ZEUGMA BIOLOGICAL SCIENCE

ZEUGMA
BIOLOGICAL SCIENCE

2022
v:3 n:3 p:1-9

Hormone`s role in development and energy regulation (Review Article)

Ishtar Imad[1], Suhail Bayati[2],

[1] Uruk university, Baghdad, 10610, Iraq,

[2] Al-Hadi University College. Baghdad, 10610, Iraq.

dr.suhail@huc.edu.iq

Abstract:

Asprosin, in addition to performing a glucogenic function, is a centrally acting orexigenic hormone that represents a potential therapeutic target for the treatment of obesity and diabetes. Perturbations in the action of T3 and T4 affect normal metabolic pathways. The sensitivity of lipid biomarkers such as LDL-C, HDL-C, TC, TG, Apo-A, and Apo-B after rehabilitation of the thyroid profile to achieve a euthyroid state was determined.

Keywords: Asprosin, T3, T4, HDL-C, TC, TG, Apo-A, Apo-B, adropin, and preptin.

Introduction

Thyroid hormones play an important role in normal development and energy regulation mechanisms, as well as in signaling mechanisms that influence energy flow through central and peripheral pathways. A study aimed to determine the effect of thyroid dysfunction on the levels of adoption, asprosin, and preptin in rats. Methods a study was performed on 38 male Wistar-albino rats. The experimental groups were designed as follows. 1-Control, 2-Hypothyroidism; To induce hypothyroidism, PTU was administered intraperitoneally at a dose of 10 mg/kg/day for 2 weeks. 3-Hypothyroidism + Thyroxine; Previously, animals were raised with hypothyroidism after 1 week of PTU application, and then l-thyroxine was administered intraperitoneally at a dose of 1.5 mg/kg/day for 1 week. 4-hyperthyroidism; Rats were exposed to hyperthyroidism after 3 weeks of l-thyroxine (0.3 mg/kg/day). 5-Hyperthyroidism + PTU; Animals were boosted with l-thyroxine in groups of 4, followed by 1 week of PTU to treat hyperthyroidism. At the end of supplementation, animals were sacrificed and blood samples were collected for analysis of FT3, FT4, adropin, asprosin, and preptin. Results FT3 vs FT4 levels were significantly decreased in hypothyroidism, while increased in hyperthyroidism ($p<0.001$). Hypothyroidism resulted in decreased levels of adropin, asprosin, and preptin. And

hyperthyroidism also reduced adropin and preptin levels ($p<0.001$). Conclusions The results of the study show that experimental hypothyroidism and hyperthyroidism lead to a significant change in the levels of adropin, asprosin, and preptin. However, correction of thyroid function caused normal levels of asprosin and preptin (Mogulkoc, et.al. 2020).

In patients with T2DM, serum concentrations of asprosin were significantly higher than in healthy controls (4.18 [IQR: 4.4] vs. 3.5 [IQR: 1.85], $P < 0.001$). Asprosin concentrations were significantly correlated with body mass index (BMI) and fasting blood glucose (FBG) in healthy subjects and with BMI, FBG, hemoglobin A1c (HbA1c), homeostatic model assessment of insulin resistance (HOMA-IR), and quantitative insulin control index (QUICKI). triacylglycerol (TAG) and total cholesterol/high-density lipoprotein cholesterol (TC/HDL-C) ratio in the T2DM group. In the fully adjusted model, the odds ratio (OR) of T2DM with serum asprosin concentrations was approximately 1.547 (95% CI 1.293–1.850, $P < 0.001$) compared with the control group. Multiple stepwise regression analysis showed that FBG and HOMA-IR were independently associated with asprosin in T2DM. findings showed that serum concentrations of asprosin are elevated in patients with T2DM. Asprosin also correlates with insulin resistance and TC/HDL-C ratio (atherosclerotic cardiovascular disease risk factor) in T2DM patients (Naiemian, et.al. 2020).

Asprosin is a newly discovered starvation-induced hormone that promotes glucose production in the liver. Here we show that plasma asprosin crosses the blood-brain barrier and directly activates orexigenic AgRP+ neurons via a cAMP-dependent pathway. This signaling leads to inhibition of downstream anorexigenic POMC+ neurons in a GABA-dependent manner, resulting in the stimulation of appetite and the drive to accumulate adiposity and body weight. Genetic deficiency of asprosin in humans results in a syndrome characterized by low appetite and extreme thinness, which is phenocopied by mice carrying similar mutations, and which can be fully rescued by expression of asprosin. Also, the study found that obese humans and mice exhibit pathologically elevated concentrations of circulating asprosin, and neutralization of plasma asprosin using a monoclonal antibody reduces appetite and body weight in obese mice, in addition to improving their glycemic profile. Therefore, asprosin, in addition to performing a glucogenic function, is a centrally acting orexigenic hormone that represents a potential therapeutic target for the treatment of obesity and diabetes (Duerrschmid, et.al. 2017).

Perturbations in the action of T3 and T4 affect normal metabolic pathways. The sensitivity of lipid biomarkers such as LDL-C, HDL-C, TC, TG, Apo-A, and Apo-B after rehabilitation of

the thyroid profile to achieve a euthyroid state was determined. A total of 179 age-matched subjects of both sexes were recruited for this research. 60 healthy controls, 34 subclinical, 50 overtly hyperthyroid, and 35 follow-up subjects with 3 months of carbimazole therapy were included. Biochemical analysis was performed using a chemical analyzer, RIA and ELISA. One-way ANOVA was used for statistical analysis, while the significance of means was compared by the Student-Newman-Keuls (SNK) test. A significant reduction of cholesterol was observed overtly compared to control and subclinical, while a significant improvement was demonstrated at follow-up. A prominent increase in TG at follow-up was demonstrated compared to control. Overt showed a significant reduction in HDL-C compared to subclinical and controls (and), respectively. A significant increase () of HDL-C was demonstrated after treatment. Apparent represented a reduction in LDL-C compared to subclinical and control (and in that order). The observation group showed a significant improvement in LDL-C after treatment and an increase compared to the control. It presented a reduction of Apo-B compared to subclinical and control. Improvement in Apo-B was demonstrated at follow-up. Apo-A was decreased at overt compared to control and increased at follow-up compared to overt. Improvement after treatment was demonstrated in the lipid profile (Naiemian, et. al. 2020).

There is a -ve association between asprosin and body mass index (BMI) in the Mets + obese group. Among asprosin and urea and fasting insulin (FI) levels in the MetS group were positive and statistically significant ($p < 0.05$). While there was a statistically significant -ve relation ($p < 0.05$) between visfatin and BMI in the MetS + Obese group, the relation with waist diameter in the MetS + Obese and MetS groups was statistically significant and -ve ($p < 0.05$. There is a direct relationship between circulating amounts of asprosin with age, weight, and height. That's why, the hormone asprosin are a new signal of metabolic disorders (Ugur, et. al. 2022).

Serum asprosin levels found to be higher in obese subjects [3.7 ng/ml (2.6–5.0)] than in T2DM/obese [0.1 ng/ml (0.0–0, 4)] and controls [0.2 ng/ml (0.1–0.3)].] ($p < 0.001$). In the T2DM/obese group, users of metformin alone or in combination had significantly lower asprosin levels than those with no known medication history [0.03 ng/ml (0.02–0.05) vs 0.2 ng/ml (0 .1–0.4); $p < 0.001$]. Stepwise multiple linear regression analysis revealed that only glucose, insulin, and adiponectin were the most important predictors of asprosin, explaining 61.3% ($p < 0.001$) of the variance. Asprosin levels are combined with IR markers without the adiposity and inflammation and are influenced by oral hypoglycemics, especially metformin (Al-Daghri, et. al. 2022). Another study included 143 samples who have been separated into 3 parts: normal glucose regulation (NGR), impaired glucose regulation (IGR), and newly

diagnosed type 2 diabetes mellitus (nT2DM). The study showed that higher plasma asprosin was found in the IGR and nT2DM groups in comparison with the NGR group, especially in the IGR subjects. Asprosin was +vely associated with the homeostasis evaluation for IR (HOMA-IR) when it was -vely combined with the homeostasis model assessment for β-cell functioning (HOMA-β) (Wang, et al. 2018).

Irisin is a newly discovered myokine and adipokine that increases total body energy expenditure. This study aimed to determine the effect of experimental hypothyroidism and hyperthyroidism on irisin levels in heart tissue in rats. The study was conducted on 40 male Sprague-Dawley rats. The experimental groups were designed as; Control, hypothyroidism, hypothyroidism + L-thyroxine, hyperthyroidism, and hyperthyroidism + PTU. After 3 weeks of the experimental period, irisin levels in heart tissue were determined. Irisin values in the hypothyroid group were higher than in the control group but lower than in the hyperthyroid group. The hyperthyroid group had the highest levels of cardiac irisin. The results of the study explain that experimental hypothyroidism and hyperthyroidism increased cardiac irisin levels, but the elevate in the hyperthyroid group was much more elevated than that in the hypothyroid group. Treatment of hypothyroidism and hyperthyroidism modified cardiac irisin levels (Atici, et.al. 2018).

There are four varied topics of diabetes: type 1 diabetes, type 2 diabetes, gestational diabetes mellitus (GDM), and other certain types of diabetes (Amer, 2014). Several published studies have focused on associations between circulating asprosin concentrations and IR, as well as diabetes in mice and humans. It has been reported that elevated plasma levels of asprosin can be observed in human subjects and mice with IR (Romere, et.al. 2016). Add more, a hospital-based case-control study involving 170 samples have high serum asprosin value in adults with T2DM when compared with controls and a dissociation between fasting glucose and serum asprosin in T2DM, consistent with many studies (Wang, et. Al. 2018 and Li, et.al. 2018). Furthermore, there is an impaired or blunted response of serum asprosin levels to glycemic fluctuations in patients with type 1 diabetes mellitus (T1DM) and T2DM (Zhang, et. al. 2019 Groener, et. al. 2019). An in vitro study demonstrated the effect of asprosin on inflammation and changes in the function of pancreatic β-cells. This study found that palmitate increased asprosin secretion in MIN6 mouse insulinoma cells, and asprosin resulted in inflammation, cellular dysfunction, apoptosis, and decreased glucose-induced insulin production in β-cells through upregulation of the TLR4/JNK-mediated pathway. Interestingly, these changes could be reversed through siRNA-mediated suppression of asprosin (Lee, ET.AL. 2019).

It has been newly reported that asprosin values in the serum of gestated women with GDM and the umbilical cord of their neonates are higher than in controls (Baykus, et al. 2019). Another evaluation found increased liver levels of asprosin in T1DM mice as well (Ko, et. al. 2019). That's why, serum asprosin, which may be a marker, may share in the early diagnosis of diabetes.

The main pathological characteristics of T2DM are elevated fasting and postmeal blood glucose levels caused by continued high liver glucose elaboration, IR, and β-cell disorders (Titchenell, et. al. 2017 Unger, 2003).

Romero et al. say that one dose of recombinant asprosin being injected Sub-cut into mice led to hyperglycemia and hyperinsulinemia, and neutralization of asprosin with asprosin-specific antibodies resulted in an improvement in IR and a decrease in plasma glucose, insulin levels, and body weight. This suggests that asprosin depletion could represent a therapeutic strategy against T2DM (Romere, et.al. 2016).

The function that asprosin acts in the inflammatory process, ER stress, and IR in skeletal muscle has been investigated. The in vitro and in vivo results of this report demonstrated that asprosin treatment leads to impaired skeletal muscle insulin sensitivity and impaired glucose and insulin tolerance in mice via ER stress/inflammatory ways linked with PKC8. This was pointed out by the reality that intraperitoneal therapy of myocytes with asprosin and mice with recombinant mouse asprosin impaired insulin signaling, including reduced insulin-induced phosphorylation of IRS-1 and Akt. As far, asprosin-induced results are eliminated by shutting down PKCδ expression with siRNA (Jung, et.al. 2019). A new study in mice with streptozotocin (STZ)-induced T1DM revealed that aerobic exercise reduces hepatic asprosin levels and thus leads to improvement in diabetes-related parameters. Therefore, it could be useful for the treatment of TIDM by regulating asprosin levels or pathways downstream of asprosin (Ko, et. al. 2019). Also, there is a clear linkage between asprosin and the prognosis of diabetes, and asprosin may give a patent target for tomorrow's management and therapeutics of DM. It should be noted that the consequences between elevated asprosin levels and diabetes cannot be well known, as elevated asprosin is a protective feedback mechanism for diabetes or a result of metabolic disorders that need more investigation.

The latest research finds that asprosin plays a key and contradictory role in obesity. Numerous studies have reported increased concentrations of asprosin in obese humans and mice. Serum levels of asprosin have been reported to be pathologically elevated in obese adults, children,

and mice, whereas reduced body weight and food intake could be observed in obese mice using an asprosin-specific antibody (Duerrschmid, et.al. 2017, Wang, et. al. 2019, and Wang, et. al. 2019). In addition, a positive relationship can be observed between circulating asprosin concentrations and waist circumference and triglycerides (TG) (Wang, et. al. 2018 Wang, et. al. 2019). Interestingly, another study noted that human salivary glands were able to synthesize asprosin. As subjects' body mass index (BMI) increased, low-density lipoprotein cholesterol (LDL-C) and asprosin levels in saliva and blood also increased (Ugur and Aydin 2019).

Cohort research includes one hundred and seventeen obese samples with BMI > 35 kg/m2 & 57 normal samples and found that preprandial asprosin levels were statistically higher in obese samples than in control samples. In addition, the research revealed that samples with higher circulating asprosin before bariatric surgery have a more regression in body weight 6 months post-surgery. Especially, this research found that preoperative asprosin levels in patients with an effective response (percentage of body weight loss within 6 months after surgery >55%) were significantly higher than in patients who did not respond (percentage of body weight loss within 6 months after surgery <35%). The sensitivity and specificity for asprosin levels to predict an effective response was 76% and 75%, respectively (Wang, et. al. 2019).

Surprisingly, the study by Ma et al. investigated the therapeutic effects of AM6545, a neutral peripheral cannabinoid receptor antagonist, on monosodium glutamate (MSG)-induced hypometabolic and hypothalamic obesity. They found that AM6545 was able to reduce serum asprosin levels, which may accordingly lead to amelioration of obesity and IR in MSG mice (Ma, et. al. 2018). However, asprosin may be a biomarker for fat tissue mass and a target in the treatment of overweight; regardless, observational studies are unable to confirm a cause-and-effect relationship between asprosin and obesity, and further in vitro and in vivo research is needed.

Also, other studies reported inapposite effects. Jung et al. showed that in opposite to an old study, the total body weight of mice did not change when recombinant asprosin was injected (Jung, et.al. 2019). Another cross-sectional study raised a result that serum asprosin concentrations were significantly lowered in obese children aged 6 to 14 years when compared with intact children of healthy weight. Asprosin was negatively linked with BMI when tuned for age and gender, which is discontinuous with the values of the last mentioned studies; this shows an unclear role for asprosin in overweight patients (Long, et. al. 2019).

The mechanism by which asprosin targeted obesity has not been fully elucidated. NPS patients and mice with an NPS-associated mutation showed reduced plasma asprosin, appetite, and extreme leanness (Romere, et.al. 2016 Duerrschmid, et.al.2017). This leads to that asprosin associated with obesity in part by raising appetite. The previously mentioned study shows that serum asprosin contributes to passing the blood-brain barrier and activated AgRP neurons through a cAMP-dependent mechanism to activated starvation, which may lead to more energy eating and getting fats (Duerrschmid, et.al. 2017).

References:

Mogulkoc, Rasim & Dasdelen, Dervis & Baltaci, Saltuk & Baltaci, Abdulkerim Kasim & Sivrikaya, Abdullah. (2020). The effect of thyroid dysfunction and treatment on drop-in, asprosin, and preptin levels in rats. Hormone Molecular Biology and Clinical Investigation. -1. 10.1515/hmbci-2020-0058.

Naiemian, S., Naeemipour, M., Zarei, M. et al. (2020). Serum concentration of asprosin in new-onset type 2 diabetes. Diabetol Metab Syndr 12, 65https://doi.org/10.1186/s13098-020-00564-w.

Duerrschmid C, He Y, Wang C, Li C, Bournat JC, Romere C, Saha PK, Lee ME, Phillips KJ, Jain M, Jia P, Zhao Z, Farias M, Wu Q, Milewicz DM, Sutton VR, Moore DD, Butte NF, Krashes MJ, Xu Y, Chopra AR. (2017). Asprosin is a centrally acting orexigenic hormone. Nat Med. Dec;23(12):1444-1453. doi: 10.1038/nm.4432. Epub 2017 Nov 6. PMID: 29106398; PMCID: PMC5720914.

Naiemian, Shakiba and Naeemipour, Mohsen, el al . (2020). The serum concentration of asprosin in new-onset type 2 diabetes. Diabetology & Metabolic Syndrome. 65: 12: 1. Asprosin, a newly identified adipokine, is pathologically increased in individuals with insulin resistance. However, the available evidence on the association of asprosin and type 2 diabetes mellitus (T2DM) status is still scarce. Therefore, this study aimed to determine the relationship between serum concentrations of asprosin and T2DM status.1758-5996.https://doi.org/10.1186/s13098-020-00564-w.bvgbbfB.

K. Ugur, F. Erman, S. Turkoglu, Y. Aydin, A. Aksoy, A. Lale, Z.K. Karagöz, İ. Ugur, R.F. Akkoc, M. Yalniz. (2022). Asprosin, visfatin, and subfatin as new biomarkers of obesity and metabolic syndrome. Eur Rev Med Pharmacol Science. Vol. 26 - N. 6. 2124-2133.DOI: 10.26355/eurrev_202203_28360.

Al-Daghri, Nasser M., Reem M.I. Alokeel, Abir Alamro. (2022). Serum asprosin levels are associated with obesity and insulin resistance in Arab adults. Journal of King Saud University – Science. Volume 34, Issue 1.

Atici E, Menevse E, Baltaci AK, Mogulkoc R. (2018). Both experimental hypothyroidism and hyperthyroidism increase cardiac irisin levels in rats. Bratislavske Lekarske Listy.119(1):32-35. DOI: 10.4149/bll_2018_007. PMID: 29405728.

Romere C, Duerrschmid C, Bournat J, Constable P, Jain M, Xia F, et al. (2016). Asprosin, is a fasting-induced glucogenic protein hormone. Cell. 165:566–79. doi: 10.1016/j.cell.2016.02.063.

Lee T, Yun S, Jeong JH, Jung TW. (2019). Asprosin impairs insulin secretion in response to glucose and viability through TLR4/JNK-mediated inflammation. Mol Cell Endocrinol. 486:96–104. doi: 10.1016/j.mce.2019.03.001.

Duerrschmid C, He Y, Wang C, Li C, Bournat JC, Romere C, et al. (2017). Asprosin is a centrally acting orexigenic hormone. Nat Med. 23:1444–53. doi: 10.1038/nm.4432.

Jung TW, Kim HC, Kim HU, Park T, Park J, Kim U, et al. (2019). Asprosin attenuates the insulin signaling pathway through PKCdelta-activated ER stress and inflammation in skeletal muscle. J Cell Physiol. 234:20888–99. doi: 10.1002/jcp.28694.

Amer Diabet A. (2014) Diagnosis and classification of diabetes mellitus. Diabetes Care. 37:S81–90. doi: 10.2337/dc14-S081.

Wang Y, Qu H, Xiong X, Qiu Y, Liao Y, Chen Y, et al. (2018) Plasma asprosin concentrations are increased in individuals with glucose dysregulation and correlated with insulin resistance and first-phase insulin secretion. Med Inflam. 2018:9471583. doi: 10.1155/2018/9471583.

Zhang X, Jiang H, Ma X, Wu H. (2019). Increased serum level and impaired response to glucose fluctuation of asprosin are associated with type 2 diabetes mellitus. J Diabetes Investig. doi: 10.1111/jdi.13148.

Li X, Liao M, Shen R, Zhang L, Hu H, Wu J, et al. (2018). Plasma asprosin levels are associated with glucose metabolism, lipid, and sex hormone profiles in females with metabolic-related diseases. Med Inflam. 2018:7375294. doi: 10.1155/2018/7375294.

Groener JB, Valkanou A, Kender Z, Pfeiffenberger J, Kihm L, Fleming T, et al. (2019). Asprosin response in hypoglycemia is not related to hypoglycemia unawareness but rather to

insulin resistance in type 1 diabetes. PLoS ONE. 14:e0222771. doi: 10.1371/journal.pone.0222771.

Baykus Y, Yavuzkir S, Ustebay S, Ugur K, Deniz R, Aydin S. (2019). Asprosin in the umbilical cord of newborns and maternal blood of gestational diabetes, preeclampsia, severe preeclampsia, intrauterine growth retardation, and macrosomic fetus. Peptides. 120:170132. doi: 10.1016/j.peptides.2019.170132.

Ko JR, Seo DY, Kim TN, Park SH, Kwak HB, Ko KS, et al. (2019). Aerobic exercise training decreases hepatic asprosin in diabetic rats. J Clin Med. 8:666. doi: 10.3390/jcm8050666.

Titchenell PM, Lazar MA, Birnbaum MJ. (2017). Unraveling the regulation of hepatic metabolism by insulin. Trends Endocrinol Metab. 28:497–505. doi: 10.1016/j.tem.2017.03.003.

Unger RH. (2003). Lipid overload and overflow: metabolic trauma and the metabolic syndrome. Trends Endocrinol Metab. 14:398–403. doi: 10.1016/j.tem.2003.09.008.

Wang CY, Lin TA, Liu KH, Liao CH, Liu YY, Wu VC, et al. (2019). Serum asprosin levels and bariatric surgery outcomes in obese adults. Int J Obesity. 43:1019–25. doi: 10.1038/s41366-018-0248-1.

Wang M, Yin C, Wang L, Liu Y, Li H, Li M, et al. (2019). Serum asprosin concentrations are increased and associated with insulin resistance in children with obesity. Ann Nutr Metab. 75:205–12. doi: 10.1159/000503808.

Ugur K, Aydin S. (2019). Saliva and blood asprosin hormone concentrations are associated with obesity. Int J Endocrinol. 2019:2521096. doi: 10.1155/2019/2521096.

Ma H, Zhang G, Mou C, Fu X, Chen Y. (2018). Peripheral CB1 receptor neutral antagonist, AM6545, ameliorates hypometabolic obesity and improves adipokine secretion in monosodium glutamate-induced obese mice. Front Pharmacol. 9:156. doi: 10.3389/fphar.2018.00156.

Long W, Xie X, Du C, Zhao Y, Zhang C, Zhan D, et al. (2019). Decreased circulating levels of asprosin in obese children. Horm Res Paediatr. 91:271–7. doi: 10.1159/000500523.