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COMMENTARY

Are the polyol pathway and hyperuricemia partners in the development of non-alcoholic fatty liver disease in diabetes?

Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver disorders worldwide. NAFLD is considered to be the hepatic component of metabolic syndrome, because its features are very similar to those of metabolic disorders, such as obesity, inflammation, insulin resistance and type 2 diabetes. It is clear that NAFLD and type 2 diabetes have a close relationship. However, the exact mechanisms underlying the pathogenesis and progression of NAFLD are still incompletely understood[1–3]. It is well known that the regulation of glucose and lipid metabolism in the liver is properly carried out by insulin through either direct or indirect mechanisms. Therefore, two possible hypotheses are proposed to explain their pathogenesis. As one possibility, insulin resistance and excessive fatty acids in the bloodstream lead to simple hepatic steatosis. The second hypothesis implicates oxidative stress, lipid peroxidation and mitochondrial dysfunction. Hepatic rho-associated coiled-coil-containing kinase 1 has been introduced as a new possible pathogenesis of NAFLD, playing an important role in high-fat diet-induced hepatic lipogenesis through the inhibition of adenosine 5′-monophosphate-activated protein kinase[3]. This hypothesis occurs under the condition of a high-fat diet. This approach and the data are highly useful and meaningful in view of the current diet therapy for patients with diabetes. Recently, a very attractive and interesting hypothesis of the pathogenesis of NAFLD was proposed from the viewpoint of excessive intake of fructose (sugar or corn syrup)[2]. This completely new theory has a close connection with the polyol pathway hyperactivity activated by uric acid.

It is well known that hyperglycemia-induced polyol pathway hyperactivity can lead to the development of diabetic complications, such as microangiopathies, macroangiopathies and others[4–7]. Furthermore, it has been thoroughly confirmed by many studies that the inhibition of aldose reductase (AR), a key enzyme in this pathway, is useful to prevent these complications. The polyol pathway consists of just two steps: glucose is first reduced to sorbitol by AR, and the resulting sorbitol is then changed to fructose by sorbitol dehydrogenase (Figure 1). During normoglycemia, the use of glucose through the polyol pathway accounts for <3% of glucose consumption in cells. However, during hyperglycemia, the utilization of glucose through this pathway represents up to 30%, resulting in the progress of diabetic complications in target tissues[7]. The mechanisms of diabetic complications induced by hyperglycemia-activated polyol pathway hyperactivity are not as simple as we expect. Generally, metabolic factors, such as protein kinase C, glycation, oxidative stress and others, are involved in the lower reaches of this pathway and contribute to the progress of diabetic complications with complex issues[6,7]. Furthermore, the following factors in relation to polyol pathway hyperactivity might also be partially involved, depending on the types of diabetic complications: inflammation, endothelial nitric oxide synthase, thromboxane, matrix metalloproteinases, nicotineamide phosphoriboxyl transferase, nitric oxide, tissue factor, vascular cell adhesion molecule and the expression of multiple genes of the transforming growth factor-β pathway[6,7].

Recently, Sanchez-Lozada *et al.*[2] proposed a very interesting and attractive hypothesis of the pathogenesis of the development of NAFLD through uric acid-induced polyol pathway hyperactivity. The concept of that study is based on the fact that the two primary sweeteners, sugar (sucrose) and high fructose corn syrup, induce fatty liver in animals. Furthermore, previous studies by this group have shown that the pathogenesis of inducing fatty liver using fructose is due to the generation of uric acid in the course of fructose metabolism, resulting in mitochondrial oxidative stress and an impairment of adenosine triphosphate production. They also confirm that hyperuricemia itself is not only strongly related with hypertriglyceridemia and NAFLD, but also predicts the progression of NAFLD. Furthermore, they found that uric acid upregulated fructokinase/ketohexokinase (KHK) and fructose metabolism through the activation of the transcription factor, carbohydrate response element-binding protein. Their recent study based on these facts evaluates whether uric acid regulates AR expression both in cultured hepatocytes (HepG2 cells) and in the liver of hyperuricemic rats, and also whether this stimulation is associated with endogenous fructose production and fat (triglyceride) accumulation.

Their latest results are summarized as follows[2]. In human HepG2 cells exposed to uric acid of 4 mg/dL (normouricemia), 8 mg/dL and 12 mg/dL (hyperuricemia) for 72 h, AR expression was upregulated by uric acid in a dose-dependent manner,

*Corresponding author. Nigishi Hotta
Tel.: +81-52-652-5511
Fax: +81-52-652-5623
E-mail address: hotta@chubuh.johas.go.jp
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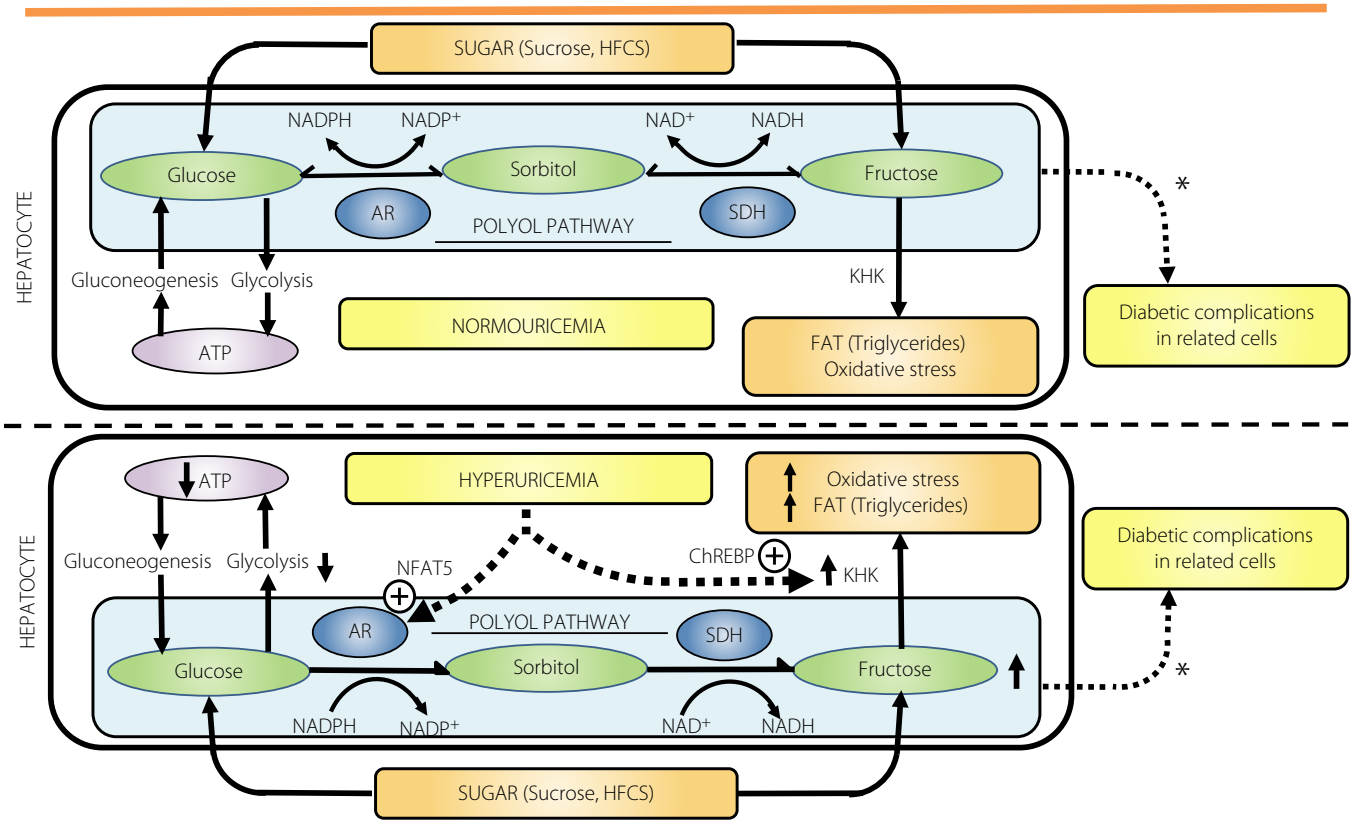

AR: aldose reductase, ATP: adenosine triphosphate, HFCS: high fructose corn syrup, ChREBP: carbohydrate response element binding protein, KHK: ketohexokinase, NAD: nicotinamide adenine dinucleotide, NADH: reduced form of nicotinamide-adenine dinucleotide, NADP: nicotinamide adenine dinucleotide phosphate, NADPH: reduced form of nicotinamide adenine dinucleotide phosphate, NFAT5: nuclear factor of activated T cells 5, SDH: sorbitol dehydrogenase.

Figure 1 | Effects of hyperuricemia through the activation of the polyol pathway for the induction of hepatic fat accumulation. Aldose reductase (AR), a key enzyme of the polyol pathway, activated by uric acid through an enrichment of nuclear factor of activated T cells 5 (NFAT5), shifts from glucose to sorbitol, contributing to an increment in fructose production. This increase of endogenous fructose results in triglyceride accumulation in the liver through the upregulation of ketohexokinase (KHK) by the transcription factor, carbohydrate response element-binding protein (ChREBP), activated by uric acid. In the course of promoted fructose metabolism, mitochondrial oxidative stress and an impairment of adenosine triphosphate production are induced. *It is well known that hyperglycemia-induced polyol pathway hyperactivity in diabetic complications of related tissues contributes to the development of diabetic complications. Thus, there is the possibility that hyperuricemia-induced polyol pathway hyperactivity in target cells could cause the development of diabetic complications, and further their progression while in a hyperglycemic condition compared with a non-hyperglycemic state.

and significant upregulation of sorbitol dehydrogenase and fructokinase/KHK was also observed. Interestingly, coexistence of uric acid and probenecid, a uric acid transporter inhibitor, prevented AR upregulation, signifying the regulation of AR expression by intracellular uric acid. However, as sorbitol and fructose did not increase in AR-deficient cells, it is clear that these products in the polyol pathway were mediated through the upregulation of AR. In the next step, they observed that uric acid-dependent AR expression was mediated by increased transcriptional activity. Namely, they found a significant enrichment of the transcription factor, nuclear factor of activated T cells 5 (NFAT5) in pure nuclear fractions of HepG2 cells exposed to uric acid. Furthermore, AR upregulation by uric acid decreased remarkably in NFAT5-deficient cells. It is interesting to note that the luciferase signal system (obtained by cloning the human AR promoter upstream) activated by uric acid was strongly prevented by the anti-oxidant molecule, apocynin, suggesting that NFAT5-dependent activation of AR is induced by oxidative stress. Finally, they attempted to confirm whether the activation of AR can shift glucose into the polyol pathway for endogenous fructose production and metabolism, and then fat accumulation in human hepatocytes and in rats. They observed that AR upregulation induced from high glucose (25 mmol/L) led to a marked increase in both sorbitol and fructose in hepatocytes, resulting in the elevation of intracellular triglycerides. However, none of these increments was found in AR-deficient cells. Intracellular oxidative stress, as well as sorbitol, fructose and triglycerides, were markedly greater in HepG2 cells exposed to both high glucose (12.5 and 25 mmol/L) and high uric acid

(12 mg/dL), as compared with the control group. They also found that elevated hepatic uric acid induced upregulation of AR and KHK in rats, as well as an increase in intrahepatic sorbitol and fructose levels, and an increase of NFAT5 expression appeared in the nucleus of hyperuricemic rats as compared with the control or allopurinol, xanthine oxidase inhibitor-treated animals. In Figure 1, their new results are summarized, along with their previous data that uric acid also upregulated KHK and fructose metabolism through the activation of the transcription factor, carbohydrate response element-binding protein.

This observation by Sanchez-Lozada *et al.*[2] is very important, because it means that hyperglycemia-induced polyol pathway hyperactivity in diabetes might cause further activation with uric acid, contributing not only to the development of NAFLD, but also the progress of diabetic complications in related tissues. Incidentally, the relationship between uric acid and diabetes is still inconclusive. However, a recent study of non-diabetic individuals showed that uric acid levels in plasma increase with 2-h plasma glucose, but not with fasting plasma glucose, and uric acid levels are inversely associated with both fasting plasma glucose and 2-h plasma glucose in the diabetic population[8]. Furthermore, uric acid levels correlate well with clinical and electrophysiological severity of diabetic sensorimotor polyneuropathy[9]. Thus, the management of uric acid in patients with diabetes is important and necessary for the prevention of diabetic complications together with NAFLD. Therefore, we cannot ignore the management of uric acid while maintaining good long-term glucose control and carrying out proper diet therapy to avoid foods and drinks containing high fat and high fructose. Due to the fact that both NAFLD and diabetic complications are markedly related with polyol pathway hyperactivity, it would not be surprising that the suppression of AR, a key enzyme in the polyol pathway, by AR inhibitors might be useful as a tool to manage these disorders. In addition, it is supposed that sodium–glucose cotransporter 2 inhibitors, a type of oral hypoglycemic agent, might be helpful to prevent the development of either NAFLD or diabetic complications caused by hyperuricemia, because it is well known that sodium–glucose cotransporter 2 inhibitors can reduce serum uric acid through the urinary excretion of uric acid[10]. Actually, sodium–glucose cotransporter 2 inhibitor in a clinical trial was shown to reduce hepatic fat content in type 2 diabetes patients[11].

DISCLOSURE

The authors declare no conflict of interest.

Nigishi Hotta[1]*, Takahiko Kawamura[1,2], Toshitaka Umemura[3]
[1]*Department of Endocrine Internal Medicine, Chubu Rosai Hospital, Japan Organization of Occupational Health and Safety, Nagoya, Japan,* [2]*Preventive Medical Center, Chubu Rosai Hospital, Japan Organization of Occupational Health and Safety, Nagoya, Japan,* [3]*Department of Neurology, Chubu Rosai Hospital, Japan Organization of Occupational Health and Safety, Nagoya, Japan*

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[Correction added on 27 March and 13 April 2020, after first online publication: Reference no. 7's publication year and reference no. 5's page details have been corrected.]