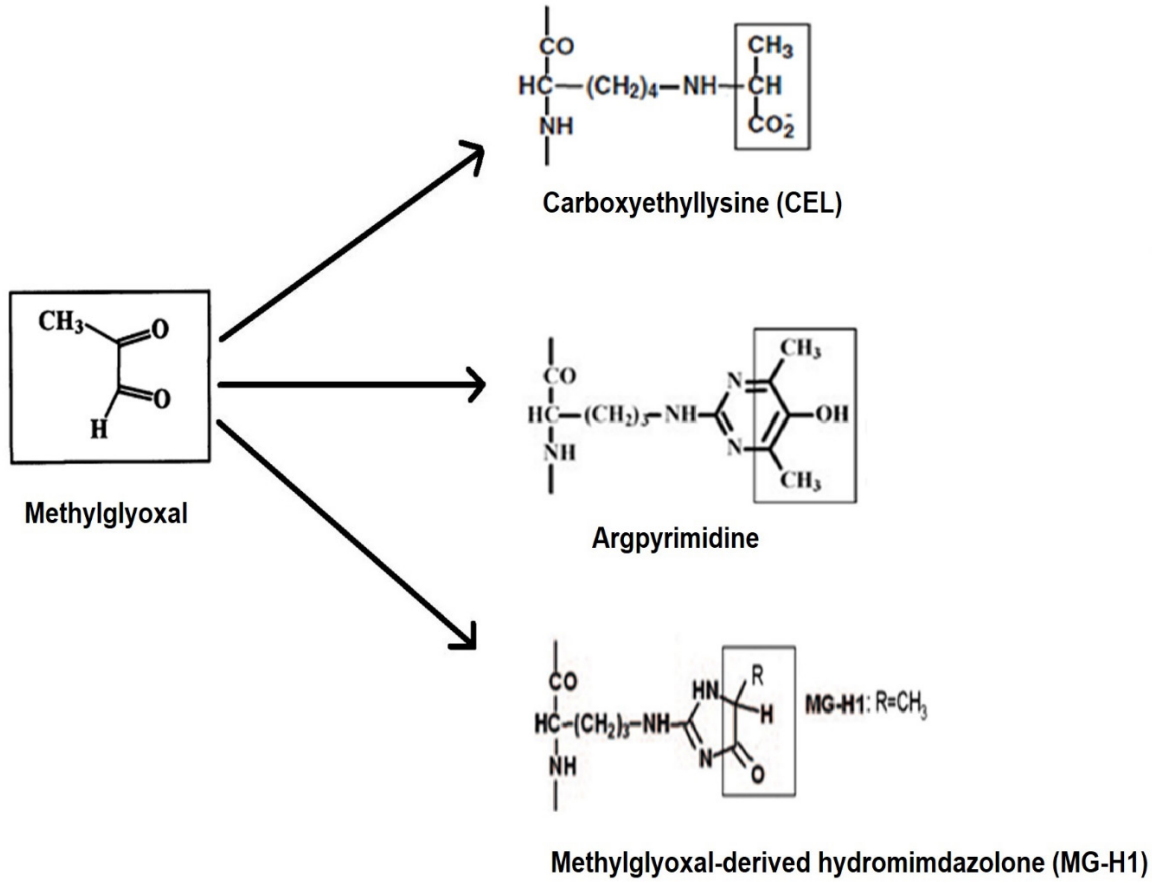

Figure 1 Chemical structures of MG-derived AGE adduct. AGE adducts formed at lysine (N-carboxyethyllysine) or arginine residues (argpyrimidine, MG-derived hydroimidazolone) on protein are shown.

abnormalities like dyslipidaemia, mitochondrial dysfunction, cell detachment, and apoptosis [22, 23]. AGE adducts have been linked to several diseases due to their interactions with the Receptor for AGEs (RAGE) [24-26]. RAGE activation has been reported to be primarily responsible for the pathogenicity associated with AGEs [27, 28]. AGE–RAGE interaction has been found to stimulate the growth of human pancreatic cancer cells [29, 30].

Antiviral activity of MG

MG has been reported to exhibit antiviral property against foot-and-mouth disease virus [31], and Newcastle disease virus [32] via interaction with viral RNA. MG exhibited antiviral activity against multiple influenza virus strains (including H1N1, H3N2, H5N2, and oseltamivir-resistant H1N1) [33], in addition to its synergistic effect when administered as a co-treatment with neuraminidase inhibitors. Synergistic combinations have been reported to reduce the dose needed to inhibit viral growth [34, 35]. Antiviral activity of MG has been reported against influenza A [33] as well as both neuraminidase-sensitive and neuraminidase-resistant influenza B viruses [36]. MG was demonstrated to suppress tumor necrosis factor-α-induced NF-κB activation, in the process inhibiting viral replication in a strain-independent manner [36] (**Figure 2**).

MG was found to exhibit hemagglutination inhibition effect indicating that it may directly interact on the virus surface and interfere with the interaction between viruses and host cells. The presence of very high concentrations of MG in manuka honey was proposed to contribute to its anti-influenza viral activity [37]. A combined use of anti-influenza drugs with manuka honey demonstrated synergistic anti-influenza virus effects [38]. Natural honey has been reported to exhibit antiviral activities against rubella virus [39], varicella-zoster virus (VZV) [40], and is used to treat recurrent herpes simplex lesions [41].

Susceptibility of SARS-CoV-2 proteome to MG modification

A recent study has proposed that the enrichment of arginine residues in functional domains of the SARS-CoV-2 proteome allows the possibility of an arginine-modifying agent strategy for inactivation of the virus [42]. In the SARS-CoV-2 proteome there are a large number of arginine residues activated by neighbouring groups for reaction with MG. These arginine residue targets are in key proteins: nucleoprotein, M-protein, and Spike protein. A further important feature for susceptibility of viral proteins to MG modification is protein abundance: high abundance of a protein increases its susceptibility to reaction with MG. Earlier studies of the SARS virion suggested proteins of highest abundance were: nucleoprotein, M-protein, Spike protein and nsp3 [43]. Increasing cellular MG in virally-infected cells is expected to increase the modification of arginine residues of viral proteins – particularly nucleoprotein, spike protein and M-protein.

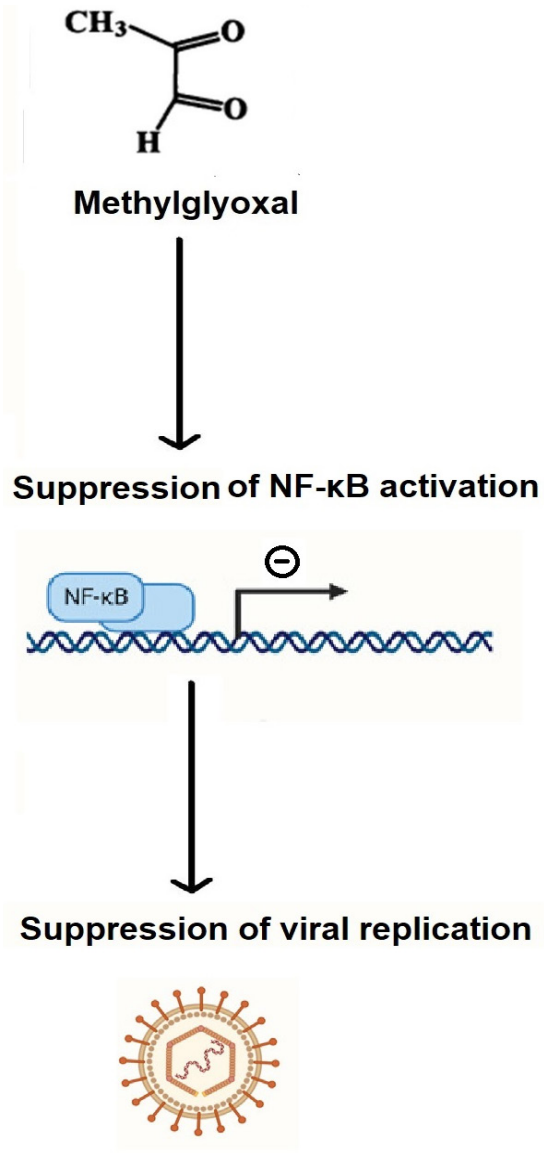

Figure 2 Schematic outline of anti-influenza activity of MG. MG was proposed to inhibit viral replication by suppression of NF-κB activation.

Several MG modification sites have been found in the Receptor Binding Domain (RBD) of viral proteins, indicating that pharmacological increase of endogenous MG concentration is likely to modify the viral proteome at multiple susceptible and functional sites, producing protein inactivation and antiviral response. Modification in functional sites of viral proteins, typically highly structured domains, converts cationic, hydrophilic arginine residues to uncharged hydrophobic MG-H1 residues. This induces protein misfolding, binding of misfolded proteins by heat shock proteins and ubiquitin ligases for degradation. Replication of SARS-CoV-2 is thereby slowed or terminated. Where viral proteins are modified by MG before folding, the change in hydrophobicity will likely impair correct folding and also direct the nascent polypeptide for ubiquitination and proteolysis. If some virions escape this proteotoxicity, MG modification on the spike protein may block or impair cell infectivity and thereby

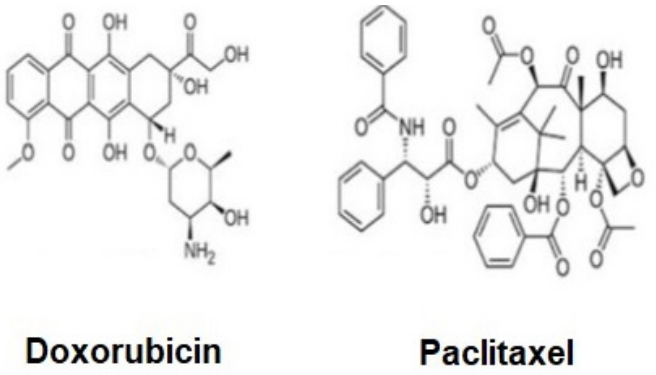

Figure 3 Molecular structures of clinical antitumor drugs. Structures of antitumor drugs doxorubicin and paclitaxel.

enhance viral immunogenicity; cf. β-propiolactone – an approach used in a SARS-CoV-2 vaccine in clinical evaluation [44].

Repurposing of drugs for treatment of COVID-19 disease

Clinical antitumor agents, doxorubicin and paclitaxel (**Figure 3**) exert their antiproliferative activity by increasing the cellular concentration of MG in human host tissues. Vulnerability of SARS-CoV-2 to modification and inactivation by MG provides a mechanistic rationale for repurposing of these drugs against SARS-CoV-2. Increase of MG may decrease viral load and decrease risk of vascular and renal complications of COVID-19. Relatively short-term treatment with drugs increasing cellular MG may be beneficial in patients with COVID-19. In conclusion, doxorubicin and paclitaxel may have therapeutic potential for the treatment of COVID-19 and can be considered in near future for evaluation in SARS-CoV-2 live virus cultures and animal models.

Conclusions and future directions

The studies on the antiviral property of MG reported till date opens up a possibility for further investigation in future. For example, it will be interesting to study the inhibitory activity of MG against highly pathogenic H5N1 and H7N9 influenza strains as well as other pathogenic viruses (e.g. zika virus, chikungunya virus, etc.) which has not been carried out earlier. Most vaccines against SARS-CoV-2 in development contain whole or fragments of the spike protein. Further investigations may be planned to use the MG modification strategy to produce inactive virus for vaccine development studies. In addition, the clinical antitumor drugs may be further explored to assess their antiviral activity against infectious viruses other than COVID-19, which may provide additional insight on the role of MG in viral inactivation. Increase of cellular MG to virucidal levels with anticancer drugs is achievable pharmacologically and sustainable over a virus life cycle. Selective toxicity of MG to the virus compared to the human host is required for a successful treatment with MG-increasing drugs, which can turn out to be an effective strategy for tackling with viral diseases.

The present review article also highlights possibilities to carry out further studies on the characterization of MG-induced

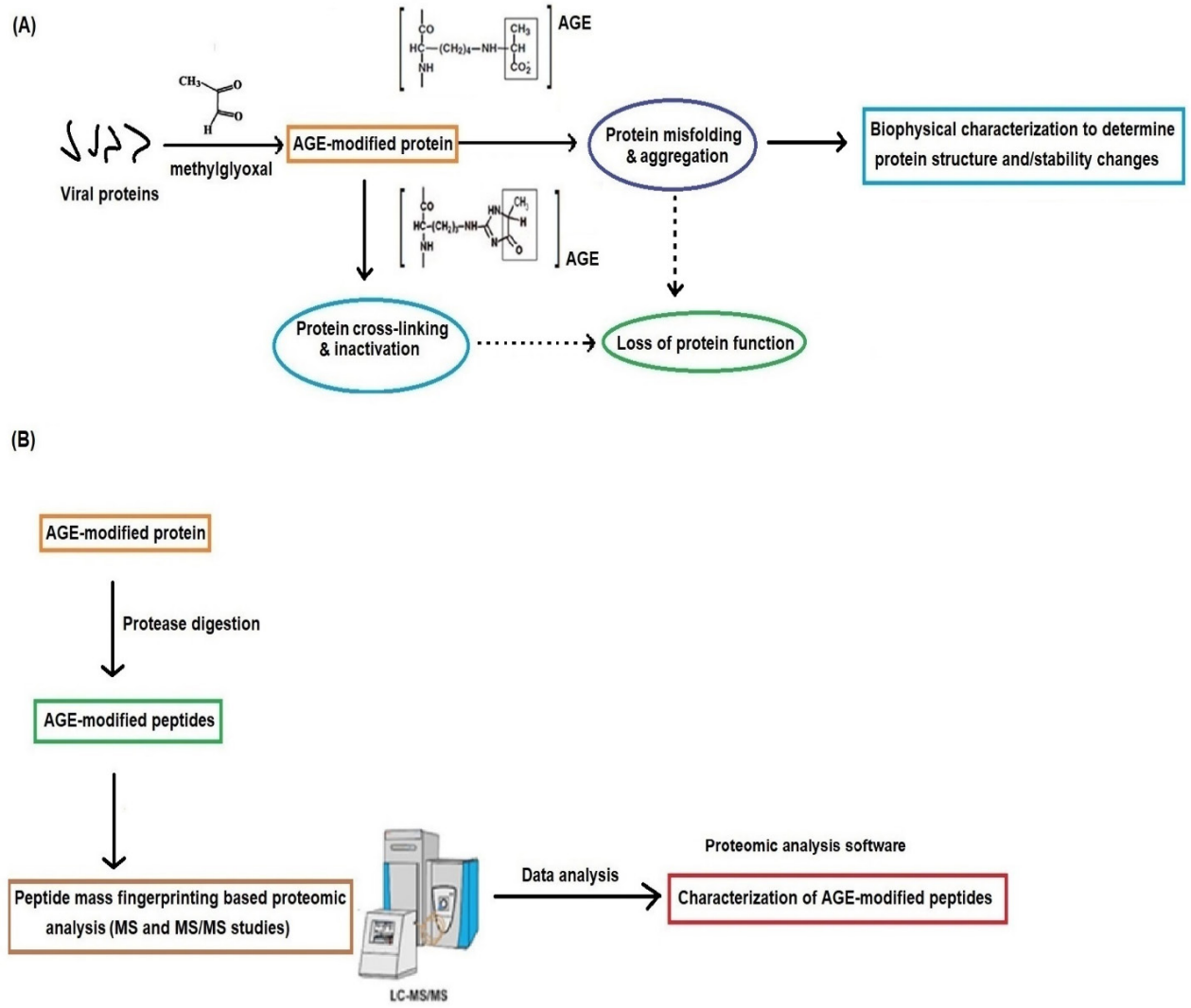

Figure 4 Schematic outline of structural characterization strategy of MG-modified viral proteins. (A) MG mediated AGE-induced changes in structure and stability of viral proteins can be characterized by standard biophysical techniques. (B) AGE-modified proteins may be further analysed by proteomic studies (MS and MS/MS methods) to identify and characterize the sites and nature of MG modifications (AGE adducts).

modification of viral proteome. For example, in case of influenza virus, MG may directly modify/alter the structures of the important surface glycoproteins, hemagglutinin and neuraminidase, as well as essential viral proteins responsible for infection. It will be interesting to investigate MG-mediated secondary and/tertiary structural alterations of viral proteins by different biophysical and spectroscopic methods in future studies. Subsequent proteomic analysis (including peptide mass fingerprinting studies) may be conducted to detect and characterize the sites (amino acid residues) and nature of MG modifications (AGE adducts) to gain information at the molecular level regarding MG-induced modification of viral proteins. A schematic representation outlining MG-mediated inactivation of viral proteins and subsequent biophysical characterization of MG-modified proteins is shown in (**Figure 4**). The studies are likely to provide a detailed insight on the mechanism of MG-mediated inactivation of specific viral proteins to gain further information on the antiviral property of the α-dicarbonyl compound.

Funding

The authors duly acknowledge ICMR-DHR (Memo No: V.25011/384/2014-HR-VDL dated 16.03.2022) for their generous funding and support.

Conflict of Interest

The authors have no potential conflicts of interest to disclose.

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