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Influence of LEAP2 (Liver Expressed Antimicrobial Peptide-2) and Ghrelin Binding to GHSR Gene Receptor as Factors Obesity Incidence: A Literature Review

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Abstract

Obesity is a serious issue in global health, which requires a more comprehensive understanding for the development of effective therapies. This study explores the role of Liver-Expressed Antimicrobial Peptide 2 (LEAP2) and its interaction with Ghrelin in regulating Growth Hormone Secretagogue Receptor (GHSR) as a potential obesity event. This method used in this review is a systematic literature analysis. The results obtained show that LEAP2, originally known as an antimicrobial, plays a significant role in metabolic regulation and body weight regulation. LEAP2 acts as a Ghrelin antagonist, reduces orexigenic effects and inhibits food intake, and exerts positive effects in tackling the effects of obesity such as hyperlipidemia and inflammation. The study also highlighted the potential of LEAP2 as a therapeutic target in obesity treatment, with palmitoylation modification showing increased stability and effectiveness of LEAP2. However, further understanding and clinical trial studies are needed to validate the preclinical findings and evaluate the long-term effects of LEAP2 regulation on human body weight and metabolic health, thus providing a basis for exploring potential clinical applications in future anti-obesity drug development

Keywords: *GHSR; Ghrelin; LEAP2; Obesity*

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INTRODUCTION

Obesity is one of the global health problems, and has been classified as an epidemic scale (World Health Organization, 2020). The obese population for two decades has increased especially in children and adolescents, In Indonesia, it was also reported that the prevalence of obesity in teenagers increased significantly in 2007 by 10.5%, then in 2013 it increased to 14.8%, and finally in 2018 there was still an increase to 21.8% (Ministry of Health of the Republic of Indonesia, 2018). Food intake habits such as eating snacks, overeating, and low physical activity are among the external factors of risk for increased obesity (Friedenreich et al., 2021). In addition to external factors that cause obesity, internal factors, namely heredity or genetics, also cause obesity (Ghalandari et al., 2015). Growth hormone secretagogue receptor (GHSR) is a gene reported as one of the causes of obesity because it is directly related to dietary regulation (Lee et al., 2021). GHSR encodes the growth hormone secretagogue receptor, which is an important receptor in signaling the Ghrelin hormone system in influencing appetite habits (Luglio et al., 2014).

Growth hormone secretagogue receptor (GHSR) is a G protein-coupled receptor (GPCR) located in the cerebrum, the signaling mechanism of GHSR has various controlling functions including food entry, the secretion of growth hormone, and glucose homeostasis (Wellman & Abizaid, 2015). The GHSR has a ligand, Ghrelin. Ghrelin is an acylated peptide produced in the gastrointestinal tract (Cornejo et al., 2019). In 1999, the ligand of endogenous GHSR-1A was found from rat stomach by Kojima et al., (1999) which was then named Ghrelin, Ghrelin is drawn from a proto-Indonesian-European language "ghre" which means to grow (Perelló et al., 2023). Ghrelin has 28 peptide residues that are acylated at the third serine residue to produce its active form, acyl-Ghrelin (Lu et al., 2021).

Ghrelin is a hormone produced from the gastric enteroendocrine cell population, Ghrelin has a function to assist the agency to react to altered metabolic conditions by involving GHSR expression in GHSR-expressing neurons and in peripheral muscles to regulate patterns of intake of food, body weight, and glucose (Ge et al., 2018). It also triggers the release of growth hormone, stimulates digestion, stimulates stomach acid secretion, and has antidepressant characteristics (Gupta et al., 2021). The orexigenic function was also found and identified to act on GHSR through neuropeptides, in general Ghrelin is a GHSR agonist to stimulate appetite (Howick et al., 2017).

For nearly 20 years Ghrelin was recognized as an Endogenous GHSR-1A ligand, but a study conducted by Lu et al., (2021); Ge et al., (2018) reported that liver-expressed antimicrobial peptide (LEAP2) became an Endogenous inhibitor of GHSR-1A. Liver-expressed antimicrobial peptide-2 (LEAP2) can be a secretory peptide first discovered in 2003 isolated in human blood filtrate (Wang et al., 2019). The structure of LEAP2 is a bicyclic peptide composed of 40 amino acids containing two disulfide bonds, despite the fact that it incorporates a bicyclic structure, LEAP2 can bind to various peptide hormones (Ge et al., 2018). At first, a study Ge et al., (2018) recognized that LEAP2 could be a non-competitive opponent of GHSR-1A, but later consideration by Varimo (2022) found that LEAP2 actually competes with the authoritative receptor Ghrelin and also reduces the constitutive action of GHSR-1A.

In Mani (2019) found that the plasma level of LEAP2 was inversely related to Ghrelin approved metabolic status in related living beings, and was unequivocally related to body mass (IBM). Since then, LEAP2 has been taken into view as a flag for effective vitality overflow as a vitality adjustment controller, but not many think about have detailed authoritatively about the relationship of LEAP2 with Ghrelin as a GHSR-1A inhibitor in body weight frequency.

Therefore, this survey article will review recent findings regarding the relationship between LEAP2 and Ghrelin as inhibitors of GHSR1A, and their potential in the pathophysiology of obesity. This topic is particularly important because to date there have been no studies in Indonesia that specifically report the influence of LEAP2 and Ghrelin on GHSR-1A in the regulation of body weight. This article is expected to serve as an initial basis in the development of further research to understand the role of LEAP2 in modulating the pathophysiology of obesity as well as finding effective ways to address the problem. In this paper, we summarize the mechanism of action of LEAP2 on Ghrelin and analyze recent findings related to its role in obesity incidence. These findings are expected to provide new insights and serve as a foundation for further research development, especially in the effort to design effective anti-obesity drugs. The knowledge gained from this review is expected to not only enrich the scientific literature, but also encourage innovation in the field of obesity treatment.

METHOD

The method used in this study is included in the type of systematics literature review. This method was chosen because it is able to answer clearly formulated questions through a systematic and explicit process of identifying, selecting, critically appraising, and collecting and analyzing data from relevant research. This review includes a systematic search of published and unpublished works, and presents a systematic synthesis of findings to minimize subjectivity and bias (Siddaway et al., 2018). The topic discussed was the effect of the relationship between LEAP2 and Ghrelin on the GHSR-1A receptor as a causative factor in obesity. Literature collection was obtained from electronic databases, namely Google Scholar, PubMed, Scopus, ScienceDirect, and Oxford Academic Journal by including keywords that match the research inclusion criteria. The article/journal search used keywords such as "(LEAP2) AND (Ghrelin) AND (GHSR) AND (Obesity)".

The article exclusion criteria are articles/journals that discuss other than the effect of the relationship between LEAP2 and Ghrelin on GHSR-1a. The following are the inclusion criteria for articles/journals (Palumbo et al., 2022):

a. Articles/journals that discuss the effect of the relationship between LEAP2 and Ghrelin on GHSR-1A as a potential obesity
b. Articles/journals are available in English
c. Articles/journals published in the last 10 years (2014-2024)
d. Articles are available in full text

The interpretation of the results of several journals included in the inclusion criteria is descriptive, namely in the form of findings from the mechanism of the

relationship between LEAP2 and Ghrelin to GHSR-1A on the incidence of obesity and tries to explain the phenomenon studied.This is the main body of the literature review. The process of collecting selected articles/journals will be outlined in Figure.1. The results of the 10 selected articles/journals will be detailed in table 1 to determine the effect of the relationship between LEAP2 and Ghrelin on GHSR-1a as a potential obesity.

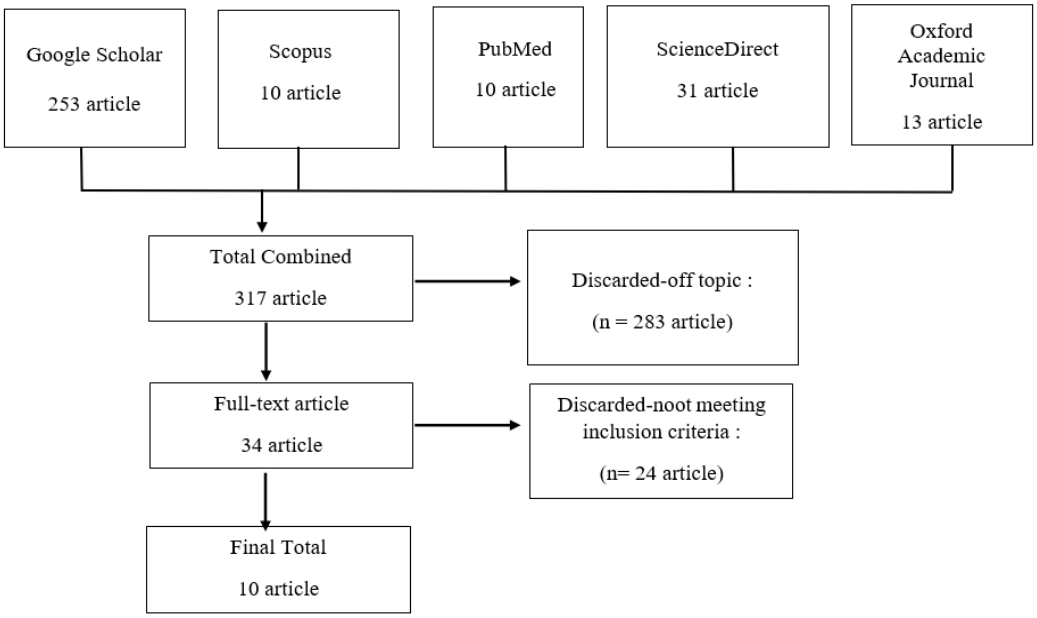

Figure 1. PRISMA flowchat

RESULT AND DISCUSSION

The discovery of the LEAP2 hormone in recent decades has been a major focus in science as it can influence metabolism and regulation of body weight. In obesity, LEAP2 hormone activity is thought to correlate with the hormone Ghrelin in activating the GHSR-1A receptor that regulates food intake. In general, Ghrelin stimulates GH release in pituitary cells and increases GH secretion. However, in recent years the discovery of the LEAP2 hormone which correlates with the incidence of obesity has become an interesting topic, several studies have been conducted but in Indonesia itself there have been no studies that discuss the effect of LEAP2 on the incidence of obesity. Based on the results of the literature review we found several case findings that discuss the incident.

Table 1. Summary of case control studies on LEAP2 and its Role in Obesity

Author	Country	Research Design	Research Object	Result
(Holm et al., 2022)	Denmark	Case control study	Obese and non-obese mice	LEAP2 expression in the livers of obese mice compared to non-obese mice. In addition, this study also confirmed that LEAP2 levels in circulating plasma are significantly higher in obese humans compared to non-obese mice.
(Bhargava et al., 2023)	English	Case control study	Plasma LEAP2 levels in humans	Plasma LEAP2 levels increased and acetyl-Ghrelin decreased after eating, showing a negative correlation. However, there was no significant correlation with appetite or brain activity.
(Hagemann et al., 2022)	Denmark	Case control study	Human and mice	LEAP2 infusion decreased glucose, growth hormone and the food intake in people and mice, partly through a GHSR receptor. Therapeutic implications of LEAP2 for metabolic diseases and obesity were also demonstrated.
(Varimo et al., 2022)	Finland	Case control study	Human	Negative association between LEAP2 and acyl-Ghrelin, with LEAP2 decreasing Ghrelin-induced GHSR activity. The changes in LEAP2 levels are reflective of the state of adolescent metabolism and may be an adverse indicator of glucose and lipid metabolism.

Table 2. Summary of experimental studies on LEAP2 and its Role in Obesity

Author	Country	Research Design	Research Object	Result
(Mani et al., 2019)	United States	Experimental studies	Rats and Human	LEAP2 levels correlated with body weight and lipid mass in rats and people. In obese mice, the plasma concentrations are higher, while in humans it is associated with obesity and metabolic effects.
(Gupta, Dowsett, et al., 2021)	United States	Experimental studies	Diet-obese mice	Plasma levels are elevated in diet-obese mice, while Ghrelin increases intake of food and LEAP2 blocks Ghrelin's effects, affecting the signal balance that regulates obesity.
(Shankar et al., 2021)	Untided States	Experimental studies	Mice	LEAP2 acted as a selective antagonist of GHSR. At certain doses, it can lock the acyl-Ghrelin effect, which plays a role in inducing food entry and GH secretion in mice. In addition, deletion of LEAP2 in mice increases the action of Ghrelin as an either orexigen and growth hormone, meaning LEAP2 is a key regulator of Ghrelin tolerance.
(Nabekura et al., 2023)	Japan	Experimental studies	Human	Serum LEAP2 levels are correlated with body mass index (BMI), visceral fat area, and triglycerides. In addition. LEAP2 affects Ghrelin response and growth hormone secretion in vivo.
(Lang et al., 2023)		Experimental studies	Obese mice	Reduced LEAP2 levels could improve the heart condition of obese mice by ameliorating hyperlipidemia, inflammation, and myocardial injury. LEAP2 also reverses macrophage polarization and involves regulation of inflammatory responses and M2 polarization. At the cellular level, LEAP2 interacts with GHSR in macrophages, and its decrease increases the interplay of GHSR and Ghrelin.
(Holá et al., 2022)	Czech Republic	Experimental studies	Rats	Palmitoyl-modified LEAP2 has high affinity to GHSR-1A receptor, good plasma stability, and antagonistic effect to Ghrelin. Palm-LEAP2 effectively reduces food intake and inhibits the effects of Ghrelin in rats.

Activity of LEAP2 Hormone towards Ghrelin Hormone

Liver-expressed antimicrobial peptide 2 (LEAP2) an antimicrobial peptide that functions as part of the immune system, this is due to its antibacterial effect, LEAP2 can create a cavity in the membranes of gram-positive bacteria due to its strong basic properties due to the presence of disulfide bonds (Henriques et al., 2010). LEAP2 is also an agonist and inverse antagonist of GHSR-1A despite its antibacterial effect (Stoyanova & Lutz, 2021). This is also supported by findings by Gupta et al., (2021) which showed that plasma levels of LEAP2 were found to be increased in diet induced obese mice relative to non-fat controlled mice. Moreover, Ghrelin and LEAP2 have opposite effects on food intake, Ghrelin increases food intake and LEAP2 blocks Ghrelin-induced food intake. The balance between Ghrelin and LEAP2 signaling is involved in regulating the incidence of obesity (Gupta et al., 2021). Research conducted by Varimo (2022) also makes it clear that LEAP2 and Ghrelin have a negative relationship, LEAP2 has the effect of reducing GHSR-1A activity induced by the hormone Ghrelin. The negative effect between LEAP2 and Ghrelin can be seen in Figure 2. LEAP2 blocks GHSR-1A whereas Ghrelin activates GHSR-1A on target cells, e.g. Neuropeptide Y (NPY)/Agouti-Related Peptide (AgRP) and b cells that function to upregulate GH secretion, appetite, and Glucose-Stimulated Insulin SecretionShould discuss the relevant existing literature related to the presented case.

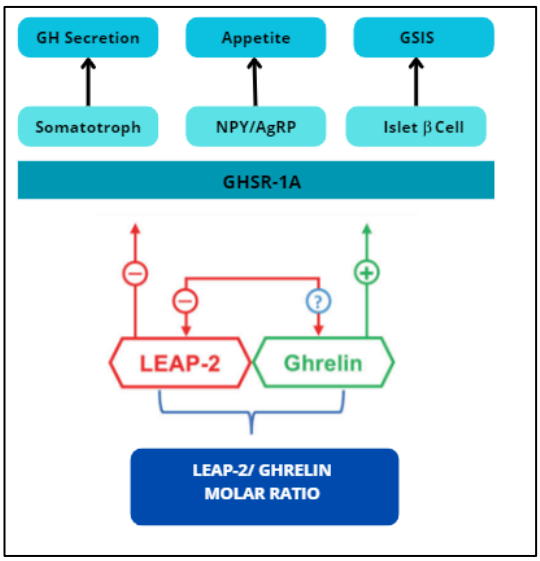

Figure 2. Association between LEAP2 activity and Ghrelin (Lu et al., 2021)

Effect of LEAP2 and Ghrelin on GHSR-1A Receptor

Growth hormone secretagogue receptor (GHSR) is a receptor involved in responding to the hormone Ghrelin in the body (M'Kadmi et al., 2019). The hormone Ghrelin is known for playing an essential in regulating appetite and stimulates the production of growth hormone. The main function of GHSR is activated by G protein activity which triggers the body's response to Ghrelin, in the presence of Ghrelin, GHSR is active at about 50% of its capacity which means the receptor maintains its activity to influence the secretion of growth hormone and appetite (Yin et al., 2014).

LEAP2 is another substance in the body that has a role as a regulator of GHSR, LEAP2 is a GHSR inhibitor that can inhibit growth hormone secretion and reduce appetite (Lugilde et al., 2022). Based on the findings of Hagemann et al., (2021) which states that infusion of LEAP2 reduces postprandial plasma glucose, growth hormone concentration, and food intake in humans and rats. In addition, it was found that the glucose-lowering and appetite-suppressing effects of LEAP2 were induced at least in part through the growth hormone secretagogue receptor (GHSR). Supporting research was also conducted by Shankar et al., (2021) which states that LEAP2 acts as a selective antagonist of GHSR. At certain doses, it can block the effects of acyl-Ghrelin which plays a role in inducing food intake and GH secretion in mice. In addition, deletion of LEAP2 in mice enhances the action of Ghrelin as an orexigen and growth hormone, which means LEAP2 is a major determinant of Ghrelin resistance to GHSR (Shankar et al., 2021).

One of the effects of LEAP2 is that as an inverse agonist, LEAP2 can also alter the polarization of NPY neurons that play a role in regulating (Mustafá et al., 2021). As a Ghrelin antagonist, LEAP2 competes with Ghrelin directly. LEAP2 and Ghrelin bind to the same spot on the GHSR-1A receptor and both have similar roles (Li et al., 2023). The common binding point for LEAP2 and Ghrelin based on mutational analysis is Phe279 on GHSR-1A, unlike Ghrelin LEAP2 does not cause receptor internalization after binding (Ribeiro et al., 2021). Overall, LEAP2 inhibits GHSR-1A function by reducing consitutive activity and displacing Ghrelin from the binding site and reducing intracellular signaling through receptor internalization, LEAP2 being a specific and effective inhibitor (Barrile et al., 2019).

Association of LEAP2 in the Incidence of Obesity

The relationship of the LEAP2 hormone to the incidence of obesity was found in several studies, including by previous studies highlighting the importance of serum LEAP2 levels in influencing body mass index (BMI), the results showed that participants with a BMI of 32 to 50kg had higher LEAP2 levels compared to controls who had normal body weight, besides that participants with a BMI of more than 50kg showed lower LEAP2 concentrations (Nabekura et al., 2023). These findings are also supported by Bhargava et al., (2023) who highlighted the potential of LEAP2 in altering the body's prosprandial response to food, in his research found an increase in plasma LEAP2 levels after eating which was followed by a decrease in acetyl-Ghrelin (AG) which showed a negative correlation between the two. Meanwhile, studies conducted by Mani et al., (2019) and Holm et al., (2022) provide additional support for the role of LEAP2 in the incidence of obesity. The discovery of LEAP2 levels correlating with body weight and fat mass in mice and humans means this association may involve similar mechanisms across. Moreover the decrease in LEAP2 levels after bariatric surgery suggests that changes in LEAP2 may be a more competitive target for obesity management, in addition the increased expression of LEAP2 in the liver in obese mice may provide support about the role of specific tissues in the production of LEAP2 regulation (Mani et al., 2019). These findings may form the basis for further understanding of the relationship between LEAP2 and the incidence of obesity, so the

potential implications of these findings may involve the potential development of anti-obesity drugs for future LEAP2-based obesity therapy.

Impact of LEAP2 in Addressing Obesity Risk at the Cellular Level

In some findings LEAP2 function is used as an antidote to the incidence of obesity, some findings conducted by Lang et al., (2023) stated that in obese mice, it was found that LEAP2 which is a regulatory protein, has a crucial role in reducing the negative effects of obesity at the cellular and hormonal levels. The results showed that obesity in mice caused hyperlipidemia, increased proinflammatory substances, and damage to the heart. However, when LEAP-2 was inactivated, there was an improvement in hyperlipidemia caused by a high-fat diet, as well as a decrease in inflammation and injury to the heart. LEAP-2 also modified macrophage cells, changing polarization from M1 to M2, which plays a role in the recovery process. Thus, LEAP-2 proves its role in overcoming the negative effects of obesity at the cellular level (Lang et al., 2023). Then this is also supported by research conducted by Holá et al., (2022) still in a related context, research on palmitoylation on LEAP2 shows promising results. Modification with palmitoyl increased the affinity of LEAP2 to the GHSR-1A receptor and showed high stability in mouse blood. This modified LEAP2 was also able to produce stronger anorexigenic effects and inhibit the effects of Ghrelin in mice more effectively than LEAP2 without palmitoyl modification. These findings provide a new understanding of the possibility of modifying LEAP2 to enhance its effectiveness as a potential therapy for obesity. By better understanding the role of LEAP-2 at the cellular and hormonal levels, it can be the basis for the development of anti-obesity drugs in addressing the problem of obesity in the future.

CONCLUSION

Based on the results of the review, it can be concluded that LEAP2 has a close correlation with body weight, fat mass, and obesity in mice and humans. The relationship of LEAP2 with Ghrelin shows the complexity of the interaction at the cellular level, where LEAP2 can act as an agonist or antagonist to the GHSR-1A receptor. Potential therapeutic implications of LEAP2 in obesity require further clinical research to validate preclinical findings and evaluate the long-term effects of LEAP2 regulation on human body weight and metabolic health, so that it can be the basis for future anti-obesity drug development.

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