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Review article

Glycative stress and anti-aging: 10. Glycative stress and liver disease.

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Abstract

The liver is a vital organ which has a basal metabolic rate of 25%. Liver diseases include hepatitis, cirrhosis and fatty liver disease. Causes of fatty liver disease are obesity, excessive energy consumption, such as through alcohol and carbohydrates, diabetes, and lack of exercise. Chronic and excessive alcohol consumption in patients with a fatty liver induces alcoholic liver disease (ALD) at a ratio of 10-20%. Contrarily, fatty liver disease includes pathological conditions designated as nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). NASH occurs in those with a background of fatty liver due to overeating, lack of physical activity, obesity, diabetes, and even lipid abnormalities all without a drinking history. Leaving fatty liver disease untreated is a risk factor which may lead to cirrhosis or hepatoma. Among the various types of AGEs (advanced glycation end products) formed *in vivo*, glyceraldehyde-derived AGEs (Glycer-AGEs) and acetaldehyde-derived AGEs (AA-AGEs) are involved in liver diseases. There is a possibility that Glycer-AGEs and AA-AGEs induce protein dysfunction and influence nerve cells or liver cells, which are involved in the onset and progression of alcoholic liver disease (ALD). Moreover, varied AGEs, mainly glucose-derived AGEs (Glc-AGEs), are produced in food during heating or processing. Intake of food containing high levels of GLc-AGEs may induce the accumulation of Glc-AGEs and Glycer-AGEs in the liver. Therefore, food-derived AGEs and postprandial hyperglycemia may increase levels of Glycer-AGEs, and induce liver diseases.

KEY WORDS: alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), glyceraldehyde-derived AGEs (Glycer-AGEs), acetaldehyde-derived AGEs (AA-AGEs)

1. Introduction: liver diseases

The liver, which is a vital organ with a basal metabolic rate of 25%, metabolizes carbohydrates, lipids, protein and vitamins, detoxifies substances and secretes bile. Furthermore, the liver has a high regenerative capacity and thus, is a regeneratable organ, even if liver cells are destroyed. Liver diseases include hepatitis, cirrhosis and fatty liver disease. As patients with liver diseases rarely have subjective symptoms, the liver is called a silent organ.

Hepatitis is classified, according to clinical conditions; mainly into acute hepatitis and chronic hepatitis (inflammation lasts for six months or longer). Based on the causes, hepatitis is categorized into viral (A, B, C and others), alcoholic, drug-induced, autoimmune hepatitis and others [1].

Hepatitis A is an infectious disease affecting the digestive organs, which is caused by the hepatitis A virus (HAV). Consumption of virus contaminated shellfish is a major cause of hepatitis A, which is commonly seen in regions with unsanitary living conditions. Infection of children mostly results in inapparent infection, while infection of adults frequently induces an onset of hepatitis A. Hepatitis B, which is caused by the hepatitis B virus (HBV), is classified into transitory and persistent disease. In most cases of the persistent type of hepatitis, the virus is passed from mother to infant. Acute hepatitis occurs rather than chronic hepatitis. Hepatitis C, which is caused by the hepatitis C virus (HCV), occurs regardless of season, age or sex. Hepatitis C accounts for the majority of blood-transfusion-induced hepatitis cases, and has a high probability to become chronic.

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Until recently, causes of hepatoma, which is one of the liver diseases, was mostly through viral liver diseases, such as hepatitis C. However, the number of nonalcoholic cases has been increasing as a cause of hepatoma, where a fatty liver is considered as a cause in many cases. A fatty liver is induced by obesity, excessive energy consumption, such as alcohol and carbohydrates, diabetes and lack of physical activity. Consumption of excessive alcohol as much as intaking five *go* (900 mL) of Japanese sake per day for seven consecutive days can lead to the onset of a fatty liver, even in a healthy person [2-4]. Chronic and excessive alcohol consumption of people with alcoholic fatty liver disease causes the onset of alcoholic liver disease (ALD) at a ratio of 10-20%. The spectrum of liver disease is the following: ADL develops into alcoholic fatty liver, alcoholic hepatitis and alcohol-related cirrhosis.

Contrarily, fatty liver diseases include nonalcoholic clinical conditions designated as nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). NASH occurs in those with a background of fatty liver due to overeating, lack of exercise, obesity, diabetes, and even lipid abnormalities all without a drinking history. Leaving NFLD without any treatments or interventions for five-ten years has a 5-20% chance to lead to the development of cirrhosis or hepatic cancer in patients with NFLD. NASH and ALD show resemblances in histological images of liver.

2. Liver diseases and AGEs

Among diversified types of AGEs (advanced glycation end products) formed *in vivo*, glyceraldehyde-derived AGEs (Glycer-AGEs) and acetaldehyde-derived AGEs (AA-AGEs) are involved in liver diseases [5].

It has long been recognized that AGEs are formed *in vivo* mainly from glucose and protein. However, it has also been confirmed that AGEs are formed from the metabolic intermediates and degradation products of glucose, the intermediates of glycation, and fructose (***Fig. 1***) [6, 7]. Furthermore, intermediates of glycation and aldehyde-derived AGEs form AGEs at a faster rate in comparison to glucose-derived AGEs (Glc-AGEs) and fructose-derived AGEs (Fru-AGEs). For example, in the glycation with protein of bovine serum albumin (BSA), the speed of AGE formation is the fastest in Glycer-AGEs, followed by glycolaldehyde-derived AGEs (Glycol-AGEs), methylglyoxal-derived AGEs (MGO-AGEs), glyoxal-derived AGEs (GO-AGEs), 3-deoxyglucosone-derived AGEs (3-DG-AGEs), Fru-AGEs and Glc-AGEs (Glycer-AGEs, Glycol-AGEs > MGO-AGEs, GO-AGEs >> 3-DG-AGEs >>> Fru-AGEs > Glc-AGEs).

Particularly, Glycer-AGEs are strongly involved, via receptor for AGEs (RAGE), in the onset and progression of diabetic vascular complications [7, 8]. When Glycer-AGEs are

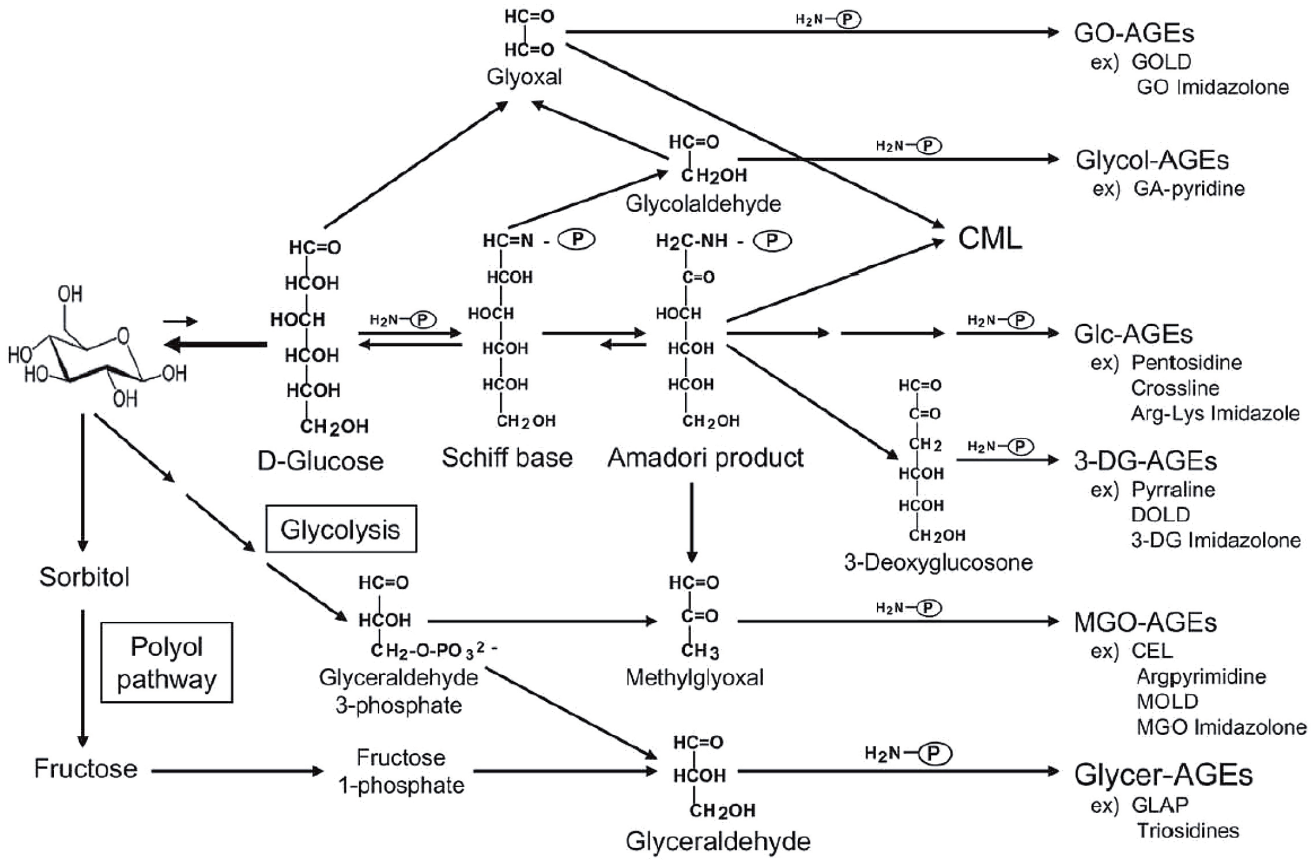

Fig. 1. **Alternative routes for the formation of AGEs *in vivo*.**

Glc-AGEs, glucose-derived AGEs; Glycer-AGEs, glyceraldehyde-derived, AGEs; Glycol-AGEs, glycolaldehyde-derived AGEs; MGO-AGEs, methylglyoxal (MGO)-derived AGEs; GO-AGEs, glyoxal (GO)-derived AGEs; 3-DG-AGEs, 3-deoxyglucosone (3-DG)-derived AGEs; CML, N-(carboxymethyl)lysine; P-NH2, free amino residue of protein. GOLD, GO-lysine dimmer; GA-pyridine, 3-hydroxy-4-hydroxymethyl-1-(5-carboxypentyl) pyridinium cation; DOLD, 3-DG-lysine dimmer; CEL, N-(carboxyethyl)lysine; MOLD, MGO-lysine dimmer; GLAP, glyceraldehyde derived pyridinium compound. The figure is adapted from Reference 7.

added to a hepatocyte culture system, there is an increase in an inflammatory marker known as the C-reactive protein (CRP). Furthermore, added into the culture system of hepatic stellate cell, which is associated with liver fibrosis, Glycer-AGEs induce glycative stress via RAGE and elicit inflammation [9]. Glycer-AGEs are accumulated in patients with NASH, which do not have impaired glucose tolerance [10]. When glyceraldehyde is added into the cell culture system of Hep3B, derived from a hepatic cancer cell in humans, apoptosis is induced in hepatocyte cells along with an increase in the amount of Glycer-AGEs. Furthermore, the activity of heat shock cognate 70 (Hsc70), which is a molecular chaperon, is lowered, when modified by glyceraldehyde to Glycer-AGEs. Subsequently, through protein dysfunction, hepatocellular injury may develop [11].

Contrarily, acetaldehyde, which is a metabolite of alcohol, is bound with protein to form AA-AGEs (*Fig. 2*). AA-AGEs have strong effects on hepatocellular injury. AA-AGEs are formed mainly in hepatic cells around central venules (Zone 3) and are involved in the onset and progression of ALD [12]. AA-AGEs are distributed in the blood or in the brain of alcohol-dependent patients [13]. It has been reported that AA-AGEs were formed mainly in hepatic cells around central venules in a chronic alcohol-treated rat model. Judging from these reports, even after acetaldehyde is metabolized and disappears from the blood, AA-AGEs may be involved in the onset and progression of alcoholic hepatopathy, affecting nerve cells or liver cells with toxicity.

3. Influences of food-derived AGEs on the liver

Varied AGEs are produced in food during heating or processing. Commercial food tends to contain AGEs, mainly Glc-AGEs or Fru-AGEs. An examination in influences of Glycer-AGEs on a RAGE expression system, where beverages containing high levels of GLc-AGEs were orally supplied to normal rats, demonstrated that the expression of vascular endothelial growth factor (VGEF) gene increased, and Glc-AGEs and Glycer-AGE accumulated [14].

An experimental system offering a limited food supply to type 2 diabetes model rats, confirmed that Glycer-AGEs were formed due to postprandial blood glucose elevation [15]. In the case of the administration of α-glucosidase inhibitor to patients with type 2 diabetes, in-blood levels of Glycer-AGEs were significantly reduced in comparison to the levels before administration [16]. Moreover, according to a survey of patients with NAFLD, the dietary intake of sweet beverages was five times higher in patients with NAFLD than in healthy people. Excessive consumption of sugar or high fructose corn syrup containing 55% fructose, which is added to beverages as a sweetener, is associated with the onset and progression of NAFLD [17]. Judging from these, there are possibilities that food-derived AGEs and postprandial hyperglycemia could increase levels of Glycer-AGEs, augment the interaction of the RAGE expression system due to Glycer-AGEs, and induce liver diseases [18].

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Conflict of Interest Statement

The authors claim no conflict of interest in this study.

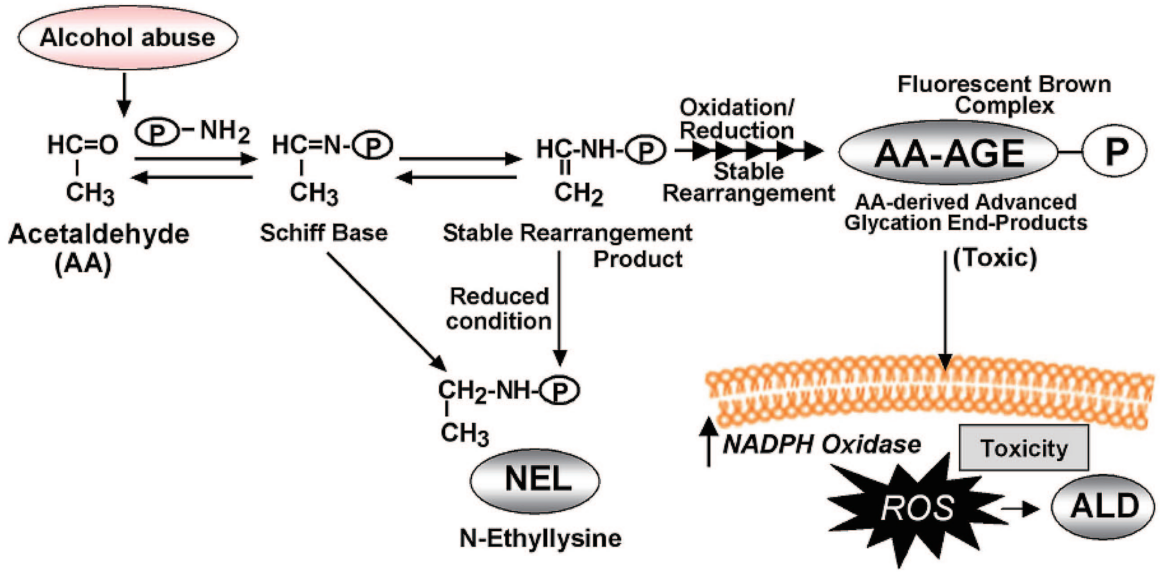

Fig. 2. **Schematic representation of the formation of AA-AGE from acetaldehyde, production of ROS, and pathogenesis of ALD.**

AA-AGE, acetaldehyde-derived AGE; NEL, *N*-ethyllysine; NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; ALD, alcoholic liver disease. The figure is adapted and modified from Reference 13.

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