International Journal of Biological Macromolecules 100 (2017) 67–74

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

journal homepage: www.elsevier.com/locate/ijbiomac

Review

The status of glycation in protein aggregation

Fereshteh Taghavi[a,b,c], Mehran Habibi-Rezaei[d], Mojtaba Amani[e], Ali Akbar Saboury[a,f], Ali Akbar Moosavi-Movahedi[a,b,f,*]

[a] Institute of Biochemistry and Biophysics, University of Tehran, Tehran, Iran
[b] UNESCO Chair on Interdisciplinary Research in Diabetes at University of Tehran, Iran
[c] Faculty of Bio Science, Tarbiat Modares University, Tehran, Iran
[d] Schools of Biology, University of Tehran, Tehran, Iran
[e] Department of Biochemistry, Faculty of Medicine, Medical University of Ardabil, Ardabil, Iran
[f] Center of Excellence in Biothermodynamics, University of Tehran, Tehran, Iran

ARTICLE INFO

Article history:
Received 15 December 2015
Accepted 28 December 2015
Available online 2 January 2016

Keywords:
Glycation
Oxidative stress
Aggregation
Amyloid
Non amyloid

ABSTRACT

Protein crucial function and flexibility directly depend on its whole structure which is determined by the native distribution of structural elements. Any disturbances in a protein architecture leads to many kind of abnormalities and intra- or extracellular accumulation of misfolded proteins which are the basis of conformational diseases. Glycation is one of the most important unwanted post-translational modifications (PTM) which modifies protein three dimensional decoration and triggers its abnormalities. In current review, we take a look at the brief history of protein glycation, its mechanism and kinetics, glycation consequences and toxic products and its involvement in protein chemical modification, aggregation amyloids and fibril formation and different mechanisms induced by such alterations.

Contents

* Corresponding author. Fax: +98 21 66404680.
E-mail address: moosavi@ut.ac.ir (A.A. Moosavi-Movahedi).

http://dx.doi.org/10.1016/j.ijbiomac.2015.12.085
0141-8130/

1. Introduction

Proteins (the word derived from the Greek word 'proteios', meaning primary or standing in the front +in) not only are considered as structural constituents of the living organisms but also, biological functions are predominantly stands on them [1]. They are considered as valuable resource macromolecular machines in all living things, and nowadays have gained notable positions in the translational sciences and applied approaches.

The primary structure of protein is a flexible polypeptide sequence which is decorated with functional groups [2]. Protein local arrangement determines its secondary structure under complex folding process. The correct distribution of secondary elements (helix, sheet and random coil) not only determines protein's three-dimensional compact structure [3] but also establishes its native biological properties. Protein total flexibility is another important matter which is also crucial for biological function [4].

The alteration of protein's normal structure makes it prone to be aggregated, and aggregation events are directly governed by intrinsic and extrinsic factors including; amino acid sequences, mutations, and environmental stresses. Numerous extrinsic factors (e.g. pH, temperature, agitation, chemical species and oxidative agents) bring about turbulence and consequent disturbance in the protein native structure, denaturation and finally protein malfunctionality [3]. Therefore, unfolding energy barrier is overpassed and protein unfolding is occurred [5].

Among them, both of exogenic and endogenic stresses by oxidative and carbonyl stresses play important role in structural and functional damaging of biomacromolecules, that is followed by cellular dysfunction and death. More importantly, glycation as an out of control physicochemical redox process between macromolecules and oxidative agents involve in many chronic and degenerative diseases like diabetes mellitus, cardiac dysfunction [6,7], visual disorders [8], nephropathy [9], vascular disorders [10] and diabetic atherosclerosis [11].

Although, the term "glycation" was originally recommended by the Nomenclature Committee of International Union of Biochemistry (IUB) and the International Union of Pure and Applied Chemistry (IUPAC) in 1985 as "all reactions that link a sugar to a protein or a peptide, whether or not catalyzed by an enzyme" but, in 1993, the enzymatic and non-enzymatic modification of proteins by sugars was distinguished as glycosylation and glycation, respectively [12].

The occurrence of this process depends on characteristic of involved initiators, such as half-life of protein, reactivity and concentration of glycation agents, the involvement of environmental factors (metals, buffer ions and oxygen), physiological pH and temperature [13].

In this review, we focus on the concepts of protein glycation and its relationship with oxidative stress, glycotoxins which are involved in chemical modification, its interference with chemical language of body, and the mechanisms which seems to be involved in protein aggregation, amyloids and fibril formation and different related mechanisms.

1.1. Historical background of the glycation

The glycation time line is started at the first of 20th century. *Louis Camille Maillard* studied the reaction between reducing sugars and amine containing compounds in 1912. The brown pigmented product or melanoids were reported as the Schiff base adducts of initial interaction between amines and saccharides [14]. The non-enzymatic reaction of amino acids with sugars now is named the "Maillard reaction". About 40 years later, in 1953, *Hodge* constructed a precise diagram for describing Millard process and put it on the scientists concern [15].

Mario Amadori demonstrated two structurally different isomers without anomeric relationship in condensation of D-glucose with aromatic amines in 1929. Isomers were characterized as the labile and stable species [16]. Then, the structure of the Amadori's stable isomer has expressed as the unbranched N-substituted 1-amino-1-deoxy-2-ketose by *Kuhn* and *Weygand* in 1937 and the involved reaction was called Amadori rearrangement [17].

The reactive α-oxoaldehyde products as a middle product of Maillard reaction was found by Rahbar and his coworkers [18].

Similar reaction in physiological systems and in the presence of reactive α-oxoaldehyde compounds due to glucose degradation and the formation of these compounds from fragmentation of the saccharide were proposed by *Pinkus* [19] and *Hayashi* and *Namiki* [20] separately.

Wallenius and *Kunkle* reported glycated hemoglobin in 1955 [21]. The reaction of amino acids with glyoxal derivatives was found by *Takahashi* in 1977 [22] and free radical degradation of Maillard intermediates were investigated by *Namiki* and co-workers, in 1986[23].

The monosaccharide autoxidation under physiological conditions and the formation of α-oxoaldehyde and hydrogen peroxide were reported by *Wolff* and co-workers [24].

Brown fluorescent pigments due to fructosamin degradation, as protein cross linkers with first used the term of advanced glycation end products (AGE) was reported by *Cerami* in 1986 [25].

Gradually other AGEs like Nε-carboxymethyl-lysine (CML) and pentosidine were discovered by *Baynes* and his coworkers [26] and *Monnier* and *Sell* in 1989 [27].

The receptor for Advanced Glycation End products (RAGE) from bovine lung endothelial cells was investigated by *Stern* and his co-workers in 1992 [28].

Thornalley and his co-workers reported the significant modifications of arginine and lysine in glycated protein [29]. All of these researches have happened but the nature of glycation and its relationship with degenerative diseases are still attractive for scientists and made it as a valuable field of outstanding interest and innovative researches in broad range of sciences.

2. Glycation

Native homeostatic modifications of proteins can trigger many important cellular processes [2] but glycation is one of the most important unwanted post-translational modification (PTM) with biochemical mechanism which modifies protein covalently through adding functional groups to its amino-acid residues like phosphorilation [30,2]. Amino acid properties can be changed by PTM based on developmental or physiological time scale. PTMs of protein are involved in determining of protein's tertiary and quaternary structures and modulate their biological activity [2].

Oxidation due to oxidative stress and glycation due to carbonyl stress is the major non-enzymatic post-translational modification mechanisms which alter and damage the structure and function of biological macromolecules specially proteins. Numerous metabolites like sugars and their reactive derivatives [6], can expose blood plasma proteins continuously and start glycation. The oxidative chemical reaction of reducing sugars with protein primary amino groups produced a new meaningful term as glycoxidation [31].

2.1. Kinetics of glycoxidation

Protein glycation is completely different from glycosylation which comprises an enzyme-catalyzed reaction and site specific addition of carbohydrate moieties [31,32]. This oxidative processes as Maillard reaction [33] is a collection of complex network reactions, time-consuming and non-enzymatic process which take