Glycated protein generates active oxygen
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Medical, biochemical and chemical studies of active oxygen are becoming increasingly intensive and recent findings may be reviewed in the monograph\(^1\), symposium records\(^2,3\) and international meeting abstracts\(^4,5\). The study of autooxidation of sugars is not new, but little has been studied about superoxide, SOD and hydroxyl radical associated with diseases and aging\(^6\). The autooxidation reaction of sugars as oxygen radical-generating system has been recently unveiled\(^6,7\), while the study of amino-carbonyl reactions is developing in a new direction ately\(^8\). Furthermore, it has been found that the Amadori rearrangement compounds (1-amino-1-deoxyketoses) generate
active oxygen species under physiological conditions\textsuperscript{9,10}). The Amadori compound is an important intermediate product in the Maillard reaction and has long been studied extensively as applied to the field of food chemistry. But, more recently, it has been noticed as a reaction intermediate product found between proteins and reducing sugar in vivo and considered to be associated with diabetes mellitus or aging. This reaction is called glycation, and the product is called glycated proteins, which are studied as being different from N- or O-glycosylated proteins.

The reducing sugars generate active oxygen under physiological conditions as shown in Fig. 1\textsuperscript{6}), and induce cleavage of nucleic acid and inactivation of viruses\textsuperscript{9,10}). The Amadori compounds such as oximes and hydrazones, also generate active oxygen involving enaminol anion as an intermediate product. The rates of production of superoxide are when measured by reducing reaction of cytochrome c are shown in Fig. 2\textsuperscript{10}). These autoxidation reactions are far weaker than those of reductone, and under physiological conditions they do not seem to occur unless the quantity of the substrate is extremely large, but when the reducing sugar is chemically modified, the reactivity is intensified. It is increased in particular in sugar phosphates and trioses to pentoses. It is therefore speculated that various sugar phosphates may also produce in vivo active oxygen in autoxidation, and exert influences on the cell functions\textsuperscript{7}).

![Fig. 1. Formation of active oxygen by the autoxidation of reducing sugars](image-url)
As shown in Fig. 3, the glycation reaction in vivo is important and complicated in the step following the production of the Amadori compounds. From this decomposition reaction, resulting formations of deoxyosone and carboxymethyl lysine have been proved. Now the formation of active oxygen has been added to the list. The method of detection involves reduction of cytochrome c, reduction of NBT, and chemical luminescence. At the present, formation of superoxide is being reported for typical glycated proteins, using these methods. Superoxide is transformed into hydrogen peroxide right after its formation. Active oxygen-producing reactions of reducing sugars are specifically promoted by Cu$^{2+}$. As inactivation of viruses and cleavage of DNA were noted for reducing sugars in the presence of Cu$^{2+}$, it was also attempted to check for glycated proteins. As a result, cleavage reactivity of bacteriophage DNA was observed. These DNA cleavage reactions are believed to be caused when Cu$^{+}$ which is reduced and produced by superoxide on the DNA molecule, reacts with H$_2$O$_2$, to produce OH$^-$, which then attacks the neighboring nucleic acid base. The phosphodiester bond is finally cleaved by elimination reaction preceded by the dissociation of the glycoside bond due to the modification of the base.
Glycated protein, thus, bear a kind of nucleosidase activity. If the base specificity, hitherto shown by simple reducing sugars\textsuperscript{15}, is proved in glycated proteins, it will be very interesting. It is also of interest to see how far the radical formation reaction is inhibited by SOD.

We don't know how much active oxygen is formed from glycated proteins \textit{in vivo}. As it is known that a considerable amount of glycated proteins is formed in diabetes, cataract, and aging, it is desired to determine exactly the quantity in the future. The role of active oxygen and the possibility of biological damage are not clear yet. Since glycated proteins induce very complicated reactions after Amadori rearrangement even in the absence of oxygen, the analysis is very difficult. Current studies are concentrated on the polymerization reaction of proteins and formation of substances. The effects of oxygen radicals on
these two reactions will be investigated in the first place.

It is interesting to see whether the Amadori rearrangement product in glycated proteins undergoes enzymic decomposition or not. Very recently a group in Japan has discovered an enzyme which oxidizes and decomposes an Amadori product of amino acids\textsuperscript{16}). On the other hand, the reaction for enzymatically reducing the glycosones, nonenzymatic decomposition products of the Amadori compound has been studied lately\textsuperscript{17}). In the future, this line of researches may be promoted from the viewpoint of defense against glycation reaction in relation with the oxygen radicals and autooxidation.

The study of the glycation of SOD is at an advanced stage. SOD has been found to be a protein that is very easily glycated\textsuperscript{18}). In this case, too, formation of the Amadori rearrangement product seems to occur and it may be important to investigate the effect of autooxidation on the fine mechanism of enzymatic dismutation of superoxide by SOD.

Finally, recent interest has also been shown in the glycation of nucleic acid \textit{in vivo}, together with proteins. Although there is no direct proof, the reaction is investigated by a spectroscopic method\textsuperscript{19}), and its biochemical significance\textsuperscript{20}) is presented. Is there really any chemical modification or autooxidation of nucleic acids \textit{in vivo} for which reducing sugar or active oxygen is responsible?

References


Lectin: The Protein with Carbohydrate-recognition Sites
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Lectin used to be defined as a protein that has multiple carbohydrate-binding sites (polyvalent) and hence effects cellular agglutination, which rules out antibodies and enzymes that are capable of binding with carbohydrates (1). In recent years, nevertheless, a large number of lectins with enzymatic activity or a single carbohydrate-binding site (monovalent) have been found one after the other, which calls for a reconsideration of the original definition. It seems more appropriate to describe this protein not as an antibody but as a protein which has one or more carbohydrate-recognition sites other than the active sites of carbohydrate-related enzymes. There has been an increasing number of instances in which the