J Prev Epidemiol. 2022;7(1):e14 Mini Review

doi 10.34172/jpe.2022.14 Journal of Preventive Epidemiology http jprevepi.com

Asprosin; effects and associations

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Received: 27 Sep. 2021
Accepted: 1 Nov. 2021
ePublished: 5 Nov. 2021

Keywords: Asprosin, Appetite, Glucose metabolism, Insulin resistance

Citation: Hassanzadeh S, Nasri P. Asprosin; effects and associations. J Prev Epidemiol. 2022;7(1):e14. doi: 10.34172/jpe.2022.14.

Abstract

Asprosin is a hormone that is released by the white adipose tissue. It stimulates the release of glucose, which is produced in the liver, into the blood. Asprosin targets many organs including the skeletal muscle, pancreas, liver, and cardiac system. In addition, asprosin stimulates appetite leading to weight gain. It also influences glucose metabolism, cell apoptosis, and insulin resistance. Furthermore, it has been implicated in some medical conditions such as obesity and diabetes.

Introduction

Asprosin is a hormone that is released by the white adipose tissue which stimulates the release of glucose from the liver into the blood circulation. The white adipose structure is the main resource of asprosin. Asprosin is a cleavage product of the C-terminal of profibrillin which is encoded by the FBN1 gene (1). Romere et al were the first to introduce asprosin as a new adipokine in 2016. They reported that patients with neonatal premature aging (NPS) have decreased appetite, lean bodies, low insulin levels with normal blood glucose levels. They noticed that these patients do not produce asprosin. Therefore, they concluded that asprosin may influence the metabolism of carbohydrates and lipids (1).

The plasma level of asprosin increases during fasting. Appetite is controlled by the hypothalamus through its receptor on the pro-opiomelanocortin (POMC) neurons (which have anorexigenic effects) and the orexigenic agouti-related peptide (AgRP) neurons (which have orexigenic effects) (2). Asprosin activates the AgRP+ neurons and inhibits POMC neurons. This results in the stimulation of appetite and increased fat tissue and weight (2, 3). The main target organs of asprosin include the skeletal muscle, pancreas, liver, and cardiac system. This hormone has a regulatory effect on glucose metabolism, appetite, cell apoptosis, and insulin resistance (3). It has been associated with some medical conditions such as obesity, diabetes, and cardiovascular disorders (CVDs) (3). Asprosin has also been reported to have implications in pregnant women with GDM, their neonates, and obese children (4-8).

Key point

Asprosin has a regulatory effect on glucose metabolism, appetite, cell apoptosis, and insulin resistance

Basu et al have recently proposed a new subclass of protein hormones called 'caudamins', which include asprosin, that may be used in therapeutic drugs to treat metabolic syndrome, cancer, and other diseases (9). In this review we aimed to present the mostly recent publication on asprosin.

Method of the study

For this narrative review study, relevant articles were searched in Scopus, Embase, EBSCO, Web of Science and Google Scholar and also in PubMed/Medline. The following search terms such as asprosin, appetite, glucose metabolism and insulin resistance were employed to retrieve the published papers on this subject.

Asprosin and its effects on the neurons and central nervous system

Asprosin crosses the blood-brain barrier (BBB) and impacts the central nervous system (CNS). It increases the activity of the AgRP neurons through a G proteins-cAMP-PKA pathway. This results in the inhibition

of the POMC neurons leading to appetite stimulation, food consumption, and weight gain (1,3,10).

Asprosin and its effects on the hypothalamus

Asprosin increases the activity of the AgRP neurons through the activation of the G proteins-cAMP-PKA pathway in the hypothalamus and, in turn, stimulates appetite.

Asprosin and its effects on the liver

Asprosin increases the production and release of glucose in the liver by binding to OLFR734 and through the GPCR (G protein-coupled receptor), which stimulates the CREB (adenylyl cyclase-PKA-cAMP responsive element binding) pathway.

Asprosin and its effects on the pancreatic β-cells

Asprosin binds to Toll-like receptor 4 (TLR4) and through the TLR4/JNK pathway in the pancreatic β-cells, stimulates the production of reactive oxygen species (ROS) and cytokines leading to inflammation, cellular dysfunction, apoptosis of pancreatic β-cells, and decreased insulin secretion. In addition, the β-cells of the pancreas can excrete asprosin during hyperlipidemia (11, 12).

Asprosin and its effects on the skeletal muscle

Asprosin affects the skeletal muscle by the inflammation and endoplasmic reticulum (ER) stress through the PKCδ/SERCA2-mediated pathway. This leads to insulin resistance (IR) and glucose intolerance (3, 13).

Asprosin and its effects on the myocardial mesenchymal cells

Asprosin inhibits the apoptosis (induced by oxidative stress) of myocardial mesenchymal cells (MSCs) through the activation of the ERK1/2-SOD2 pathway (3, 14).

Asprosin and its effects on glucogenesis

Some studies have reported that asprosin has glucogenic effects. On the other hand, some studies could not confirm the glucogenic effects of asprosin. Consequently, the glucogenic effects of asprosin are still controversial (3).

Asprosin and its effects on appetite

Some studies have reported that asprosin has orexigenic and appetite-stimulating effects. On the other hand, some studies could not confirm the orexigenic effects of asprosin. Consequently, the orexigenic effects of asprosin are still controversial (3).

Asprosin and its effects on other hormones

It has been reported that asprosin does not affect the serum levels of glucogenic hormones including glucagon, epinephrine, norepinephrine, and glucocorticoids (1). On the other hand, an association between asprosin and ghrelin (an orexigenic hormone) is also existed. Both of these substances can activate a common part of AgRP neurons. Although decreased levels of asprosin decrease the activating effects of ghrelin on AgRP neurons, the receptors of ghrelin do not affect the activating effects of asprosin on AgRP neurons. Furthermore, studies have reported that asprosin does not affect leptin, an anorexigenic hormone (3,10).

Asprosin and its association with obesity

The effect of asprosin on obesity is controversial and the mechanism by which asprosin affects obesity is still unclear. Patients with NPS have decreased serum asprosin levels and appetite, and lean bodies which indicate a role for asprosin in obesity by affecting appetite (1,10). Several studies have reported an increased serum level of asprosin in obese individuals and mice and a positive association between serum asprosin levels and waist circumference and triglyceride (TG) (15,16). A study reported that the levels of asprosin before bariatric surgery are associated with more decrease in body weight at six months after surgery. However, a study reported that asprosin did not change the whole bodyweight of mice (13). There is a positive association between serum asprosin levels and waist circumference and TG (15,16). Asprosin activates the $AgRP^{+}$ neurons (which have orexigenic effects) and inhibits POMC neurons (which have anorexigenic effects). This results in the stimulation of appetite and increased fat tissue and weight (2,3).

Asprosin and its association with diabetes

Increased plasma levels of asprosin have been reported in patients with IR, impaired glucose regulation (IGR), and newly diagnosed type 2 diabetes mellitus (T2DM) (1,15). In addition, there is an independent link between the serum levels of fasting glucose and asprosin levels in patients with T2DM (3,15). Furthermore, a study on type 1 diabetic mice reported that they had increased levels of asprosin (17). The response of serum asprosin levels to the alterations in the serum levels of glucose is also impaired in patients with T1DM and T2DM. Furthermore, the plasma levels of asprosin are increased in pregnant women diagnosed with gestational diabetes mellitus (GDM) and the umbilical cords of these patients' neonates (3,4).

Asprosin and its association with polycystic ovary syndrome

Studies have reported that female patients with polycystic ovary syndrome (PCOS) have significantly increased serum asprosin levels. In addition, there has been a positive association between serum asprosin levels and serum levels of HbA1C (hemoglobin A1c), Apolipoprotein B (ApoB), low-density lipoprotein-cholesterol (LDL-c), and testosterone. In addition, the serum asprosin level is an independent risk factor for PCOS (3,18,19).

Asprosin and its association with cardiovascular disorders

It has been reported that asprosin could be a potential biomarker for diagnosing unstable angina and assessing the severity of acute coronary syndrome (ACS) with unstable angina (20). In addition, pretreatment of asprosin on MSCs promoted the homing of MCSs, enhanced the ejection function, and decreased myocardial remodeling after myocardial infarction (MI). The apoptosis of MSCs which is induced by hydrogen peroxide (H_2O_2) was inhibited via the activation of the ERK1/2-SOD2 pathway (3, 14).

Asprosin in pregnant women and their newborns

The plasma levels of asprosin are increased in pregnant women with GDM, preeclampsia (PE), severe preeclampsia (SPE), and macrosomic fetus (MF) and are also increased in their neonates. However, the level of asprosin is lower in both pregnant women with intrauterine growth restriction (IUGR) and their newborns. In addition, the plasma levels of asprosin in pregnant women diagnosed with GDM are associated with the plasma levels of asprosin in their neonates. The level of asprosin has been reported to be higher in female neonates compared to males Asprosin has also been reported to be expressed in the placenta (4-6).

Asprosin in obese children

The level of asprosin has been reported to be increased in obese children with higher levels in the female gender compared to males (6-8).

A summary of the effects of asprosin and its implications in some disorders are shown in Tables 1-3.

Authors' contribution

Both authors, SH and PN have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Conflicts of interest

The authors report no conflict of interest.

Ethical issues

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the authors.

Funding/Support

None.

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Table 1. The effects of asprosin (1,3,10-14)

	Effects of asprosin
Neurons and the CNS	Asprosin crosses the BBB and impacts the CNS. Asprosin increases the activity of the AgRP neurons through G proteins-cAMP-PKA pathway via the inhibition of the POMC neurons leading to appetite stimulation, food consumption, and weight gain.
Hypothalamus	Asprosin increases the activity of the AgRP neurons by the activation of G proteins-cAMP-PKA pathway resulting in appetite stimulation.
Liver	Asprosin increases the production and release of glucose in the liver by binding to OLFR734 and through the GPCR stimulates the CREB pathway.
β-cells of the pancreas	Asprosin binds to TLR4 and through the TLR4/JNK pathway, stimulates the production of ROS and cytokines resulting in inflammation, cellular dysfunction, apoptosis of pancreatic β-cells, and decreased insulin secretion The β-cells of the pancreas can excrete asprosin during hyperlipidemia.
Skeletal muscle	Asprosin affects the skeletal muscle by the inflammation and ER stress through the PKCδ/SERCA2-mediated pathway leading to IR and glucose intolerance.
MSCs	Asprosin inhibits the apoptosis of MSCs which is induced by oxidative stress by activating the ERK1/2-SOD2 pathway.
Glucogenesis	The glucogenic effects of asprosin are still controversial. Some studies have reported that asprosin has glucogenic effects. Other studies could not confirm the glucogenic effects of asprosin.
Appetite	The orexigenic effects of asprosin are still controversial. Some studies have reported that asprosin has appetite-stimulating effects. Other studies could not confirm the orexigenic effects of asprosin.
Other hormones	Asprosin does not affect the serum levels of glucogenic hormones (glucagon, epinephrine, norepinephrine, glucocorticoids). There is an association between asprosin and ghrelin (an orexigenic hormone). Decreased levels of asprosin decrease the activating effects of ghrelin on AgRP neurons. The receptors of ghrelin do not affect the activating effects of asprosin on AgRP neurons. Both asprosin and ghrelin can activate a common part of AgRP neurons. Asprosin does not affect leptin (an anorexigenic hormone).

Abbreviations: Blood-brain barrier (BBB), Central nervous system (CNS), Myocardial mesenchymal cells (MSCs), Agouti-related peptide (AgRP), Proopiomelanocortin (POMC), G protein-coupled receptor (GPCR), Adenylyl cyclase-PKA-cAMP responsive element binding (CREB), Toll-like receptor 4 (TLR4), Reactive oxygen species (ROS), and endoplasmic reticulum (ER).

Table 2. Asprosin's association with some medical disorders (1-4,7,10,13-21)

	Asprosin's association with some medical disorders
Obesity	The effect of asprosin on obesity is controversial and the mechanism by which asprosin affects obesity is still unclear. Patients with NPS have decreased serum asprosin levels and appetite, and lean bodies indicate a role for asprosin in obesity by affecting appetite. Several studies have reported an increased serum level of asprosin in obese individuals and mice and a positive association between serum asprosin levels and waist circumference and TG. A study reported that the asprosin levels before bariatric surgery is associated with more decrease in body weight at 6 months after surgery. However, a study reported that asprosin did not change the whole bodyweight of mice. Asprosin activates the AgRP+ neurons (which have orexigenic effects) and inhibits POMC neurons (which have anorexigenic effects). This results in the stimulation of appetite and increased fat tissue and weight.
Diabetes	Plasma asprosin levels are increased in patients with IR, IGR, newly diagnosed T2DM. There is an independent link between the serum fasting glucose and asprosin levels in patients with T2DM. There are increased levels of asprosin in type 1 diabetic mice. The response of serum asprosin levels to the alteration of serum glucose levels is impaired in patients with T1DM and T2DM. The plasma levels of asprosin is increased of pregnant women with GDM and in the umbilical cords of these patients' neonates.
PCOS	Female patients with PCOS have significantly increased serum asprosin levels. There is a positive association between the asprosin levels and serum levels of HbA1C, ApoB, LDL-C, testosterone. The serum asprosin level is an independent risk factor for PCOS.
CVDs	Asprosin could be a potential biomarker for diagnosing UA and assessing the severity of ACS with UA. Pretreatment of asprosin on MSCs promotes the homing of MCSs, enhances the EF, and decreases myocardial remodeling after MI The apoptosis of MSCs which is induced by H_2O_2 is inhibited by the activation of the ERK1/2-SOD2 pathway.

Abbreviations: Triglyceride (TG), Insulin resistance (IR), Impaired glucose regulation (IGR), Type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), Polycystic ovary syndrome (PCOS), HbA1C (hemoglobin A1C), Apolipoprotein B (ApoB), LDL-C (low-density lipoprotein-cholesterol (LDL-C), Cardiovascular disorders (CVDs), Unstable angina (US), Acute coronary syndrome (ACS), Ejection function (EF), and Myocardial infarction (MI).

Table 3. Asprosin in certain populations (4-8)

	Asprosin in certain populations
Pregnant women and their newborns	The plasma levels of asprosin are increased in pregnant women with GDM, PE, SPE, and MF and their neonates. The plasma levels of asprosin in pregnant women with GDM are associated with the plasma levels of asprosin in their neonates. The level of asprosin is lower in both pregnant women with IUGR and their newborns. The level of asprosin is higher in female neonates compared to males. Asprosin is expressed in the placenta.
Obese children	The level of asprosin is higher in obese children with higher levels in female obese children compared to males.

Abbreviations: Gestational diabetes mellitus (GDM), Preeclampsia (PE), Severe preeclampsia (SPE), Macrosomic fetus (MF), and Intra-uterine growth restriction (IUGR).

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