EDITORIAL

ASPROSIN AND TYPE 2 DIABETES MELLITUS: A NOVEL POTENTIAL THERAPEUTIC IMPLICATION

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Diabetes is a group of metabolic disorders that is characterized by hyperglycemia which increases the risks of cardiovascular, microvascular, and macrovascular complications. Innovative therapeutic trials regarding diabetes control and management are continually being undertaken. The present review was aimed to explore the potential effects and mechanisms that lead to the pathogenesis of type 2 diabetes mellitus (T2DM) and its relation with asprosin. Asprosin is a newly discovered hormone that is encoded by protein fibrillin 1 (FBN1 gene), secreted by white adipose during fasting conditions at 5–10 nM levels, which acts on the liver through cell membrane receptors and activates the G protein cAMP- PKA pathway. Asprosin secretion is increased during fasting as the compensatory mechanism in hypoglycemia. Asprosin concentration is higher in patients with T2DM and impaired glucose regulation compared to healthy subjects. Genetic deficiency of asprosin may cause problems of poor appetite and extreme leanness in humans. Attenuating asprosin activity or depleting asprosin may serve as a novel therapeutic innovation for the treatment of T2DM and obesity. Hence, asprosin may serve as a beacon for the target of a future therapy in diabetes management.

Asprosin is a newly discovered hormone and is correlated with insulin secretion; a lot is still to be revealed about it. The primary objective of the present review was to assess plasma asprosin concentrations in the case of T2DM, and to explore the potential effects and mechanisms that lead to the pathogenesis of T2DM and its relation with asprosin. Fig. 1 shows the conceptual framework of the review.

Asprosin may serve as an ideal for future therapy in the management of diabetes which would help clinical practitioners (especially endocrinologists and laboratory technicians) to consider novel hormone asprosin as a reference for diabetes diagnosis and its subsequent management.

Asprosin biology

Asprosin is encoded by protein fibrillin 1 (FBN1 gene) (140 amino acid residues 2732-2871, molecular weight 30 kDa), and this gene also encodes fibrillin. The encoded pre-protein is processed by proteolysis to generate two proteins-fibrillin-1 and asprosin (1-4). Fibrillin-1 insufficiency interferes with

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wound healing in the connective tissue damaged by inflammatory diseases. Asprosin has a prime role in hepatic glucose synthesis and in the regulation of glucose homeostasis and is also linked to wound healing (2). The ultimate two exons of FBN1 are responsible for the encoding: exon 65 encodes 11 amino acids, while exon 66 encodes 129 amino acids (3). Romere et al. identified a fasting-induced protein hormone modulating hepatic glucose release to maintain glucose homeostasis in the body and termed this C-terminal cleavage product of profibrillin as 'asprosin' (3, 5-10).

Mammalian-generated asprosin (plasma half-life ~145 min) is about twice the molecular weight of the bacterially-generated asprosin (plasma half-life ~20 min) due to the glycosylation of the mammalian-generated protein. They found that 60 mcg subcutaneous injections produced a peak plasma level of 40 nM. There was a latent phase of a few hours after its injection before the appearance of the orexigenic effect, differentiating it from the more acute-acting orexigenic peptide hormone ghrelin (secreted from the stomach) (8, 9). Duerrschmid et al. reported that asprosin level in cerebrospinal fluid (CSF) is increased by overnight fasting in a similar way to that of plasma asprosin in 6- to 12-week-old male wild-type mice, but CSF concentrations of asprosin were four to five times below the plasma concentrations (9).

Asprosin discovery and chemistry

Asprosin is a novel adipokine discovered by Romere et al. (under the guidance of medical geneticist Dr. Atul Chopra at Baylor College of Medicine, Houston, USA) as a fasting-induced glucogenic protein hormone. They discovered it whilst analyzing the genome of patients with the extremely rare Wiedemann-Rautenstrauch

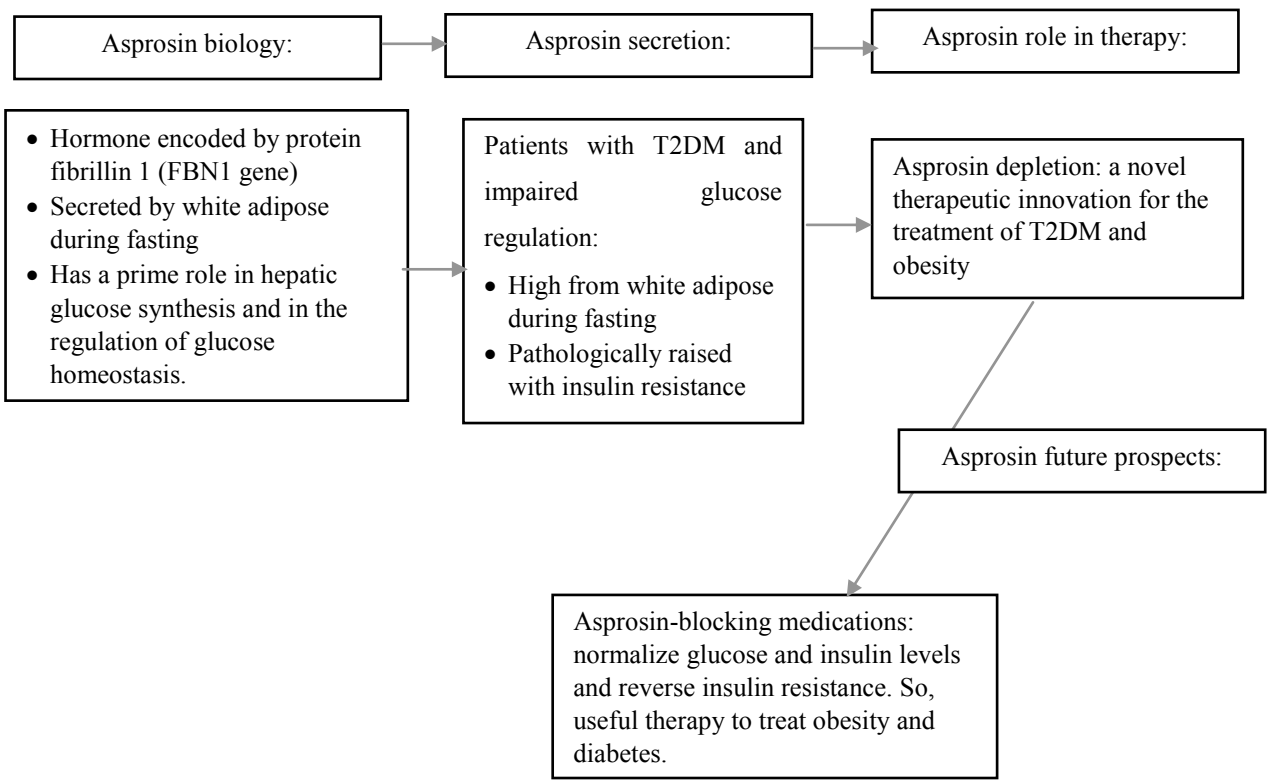

Fig. 1. *Conceptual framework of role of asprosin in diabetes therapy.*

syndrome (i.e., NPS) (3, 11). Romere et al. further assessed daily fluctuations in circulating asprosin concentrations. They concluded that glucose has a negative influence on plasma asprosin levels in a negative feedback manner (3).

Asprosin and diabetes mellitus

Asprosin has the potential therapeutic intervention for diabetes mellitus. Protein hormones are mainly the byproduct of the cleavage of a larger proprotein and circulate to the target organ on secretion, where they bind the target cell using the cell-surface receptor and stimulate rapid signal transduction via the second messenger system, and ultimately result in a measurable physiologic effect. This is the principle under consideration for asprosin in the diagnosis and management of diabetes. Hepatic glucose release into the blood circulation is essential for the smooth regulation of the brain function and survival during periods of fasting (3). The detection range for asprosin is 1–32 nmol/L with ELISA, and levels are high in obese and T2DM patients (11).

Romere et al. reported that the absence of asprosin in humans results in metabolic dysregulation (namely partial lipodystrophy) along with reduced plasma insulin. Asprosin is pathologically raised with insulin resistance in mammals including humans and mice. The reduction of asprosin protects against hyperinsulinism (3). Wiecek et al. also concluded that asprosin concentration is higher in patients with T2DM and impaired glucose regulation compared to healthy subjects (11).

A recent study by Li et al., reported that OLFR734 is a receptor of asprosin and promotes hepatic glucose production during fasting and in obesity. This study also highlighted that deficiency of Olfr734 decreases gluconeogenesis and increases insulin sensitivity (12).

Asprosin and neonatal progeroid syndrome patients

Romere et al. found that mutations in the gene encoding profibrillin (FBN1) in patients with neonatal progeroid progeroid syndrome (NPS) disrupted the expression of asprosin. NPS is a rare genetic condition (i.e., caused by a genetic deficiency of asprosin), first described in humans in 1977 and is characterized by congenital, partial lipodystrophy, poor appetite and extreme thinness (mainly affecting the face and extremities) (2, 4, 13). NPS patients have mutations in the FBN1 gene which is responsible for controlling asprosin, therefore, they have low levels of asprosin and are devoid of the fatty layer under their skin due to the defects in asprosin (2). NPS patients generally look progeroid due to facial dysmorphic features and reduced subcutaneous fat (3).

Romere et al. found that the overnight-fasted plasma insulin levels in NPS patients were two-fold lower than the unaffected subjects. They concluded that NPS mutations may reduce plasma insulin levels in humans (3). Duerrschmid et al. found orexigenic property in asprosin because it crosses the blood-brain barrier (BBB) and activates the orexigenic agouti-related neuropeptide ($AgRP^{+}$) neurons (hypothalamic neurons that promote hunger) via a cAMP-dependent pathway. They also found that genetic deficiency of asprosin may cause problems of poor appetite and extreme leanness in humans (4, 6, 7, 9, 11, 13-15).

Asprosin plasma concentration

Asprosin is secreted by white adipose during fasting conditions (i.e., glucose deprived condition) at 5–10 nM levels and acts on the liver through cell membrane receptors and activates the G protein cAMP- PKA pathway (cyclic adenosine monophosphate-protein kinase A) (2, 3, 5, 8). This leads to the rapid release of glucose into the blood circulation and insulin secretion as the compensatory mechanism. This is the nexus of asprosin with diabetes management, for which it is being investigated (3). Romere et al. also observed that asprosin-binding antibodies in diabetic mice normalized their glucose and insulin levels but asprosin did not alter the serum concentration of glucagon, epinephrine, norepinephrine and cortisol in those mice. They also presented that asprosin is present in the plasma of humans, mice, and rats at consistent nanomolar levels by calculating the plasma levels with the help of a standard curve using recombinant asprosin (rAsprosin) (3).

Asprosin secretion is increased through fasting in humans as the compensatory mechanism in hypoglycemia. Glucose serum levels below 20 mg/

dL lead to cerebral seizures or coma. Subcutaneous administration of the rAsprosin in mice increases both blood glucose and insulin (5, 8, 9). Duerrschmid et al. found that the circulating concentration of asprosin rises with fasting and acutely declines with refeeding in a biocircadian rhythmic pattern (9). Beutler et al. found that circulating asprosin levels increased with overnight fasting in mice, rats, and humans, but rapidly declined after food intake, suggesting the role of asprosin as a signal for hunger (8).

Inhibition of asprosin secretion

Duerrschmid et al., in their study on wild-type mice, concluded that AgRP+ neurons are essential for stimulation of appetite by asprosin. They confirmed its necessity by comparing the appetite level with and without $AgRP^{+}$ neurons. In the latter group, where these neurons were excised, they found a complete absence of asprosin orexigenic stimulus even after feeding the mice with a normal diet. They concluded that asprosin-mediated activation of AgRP+ neurons can be completely prevented by pretreating the cells with suramin (an inhibitor of heterotrimeric G proteins), NF449 (an inhibitor of the Gαs subunit of heterotrimeric G proteins), NKY80 (an inhibitor of adenylate cyclase), and PKI (an inhibitor of protein kinase A, PKA) (8). These all may be exploited for future clinical trials.

Therapeutic implications of asprosin

Various studies have reported that asprosin might be a novel therapeutic target for diabetes management (4, 16). Alan et al. found a raised level of asprosin in T2DM patients compared to their matched controls and its levels were positively correlated with insulin resistance in those subjects (15). Asprosin can also play a potential therapeutic target for obesity management because uncontrolled adiposity is a culprit for the dysfunction of adipokines and may lead to obesity-related disorders (1, 5, 9). Zhang et al. hypothesized that asprosin may have a link to the pathogenesis of lipid disorders because insulin resistance can lead to dyslipidemia (5).

Asprosin, when injected intravenously, crosses the BBB to activate the hypothalamic feeding circuit and this stimulates appetite and maintains adiposity in long-term applications (9). Researchers have also explored its potential implications in polycystic ovarian syndrome (PCOS), a metabolic disorder with insulin resistance (13, 15). Li et al. found the correlations of glucose, insulin, and lipid metabolism profiles in the PCOS group with the plasma asprosin level (13). Lee et al. also found that therapeutic application of rAsprosin induced inflammation and insulin resistance in skeletal muscle (7).

Romere et al. derived an interesting conclusion that asprosin treatment has no effect on the plasma levels of catabolic hormones (glucagon, catecholamines, and glucocorticoids) which are responsible for the induction of the hepatic glucose release (3). Donma et al. also reported that mice with insulin resistance and humans with pre-diabetes have elevated levels of asprosin. Hence, the administration of an asprosin-blocking medication may be a useful therapy to treat obesity and diabetes as it may normalize glucose and insulin levels and reverse insulin resistance (2). Acara et al. studied the relation of asprosin in unstable angina pectoris (UAP) patients by measuring its levels in the blood serum of the patients and the control subjects with the microELISA method. They recommended asprosin as a relevant biomarker for UAP diagnosis and treatment (17).

Asprosin mechanism of action in diabetes mellitus

Under hyperlipidemic conditions, β-cells can be a source of asprosin, and asprosin induces β-cell inflammation, dysfunction, and apoptosis through TLR4/JNK-mediated signalling. Asprosin promotes inflammation through TLR4/JNK-mediated pathway (Toll-like receptor4/cJUN N-terminal kinase) in β-cells. JNK is a serine/threonine kinase that falls under the mitogen-activated protein kinase family (6). This novel adipokine has a diabetogenic role in the body as it stimulates hepatic gluconeogenesis by elevating cellular cAMP levels, and raises blood glucose levels, which ultimately helps to develop diabetes (7) (Table I).

Duerrschmid et al. observed that mammals respond to fasting by activating the cascade of interconnected and hormone-coordinated processes. Such coordinated processes during early fasting

conditions are stimulation of appetite and subsequent release of hepatic glucose into the circulation, and these processes together provoke the mammals to take or search food to derive the nutrition for the functioning of the brain (9). Lee et al. also observed that asprosin contributes to palmitate-mediated inflammation, cellular dysfunction, and apoptosis in β-cells and human islets of Langerhans (7). Duerrschmid et al. reported that asprosin acutely inhibits ~85% of the proopiomelanocortin ($POMC^{+}$)

Table I. *Comparative review of asprosin and DM.*

References	Level of evidence[a]	Grade of evidence[a]	Findings
Zhang et al. (2017) (5)	IIa	B	Attenuating asprosin activity or depleting asprosin may serve as a novel therapeutic innovation for the treatment of T2DM and obesity.
Wang et al. (2018) (4)	IIa	B	Circulating asprosin might be a predictor of early diagnosis of DM and serve as a potential therapeutic intervention for prediabetes and T2DM.
Lee et al. (2019) (7)	Ib	A	Asprosin plays a significant role in preserving pancreatic β-cells and act as the target for the treatment of obesity-associated insulin resistance and diabetes.
Donma et al. (2018) (2)	Ia	A	Mice with insulin resistance and humans with prediabetes have elevated levels of asprosin. Administration of an asprosin-blocking medication may normalize glucose and insulin levels and reverse insulin resistance.
Romere et al. (2016)(3)	IIa	B	Circulating asprosin maintains glucose homeostasis in the body at the time of low dietary glucose by releasing liver glucose stores. Glucose has a negative influence on plasma asprosin levels in a negative feedback manner. Hence, asprosin may be a therapeutic target in T2DM.
Beutler et al. (2018)(8)	IV	C	Circulating asprosin levels increase with overnight fasting in mice, rats, humans, but rapidly decline after food intake, suggesting the role of asprosin as a signal for hunger.
Duerrschmid et al. (2017) (9)	Ib	A	Circulating asprosin rises with fasting and acutely declines with refeeding in a biocircadian rhythmic pattern.
Wiecek et al. (2018)(11)	III	B	Asprosin concentration is higher in patients with T2DM and impaired glucose regulation compared to healthy subjects.
Alan et al. (2018)(15)	IIb	B	Asprosin level is raised in T2DM patients compared to their matched controls and its levels are positively correlated with insulin resistance in those subjects.

[a]*WHO. General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine. World Health Organization 2000: 1-74. [Grade A: Evidence levels quality Ia, Ib; Grade B: Evidence levels IIa, IIb, III; Grade C: Evidence level IV].*

neurons (anorexigenic neurons within the arcuate nucleus of the hypothalamus, ARH) that perform in a coordinated way with the $AgRP^+$ neurons (9).

Asprosin future prospects in diabetes therapy

Diabetes care is continually evolving as innovative research, technology, and therapeutic approaches, such as checking serum testosterone in men with diabetes and signs and symptoms of hypogonadism, are being reported (18). Innovative therapeutic trials regarding diabetes control and management are still continually being undertaken. Holden et al. reported that patients with T2DM on simultaneous therapy with insulin plus metformin had a reduced risk of death and major adverse cardiac events (MACE) compared with those treated with insulin monotherapy (19). Glucose control remains the all-time major desired therapeutic endpoint in the management of T2DM and reduction of hyperglycemia decreases the progression of microvascular complications (20, 21), and asprosin may open a new venture in diabetes management.

Davies et al. also highlighted that diabetes self-management education and support (DSMES) program be applied to promote adherence, to adopt a healthy lifestyle, and minimize therapeutic inertia by emphasizing the coordinated chronic care model (20). Recent advancements in diabetes therapy showed promising results on cardiovascular outcomes with glucagon-like peptide 1 (GLP-1) analogues liraglutide and semaglutide (16, 22) and empagliflozin (23).

Alan et al. explored that asprosin research was mainly focused on exploring its potential application in metabolic disorders related to insulin resistance (15). Lee et al. suggested that asprosin may have therapeutic implications as a target for the treatment of obesity-associated insulin resistance and diabetes, as it plays a significant role in preserving pancreatic β-cells (7). Duerrschmid et al. described chronic asprosin loss-of-function using a pharmacological entity (9). Romere et al. developed an asprosin-specific monoclonal antibody and validated its specificity for asprosin using FBN1 wild-type and null cells (3).

Zhang et al. confirmed that information about the potential role of asprosin in T2DM is still lacking. That study also concluded that asprosin concentrations are increased in T2DM adults, suggesting it as one of the risk factors in the pathogenesis of T2DM, and attenuating asprosin activity or depleting asprosin may serve as a novel therapeutic innovation for the treatment of T2DM and obesity (5). More extensive prospective or randomized controlled trials based on these findings may be conducted in the future to establish the conclusive causal association between asprosin and T2DM, obesity.

CONCLUSION

Asprosin is a fasting-induced hormone secreted from adipose tissue that enhances glucose production in the liver and stimulates appetite regulation in the hypothalamus by initiating the cAMP signaling pathway. Asprosin concentrations are pathologically expanded in T2DM, insulin resistance and obesity patients, and a decrease of its bio-level may improve these metabolic disorders. Asprosin is a predictor for early determination of DM and may be a potential therapeutic target for prediabetes and T2DM.

Lessening asprosin action or draining asprosin may serve as a novel therapeutic innovation for the treatment of T2DM and obesity. Subsequently, a newly found protein hormone asprosin may serve as a target fo future therapeutic options in the management and treatment of diabetes.

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which is activated by caspase-1 and suppresses transcription of pro-inflammatory genes and immune responses. Since IL-37 is an inhibitor of IL-1, a potent pro-inflammatory cytokine (23), we believe that this anti-inflammatory cytokine may suppress fever and inflammation provoked by coronavirus, so as to reduce the number of deaths.

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