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Original Article

Does kisspeptin act as a neuropeptide or as an adipokine in obese people?

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الملخص

أهداف البحث: أصبحت السمنة مشكلة عالمية خطيرة تؤثر على صحة وحياة الناس في جميع أنحاء العالم. إلى جانب كون الكيسبيبتين ببتيدا عصبيا، فإنه مادة دهنية مهمة تشارك في تنظيم توازن الطاقة ووزن الجسم. تهدف هذه الدراسة إلى توضيح الدور الأساسي للكيسبيبتين في السمنة وتوضيح ما إذا كان الكيسبيبتين يعمل كببتيد عصبي أو دهني عند الأشخاص الذين يعانون من السمنة المفرطة.

طرق البحث: تضمنت دراسةالحالات والشواهد هذه ١١٠ فردا بدينا بمؤشر كتلة الجسم ٣٣.٤٥ ±٠.٣٦كجم/م^2 و٨٤ فردا بوزن طبيعي بمؤشر كتلة الجسم ٢١.٣٥ ±٠.٢٤كجم/م^2، تتراوح أعمارهم بين ٢١ و٤٥ عاما (٣١.٥٦ ±٠.٦٧عاما). تم قياس تركيز الكيسبيبتين والببتيد المنشط للعدلة الظهارية-٧٨ والجريلين باستخدام تقنية مقايسة الممتز المناعي المرتبط بالإنزيم. تم تحديد معلمات صورة الدهون باستخدام تقنيات القياس اللوني التجارية.

النتائج: كانت تراكيز الكيسبيبتين والببتيد المنشط للعدلة الظهارية-٧٨ في البلازما أعلى بشكل ملحوظ في الأشخاص الذين يعانون من السمنة (كيسبيبتين لمرضى السمنة: ٤٣٧.٦٦ ± ٣٤.٩٦ بيكوغرام/مل، كيسبيبتين لذوي الوزن الطبيعي: ٢٥٠.١٠ ±١٦.١٦بيكوغرام/مل، الببتيد المنشط للعدلة الظهارية-٧٨ لمرضى السمنة: ١٤٤.٨٠ ± ٢٣.٩٤ بيكوغرام/مل، الببتيد المنشط للعدلة الظهارية-٧٨ لذوي الوزن الطبيعي: ٥٠.٩٧ ±٣.٩١ بيكوغرام/مل). أظهر تركيز الجريلين عدم وجود فرق معنوي بين الأشخاص الذين يعانون من السمنة والأشخاص ذوي الوزن الطبيعي (الجريلين لمرضى السمنة: ٣.٦٧ ± ١.٨٤ نانوغرام/مل، الجريلين لذوي الوزن الطبيعي: ١.٧٨ ±٠.١٤). أختلفت معلمات صورة الدهون بشكل كبير في مرضى السمنة مقارنة بالأشخاص ذوي الوزن الطبيعي.

الاستنتاجات: يرتبط الكيسبيبتين بالسمنة، زيادة كتلة النسيج الدهني يمكن أن تكون مسؤولة ليس فقط عن زيادة إفراز الكيسبيبتين، ولكن عن زيادة إفراز الببتيد المنشط للعدلة الظهارية-٧٨ أيضا. قد يعمل كيسبيبتين كأديبوكين أكثر من ببتيد عصبي في الأشخاص الذين يعانون من السمنة المفرطة. هناك حاجة إلى مزيد من الدراسات على البشر لتحديد الدور الأساسي للكيسبيبتين في تمايز الخلايا الشحمية وتكوين الدهون.

الكلمات المفتاحية: الأنسجة الدهنية؛ الببتيد المنشط للعدلة الظهارية-٧٨؛ توازن الطاقة؛ جريلين؛ كيسبيبتين

Abstract

Objectives: Obesity is a serious global issue with a massive impact on the health and life of people worldwide. Besides being a neuropeptide, kisspeptin is an important adipokine involved in regulating energy homeostasis and body weight. This study aims to clarify the underlying role of kisspeptin in obesity.

Methods: This case-control study included 110 obese individuals with BMI of 33.45 ± 0.36 kg/m^2 and 84 normal-weight individuals with BMI 21.35 ± 0.24 kg/m^2. The individuals' ages ranged from 21 to 45 years (31.56 ± 0.67 year). Kisspeptin, neutrophil epithelial activating peptide (ENA-78), and ghrelin were determined using the enzyme-linked immunosorbent assay (ELISA) technique. Lipid profile parameters were determined using the commercial colorimetric techniques.

Results: Plasma concentrations of kisspeptin and ENA-78 were significantly higher in obese subjects (kisspeptine of obese: 437.66 ± 34.96 pg/ml; kisspeptine of normal-weight: 250.10 ± 16.16 pg/ml, $p< 0.0001$; ENA-78 of obese: 144.80 ± 23.94 pg/ml; ENA-78 of normal-weight: 50.97 ± 3.91 pg/ml, $p< 0.001$). Ghrelin concentrations showed no significant difference between obese and normal-

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weight subjects. The lipid profile parameters significantly differed between obese and normal-weight subjects.

Conclusion: Kisspeptin is associated with obesity. An increased mass of adipose tissue could be responsible not only for increased kisspeptin secretion but also for the increased ENA-78 secretion. Kisspeptin may act as an adipokine more than a neuropeptide in obese population. Further studies on humans are required to establish the underlying role of kisspeptin in adipocyte differentiation and lipogenesis.

Keywords: Adipose tissue; ENA-78; Ghrelin; Kisspeptin; Obesity

Introduction

Obesity is a serious global issue affecting the health and life of people around the world. Positive energy balance (also called energy homeostasis) and accumulation of white adipose tissue are linked to obesity.[1] Adipose tissue plays a central role in regulating the whole-body energy. It stores energy in the form of lipid and controls the lipid mobilization and distribution in the body. Positive energy balance means that energy intake exceeds energy expenditure and it is the main driver of weight gain.[2] Adipokines are mediators that participate in many biological processes. They play a pivotal role in the physiology of many pathological conditions such as cardiovascular diseases,[3] rheumatoid arthritis, and metabolic disorders such as obesity.[4] The secretion of adipokines from the adipose tissue is regulated by various factors including the endocrine hormones and central nerves system (CNS) signals.[2]

Kisspeptin is a neuropeptide encoded by the *KISS1* gene. It is known for regulating the reproductive system as well as metabolism.[5] It functions through a G-protein coupled receptor (GPR54). Kisspeptin and its receptor are expressed in the hypothalamus, placenta, liver, kidney, pancreas, and adipose tissue. The expression of GPR54 in the adipose tissue indicates the role of kisspeptin in mediating CNS signals which affect both the amount of adipose and the secretion of adipose tissue-related factors. On the other hand, adipose tissue is one of the major means of circulating kisspeptin in humans, indicating the paracrine/autocrine function of kisspeptin as an adipokine.[4,6] Kisspeptin and its receptor are also expressed in human monocytes and macrophages, therefore it is believed that it is implicated in the inflammation processes.[3]

Neutrophil epithelial activating peptide (ENA-78) or CXCL5 is a cytokine and a member of the family of chemokines that is involved in the chemotaxis of the inflammatory cells. ENA-78 is secreted from the macrophages that reside in the adipose tissue,[7] and it functions as an adipokine by activating the Jak2/Stat5 pathway, which reduces the insulin signalling and promotes obesity.[8] Increased white adipose tissue in obese individuals causes a chronic systemic inflammatory response. This inflammation is associated with increased macrophages infiltration, which in turn, causes increased secretion of the adipose tissue along with derived factors such as kisspeptin and ENA-78.[9]

Ghrelin is a stomach-derived peptide that promotes energy conservation by increasing appetite.[10] Ghrelin acts as a ligand for the growth hormone secretagogues receptor by stimulating growth hormone secretion.[11] A neuroanatomical study approved the existence of a neuronal bridge between kisspeptin and ghrelin in growth hormone release.[12] Another pharmacological study illustrated that in rats treated with kisspeptin, ghrelin secretion was inhibited, suggesting an anorexigenic role for kisspeptin through the ghrelin pathway.[13]

Kisspeptine is an important neuropeptide, and at the same time, it is an adipokine.[4–6] Previous studies have shown that kisspeptin, as a neuropeptide, is associated with obesity either due to direct signalling to metabolism pathways and the adipose tissue,[5,14] or because of performing an anorexigenic role through the ghrelin pathway. In both cases, kisspeptin level decreased in obese subjects.[13] Meanwhile, other studies have illustrated that the increased kisspeptin acts as an adipokine, and is associated with obesity.[7,9] The purpose of this study was to find out the exact role of kisspeptin in obesity, and figure out if it would act as an anorexigenic neuropeptide and increase the ghrelin level in obese individuals, or would act as adipokine and be secreted in large amounts along with other adipokines such as ENA-78 in response to the increased mass of adipose tissue.

Material and Methods

All the participants were healthy volunteers who had no systemic, diabetic, or reproductive issues. The study subjects were males, aged between 21 and 45 years. The case group included 110 obese individuals with body mass index (BMI) 33.45 $\pm$ 0.36 kg/m^2, while the control group included 84 normal weight individuals with BMI 21.35 $\pm$ 0.24 kg/m^2.

Blood samples were obtained by venepuncture after overnight fasting from 8 pm to 12 noon. The samples were left to clot; the sera were isolated and stored at -80 °C until used for clinical analysis. Serum kisspeptin, ENA-78, and ghrelin were determined using ELISA kits (Elabscience, USA). Lipid profile parameters (cholesterol, triglycerides, LDL, VLDL, and HDL) were determined using commercial kits based on colorimetric technique (LiNEAR, Spain).

The statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 25 (IBM SPSS statistic, NY, USA). T-test was used to determine the mean and standard error of the mean; $P<0.05$ was considered as statistically significant. Pearson correlation was used to analyse the correlation between the study parameters. All the figures were drawn using GraphPad Prism version 8.3.0 (California, USA).

Results

The plasma concentrations of kisspeptin and ENA-78 were significantly higher in obese compared to normal-

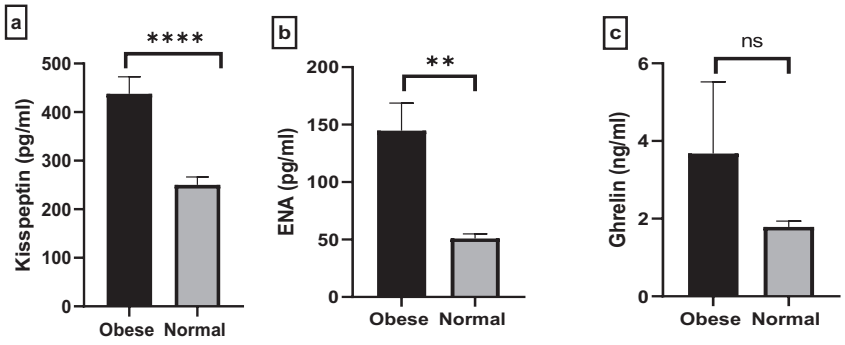

Figure 1: Mean comparison of a) kisspeptin, b) ENA-78, and c) ghrelin in obese and normal weight subjects. ****: significant at P> 0.0001, **: significant at P> 0.01, ns: non-significant.

Table 1: Mean comparison of age, BMI and lipid profile parameters between the obese and normal-weight groups.

Parameter	Obese (n = 110) Mean ± SEM	Normal weight (n = 84) Mean ± SEM	P-value
Age (year)	31.56 ± 0.67	31.35 ± 0.58	0.81
BMI (Kg/m^2)	33.45 ± 0.36	21.35 ± 0.24	0.0001
Kisspeptin (pg/ml)	437.66 ± 34.96	250.10 ± 16.16	0.0001
ENA-78 (pg/ml)	144.80 ± 23.94	50.97 ± 3.91	0.001
Ghrelin (ng/ml)	3.67 ± 1.84	1.78 ± 0.14	0.373
Total cholesterol (mg/dl)	180.43 ± 1.68	157.14 ± 0.96	0.0001
Triglyceride (mg/dl)	173.43 ± 3.0	100.92 ± 2.23	0.0001
LDL (mg/dl)	102.25 ± 1.87	80.81 ± 1.20	0.0001
VLDL (mg/dl)	34.68 ± 0.60	20.18 ± 0.44	0.0001
HDL (mg/dl)	43.49 ± 0.76	56.14 ± 0.48	0.0001

BMI: Body mass index, SEM: Standard error of mean. ENA-78: Neutrophil epithelial activating peptide. LDL: Low density lipoprotein. VLDL: Very low density lipoprotein. HDL: High density lipoprotein.

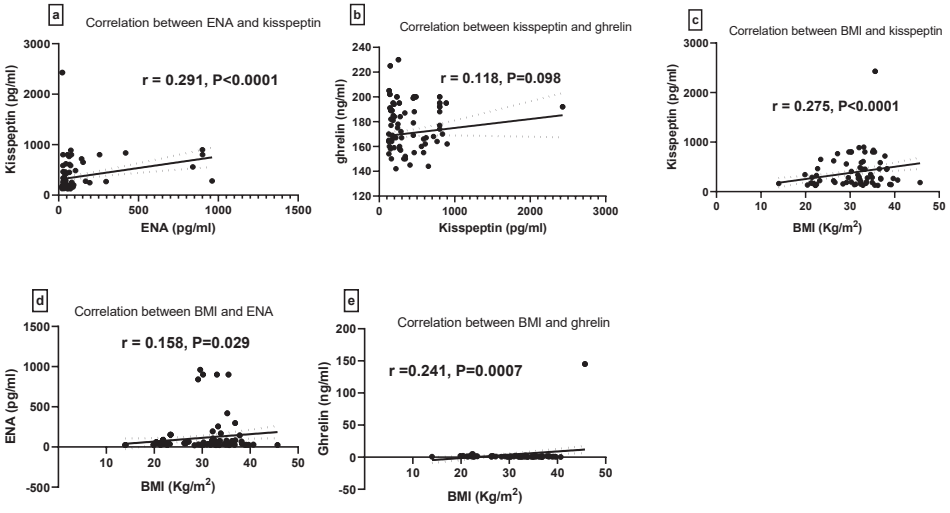

Figure 2: Correlations between kisspeptin and ENA-78 (figure a) and kisspeptin and ghrelin (figure b). The correlations between BMI and kisspeptin, ENA-78, and ghrelin each are shown in figures c, d, and e respectively. The solid lines represent the mean while the dashed lines represent the 95% confidence interval. r represents Pearson correlation and P-value represents the significance of correlation.

weight subjects (kisspeptine of obese: 437.66 ± 34.96 pg/ml; kisspeptine of normal-weight: 250.10 ± 16.16 pg/ml, P< 0.0001; ENA-78 of obese: 144.80 ± 23.94 pg/ml; ENA-78 of normal-weight: 50.97 ± 3.91 pg/ml, P< 0.001; Figure 1). Ghrelin concentration showed no significant difference between obese and normal-weight subjects (ghrelin of obese: 3.67 ± 1.84 ng/ml; ghrelin of normal weight: 1.78 ± 0.14 ng/ml, P = 0.373; Figure 1). The plasma cholesterol, triglycerides, LDL and, VLDL were significantly elevated in obese subjects compared to

normal-weight subjects, whereas plasma HDL was significantly elevated in normal-weight subjects (Table 1). There was a weak positive correlation between kisspeptin and both ENA-78 as well as ghrelin (Figure 2). Weak positive correlations were also found between BMI and kisspeptin, ENA-78, and ghrelin each (Figure 2).

Discussion

Even though previous studies have illustrated the role of kisspeptin in human metabolism, there is a persistent need to further investigate the impact of kisspeptin in obesity. This study was conducted to investigate this role.

The current study found that serum kisspeptin is significantly elevated in obese individuals ($P<0.0001$, Figure 1). Serum ENA-78 concentration was also significantly elevated in obese individuals ($P<0.001$, Figure 1); this elevation could be due to the increased mass of adipose tissue and chronic inflammation caused by obesity. A weak positive correlation was found between the kisspeptin and ENA-78 ($r = 0.291$, $P<0.0001$, Figure 2). The results of this study disagree with the results of existing animal studies which illustrated that reduced kisspeptin signalling leads to obesity and vice versa.[5,15] This disagreement could have been due to the fact that kisspeptin takes on different roles, as a neuropeptide and as an adipokine, and each role has a distinct effect, as will be seen later.

While cholesterol, LDL, VLDL, and triglyceride were significantly elevated in obese subjects (Table 1), there was no significant difference in serum ghrelin between obese and normal-weight subjects ($P = 0.373$, Figure 1). Ghrelin is a systemic orexigenic peptide hormone, and its level differs depending on factors such as energy intake, stress, and food behaviour.[16] Serum ghrelin fluctuates based on meals. It falls after food intake, especially in lean individuals; this indicates a short-term regulation of its secretion by the stomach and duodenum.[17] Most obese subjects (except Prader–Willi syndrome patients) exhibit lower serum ghrelin concentration. The reduced ghrelin levels caused by obesity can be reversed through caloric restriction.[18] In this study, it has been found that ghrelin concentration of the obese subjects does not significantly differ from that of the normal-weight subjects. There are studies agree with us and other studies do not agree with our finding. This could be due to the low postprandial suppression of ghrelin in the obese subjects as compared to the non-obese subjects, which makes the obese individuals feel a greater sense of hunger after food consumption.[19]

This study found that there is a very weak positive correlation between kisspeptin and ghrelin ($r = 0.118$, $P = 0.098$, Figure 2). This could indicate that kisspeptin, despite its significant elevation in obese subjects, has no effect on ghrelin and it is not likely to act as an anorexigenic neuropeptide especially through the ghrelin pathway. A previous experimental animal study,[13] reported that kisspeptin acts as an anorexigenic neuropeptide, and ghrelin levels in the rats decreased after they were injected with kisspeptin. This result disagrees with the results of the current study. The disagreement could be due to the fact that the kisspeptin injections in the previous study were given via third cerebral ventricle, and thus kisspeptin could have spread from the brain to the blood, that is, kisspeptin worked as a neuropeptide.

Stengel *et al*, in their experiments, found that mice injected with kisspeptin in their lateral brain ventricle exhibited low appetite post injection; kisspeptin inhibited food intake at certain levels.[19] They concluded that kisspeptin acts as an anorexigenic factor only when it is secreted as a neuropeptide from the brain. Drawing from this and based on the significant elevation of kisspeptin in the obese group in the current study, it became possible to conclude that kisspeptin does not act as an anorexigenic factor when it is secreted from the adipose tissue. Rather, it acts as an adipose tissue-related factor (adipokine) and is largely secreted in consequence to the increased mass of adipose tissue in obese individuals.

ENA-78, like other adipokines such as leptin, adiponectin, and other cytokines, is expressed in white adipose tissue. It is mainly expressed in the macrophages that reside in the white adipose tissue.[8] Its role is responsible for the local inflammation that characterises the white adipose tissue, and it also regulates insulin secretion and body weight.[20] Our results showed a significant elevation of ENA-78 in obese subjects compared to normal-weight subjects indicating that the increased inflammatory macrophages infiltration are caused by obesity. This result is consistent with Chavey *et al* who illustrated that the secretion of ENA-78 from the macrophages that reside in white adipose tissue was dramatically high in obese individuals as compared to lean individuals. They also concluded that the increased secretion of ENA-78 from the macrophages of white adipose tissue represents a link between obesity and inflammation.[9] Our results also agree with an animal study done by Nunemaker *et al*, who found that the increased concentration of serum ENA-78 is associated with obesity and it is a very sensitive marker for the inflammation that leads to diabetes mellitus in mice.[21]

Obesity alters the expression of kisspeptin and its receptor, and kisspeptin in turn regulates the glucose homeostasis and alters the body weight.[22,23] Wang *et al*, in their experiments on mice, found that the expression of GPR54 is higher in mice fed on a high fat diet. They also illustrated that the mice deficient in GPR54 have less adipose tissue mass and smaller adipocyte size. This indicates a reduced secretion of kisspeptin due to the reduced mass of adipose tissue in these mice.[24] Although theirs was an animal study, our results agree with Wang et al.

The study is limited since it detected only one adipokine (ENA-78) in addition to kisspeptin. Further research should focus on other adipokines such as leptin.

Conclusion

Increased mass of adipose tissue is responsible for increased kisspeptin. Kisspeptin could act more as an adipokine in obese people than as a neuropeptide. Further studies on humans are required to establish the underlying role of kisspeptin in adipocyte differentiation and lipogenesis.

Recommendation

The authors recommend that future research should focus on leptin and use a larger sample size.

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This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

The research was approved by the ethical committee of the College of Pharmacy, University of Kerbala, Iraq. The reference number of the ethical approval obtained on 1 February 2020 is HU001. This study adheres to the Helsinki Declaration.

Authors' contributions

SJA conceived and designed the study and wrote the initial and final draft of the article. FSA conducted research, provided research materials, and collected and organised data. IHD analysed and interpreted data, and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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