Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Circulating neuromedin U levels are similar in subjects with NGT and newly diagnosed T2DM and do not correlate with insulin secretion

Mingzhu Han [a,1], *Yanhong Xu* [a,1], *Jing Yuan* [b], *Yi Zhu* [a], *Jianhua Zhou* [a], *Lu Liu* [a], *Xiaohua Li* [a,*], *Hongli Zhang* [a,*]

[a] *Department of Endocrinology, Seventh People's Hospital of Shanghai University of Traditional Chinese Medicine, Shanghai 200137, China*
[b] *Department of Statistics, Shandong Institute of Business and Technology, Yantai 264005, China*

ARTICLE INFO

Article history:
Received 20 October 2018
Received in revised form
5 February 2019
Accepted 12 April 2019
Available online 18 April 2019

ABSTRACT

Aims: Neuromedin U (NMU), a highly conserved peptide, is implicated in energy homeostasis and is involved in regulating insulin secretion as a decretin hormone in animals. However, there have been no reports on the relationship between NMU and type 2 diabetes mellitus (T2DM). The aim of this study was to investigate circulating NMU concentrations in healthy subjects and T2DM patients and to evaluate the association between serum NMU levels and glucose-stimulated insulin secretion.

Methods: We used ELISA to analyze NMU concentrations in blood samples from newly diagnosed T2DM patients (n = 57) and age-, sex- and BMI-matched healthy control subjects (n = 50). Anthropometric parameters, oral glucose tolerance, glycosylated hemoglobin, blood lipids, insulin sensitivity, and insulin secretion were measured.

Results: No difference was observed in serum NMU levels between control subjects and newly diagnosed T2DM patients (p = 0.788). The oral glucose tolerance test (OGTT) results indicated that serum NMU concentrations did not change and did not correlate with insulin levels at fasting and 1 h, 2 h and 3 h after glucose load in both healthy controls and newly diagnosed T2DM patients.

Conclusion: Circulating NMU concentrations were similar in control subjects and newly diagnosed T2DM patients and were not associated with glucose-stimulated insulin secretion. Serum NMU is not a human decretin hormone and may not play a role in the pathogenesis of T2DM.

1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases; in 2017, it affected over 425 million people worldwide [1]. Insulin resistance and impaired insulin secretion remain the primary defects in T2DM. However, several pathophysiological abnormalities contribute to these defects [2]. Despite extensive research, the underlying mechanisms are not fully understood.

Neuromedin U (NMU) is a neuropeptide that is expressed and secreted in both the brain and the gut [3–5]. Two G-protein-coupled receptors for NMU have been identified: neuromedin U receptor 1 (NMUR1) and neuromedin U receptor 2 (NMUR2) [6–8]. NMUR1 is expressed in mainly peripheral

* Corresponding authors.
E-mail addresses: wendylee_tcm@shutcm.edu.cn (X. Li), hongliting@sina.com (H. Zhang).
[1] These authors contributed equally to this work.
https://doi.org/10.1016/j.diabres.2019.04.020
0168-8227/

tissues, particularly the gastrointestinal tract, immune system, and pancreas [9–11], whereas NMUR2 is abundant in the hypothalamus, hippocampus, and spinal cord [7–9,12]. It has been reported that NMU could play a role in energy homeostasis and in a wide variety of other physiological processes, including blood pressure, smooth muscle contraction, nociception, stress and inflammation [4,13–17]. NMU administration has been shown to decrease food intake and body weight in rodents by increasing energy expenditure, locomotor activity and oxygen consumption [5,18–20]. NMU transgenic mice are lean and hypophagic [21]; however, NMU-/- mice exhibited increased adiposity, hyperinsulinemia, and hyperlipidemia [22], suggesting that NMU is involved in insulin sensitivity and insulin secretion. Some studies have found NMUR1 mRNA expression and immunoreactivity in rodent and human pancreatic beta cells, and NMU suppressed insulin secretion in isolated rodent and human islets [10,23,24].

The incretin hormones include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), both of which are released during meals from gut endocrine cells; these hormones potentiate glucose-induced insulin secretion and are involved in glucose homeostasis [25]. It has been established that the incretin effect is severely reduced or absent in T2DM patients, and this contributes to the pathogenesis of T2DM [26]. Recently, Alfa et al. reported that NMU was a nutrient-responsive decretin hormone secreted from enteroendocrine cells that suppresses pancreatic beta cell insulin secretion [23].

To date, there have been no reports on the relationship between NMU and T2DM. The aim of this study was to investigate circulating NMU concentrations in healthy subjects and T2DM patients. Furthermore, we evaluated the association between NMU levels and glucose-stimulated insulin secretion and determined whether NMU participates in the pathogenesis of T2DM.

2. Subjects and methods

2.1. Study population

A total of 107 subjects were recruited for this study: 50 healthy control subjects and 57 newly diagnosed T2DM patients. T2DM diagnosis was based on the 2011 American Diabetes Association diagnostic criteria [27]. Subjects with impaired fasting glucose and/or impaired glucose tolerance were excluded. None of the control subjects were taking medications known to affect glucose tolerance or insulin secretion. Individuals with type 1 diabetes, gestational diabetes, active hepatitis/liver cirrhosis, chronic renal failure on hemodialysis, congestive heart failure, or other known major diseases were excluded from the study. All subjects enrolled in the study provided informed consent. The study protocol was in agreement with the guidelines of the ethics committee of our hospital.

2.2. Oral glucose tolerance test

An oral glucose tolerance test (OGTT) was performed for all of the included participants. After a 12-hour overnight fast, the patients ingested 75 g glucose, and blood samples were collected at baseline and at 30, 60, 90, 120, and 180 min after glucose intake. Blood samples for determination of NMU determination were collected in vacutainer tubes containing aprotinin. After clotting, the blood specimens were separated by centrifugation. Serum were frozen and stored at −80 °C immediately after centrifugation.

2.3. Anthropometric and biochemical measurements

Weight (without shoes and in light outdoor clothing) and height were measured, and body mass index (BMI) (kg/m^2) was calculated by dividing patient weight (kg) by height squared (meters squared). Waist circumference (WC) was measured midway between the lower costal margin and the iliac crest, and hip circumference was measured at the level of maximum extension of the buttocks. The waist-to-hip ratio (WHR) was also calculated. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured after the subjects had rested for 10 min.

Serum variables were determined at the Department of Medical and Chemical Laboratory Diagnostics at Shanghai Seventh People's Hospital of TCM. Blood glucose levels were determined using the glucose oxidase method; insulin levels were measured using chemiluminescence; and serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels were measured using enzymatic methods. Blood NMU levels were quantified using a commercially available ELISA kit (Peninsula Laboratories, San Carlos, CA, USA). The NMU ELISA was performed in duplicate according to the manufacturer's protocol. Homoeostasis model assessment for IR index (HOMA-IR) and beta cell function (HOMA-β) were calculated using the following formulas: HOMA-IR = fasting plasma glucose (FPG) (mM) × insulin (mIU/L)/22.5; HOMA-β = 20Xinsulin (mIU/L)/(FPG (mM) − 3.5) × 100%.

2.4. Statistical analysis

Statistical analysis was performed using SPSS 19.0 software (SPSS Inc., Chicago, IL). The data are presented as the mean ± SD. Continuous variables that followed normal distributions were compared via Student's t test. Variables not normally distributed were natural logarithmically transformed. Correlation coefficients were analyzed using Spearman's correlation. P values < 0.05 were considered statistically significant.

3. Results

3.1. Study population characteristics

The baseline clinical characteristics of the subgroups studied (control and newly diagnosed T2DM) are shown in Table 1. The age and sex distributions were similar between the two groups. In addition, there were no statistically significant differences between T2DM patients and control subjects with respect to BMI, WHR, blood pressure, ALT, AST, Cr, TC, LDL-C, HDL-C, and 2 h post-OGTT serum insulin. However, fasting

Table 1 – Clinical and biochemical characteristics in control subjects and in patients with T2DM.

Variable	Healthy control (n = 50)	T2DM (n = 57)	P value
Age (years)	48.74 ± 10.64	52.51 ± 11.22	0.079
Sex (M/F)	28/22	34/23	
Weight (kg)	68.00 ± 11.66	72.29 ± 13.00	0.120
BMI (kg/m^2)	24.91 ± 4.33	26.45 ± 3.66	0.085
WC (cm)	82.58 ± 8.64	84.22 ± 6.96	0.434
WHR	0.89 ± 0.05	0.91 ± 0.04	0.068
SBP (mmHg)	126.1 ± 11.21	129.3 ± 8.89	0.224
DBP (mmHg)	77.10 ± 8.14	75.10 ± 10.15	0.285
$Glucose_0$ (mmol/L)	5.46 ± 0.60	9.33 ± 2.34	0.000
$Glucose_{120}$ (mmol/L)	6.14 ± 1.02	16.87 ± 4.26	0.000
HbA1c (%)	5.54 ± 0.37	7.88 ± 1.75	0.000
TC (mmol/L)	5.01 ± 1.80	5.16 ± 1.27	0.672
TG* (mmol/L)	1.28 (0.88–2.13)	1.98 (1.27–3.16)	0.021
LDL-C (mmol/L)	2.73 ± 1.02	3.18 ± 1.04	0.058
HDL-D (mmol/L)	1.28 ± 0.34	1.19 ± 0.31	0.198
ALT* (U/L)	22.05 (12.95–28.80)	27.40 (18.05–37.00)	0.062
AST (U/L)	21.81 ± 7.81	24.04 ± 12.40	0.378
SCr (81.8 μmol/L)	60.01 ± 16.37	59.75 ± 14.73	0.944
$Insulin_0$ (pmol/L)	66.08 ± 40.19	90.38 ± 46.20	0.001
$Insulin^*_{120}$ (pmol/L)	309.7 (207.30–494.33)	364.0 (187.68–556.95)	0.809
HOMA-IR*	1.92 (1.29–2.53)	4.47 (3.23–7.13)	0.000
HOMA-β	93.79 ± 50.72	50.87 ± 33.67	0.000
Neuromedin U* (ng/ml)	4.32 (3.40–5.22)	4.56 (3.24–6.23)	0.788
BMI ≥ 25 kg/m^{2*}	4.11 (3.33–7.46)	4.52 (3.22–5.14)	0.433#
BMI < 25 kg/m^{2*}	4.36 (3.56–5.11)	4.92 (3.70–7.32)	0.424&

Abbreviations: *BMI* body mass index, *WC* Waist circumference, *WHR* waist-to-hip ratio, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HbA1c* hemoglobin A1c, *TC* total cholesterol, *TG* triglyceride, *LDL-C* low density lipoprotein cholesterol, *HDL-C* high density lipoprotein cholesterol, *ALT* alanine aminotransferase, *AST* aspartate transaminase, *SCr* Serum creatinine, *HOMA-IR* homeostasis model assessment for insulin resistance index, *HOMA-β* homeostasis model assessment for beta cell function.

Data are Means ± SD and median (25th and 75th percentiles). #: overweight/obese subjects (BMI ≥ 25 kg/m^2) VS nonobese subjects (BMI < 25 kg/m^2) in healthy control; &: overweight/obese subjects (BMI ≥ 25 kg/m^2) VS nonobese subjects (BMI < 25 kg/m^2) in T2DM group. *Log-transformed variable, values given are median (25th and 75th percentiles).

plasma glucose (FPG), fasting serum insulin, HbA1C, TG and HOMA-IR values were significantly higher in the T2DM group than in the control group ($P < 0.01$ or $P < 0.05$), and HOMA-β values were significantly lower ($P < 0.05$). No difference was observed in serum NMU levels between control subjects and newly diagnosed T2DM patients. Stratification with BMI in T2DM or control groups showed that serum NMU concentrations were similar in overweight/obese subjects (BMI ≥ 25 kg/m^2) and nonobese subjects (BMI < 25 kg/m^2) (Table 1).

3.2. *Correlation of NMU levels with insulin secretion*

We next investigated the relationship of circulating NMU levels with insulin secretion using Spearman's correlations. As we know, severe and persistent hyperglycemia resulted in loss of pancreatic beta cell function by glucotoxicity. So we selected 20 newly diagnosed T2DM patient of HbA1C <7.5% and 20 healthy control from whole group to study the relationship of circulating NMU levels with insulin secretion. The baseline clinical characteristics are shown in Table S1. During the OGTT test, 2 h post-OGTT and 3 h post-OGTT insulin levels in the newly diagnosed T2DM group were significantly higher than in the control group. This finding suggested a delay in peak insulin response and return to basal insulin levels after glucose loading in T2DM patients. However, serum NMU concentrations did not change during glucose loading in either group (Fig. 1). Serum NMU levels did not correlate with insulin levels at fasting or 1 h, 2 h or 3 h after glucose load in either newly diagnosed T2DM patients or healthy controls (control: fasting $r = 0.139$, $p = 0.058$, 1 h $r = 0.069$, $p = 0.772$, 2 h $r = 0.219$, $p = 0.364$, 3 h $r = 0.11$, $p = 0.645$; T2DM: fasting $r = 0.352$, $p = 0.128$, 1 h $r = 0.153$, $p = 0.519$, 2 h $r = 0.272$, $p = 0.246$, 3 h $r = 0.153$, $p = 0.519$ (Fig. 2). There were still no significant correlations after adjustments for age, BMI, WHR and HOMA-IR score (data not shown).

4. Discussion

Previous studies demonstrated that NMU plays a role in energy expenditure and insulin secretion. NMU may be a possible candidate for the treatment of obesity and diabetes. However, there have been no reports on the relationship between NMU and T2DM. In this study, we demonstrated for the first time that serum NMU concentrations are not different in newly diagnosed, untreated T2DM patients and control subjects. Furthermore, our study also showed that NMU is not a nutrient-responsive hormone, and it does not correlate with insulin secretion in humans. These results do not agree with a previous animal study, in which NMU was found to be a decretin hormone that inhibited insulin secretion [23].

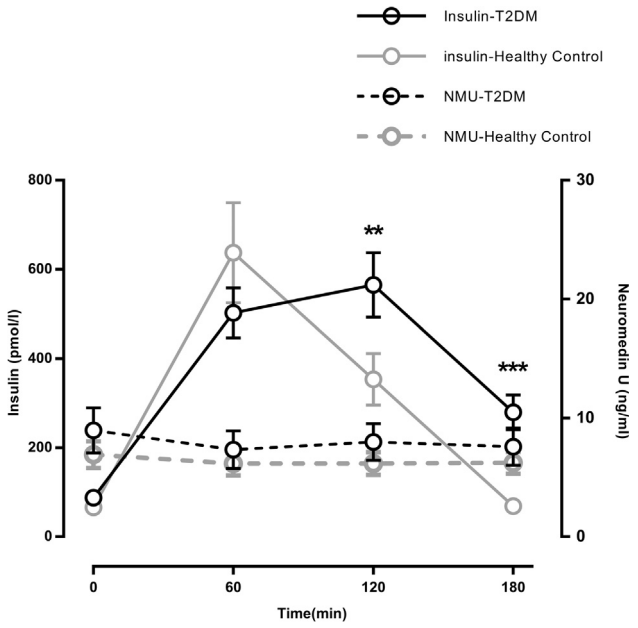

Fig. 1 – Serum insulin and NMU values before and at various time points during OGTTs in newly diagnosed T2DM patients and healthy controls. Insulin level in T2DM patients (black solid line), insulin level in healthy controls (gray solid line), NMU level in T2DM patients (black dotted line), NMU levels in healthy controls (gray dotted line). The data are presented as the mean ± SEM; $^{**}p < 0.01$, $^{***}p < 0.001$ for differences in insulin levels between T2DM patients and healthy controls.

NMU belongs to a family of neuropeptides, the neuromedins. NMU is ubiquitously distributed, but its highest levels are found in the brain and gastrointestinal tract. This protein has been implicated in energy homeostasis due to its regulation of food consumption and energy expenditure. Central and peripheral NMU administration has been shown to decrease body weight and improve glucose homeostasis in rodents by increasing energy expenditure and oxygen consumption [19,20,28]. Mice lacking the gene encoding NMU become obese, and in humans, a genetic variation in the NMU gene has been associated with overweight and obesity [22,29]. Although these studies have made NMU a possible candidate for treating obesity and diabetes, the role of NMU in diabetes has not been clearly established. In our study, we first investigated circulating NMU concentrations in healthy subjects and newly diagnosed type 2 diabetes patients. Because a previous study reported very low circulating concentrations of NMU in rodents [30], we treated our blood samples with aprotinin according to the ELISA kit manual. The range of NMU concentrations we detected in our population is similar to those reported in other papers [31]. In our study, we found that NMU concentrations were not different in subjects with normal glucose tolerance (NGT) and newly diagnosed T2DM patients. In contrast to previous animal study results, we did not find increased NMU levels in overweight/obese diabetes patients or healthy subjects compared with the respective lean populations.

Recently, Alfa et al. described that NMU is a nutrient-responsive decretin hormone that is secreted from enteroendocrine cells and suppresses insulin secretion by pancreatic beta cells [23]. As we known, incretin hormone such as GLP1 and GIP, are secreted by enteroendocrine cells following a meal, and these hormones enhance glucose-stimulated insulin production and secretion from pancreatic beta cells [32]. Decretin hormones, which are also derived from an enteroendocrine source and are sensitive to nutrient availability, would have the opposite hallmarks of incretins. Decretin is induced by feeding and prevent excessive fluctuations in plasma insulin. There is a delay in the peak insulin response and return to basal insulin level after glucose load in T2DM patients, which implies that beta cells produce more insulin and result in hyperinsulinemia.

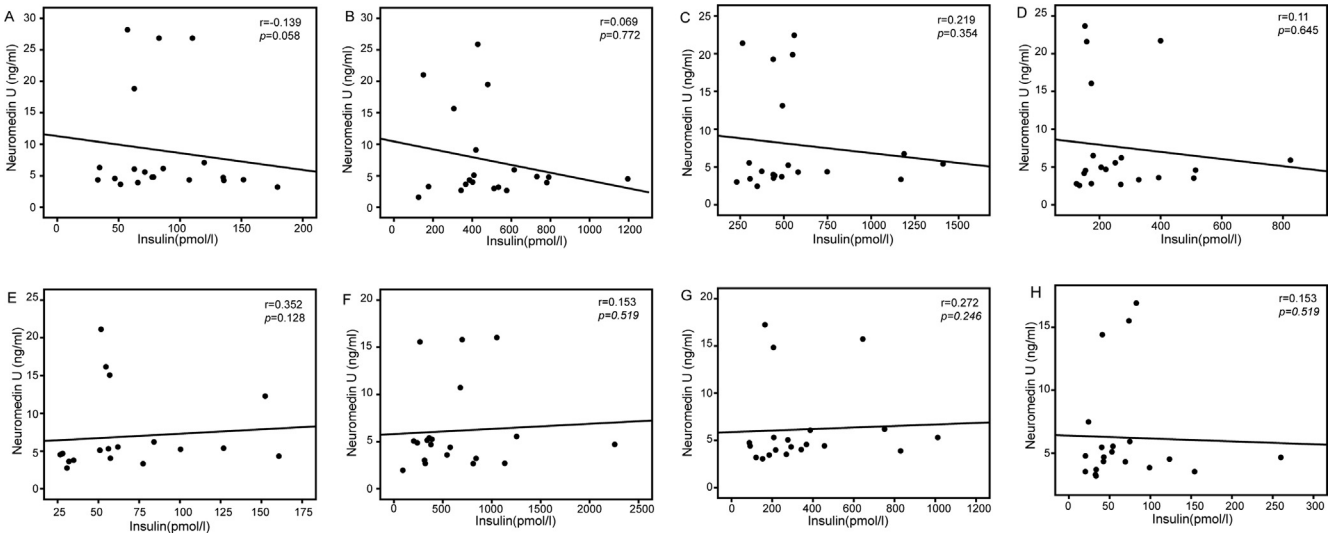

Fig. 2 – Correlation analysis between serum NMU and insulin levels. Serum NMU levels do not correlate with insulin levels at fasting (A) and 1 h (B), 2 h (C) and 3 h (D) after glucose load in newly diagnosed T2DM patients and at fasting (E) and 1 h (F), 2 h (G) and 3 h (H) after glucose load in healthy controls.

Hyperinsulinemia is the root cause of insulin resistance, obesity, and diabetes [33]. Similar to incretin defects, decretin defects might contribute to the development of T2DM. In our study, we found that neither the T2DM group nor the normal control group displayed correlations between serum NMU levels and insulin secretion in a small clinical sample. Serum NMU concentrations did not change during glucose loading. These data indicated that serum NMU did not inhibit insulin secretion, did not modulate the kinetics of insulin secretion after glucose stimulation and was possibly not a decretin hormone in humans.

Our clinical finding is inconsistent with the animal data. The reason may be attributed to the relatively low serum NMU level in humans. In animal experiments, NMU was administered by injection and resulted in a higher serum concentration than that in physiological conditions [20,34,35]. Previous studies suggested that NMU may act in a paracrine or autocrine manner to regulate physiological processes, such as modulating energy expenditure and insulin secretion [20,24,36]. Nutrition can induce a local increase in the NMU level, which suppresses insulin secretion. Due to the relatively small quantity or rapid degradation, we did not observe a change in the NMU level in circulating blood. Certainly, we cannot rule out other reasons, so a detailed mechanism still needs to be determined. While this paper was in revision, another report was published indicating that NMU did not act as a decretin in rats. They found NMU did not inhibit glucose stimulated insulin secretion and glucose did not affect NMU secretion from isolated perfused rat small intestine [37]. Such results are consistent with our observations presented here.

There are several limitations regarding the design of this study. A major limitation of this study is the small number of patients who were available for analysis. Additional follow-up studies on a larger number of subjects are needed. A second limitation is its retrospective design. The final limitation is that serial changes in serum NMU levels also need to be measured under impaired glucose tolerance conditions and at different stages of T2DM, in addition to newly diagnosed T2DM patients, to further clarify the role of circulating NMU in the pathogenesis of T2DM.

In summary, our results indicate for the first time that circulating NMU concentrations are similar in newly diagnosed T2DM patients and healthy subjects and are not associated with glucose-simulated insulin secretion in humans. Serum NMU is not a human decretin hormone and may not play a role in the pathogenesis of T2DM.

Conflict of interest statement

None of the authors have financial or other interests that might be construed as a conflict of interest with regard to the submitted manuscript.

Funding

This study was supported by the Pudong New Area Science and Technology Development Fund (PKJ2017-Y10 to H.Z.), Pudong New Area Municipal Health Commission—Summit Clinical Traditional Medicine Grant (PDZY-2018-0602 to X.L.).

Author contributions

H.M. and Y.X. contributed to data collection and analysis and wrote the manuscript. J.Y. analyzed the data and contributed to the discussion. Y.Z., J.Z., and L.L. contributed to data collection. X.L. designed the study's analytic strategy, contributed to discussion and reviewed/edited the manuscript. H.Z. conceived the project and designed the research, contributed to discussion, wrote the manuscript, and reviewed/edited the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.04.020.

REFERENCES

[1] IDF diabetes ATLAS, 8th ed.; 2017.
[2] DeFronzo RA et al. Type 2 diabetes mellitus. Nat Rev Dis Primers 2015;1:15019.
[3] Ballesta J et al. Occurrence and developmental pattern of neuromedin U-immunoreactive nerves in the gastrointestinal tract and brain of the rat. Neuroscience 1988;25(3):797–816.
[4] Mitchell JD, Maguire JJ, Davenport AP. Emerging pharmacology and physiology of neuromedin U and the structurally related peptide neuromedin S. Br J Pharmacol 2009;158(1):87–103.
[5] Howard AD et al. Identification of receptors for neuromedin U and its role in feeding. Nature 2000;406(6791):70–4.
[6] Hosoya M et al. Identification and functional characterization of a novel subtype of neuromedin U receptor. J Biol Chem 2000;275(38):29528–32.
[7] Fujii R et al. Identification of neuromedin U as the cognate ligand of the orphan G protein-coupled receptor FM-3. J Biol Chem 2000;275(28):21068–74.
[8] Graham ES et al. Neuromedin U and Neuromedin U receptor-2 expression in the mouse and rat hypothalamus: effects of nutritional status. J Neurochem 2003;87(5):1165–73.
[9] Raddatz R et al. Identification and characterization of two neuromedin U receptors differentially expressed in peripheral tissues and the central nervous system. J Biol Chem 2000;275(42):32452–9.
[10] Kaczmarek P et al. Neuromedin U receptor 1 expression in the rat endocrine pancreas and evidence suggesting neuromedin U suppressive effect on insulin secretion from isolated rat pancreatic islets. Int J Mol Med 2006;18(5):951–5.
[11] Cardoso V et al. Neuronal regulation of type 2 innate lymphoid cells via neuromedin U. Nature 2017;549 (7671):277–81.
[12] Brighton PJ, Szekeres PG, Willars GB. Neuromedin U and its receptors: structure, function, and physiological roles. Pharmacol Rev 2004;56(2):231–48.
[13] Brown DR, Quito FL. Neuromedin U octapeptide alters ion transport in porcine jejunum. Eur J Pharmacol 1988;155(1–2):159–62.
[14] Westfall TD et al. Characterization of neuromedin U effects in canine smooth muscle. J Pharmacol Exp Ther 2002;301 (3):987–92.
[15] Hanada R et al. A role for neuromedin U in stress response. Biochem Biophys Res Commun 2001;289(1):225–8.

[16] Cao CQ et al. A pro-nociceptive role of neuromedin U in adult mice. Pain 2003;104(3):609–16.
[17] Hedrick JA et al. Identification of a human gastrointestinal tract and immune system receptor for the peptide neuromedin U. Mol Pharmacol 2000;58(4):870–5.
[18] Novak CM, Zhang M, Levine JA. Neuromedin U in the paraventricular and arcuate hypothalamic nuclei increases non-exercise activity thermogenesis. J Neuroendocrinol 2006;18(8):594–601.
[19] Nakazato M et al. Central effects of neuromedin U in the regulation of energy homeostasis. Biochem Biophys Res Commun 2000;277(1):191–4.
[20] Peier AM et al. Effects of peripherally administered neuromedin U on energy and glucose homeostasis. Endocrinology 2011;152(7):2644–54.
[21] Kowalski TJ et al. Transgenic overexpression of neuromedin U promotes leanness and hypophagia in mice. J Endocrinol 2005;185(1):151–64.
[22] Hanada R et al. Neuromedin U has a novel anorexigenic effect independent of the leptin signaling pathway. Nat Med 2004;10(10):1067–73.
[23] Alfa RW et al. Suppression of insulin production and secretion by a decretin hormone. Cell Metab 2015;21 (2):323–34.
[24] Zhang W et al. Neuromedin U suppresses glucose-stimulated insulin secretion in pancreatic beta cells. Biochem Biophys Res Commun 2017;493(1):677–83.
[25] Creutzfeldt W. The [pre-] history of the incretin concept. Regul Pept 2005;128(2):87–91.
[26] Opinto G, Natalicchio A, Marchetti P. Physiology of incretins and loss of incretin effect in type 2 diabetes and obesity. Arch Physiol Biochem 2013;119(4):170–8.
[27] Basevi V et al. Comment on: American Diabetes Association. Standards of medical care in diabetes–2011. Diab Care 2011;34(Suppl. 1):S11–61. Diab Care; 2011:34(5);e53; author reply e54.
[28] Ivanov TR et al. Evaluation of neuromedin U actions in energy homeostasis and pituitary function. Endocrinology 2002;143(10):3813–21.
[29] Panetta R et al. Functional genomics of the rat neuromedin U receptor 1 reveals a naturally occurring deleterious allele. Physiol Genomics 2013;45(2):89–97.
[30] Domin J et al. Neuromedin U–a study of its distribution in the rat. Peptides 1987;8(5):779–84.
[31] Ketterer K et al. Neuromedin U is overexpressed in pancreatic cancer and increases invasiveness via the hepatocyte growth factor c-Met pathway. Cancer Lett 2009;277(1):72–81.
[32] Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. Cell Metab 2013;17 (6):819–37.
[33] Corkey BE. Banting lecture 2011: hyperinsulinemia: cause or consequence? Diabetes 2012;61(1):4–13.
[34] Dalboge LS et al. Neuromedin U inhibits food intake partly by inhibiting gastric emptying. Peptides 2015;69:56–65.
[35] Nagai H et al. Differential effects of selective agonists of neuromedin U1 and U2 receptors in obese and diabetic mice. Br J Pharmacol 2018;175(2):359–73.
[36] Mitchell JD et al. Expression and vasoconstrictor function of anorexigenic peptides neuromedin U-25 and S in the human cardiovascular system. Cardiovasc Res 2009;81(2):353–61.
[37] Kuhre RE et al. Neuromedin U Does Not Act as a Decretin in Rats. Cell Metab. 2019;29(3):719–26.