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Gastric X/A-Like Cell-Derived Peptides Participate Global Lipid Metabolism Regulation

Ruili Yu*; Lingfei Kong

Department of Pathology, Henan Provincial People's Hospital, People's Hospital of Zhengzhou University, People's Hospital of Henan University, 7 Weiwu Road, Zhengzhou, 450003, Henan Province, China.

****Corresponding Author:** Ruili Yu*

Tel: +86-188-1179-2879; Email: yyyrrrlll@126.com

Abstract

The X/A-like cell is an enteroendocrine cell that was initially poorly understood but has gained significant attention due to its peptide products, including ghrelin, desacyl-ghrelin, obestatin and nesfatin-1. While these peptides are primarily known for their roles in controlling food intake, they also play various roles in gastrointestinal motility, mood, sleep, cardiovascular function, immunity, inflammation, and more. Importantly, a wealth of evidence confirms their important roles in regulating energy metabolism, including glucose and lipid homeostasis, making them potential targets for the treatment of metabolic diseases. This review will explore the X/A-like cell and its peptide products, with a focus on their roles in lipid metabolism regulation.

Keywords: X/A-like cell; Lipid metabolism; Ghrelin; Desacyl-ghrelin; Obestatin; Nesfatin-1.

Introduction

Lipids, proteins, and nucleic acids are the fundamental building blocks of all cells and have a variety of functions in different processes [1]. As the principal component of biological membranes, lipids play a key role in membrane consistency, energy storage and metabolism, and act as signaling molecules for many cellular activities [2-5]. Given their biological importance, the regulation of lipid metabolism is essential for maintaining cellular homeostasis. Abnormal regulation of lipid metabolism can lead to lipid metabolic disorders, resulting in obesity, Non-Alcoholic Fatty Liver Disease (NAFLD), and other metabolic diseases [6,7]. Therefore, studying the lipid metabolism regulation is of great significance.

The gastrointestinal tract plays a central role in food digestion and nutrient absorption, providing materials (such as lipids, glucose and proteins) and energy to the human body [8,9]. It also has a multitude of endocrine cells, being the largest endocrine organ [10]. Enteroendocrine cells, which include X/A-like cells, L cells, G cells, K cells, I cells, enterochromaffin cells, and D cells are scattered throughout the gastrointestinal mucosa in the crypts and villi [11]. They can sense luminal content, produce and secrete various hormones and neuropeptides that act on different targeting cells, thus playing important roles in modulating multiple physiological and homeostatic functions, including energy metabolism [12,13]. Gastrointestinal hormones can also activate neural circuits that regulate peripheral tissues, for instance the liver, pancreatic islets, adipose tissue, and skeletal muscle, coordinating overall energy absorption, storage, and utilization [14,15]. It is undoubtable enteroendocrine cells play important roles in lipid metabolism regulation, directly or indirectly.

The X/A-like cell is a unique enteroendocrine cell population located in the oxyntic mucosa of stomach, representing 20-30% of the total endocrine cell population [16]. At first, its function was unknown. However, over the past years, with the discovery of hormones produced by the X/A-like cell, particularly ghrelin and nesfatin-1, this cell has attracted much attention [17,18]. Studies have confirmed that the X/A-like cell and its products participate in regulating energy metabolism, specifically the glucose and lipid metabolism regulation [19]. Functions of the X/A-like cell in the lipid metabolism regulation will be discussed in this review, with an emphasis on the effects of ghrelin, desacyl-ghrelin, obestatin, and nesfatin-1 produced by the X/A-like cell.

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The X/A-like cell is a unique cell population

In the stomach, the X/A-like cell has been identified as a fifth distinct endocrine cell type following the discovery of G cells producing gastrin, D cells releasing somatostatin, enterochromaffin-like cells secreting histamine, and enterochromaffin cells containing serotonin [20]. When this unique cell population was first discovered, it was called X cell because its function was unknown [16]. In rats, it was also named A-like cells because the morphology of this cell has been described as similar to pancreatic A cells [21]. Therefore, in rodents, this endocrine cell type was termed X/A-like cell [22,23]. In humans, it was named P/D1 cell, characterized by secretory granules, which were compact and round in the electron microscope, distinguishing it from other endocrine cells [24].

The X/A-like cell is the second most plentiful endocrine cell population in the stomach, primarily located in the oxyntic mucosa [25]. Besides the mucosal layer of the stomach, the X/A-like cell also exists in the intestinal mucosa [26,27]. Most X/A-like cells are present in gastric body, followed by the duodenum, while only a few can be observed in the colon, ileum and cecum [28].

According to their morphology, there are two types of X/A-like cells: Opened type and closed type. Opened-type cells are triangular or elongated with contact to the lumen, while closed-type cells have small and round shapes without any connection to the lumen [29]. These distinct relationships with the lumen suggest that the regulatory mechanisms of opened-type and closed-type X/A-like cells may differ. The former, with direct connection to luminal contents, are likely modulated by luminal signals, for example pH and nutrients [22,26,30]. On the other hand, closed-type cells, situated in the base of the mucosal layer without any connection to luminal contents, may be regulated by mechanical stimulation, hormones, or neuronal signals. The distribution of them also differs, with opened-type X/A-like cells mainly found in the intestine, and their numbers gradually increasing from the duodenum to the colon. In contrast, the majority of closed-type X/A-like cells are found in the stomach, where only a few opened-type cells are observed [29,31,32]. These differences in distribution suggest that X/A-like cells may have various functions in different parts of the gastrointestinal tract.

For a long time, functions of the X/A-like cell remained unknown until the discovery of ghrelin in 1999, which was found to be produced and secreted by the X/A-like cell and the only hormone known to increase appetite peripherally [17,33]. This discovery brought significant attention to products and functions of X/A-like cells. Over the years, other products derived from the X/A-like cell, such as desacyl-ghrelin, obestatin, nesfatin-1, have also been identified.

Peptides derived from X/A-like cells regulate lipid metabolism in distinct ways

GHRL is the encoding gene for ghrelin, desacyl-ghrelin and obestatin, which encodes a 117 amino-acid peptide, prepro-ghrelin [34]. Prepro-ghrelin is then cleavaged to mature ghrelin and obestatin [35-37]. Catalyzed by the Ghrelin O-Acyltransferase (GOAT), ghrelin is activated by a unique post-transcriptional modification, which the third amino acid serine is octanoylated [38]. Nesfatin-1, a hormone cleavaged from the precursor Nucleobindin 2 (NUCB2), is encoded by *NUCB2* gene [18]. The discovery of these products has led to the identification of the X/A-like cell's functions in energy metabolism regulation. For instance, active (acyl-) ghrelin has been demonstrated to enhance growth hormone secretion, stimulate food intake, and promote adiposity, while desacyl-ghrelin, the inactive form of ghrelin, has been suggested to have opposite effects. On the other hand, obestatin, has been found to inhibit food intake, delay gastric emptying, leading to reduced body weight and fat mass. Nesfatin-1, has been observed to inhibit food intake, reduce body weight, improve glucose homeostasis.

In addition to their effects on energy metabolism, X/A-like cell products have been implicated in lipid metabolism regulation. Ghrelin as well as desacyl-ghrelin has been observed to stimulate lipogenesis, inhibit lipolysis, leading to increased fat storage. Conversely, obestatin has been suggested to increase lipolysis and promote lipid oxidation, leading to decreased fat storage and improved lipid metabolism. Nesfatin-1 has also been shown to improve lipid metabolism by reducing triglyceride levels and increasing fatty acid oxidation. Overall, the X/A-like cell and its products have emerged as key regulators of energy and lipid metabolism, with potential implications for the treatment of obesity and other metabolic diseases.

Ghrelin stimulates lipid accumulation in liver and adipose tissue by promoting lipogenesis and inhibiting lipolysis

Although acyl-ghrelin only accounts for 10-20% of the total circulating ghrelin, only acyl-ghrelin can bind to its receptor, Growth Hormone Secretagogue Receptor 1a (GHS-R1a) [39]. The wide distribution of ghrelin and GHS-R1a in various tissues indicates multiple physiological functions of ghrelin [40-44]. Its classic function is to increase growth hormone secretion synergistically with growth hormone-releasing hormone through a hypothalamus-pituitary mechanism [17,45]. Ghrelin also increases appetite through GHS-R1a via both the central mechanism and vagal signaling, and it is the only hormone produced peripherally that stimulates food intake [33,46-51]. As a hormone produced by the gastrointestinal tract, ghrelin accelerates gastric emptying and decreases small intestine transit time, as well as triggers the migrating motor complex in fasting conditions [52-55]. Ghrelin exerts favorable functions in sleep, memory, and may exert anxiolytic and anti-depressant effects in humans and animals, although this remains controversial [56-58]. It exerts protective effects on cardiovascular function, dilates vessels, increases myocardial contractility, and protects cardiomyocytes and endothelial cells via both peripheral and central mechanisms [59-62]. Ghrelin also promotes lymphocyte development, exerts immune-regulatory function, inhibits pro-inflammatory factors and chemokines, and suppresses the immune response, thus exerting anti-inflammatory function [63,64]. Furthermore, ghrelin regulates the glucose metabolism. In pancreatic islets, ghrelin inhibits insulin secretion by directly acting on b-cells and indirectly via somatostatin [65,66]. It also stimulates the secretion of glucagon by directly acting on a-cells to regulate glucose metabolism [67]. In addition, ghrelin impairs insulin sensitivity in insulin-targeted tissues, for example the skeletal muscle, adipose tissue and liver [68-70].

Of note, ghrelin participates global lipid metabolism. Exogenous ghrelin, both centrally and peripherally, increases lipid content in circulation. For example, intracerebroventricular injections of ghrelin in rats for five days significantly increased circulating lipid contents, such as free fatty acid, cholesterol, and triglyceride [71]. In anorexia nervosa patients, intravenous infusion of ghrelin twice a day for fourteen days significantly increased the plasma triglyceride levels [72].

Liver

Ghrelin has been reported to act on hepatic lipid metabolism. Intracerebroventricular injections of ghrelin in fish increased lipogenesis and decreased the oxidation of fatty acid in the liver [73]. In line with this finding, central ghrelin administration in rats promoted hepatic de novo lipogenesis and inhibited lipid mobilization, as evidenced by increased expression of lipogenesis-related genes and reduced Carnitine Palmitoyltransferase 1 (CPT1) expression, a key enzyme for the oxidation of fatty acid [74]. However, mechanisms of central ghrelin in hepatic lipogenesis and lipid mobilization were different, since the former was in a GH-independent manner, while the latter was in a GH-dependent manner. Ghrelin also acts peripherally to regulate hepatic lipid metabolism. Subcutaneous injection of ghrelin for four days significantly increased the level of hepatic triglyceride, and induced expressions of genes related to hepatic lipogenesis, for example Fatty Acid Synthase (FAS), Acetyl-Coa Carboxylase (ACC), while reduced CPT expression, and decreased phosphorylated AMP-Activated Protein Kinase (AMPK) [75]. Chronic Intravenous infusion of acyl-ghrelin induced hepatic steatosis in rats, evidenced by increased lipid droplet number and triglyceride content, which was mediated by a GHS-R1a-dependent mechanism [76]. Subcutaneous infusion of exogenous ghrelin for 14 days in mice increased lipid deposition in the liver by promoting lipid synthesis, evidenced by increased expression of genes promoting lipogenesis, including Peroxisome Proliferator-Activated Receptors g (PPARg) and Sterol Regulatory Element Binding Protein 1 (SREBP1) [77]. These effects were also confirmed in primary hepatocytes isolated from mice. Furthermore, ghrelin receptor antagonist or ghrelin receptor gene knockout significantly inhibited hepatic lipogenesis and alleviated obesity-associated hepatic steatosis in mice. In vitro experiment indicates ghrelin regulates lipid metabolism in the liver via directly activating GHS-R1a. In terms of the underlying mechanism, this study uncovered the mammalian Target Of Rapamycin (mTOR)-PPARg signaling mediated ghrelin's effects on hepatic lipid metabolism, since both mTOR inhibitor and PPARg antagonism or *PPARg* gene knockout significantly attenuated the ghrelin's stimulatory effect on hepatic lipogenesis. Moreover, knockout of *mTOR* specifically in X/A-like cells elevated circulating ghrelin level, increased hepatic lipogenesis, while activation of mTOR pathway specifically in X/A-like cells reduced the expression of ghrelin, improved hepatic steatosis in obese mice, which was partly reversed by exogenous ghrelin administration [78]. These evidence support the notion that ghrelin regulates lipid metabolism in the liver through promoting lipogenesis while inhibiting the oxidation of fatty acid. In contrast, there are a few reports suggest that ghrelin attenuates hepatic lipid accumulation. For instance, intracerebroventricular infusion of ghrelin by mini-pumps for seven days in mice was reported to increase the breakdown of triglyceride in liver, resulting in reduced hepatic triglyceride content [79]. Ghrelin administrated subcutaneously twice weekly for two weeks reduced the triglyceride content in mice, accompanied with autophagy induction, and in vitro ghrelin treatment decreased the triglyceride content in LO2 cells stimulated by free fatty acids [80].

White adipose tissue

Ghrelin has also been found to increases lipid accumulation in adipose tissue. Studies have shown that chronic central ghrelin infusion promotes the expression of enzymes related to fat storage, including Stearoyl-Coa Desaturase-1 (SCD-1), while decreases the expression of CPT1a in white adipocytes, leading to lipid accumulation and increased adipose tissue weight [81]. These effects occurred independently of ghrelin-induced hyperphagia [82]. Ghrelin administration through daily intraperitoneal injection or mini-pumps for seven to fourteen days in rodents has been shown to significantly increase fat mass and adipose tissue weight, along with enlarged adipocytes and elevated triglyceride content in white adipose tissues, which was caused by reducing fat utilization [83,84]. Consistent with this notion, another study has been shown that chronic intravenous infusion of acyl-ghrelin increased white adipose tissue mass in rats resulted from reduced lipid export and increased lipogenesis with no change in food intake, since ghrelin decreased serum free fatty acid level, as well as ATP-Binding Cassette Transporter G1 (ABCG1) expression, but elevated SREBP1c expression in white adipose tissues [76]. Furthermore, transcriptional blockade of GHS-R1a abolished these alterations, suggesting that these effects of ghrelin were in a GHS-R1a-dependent manner. *GHS-R* ablation reduces lipid uptake and lipogenesis in white adipose tissues, and protects mice from diet-induced obesity [85,86]. There are also other studies indicating that ghrelin promotes adipogenesis and inhibits lipolysis in adipocytes independent of GHS-R1a [87,88]. The stimulatory effect of ghrelin on lipid accumulation in adipocytes has also been confirmed in vitro. Ghrelin treatment significantly elevated expressions of lipogenesis-related genes, such as PPARg, SREBP1, ACC, FAS, and proteins related to fat storage, such as Lipoprotein Lipase (LPL), perilipin in human omental adipocytes [89]. Ghrelin was shown to suppress lipolysis in rat adipocytes [88]. In fish, ghrelin was also reported to stimulate synthesis of triglycerides, but increase lipolysis in isolated adipocytes [90].

Brown adipose tissue

Ghrelin is also involved in regulating thermogenic function of brown adipose tissue. Chronic central ghrelin infusion has been shown to decrease the expression of mitochondrial Uncoupling Proteins (UCP) 1 and 3, which are related to thermogenesis, and this may be mediated by the sympathetic nervous system [81]. Similarly, chronic repeated ghrelin treatment for seven days in mice decreased UCP1 mRNA expression in brown adipose tissue [83]. In cultured brown adipocytes, ghrelin treatment inhibited the expression of adipogenic and thermogenic genes, but the antagonist for GHS-R eliminated the effect of ghrelin [85]. Furthermore, both the antagonist for GHS-R in vitro and *GHS-R* ablation in vivo increased UCP1 expression in brown adipose [85,91], suggesting that the effect of ghrelin in brown adipose tissue is GHS-R dependent.

The effect of ghrelin on lipid accumulation of liver and adipose tissue, and its role in the thermogenic function of brown fat suggest that ghrelin may serve as a potential target to combat obesity, NAFLD and other lipid disorders.

Desacyl-ghrelin either inhibits or promotes lipid accumulation depending on the specific tissues or cells

Desacyl-ghrelin is the nonacylated form of ghrelin, accounting for the most abundant form of ghrelin in the circulation [92,93]. Although previously thought to be inactive, recent studies have shown that desacyl-ghrelin has functions that mostly opposed to acyl-ghrelin [94-98]. Desacyl-ghrelin is found to reduce appetite, decrease food intake, and delay gastric emptying through a central mechanism independent of the vagal afferent pathway [94,99-101]. In the cardiovascular system, desacyl-ghrelin inhibits cell death of cardiomyocytes and endothelial cells [102,103],

and decreases anxiety-like behavior [104,105]. With regard to the glucose metabolism, desacyl-ghrelin enhances insulin secretion by increasing the number and inhibiting the apoptosis of b-cells [106]. Furthermore, it acts on the adipose tissue, skeletal muscle and liver to improve the insulin sensitivity and glucose tolerance [107-110].

In terms of the lipid metabolism, the lipid content in the blood, which is elevated by ghrelin, has been reported to be decreased by desacyl-ghrelin. Administration of desacyl-ghrelin in humans decreased free fatty acids levels in the circulation [111,112] In addition, desacyl-ghrelin overexpression was observed to decrease plasma free fatty acid levels in mice [113].

Liver/muscle

There is limited research about the function of desacyl-ghrelin in hepatic lipid metabolism. However, a study using microarrays to investigate the rapid effects of desacyl-ghrelin on metabolic profile in *GHS-R* ablated mice found that desacyl-ghrelin acutely regulated hepatic genes related to lipid metabolism in a GHS-R-independent manner [108]. Acute desacyl-ghrelin treatment upregulated adipogenic pathway gene sets, including PPARg, which was confirmed by quantitative PCR. Consistent with this finding in vivo, desacyl-ghrelin treatment significantly increased triglyceride content in primary hepatocytes from rats, as well as the expression of lipogenesis-related genes, for example Diacylglycerol Acyltransferase (DGAT1) [114]. Desacyl-ghrelin also elevated phosphorylation rates of AMPK and ACC, indicating that it stimulated AMPK-activated mitochondrial fatty acid b-oxidation. In addition, studies reported that desacyl-ghrelin increased the lipid content as well as ACC expression in mouse myoblast C2C12 cells, while reducing the expression of UCP2 and UCP3 [115]. Desacyl-ghrelin was observed to stimulate fatty acid oxidation, accompanied by an increase in ACC phosphorylation, and blunt epinephrine-stimulated lipolysis in isolated muscle from rats [116,117].

Adipose tissue

Studies have shown that in vivo, desacyl-ghrelin inhibits lipid accumulation in adipose tissues. In fact, overexpressing of desacyl-ghrelin in mice decreased fat pad mass weight [100], and in adipose tissues, it decreased epididymal and perirenal fat masses, thus resisting to high-fat diet-induced obesity [107]. However, studies have found desacyl-ghrelin promotes lipogenesis in adipocytes in vitro. Desacyl-ghrelin markedly elevated the expression of genes promoting lipogenesis, for instance PPARg, SREBP1, FAS. ACC, leading to increased lipid contents in omental adipocytes [89,118]. Additionally, desacyl-ghrelin has inhibitory effects on lipolysis, as evidenced by studies in vivo and vitro. An overnight intravenous infusion of desacyl-ghrelin was shown to inhibit lipolysis in healthy humans [112], while in rats, it blunted b3-adrenergic receptor-induced lipolysis in mature subcutaneous and visceral adipose tissue depots, which was mediated by reducing activation of hormone-sensitive lipase (HSL), a key lipid hydrolase [119]. Desacyl-ghrelin also inhibited lipolysis in rat and 3T3-L1 adipocytes in both a GHS-R1a dependent and independent manner [88,120,121]. Furthermore, with regard to brown adipose tissue, desacyl-ghrelin and its analog stimulated expression of mitochondrial function markers and enhanced thermogenesis [122].

In conclusion, desacyl-ghrelin not only antagonizes ghrelin in the regulation of lipid metabolism, but also exerts actions similar to ghrelin in some aspect, such as promoting lipid accumulation in liver. The discrepant effects on lipid metabolism in different tissues/cells may due to the distinct receptor distribution or downstream intracellular pathways. However, the study of desacyl-ghrelin has entered a stagnant period due to the lack of identification of its receptor. Identification of desacyl-ghrelin receptors in the future will largely increase our knowledge about its function and mechanism. Moreover, the clinical importance of desacyl-ghrelin is increased by evidence linking elevated acyl-ghrelin/desacyl-ghrelin ratios to obesity and diabetes [110,123,124].

Obestatin has complex effects on lipid metabolism

Obestatin, a 23 amino-acid peptide, was named after the Latin words “obedere” and “statin”, meaning obesity suppression. Initially, obestatin was found to reduce body weight and suppress the motility of the gastrointestinal tract via GPR39, exerting functions that opposed to ghrelin [37]. However, the function of obestatin on food intake is under debating with either suppress or has no effect [125-127]. Obestatin is also found to act in brain to inhibit thirst, although other studies have challenged this claim [128,129]. In addition, obestatin has been shown to promote sleep, improve memory and cause anxiolytic effect [130-132]. It also promotes cardioprotection and is involved in muscle regeneration and the determination of fiber type [133-136]. Additionally, it regulates immune cell functions and reduces imflammation [137,138]. The function of obestatin in the glucose metabolism is more complex and contradictory. It is demonstrated to improve the survival of b-cell by increasing proliferation and reducing apoptosis via GLP-1R [139,140]. Some studies show that obestatin promotes the secretion of insulin stimulated by glucose via GHS-R, while others show an inhibitory effect on insulin secretion [141-144].

Most studies suggest that obestatin has a beneficial effect on lipid metabolism regulation. Obestatin reduces circulating lipid levels, as shown by a fourteen-day infusion of a stable obestatin analog in Sprague-Dawley rats, which significantly reduced plasma triglyceride levels without affecting cholesterol levels or food intake [145]. Obestatin, as well as its N-terminal fragment and Nt8U, the N-terminal fragment analog, have also been observed to decrease circulating triglyceride levels in mice [146]. In addition, chronic intraperitoneal administration of obestatin in rats was found to reverse hyperlipidemia induced by high-fat diet [147]. Chronic obestatin treatment also reduced total cholesterol and low-density lipoprotein fractions of cholesterol, while increasing high-density lipoproteins cholesterol content in type 2 diabetic mice [148]. Moreover, a significant correlation between the serum obestatin levels and lipoprotein subfractions was reported in non-diabetic obese patients [149].

Liver

Obestatin also regulates lipid metabolism in the liver. Chronic obestatin treatment significantly decreased hepatic triglycerides and cholesterol contents, and reduced hepatic lipid deposition in rodents [147,148]. Obestatin altered the expression of hepatic genes related to lipid metabolism, with elevated expressions of adiponectin receptors (adipoRII), CPT1, PPARa. Obestatin may regulate hepatic lipid metabolism through AMPK, as studies have shown that obestatin increases AMPK phosphorylation in the liver. Moreover, one study reported that hepatic dysmetabolism in obese Wistar rats was related to obestatin suppression and that restoring obestatin improved hepatic lipid metabolism [150]. These findings suggest that obestatin improves the hepatic lipid metabolism.

Adipocytes

Obestatin has been shown to regulate lipid metabolism in adipocytes by affecting free fatty acid uptake, adipogenesis and lipolysis. In differentiated 3T3-L1 adipocytes, obestatin treatment was found to increase free fatty acid uptake [120]. Additionally, obestatin was reported to enhance adipogenesis by regulating the expression of adipogenic genes, for instance PPARg, FAS, CCAAT-Enhancer-Binding Proteins (C-EBP) in 3T3-L1 adipocyte cells [151,152]. In mice, peripheral obestatin treatment significantly upregulated the expressions of genes involved in glycerolipid metabolism and lipogenesis including PPARg in the white adipose tissue [127,146]. Obestatin was also observed to inhibit lipolysis in 3T3-L1 adipocytes, rat preadipocytes, human subcutaneous and omental adipocytes, accompanied by increased AMPK phosphorylation [120,153,154]. However, the role of obestatin in adipogenesis and lipolysis is still being debated. For example, in isolated adipocytes of rats, obestatin was reported to inhibit both basal and insulin-stimulated lipogenesis and promote adrenalin-stimulated lipolysis, which might be mediated by GPR39 receptor [155]. Some studies suggest that the regulation of lipogenesis and lipolysis by obestatin may vary during the differentiation of preadipocytes. For instance, in the early stages of 3T3-L1 cell differentiation, obestatin was found to be adipogenic and increase lipid accumulation, whereas in mature adipocytes, the lipid accumulation was decreased after obestatin treatment [156]. Similarly, obestatin suppresses lipolysis at the early stage of rat preadipocyte differentiation, while stimulates lipolysis at the late stage of adipogenesis [153]. Furthermore, obestatin may act on the transport of cholesterol. A study in cows found that continuous infusion of obestatin for eight weeks led to an obvious reduction in ATP-Binding Cassette A1 (ABCA1) expression, a key cholesterol transporter, in adipose tissue [157].

Given the complex and controversial effects of obestatin and the fact that its specific receptor is still unknown, obestatin is still a debated peptide. However, considering its potential as a treatment target for lipid metabolic diseases, further research is warranted.

Nesfatin-1 exerts a favorable action on the lipid metabolism by inhibiting lipid accumulation and accelerating lipid decomposition

Nesfatin-1, composed of 82 amino acids, is a post-translationally modified product of NUCB2 [158]. Although nesfatin-1 and ghrelin are produced and secreted by the same X/A-like cell, nesfatin-1 exerts functions that are almost completely opposite to ghrelin. Nesfatin-1 was initially found to inhibit food intake and is named of nesfatin-1 after being identified as a satiety and fat-influencing protein [18]. It has been reported to reduce water intake via hypothalamic mechanisms, with the reduction in water intake being more pronounced than that of food [159]. Nesfatin-1 inhibits gastric and duodenal motility, decreases gastric emptying, and regulates the secretion of gastric acid, which is mediated by a central vagal mechanism [160]. Nesfatin-1 reduces rapid eye movement sleep and intermediate stage of sleep, while increasing passive wake [161,162]. In addition, it promotes anxiety-like behavior and increases depression-like behavior, exerting effects opposite to ghrelin [163-166]. In cardiovascular physiology, nesfatin-1 exerts a hypertensive action mediated via the central nervous system and peripheral blood vessel, and induces apoptosis of cardiomyocytes [167-170]. Unlike ghrelin, nesfatin-1 reduces the inflammatory response, exerting an anti-inflammatory action [171-173]. Studies have shown nesfatin-1 plays important roles in reproductive maturation and function, but the downstream mediators of nesfatin-1 have not been identified yet [174-176]. In terms of glucose homeostasis regulation, nesfatin-1 acts in opposition to ghrelin. Nesfatin-1 promotes the secretion of insulin from b-cells in pancreatic islets, stimulating the utilization of glucose [177-179]. Moreover, it improves insulin sensitivity in insulin-targeted tissues, for instance the muscle, liver and adipose tissue, increasing glucose uptake [180,181].

Dyslipidaemia, characterized by abnormal lipid metabolism, can lead to hypertriglyceridemia and hypercholesterolemia. Studies have reported that nesfatin-1 can improve lipid levels through both peripheral and central mechanisms. For instance, intravenous administration of nesfatin-1 for six days normalized plasma free fatty acid contents in mice with type 2 diabetes mellitus induced by streptozotocin [182]. Similarly, continuous subcutaneous administration of nesfatin-1 for fourteen days eliminated the increase in plasma cholesterol and triglyceride level of mice fed on high-fat diet [183]. Furthermore, exogenous nesfatin-1 infused from the central decreased circulating free fatty acid content in mice with type 2 diabetes mellitus, providing further evidence of its regulatory function in plasma lipid levels [184].

Liver

Nesfatin-1 is involved in regulating hepatic lipid metabolism. In mice with hepatic steatosis induced by high-fat diet, continuous subcutaneous infusion of nesfatin-1 for fourteen days significantly reduced the triglyceride content in the liver and decreased the lipid droplet size [183]. This effect was independent of food intake and was achieved by decreasing lipogenesis and increasing fatty acid oxidation. The expression of transcriptional factors promoting lipogenesis including PPARg, SREBP1, as well as the expression of rate-limited enzyme related to lipogenesis including ACC, FAS, was markedly reduced, while expressions of genes related to b-oxidation were increased. The AMPK pathway mediated the beneficial function of nesfatin-1 in the hepatic lipid metabolism, attenuating lipid accumulation in hepatocytes. Another study also supports this finding and reported that nesfatin-1 treatment led to a reduction in size of lipid droplet in hepatocytes, and decreased expressions of genes involved in lipogenesis [185]. Similarly, in fish, intracerebroventricular nesfatin-1 treatment decreased hepatic lipogenesis while promoted the oxidation of fatty acid, as evidenced by a reduction in the expression of transcriptional factors involved in lipogenesis and an increase in the expression of genes involved in the oxidation of fatty acid [186]. These finding suggest nesfatin-1 not only directly acts on liver, but also has an indirect effect through the central.

Adipose tissue

The specific distribution of nesfatin-1 in the adipose tissue, suggests it plays a role in adipose tissue [187]. Nesfatin-1 has been reported to activate the mobilization of lipid. Nesfatin-1 treatment increased the expression of Adipose Triglyceride Lipase (ATGL), a gene related to lipolysis, in primary brown adipocytes [188]. Similarly, central administration of nesfatin-1 in mice activated the mobilization of lipid through HSL and ATGL, which was mediated by the sympathetic nervous system [184]. Nesfatin-1 is involved in the lipid metabolism of adipose tissue not only through regulating genes related to lipid metabolism, but also by affecting adipocytes differentiation. *NUCB2* knockdown by short hairpin RNA in 3T3-L1 preadipocytes pro-

moted the differentiation of adipocyte [189], while another study demonstrated that NUCB2 inhibited the differentiation of adipocytes by suppressing insulin signal and cAMP production, and the nesfatin-1 domain was essential for inhibitory effects on adipocyte differentiation [190]. In contrast, in another study nesfatin-1 was demonstrated to stimulate the brown adipocytes differentiation. During the differentiation of primary brown adipocytes, the expression of nesfatin-1 was gradually reduced. Nesfatin-1 treatment led to markely enhanced UCP1 expression, a classic marker of brown adipose, with reduced activity of mTOR signaling. These alterations were reversed by activation of mTOR, suggesting that nesfatin-1 induced brown adipocyte phenotype is likely mediated by the mTOR signaling [188]. Moreover, central administration of nesfatin-1 induced heat production from brown adipose tissue which was critically dependent on b3 adrenergic stimulation [191]. This finding suggests that nesfatin-1 acts on the central to stimulate thermogenesis from brown adipose tissue, thus playing a role in lipid metabolism of brown adipose.

In conclusion, nesfatin-1 exerts a favorable function in the lipid metabolism, inhibiting lipid accumulation, accelerating lipid decomposition, which is promising in preventing and treating lipid metabolic disorders, for example NAFLD and obesity. The evidence that patients with NAFLD have lower serum nesfatin-1 levels and that nesfatin-1 has a negative correlation with body mass index suggest this unique peptide might be involved in the development of lipid-related diseases [192,193]. However, the unknown receptor for nesfatin-1 limits our understanding of this unique peptide, and further exploration is needed to understand its effects on the development of lipid metabolic diseases and potential mechanisms.

Summary

The endocrine X/A-like cell plays an essential role in regulating lipid metabolism through its peptide products, such as ghrelin, desacyl-ghrelin, obestatin and nesfatin-1 (Figure 1). These peptides appear to have antagonistic or synergistic action with each other to maintain the lipid homeostasis. Although the mechanism by which X/A-like cells regulate the production and secretion of these peptides differently according to the need of organism remains unclear. Targeting X/A-like cell and its peptide products may provide therapeutic benefits for patients with lipid metabolism disorders, such as obesity, NAFLD and diabetes.

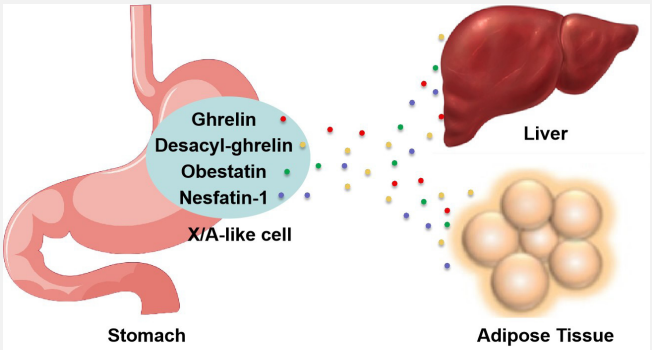

Figure 1: Gastric X/A-like Cell-Derived Peptides Participate Global Lipid Metabolism Regulation.

Declarations

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