Diabetology International (2019) 10:245–249
https://doi.org/10.1007/s13340-019-00406-9

REVIEW ARTICLE

Pathophysiological roles of nutrient-sensing mechanisms in diabetes and its complications

Shinji Kume[1]

Received: 8 July 2019 / Accepted: 6 August 2019 / Published online: 13 August 2019

Abstract

Diabetic nephropathy, which is characterized by increased albuminuria, has been the most common cause of end-stage kidney disease for many years in Japan and many other countries. Although the renal prognosis of the disease has been improving in recent years because of the clinical implementation of strict glucose, blood pressure, and lipid controls, some diabetes patients continue to exhibit treatment-resistant macroalbuminuria leading to end-stage kidney disease. Furthermore, renal function decline without macroalbuminuria in diabetes is an emerging issue in Japan, which might be partly due to aging. Thus, a novel therapeutic strategy is needed to further improve renal outcome in diabetes patients. We have recently reported the involvement of dysregulation of intracellular nutrient-sensing signals and the related cellular process, autophagy, in the pathogenesis of diabetic nephropathy and abnormal insulin secretion pattern in type 2 diabetes. This review discusses potential roles of intracellular nutrient-sensing signals and autophagy as novel therapeutic targets for type 2 diabetes and diabetic nephropathy.

Keywords Type 2 diabetes · Diabetic nephropathy · Sirt1 · AMPK · mTORC1 · Autophagy

Introduction

Metabolic alterations mediated by deficient insulin action cause vascular damage, leading to life-threatening diabetic complications such as diabetic nephropathy. Endothelial damage is thought to be a primary event in the onset of diabetic vascular complications [1]. During the development of typical diabetic nephropathy, glomerular endothelial damage initially occurs, followed by microalbuminuria; the resulting podocyte injury leads to macroalbuminuria or massive proteinuria, thereby causing proximal tubular cell damage, subsequent nephron loss, and finally renal dysfunction [2–4]. Thus, typical diabetic nephropathy is considered to be a progressive kidney disease related to the development of proteinuria. In addition, it has been recently reported that mild but significant reduction in renal function without macroalbuminuria is an emerging clinical issue in diabetes care [5, 6]. Our recent clinical diabetes cohort study showed that age-associated atherosclerosis is likely to be involved in the pathogenesis of this type of kidney injury [6]. Thus, there is a need for new therapeutic options to combat refractory massive proteinuria and prevent kidney damage related to atherosclerosis, which can further improve renal outcomes in diabetes patients.

Calorie restriction (CR) has various beneficial effects on health in animal models, such as lifespan extension, diabetes prevention, cancer prevention, and renoprotection [7–9]. Notably, cellular energy homeostasis is maintained even during long-term fasting. To endure periods of long-term fasting, mammalian cells have evolved several intracellular nutrient-sensing signals, as well as systems regulated by these signals [10]. Recently, we have found that the dysregulation of these signals and related cell functions are associated with the pathogenesis of diabetes and diabetic nephropathy [11]. This review will focus on the roles of intracellular nutrient-sensing signals and autophagy as novel therapeutic targets for diabetes and diabetic nephropathy.

✉ Shinji Kume
skume@belle.shiga-med.ac.jp

[1] Department of Medicine, Shiga University of Medical Science, Tsukinowa-cho, Seta, Otsu 520-2192, Shiga, Japan

Anti-aging role of the Sirt1-autophagy pathway in aged kidneys

The kidney is a typical target organ of age-associated tissue damage [12]; in particular, age-dependent atherosclerotic changes and subsequent renal hypoxia are involved in the pathogenesis of aging in the kidney [13, 14]. Importantly, age-dependent decline in renal function is an emerging issue in diabetes care.

CR has various beneficial effects on health, including lifespan extension and anti-aging effects [7–9]. Investigations of the mechanisms of CR-related longevity have shown that silent information regulator 2 (Sir2) is a survival factor that can prolong lifespan [15]. Sirt1 is a mammalian homolog of Sir2, and was originally identified as an NAD-dependent histone deacetylase involved in various cellular processes, including stress resistance, cell cycle, metabolism, and apoptosis in response to the cellular energy and redox status; in addition, it exhibits deacetylase activity for more than two dozen known substrates [15].

Autophagy is a process by which damaged proteins and organelles are degraded to maintain cellular homeostasis during various stress conditions, such as starvation, oxidative stress, endoplasmic reticulum stress, and hypoxia [16, 17]. We discovered that Sirt1 is a potent regulator of autophagy against hypoxic stress in the kidneys [14]. During the process of aging in the kidney, Sirt1-dependent autophagy showed reduced ability to prevent age-related atherosclerosis and subsequent kidney hypoxia, leading to accumulation of damaged mitochondria and subsequent proximal tubular cell damage. However, CR was able to restore the activity of the Sirt1-dependent autophagy-related cell protective pathway even in aged kidneys; this suggested that the activation of autophagy may serve as a therapeutic strategy to prevent kidney injury associated with atherosclerosis-related hypoxia stress, even in elderly diabetic patients (Fig. 1).

Protective role of podocyte autophagy in diabetic nephropathy

Podocyte protection is important for prevention of refractory proteinuria in diabetes, because podocytes comprise terminally differentiated cells that cannot undergo replication [18]. Previous investigations have shown that podocytes are likely to exhibit extremely high rates of autophagy even under non-stress conditions [19], suggesting that autophagy is critical for maintenance of podocyte function and survival.

What is the extent of autophagy activity in diabetic podocytes? To answer this question, we first examined the relationship among the level of proteinuria, podocyte damage, and autophagy activity in podocytes within human renal biopsy samples. Autophagy insufficiency, which was defined as the accumulation of P62 protein, was abundantly present in the glomeruli of diabetic patients with podocyte damage and related massive proteinuria, suggesting that insufficient podocyte autophagy was associated with severe podocyte injury and massive proteinuria in diabetic patients [20, 21].

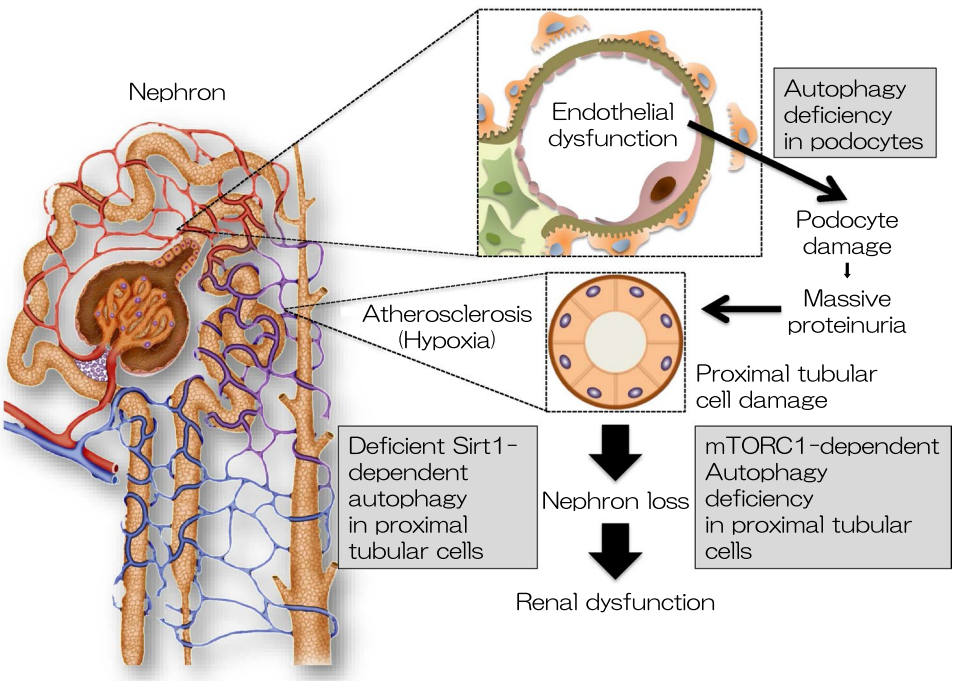

Fig. 1 Proposed pathogenesis of typical diabetic nephropathy characterized by proteinuria development and renal dysfunction related to atherosclerosis in diabetes. Autophagy insufficiency in kidney cells is involved in the pathogenesis of massive proteinuria development due to podocye damage and tubular cell damage caused by proteinuria and atherosclerosis-related hypoxic stress

To assess this causal association, we next investigated the effects of podocyte autophagy deficiency on high-fat diet-induced minimal proteinuria using a podocyte-specific autophagy-deficient mouse model. Although diabetic wild-type mice showed very mild albuminuria without podocyte injury, diabetic podocyte-specific autophagy-deficient mice developed massive albuminuria with severe podocyte injury [20, 21], suggesting that podocyte autophagy can protect cells against diabetic stress and that autophagy insufficiency combined with diabetic conditions can cause damage to podocytes (Fig. 1).

Protective role of proximal tubular cell autophagy in diabetic nephropathy

Based on the findings of a recent study by the our group, as well as the previous observation of autophagy in diabetic podocytes, the renoprotective function of autophagy may be suppressed in proximal tubular cells exposed to diabetes stress [22]. Autophagy insufficiency was confirmed in renal biopsy specimens from patients with type 2 diabetes or obesity with proteinuria. Furthermore, proximal tubular cell-specific autophagy-deficient mice developed severe tubular damage when they were exposed to experimental massive proteinuria [22], suggesting that insufficient autophagy is involved in the development of cell vulnerability to cell-toxic proteinuria in proximal tubular cells.

In that study, we also examined the mechanisms underlying autophagy deficiency in proximal tubular cells of high-fat diet-induced obese mice and patients with type 2 diabetes or obesity with proteinuria [22]. An intracellular nutrient-sensing signal, the mammalian target of rapamycin complex 1 (mTORC1), is activated by glucose, some types of amino acids, saturated fatty acids, and insulin, all of which are increased in diabetes [22]. This kinase complex serves as a strong physiological inhibitor of autophagy. We discovered that hyperactivation of mTORC1 signaling was involved in diabetes- or obesity-related autophagy suppression in proximal tubular cells.

Interestingly, obesity-mediated suppression of proteinuria-induced autophagy was corrected by dietary restriction and treatment with rapamycin, a specific inhibitor of mTORC1 signaling. A recent study showed that low-protein diet ameliorated diabetes-related tubulointerstitial damage through anti-inflammatory effects and upregulation of autophagy in diabetic Wistar fatty (fa/fa) rats [23]. Therefore, the restoration of autophagy activity may serve as a new therapeutic target to promote renal protection in diabetes patients with refractory proteinuria (Fig. 1).

Physiological role of fasting-dependent autophagy in the liver and kidney

Podocyte autophagy is constitutively active, regardless of feeding state; however, proximal tubular cell autophagy is inactive in fed conditions and becomes active during long-term fasting [22]. We next investigated the physiological role of fasting-dependent autophagy in proximal tubular cells [24, 25].

Glucose, fatty acids, and ketone bodies are energy sources to generate ATP for living mammalian cells. Of these, glucose and ketone bodies can be utilized for ATP production in the brain. Therefore, gluconeogenesis and ketogenesis are critical for the maintenance of brain energy homeostasis during starvation in mammals. The liver is a critical component of regulation of both processes. In addition, the kidney is known to support gluconeogenesis [26]. Thus, we examined the role of fasting-dependent autophagy in proximal tubular cells during starvation-induced gluconeogenesis and ketogenesis using several mouse models lacking autophagy activity in liver, kidney, or both organs [24, 25].

Deficient autophagy in any organs did not alter glucose homeostasis during long-term fasting [24]. However, liver-specific autophagy deficiency partially (but significantly) suppressed starvation-induced ketogenesis [24]. Moreover, mice-lacking autophagy in both liver and kidney showed complete reduction of ketogenesis, and demonstrated much lower physical activity during fasting [24]. These findings suggest that autophagy is involved in hepatic and renal ketogenesis during starvation, and that ketogenesis, but not gluconeogenesis, may be critical for maintenance of physical activity during prolonged fasting [24, 25].

Role of hypothalamic AMP-activated protein kinase (AMPK) in the regulation of first-phase insulin secretion in fasting and diabetes

An intracellular nutrient-sensing signal, AMPK, is one of the central regulators in whole-body energy metabolism and glucose metabolism [27]. We discovered that hypothalamic AMPK regulates first-phase insulin secretion from pancreatic β-cell. Glucose-stimulated insulin secretion (GSIS) from pancreatic β-cells is biphasic, and the suppression of first-phase GSIS is a key characteristic of β-cell dysfunction in type 2 diabetes, which results in postprandial hyperglycemia [28].

We focused on the relationship between fasting-dependent reduction in first-phase GSIS and β-cell dysfunction in

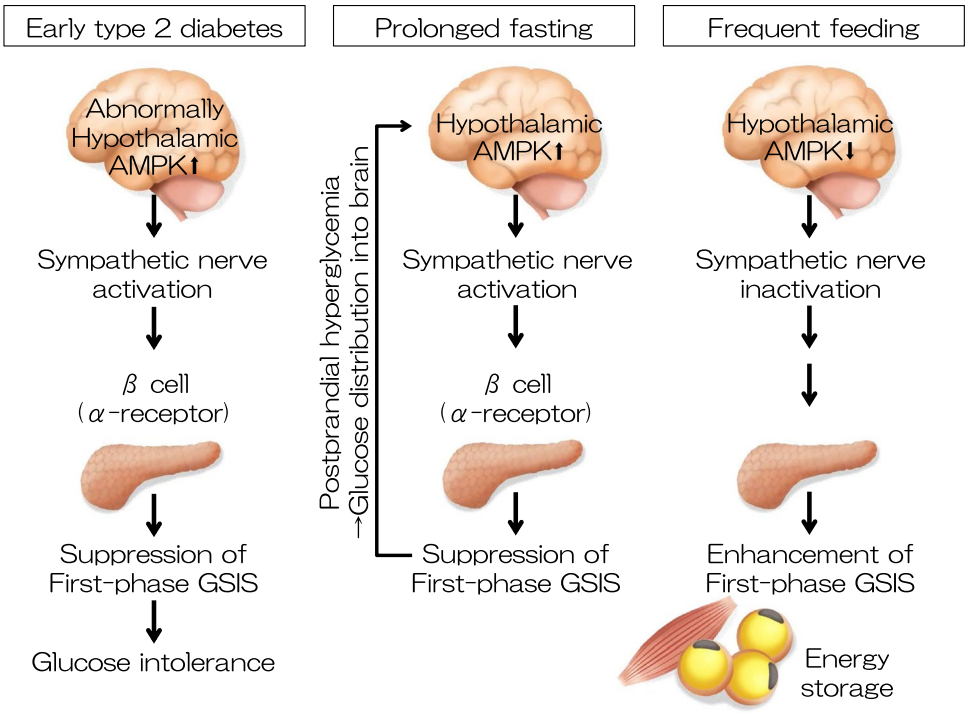

Fig. 2 Role of hypothalamic AMP-activated protein kinase (AMPK) in regulation of first-phase glucose-stimulated insulin secretion (GSIS). During prolonged fasting stimulates AMPK leading to activation of sympathetic nerve and subsequent suppression of first-phase GSIS, which is essential for postprandial brain glucose distribution (center). In contrast, frequent feeding suppresses brain-beta cell neural axis, increasing first-phase GSIS to store abundant glucose in insulin-sensitive organs such as skeletal muscle and adipose tissues (right). Furthermore, starvation-related neural system is involved in diabetes-related impairment of first-phase GSIS and glucose intolerance (left)

type 2 diabetes. Reduced first-phase GSIS after prolonged fasting decreased glucose redistribution to peripheral tissues, whereas it increased glucose redistribution to the brain; this promoted maintenance of glucose supply to the brain during refeeding after prolonged fasting. Notably, the excitation of the hypothalamic AMPK–β-cell neural axis impaired first-phase GSIS in both fasted wild-type rats and a rat model of type 2 diabetes [29]. Furthermore, surgical denervation of the pancreas dramatically improved first-phase GSIS, glycemic control, and β-cell survival in a murine model of diabetes [29].

Reduced first-phase GSIS might be a common insulin secretion pattern during times of scarcity, which may influence β-cell dysfunction in type 2 diabetes in the modern era (i.e., the "era of plenty"). Following this study, we proposed that β-cells in diabetic individuals mistakenly sense that they are under conditions that mimic those of prolonged fasting (Fig. 2). This so-called "starvation diabetes" was first observed in the 1940s [30].

Perspectives

During their evolution, mammals developed a variety of intracellular nutrient-sensing signals, many of which may have originally been used to combat starvation, a life-threatening event. However, in the recent era of plenty, these systems are likely to be unnecessary for survival because of the continuous access to food. Through the series of our nutritional study, we have learned that it is important to understand the roles of these physiological mechanisms, to better understand the pathogenesis of diabetes and its complications. Based on the series of experiments described in this review, some systems to combat starvation in cells are likely to be involved in the pathogenesis of diabetes and its complications. I hope that additional studies focusing on starvation metabolism will provide further insight into the pathogenesis of diabetes and its complications and contribute to development a therapy for the diseases.

Acknowledgements This review is a summary of my presentation in the Lilly Award Lecture at the 62nd annual meeting of the Japan Diabetes Society, Sendai, Japan. I would like to express sincere gratitude to Professor Hiroshi Maegawa, Professor Daisuke Koya, Professor Masakazu Haneda, Professor Atsunori Kashiwagi, Professor Ryuichi Kikkawa, and all members of department of medicine, Shiga University of Medical Science for their guidance and support.

Compliance with ethical standards

Conflict of interest Shinji Kume declares that he has no conflict of interest.

Statement of animal and/or human participants This article does not contain any studies with human or animal subjects.

References

1. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005;54:1615–25.
2. Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. Lancet. 1982;1:1430–2.
3. Pagtalunan ME, Miller PL, Jumping-Eagle S, Nelson RG, Myers BD, Rennke HG, Coplon NS, Sun L, Meyer TW. Podocyte loss and progressive glomerular injury in type II diabetes. J Clin Invest. 1997;99:342–8.
4. Abbate M, Zoja C, Remuzzi G. How does proteinuria cause progressive renal damage? J Am Soc Nephrol. 2006;17:2974–84.
5. Afkarian M, Zelnick LR, Hall YN, Heagerty PJ, Tuttle K, Weiss NS, de Boer IH. Clinical manifestations of kidney disease among US adults with diabetes, 1988–2014. JAMA. 2016;316:602–10.
6. Kume S, Araki SI, Ugi S, Morino K, Koya D, Nishio Y, Haneda M, Kashiwagi A, Maegawa H. Secular changes in clinical manifestations of kidney disease among Japanese adults with type 2 diabetes from 1996 to 2014. J Diabetes Investig. 2018;10:1032–40.
7. Sohal RS, Weindruch R. Oxidative stress, caloric restriction, and aging. Science. 1996;273:59–63.
8. Omodei D, Fontana L. Calorie restriction and prevention of age-associated chronic disease. FEBS Lett. 2011;585:1537–42.
9. Mattison JA, Colman RJ, Beasley TM, Allison DB, Kemnitz JW, Roth GS, Ingram DK, Weindruch R, de Cabo R, Anderson RM. Caloric restriction improves health and survival of rhesus monkeys. Nat Commun. 2017;8:14063.
10. Efeyan A, Comb WC, Sabatini DM. Nutrient-sensing mechanisms and pathways. Nature. 2015;517:302–10.
11. Kume S, Thomas MC, Koya D. Nutrient sensing, autophagy, and diabetic nephropathy. Diabetes. 2012;61:23–9.
12. Zhou XJ, Rakheja D, Yu X, Saxena R, Vaziri ND, Silva FG. The aging kidney. Kidney Int. 2008;74:710–20.
13. Tanaka T, Kato H, Kojima I, Ohse T, Son D, Tawakami T, Yatagawa T, Inagi R, Fujita T, Nangaku M. Hypoxia and expression of hypoxia-inducible factor in the aging kidney. J Gerontol A Biol Sci Med Sci. 2006;61(8):795–805.
14. Kume S, Uzu T, Horiike K, Chin-Kanasaki M, Isshiki K, Araki S, Sugimoto T, Haneda M, Kashiwagi A, Koya D. Calorie restriction enhances cell adaptation to hypoxia through Sirt1-dependent mitochondrial autophagy in mouse aged kidney. J Clin Invest. 2010;120:1043–55.
15. Haigis MC, Guarente LP. Mammalian sirtuins–emerging roles in physiology, aging, and calorie restriction. Genes Dev. 2006;20(21):2913–21.
16. Levine B, Kroemer G. Autophagy in the pathogenesis of disease. Cell. 2008;132:27–422.
17. Kroemer G, Mariño G, Levine B. Autophagy and the integrated stress response. Mol Cell. 2010;40:280–93.
18. Mundel P, Shankland SJ. Podocyte biology and response to injury. J Am Soc Nephrol. 2002;13(12):3005–15.
19. Hartleben B, Gödel M, Meyer-Schwesinger C, Liu S, Ulrich T, Köbler S, Wiech T, Grahammer F, Arnold SJ, Lindenmeyer MT, Cohen CD, Pavenstädt H, Kerjaschki D, Mizushima N, Shaw AS, Walz G, Huber TB. Autophagy influences glomerular disease susceptibility and maintains podocyte homeostasis in aging mice. J Clin Invest. 2010;120:1084–96.
20. Tagawa A, Yasuda M, Kume S, Yamahara K, Nakazawa J, Chin-Kanasaki M, Araki H, Araki S, Koya D, Asanuma K, Kim EH, Haneda M, Kajiwara N, Hayashi K, Ohashi H, Ugi S, Maegawa H, Uzu T. Impaired podocyte autophagy exacerbates proteinuria in diabetic nephropathy. Diabetes. 2016;65:755–67.
21. Yasuda-Yamahara M, Kume S, Tagawa A, Maegawa H, Uzu T. Emerging role of podocyte autophagy in the progression of diabetic nephropathy. Autophagy. 2015;11:2385–6.
22. Yamahara K, Kume S, Koya D, Tanaka Y, Morita Y, Chin-Kanasaki M, Araki H, Isshiki K, Araki S, Haneda M, Matsusaka T, Kashiwagi A, Maegawa H, Uzu T. Obesity-mediated autophagy insufficiency exacerbates proteinuria-induced tubulointerstitial lesions. J Am Soc Nephrol. 2013;24:1769–81.
23. Kitada M, Ogura Y, Suzuki T, Sen S, Lee SM, Kanasaki K, Kume S, Koya D. A very-low-protein diet ameliorates advanced diabetic nephropathy through autophagy induction by suppression of the mTORC1 pathway in Wistar fatty rats, an animal model of type 2 diabetes and obesity. Diabetologia. 2016;59:1307–17.
24. Takagi A, Kume S, Kondo M, Nakazawa J, Chin-Kanasaki M, Araki H, Araki S, Koya D, Haneda M, Chano T, Matsusaka T, Nagao K, Adachi Y, Chan L, Maegawa H, Uzu T. Mammalian autophagy is essential for hepatic and renal ketogenesis during starvation. Sci Rep. 2016;6:18944.
25. Takagi A, Kume S, Maegawa H, Uzu T. Emerging role of mammalian autophagy in ketogenesis to overcome starvation. Autophagy. 2016;12:709–10.
26. Krebs HA, Bennett DA, De Gasquet P, Gasquet P, Gascoyne T, Yoshida T. Renal gluconeogenesis The effect of diet on the gluconeogenic capacity of rat-kidney-cortex slices. Biochem J. 1963;86:22–7.
27. Hardie DG, Ross FA, Hawley SA. AMPK: a nutrient and energy sensor that maintains energy homeostasis. Nat Rev Mol Cell Biol. 2012;13:251–62.
28. Seino S, Shibasaki T, Minami K. Dynamics of insulin secretion and the clinical implications for obesity and diabetes. J Clin Invest. 2011;121:2118–255.
29. Kume S, Kondo M, Maeda S, Nishio Y, Yanagimachi T, Fujita Y, Haneda M, Kondo K, Sekine A, Araki SI, Araki H, Chin-Kanasaki M, Ugi S, Koya D, Kitahara S, Maeda K, Kashiwagi A, Uzu T, Maegawa H. Hypothalamic AMP-activated protein kinase regulates biphasic insulin secretion from pancreatic β cells during fasting and in type 2 diabetes. EBioMedicine. 2016;13:168–80.
30. Lundbaek K. Metabolic abnormalities in starvation diabetes. Yale J Biol Med. 1948;20(6):533–44.