

High levels of Nesfatin-1 in relation to the dysfunction of the hypothalamic–pituitary–adrenal and hypothalamus–pituitary–thyroid axes in depressed patients with subclinical hypothyroidism

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Abstract: Despite the increasing amount of evidence suggesting a relationship between depression and subclinical hypothyroidism (SCH), the exact mechanism underlying this relationship remains unclear. The main purpose of this study was to investigate the roles of plasma Nesfatin-1 levels and dysfunction of the hypothalamic–pituitary–adrenal (HPA) and hypothalamus–pituitary–thyroid (HPT) axes in the comorbidity of depression and SCH. Dysfunctions of the HPA and HPT axes were detected by measuring plasma corticosterone and thyroid-stimulating hormone (TSH) concentrations, respectively. Subjects in the patient group were selected from patients hospitalized at the Anhui Mental Health Center, and subjects in the control group were recruited from healthy volunteers. Healthy control subjects were matched to the patients in terms of weight and body mass index. The Hamilton Depression Rating Scale was administered to both the groups. The enzyme-linked immunosorbent assay method was used to measure plasma Nesfatin-1, corticosterone, and TSH levels. A radioimmunoassay kit was used for the measurement of the plasma-free triiodothyronine and plasma-free thyroxine. The results showed that the Hamilton Depression Rating Scale scores and average Nesfatin-1, corticosterone, and TSH levels were significantly higher in depressed patients with SCH than in the control group. Moreover, positive relationships were observed between Nesfatin-1 levels and the concentrations of corticosterone ($r=0.626$, $P<0.001$) and TSH ($r=0.229$, $P=0.036$) in depressed patients with SCH. These findings indicate that Nesfatin-1 is involved in the comorbidity of depression and SCH, and the mechanism underlying this involvement might be related to the dysfunction of the HPA and HPT axes.

Keywords: corticosterone, depression, HPA axis, HPT axis, TSH, SCH

Introduction

Depression is the most common mood disorder and is estimated to affect 350 million people worldwide according to the World Health Organization. Although several behavioral and biologic factors may be involved in precipitating and perpetuating the symptoms of depression,^{1–3} the principal causes are not clear. A correlation between thyroid dysfunction and depression has been consistently reported in recent literature.^{4,5} Clinical hypothyroidism (also known as overt hypothyroidism) has traditionally been recognized as an important cause of depression,⁶ and thyroid hormones have been used as accelerators and augmenters of an antidepressant response for several decades.^{7,8} Moreover, dysfunctions of the hypothalamus–pituitary–thyroid (HPT) axis have been documented in patients with depression.⁹

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Subclinical hypothyroidism (SCH) is characterized by elevation of the plasma thyroid-stimulating hormone (TSH) concentration above the statistically defined upper limit of the reference range when plasma-free triiodothyronine (fT3) and plasma-free thyroxine (fT4) concentrations are within their reference ranges, and it is a common thyroid dysfunction that occurs in 4%–20% of the adult population.¹⁰ Although the relationship between depression and SCH remains controversial, an increasing amount of evidence suggests that SCH is associated with neuropsychiatric disorders such as cognitive dysfunction¹¹ and depression.¹² Depression is reportedly observed more frequently among individuals with SCH than among those with overt hypothyroidism,¹³ and patients with SCH exhibit a twofold higher prevalence of depression-like symptoms relative to healthy individuals.¹⁴ Therefore, the guidelines of the American Association of Clinical Endocrinologists recommended that the diagnosis of SCH must be considered in every patient with depression.¹⁵

Nesfatin-1, a novel satiety factor, plays a role in integrating feeding, glucose homeostasis, and energy expenditure.^{16,17} Apart from the findings that Nesfatin-1 is distributed in stress-related brain regions, including the hypothalamus, and colocalized with stress-related substances,^{18,19} intracerebroventricular administration of Nesfatin-1 has been reported to be able to activate the hypothalamic–pituitary–adrenal (HPA) axis, the hyperactivity of which is proposed to be among the causal factors for triggering depressive episodes.²⁰ Similarly, the results of our previous study confirmed that intraperitoneal administration of Nesfatin-1 in a single dose or chronically resulted in depression-like behavior and HPA axis hyperactivity in rats.²¹ Furthermore, an increased plasma concentration of Nesfatin-1 and an increased hypothalamic mRNA expression of Nesfatin-1 have been observed in animal models of depression.²² Consistent with the animal results, clinical studies have reported that the plasma Nesfatin-1 level is significantly higher in patients with major depressive disorder²³ than in healthy controls and is associated with elevated scores of anxiety and depression.^{23,24} Given the roles of the HPA axis and Nesfatin-1 in the pathophysiology of depression, the plasma concentrations of Nesfatin-1 and corticosterone were further evaluated in depressed patients with SCH in the present study, and the relationship between Nesfatin-1 and corticosterone concentrations was also investigated.

Recent evidence has indicated a close relationship between Nesfatin-1 and thyroid function.²⁵ The level of Nesfatin-1 has been found to be low in children with hyperthyroidism.²⁶ In another study, the concentration of Nesfatin-1 was shown

to be higher in hyperthyroid patients than in controls, and a negative correlation was observed between Nesfatin-1 and TSH concentrations.²⁷ A similar negative correlation was reported in patients with type 2 diabetes in a recent study.²⁵ However, to the best of our knowledge, little is known about the role of the plasma Nesfatin-1 levels in depressed patients with SCH. Considering the elevated plasma TSH concentration in depressed patients with SCH, another objective of this study was to investigate the association between Nesfatin-1 and TSH concentrations in depressed patients with SCH.

Given the dysfunction of the HPT and HPA axes, together with the important role of Nesfatin-1 in the pathophysiology of depression and SCH, we hypothesized that the plasma Nesfatin-1 levels should be increased in depressed patients with SCH and that this may be associated with the hyperactivity of the HPA axis and the overproduction of TSH. To test this hypothesis, subjects in the patient group were selected from patients hospitalized at the Anhui Mental Health Center, and subjects in the control group were recruited from healthy volunteers. The plasma Nesfatin-1, corticosterone, and TSH levels were measured using the enzyme-linked immunosorbent assay, and the plasma fT3 and fT4 levels were measured using a radioimmunoassay kit. Correlations were evaluated using a Pearson correlation test.

Materials and methods

Subjects

A total of 1,234 subjects with depression, according to the *Diagnostic and Statistical Manual for Psychiatric Disorders – Fourth Version*, who were hospitalized at the Anhui Mental Health Center from February 2016 to February 2017 were scanned in the study, and 83 depressed patients with a comorbidity of SCH were selected from the above patients on the basis of the following biochemical evidence: a TSH concentration greater than the reference range (TSH >4.50 mIU/L), with fT3 and fT4 within the reference range (fT3 between 1.7 and 3.7 pg/mL, fT4 between 0.8 and 2 ng/dL). The inclusion criteria were as follows: 1) all newly diagnosed patients with a *Diagnostic and Statistical Manual for Psychiatric Disorders – Fourth Version* diagnosis of major depressive disorder, minor depressive disorder, dysthymia, or adjustment disorder (with depressed mood); 2) depressed patients with comorbid SCH (defined by elevated plasma TSH levels and normal plasma fT3 and fT4 levels); and 3) patients who were not receiving an antidepressant, electroconvulsive therapy, or antithyroid drugs. The exclusion criteria included the following: 1) patients with a psychotic illness other than depressive disorders, 2) patients with thyroid diseases other

than SCH, and 3) patients who were already on treatment for a depressive illness or thyroid dysfunction. In contrast, 60 healthy volunteers, selected on the basis of the biochemical evidence of normal thyroid function (TSH, fT3, and fT4 levels within the reference range), formed the control group. Figure 1 summarizes the recruitment process. In accordance with the principles of the Declaration of Helsinki, all subjects gave written informed consent prior to participation. This study was approved by the Ethics Committee of the Anhui Mental Health Center.

Measurements

Weight and height measurements and the body mass index (BMI) calculation were carried out meticulously for all subjects. Study nurses administered questionnaires through face-to-face interviews. After an overnight fast, blood samples were drawn in the morning at approximately 8 a.m. from a forearm vein of the participants. Tubes that had a 5-mL capacity and contained EDTA were used for collecting blood. After centrifugation of the blood at $3,000 \times g$ for 5 min at 4°C , the plasma was obtained. The separated plasma was stored in a -80°C freezer until the time of assay.

The concentrations of Nesfatin-1, corticosterone, and TSH were measured using commercially available enzyme-linked immunosorbent assay kits (Nesfatin-1: Cusabio Biotech. Co., Ltd, Wuhan, Hubei, People's Republic of China; corticosterone: Enzo Life Sciences, Inc., New York, NY, USA; TSH: Cusabio Biotech. Co., Ltd) according to the

manufacturer's instructions. The plasma fT3 and fT4 levels were measured using a radioimmunoassay kit (North Institute of Biological Technology, Beijing, People's Republic of China) and apparatus from USTC Zonkia (USTC Zonkia Scientific Instruments Co., Ltd, Anhui, People's Republic of China).

Statistical analysis

All of the statistical analyses were performed using Statistical Package for the Social Sciences version 12.0.1 (SPSS Inc., Chicago, IL, USA). Data are expressed as the mean \pm standard error of the mean, and $P < 0.05$ was considered statistically significant. A one-sample Kolmogorov–Smirnov test showed a normal distribution of the continuous variables (age, BMI, Hamilton Depression Rating Scale [HAM-D] scores, and the concentrations of Nesfatin-1, corticosterone, TSH, fT3, and fT4) in both the patient group and the control group. A Student's *t*-test was used to evaluate differences between the groups (age, BMI, HAM-D scores, and the concentrations of Nesfatin-1, corticosterone, TSH, fT3, and fT4). To analyze the sex difference between groups, the χ^2 test was used. The correlation analyses were performed using a Pearson correlation test.

Results

The demographic variables did not show any statistically significant difference between the groups. As shown in Table 1, differences between the groups were not statistically

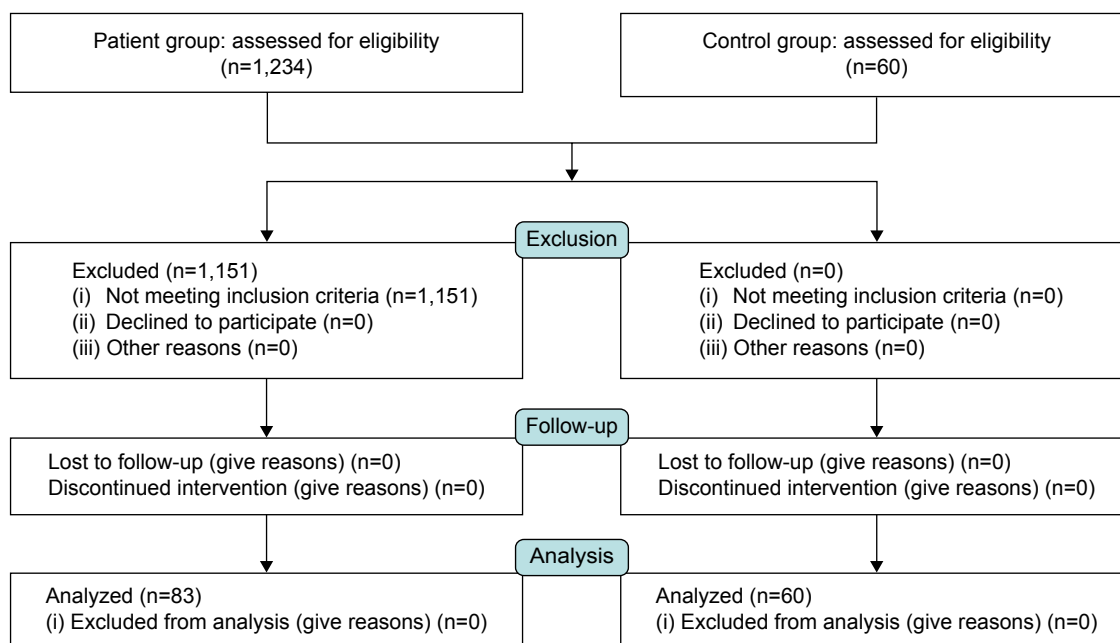


Figure 1 Flowchart showing the recruitment of participants.

Table 1 Comparison of mean values (or ratios) of age, sex, BMI, and HAM-D scores in patient group and control group (mean ± SEM)

Variables	Control group	Patient group	Statistics (t or χ^2)	P-value	Effect size (Cohen's d)	Power
Age	32.25±2.63	34.63±1.96	0.638	0.526		
Sex (female/male)	30/30	43/40	0.046 ^a	0.831		
BMI (kg/m ²)	22.79±0.30	23.27±0.19	1.275	0.206		
HAM-D	7.00±0.54	21.84±1.94	-5.40	<0.001**	1.16	1.00

Notes: ^a χ^2 score. **P<0.001 was considered statistically significant.

Abbreviations: BMI, body mass index; HAM-D, Hamilton Depression Rating Scale; SEM, standard error of the mean.

significant in terms of age, BMI, or sex. The mean HAM-D scores of the patient group were significantly higher than those of the control group (t(2,141) = -5.40, P<0.001, Cohen's d=1.67, Table 1).

The Nesfatin-1 levels of the patient group were significantly higher than those of the control group (t(2,141) = -3.70, P<0.001, Cohen's d=0.67, Table 2). Similarly, the depressed patients with SCH showed higher corticosterone levels than the healthy subjects (t(2,141) = -4.88, P<0.001, Cohen's d=1.35, Table 2). In terms of thyroid hormones, the plasma concentrations of TSH were significantly higher in depressed patients with SCH than in the control group (t(2,141) = -17.33, P<0.001, Cohen's d=4.13, Table 2), whereas no significant difference in the concentration of fT3 (t(2,141) = 0.098, P=0.922) or fT4 (t(2,141) = 1.391, P=0.168) was observed between the two groups.

Post hoc power analyses demonstrated that sufficient power was available to distinguish the above significant differences (HAM-D: power = 1.00; Nesfatin-1: power = 0.99; corticosterone: power = 1.00; TSH: power = 1.00).

The results of the Pearson correlation analysis showed that the plasma Nesfatin-1 concentrations were positively correlated with corticosterone concentrations among the depressed patients with SCH (r=0.626, P<0.001, Figure 2A). However, no such correlation was observed in the control group (r=0.012, P=0.926, Figure 2B).

Similarly, a positive correlation was found between the plasma Nesfatin-1 and TSH levels in the patient group (r=0.229, P=0.036, Figure 3A), but not in the control group (r=0.038, P=0.773, Figure 3B).

Discussion

In the present study, we demonstrated that the HAM-D scores and mean Nesfatin-1, corticosterone, and TSH concentrations were significantly higher in depressed patients with SCH than in healthy controls. Moreover, the plasma Nesfatin-1 concentrations were found to be positively correlated with corticosterone and TSH concentrations in depressed patients with SCH.

Accumulating evidence supports an association between depression and SCH.²⁸ SCH has been reported to markedly increase the risk of depression,¹³ and the prevalence of depressive symptoms in the SCH population has been reported to be 63.5%.²⁹ Consistent with this, in the present study, the prevalence of SCH in depressed patients was 6.7% (83/1,234), whereas the prevalence of SCH in healthy subjects was 0.0% (0/60) according to the results of the blood tests. These findings highlight the importance of a depressive evaluation in the management of patients with SCH and suggest that SCH might be considered as a possible risk factor for depression.

Nesfatin-1, a novel satiety molecule, is involved in various affective disorders, including anxiety disorder and depression.^{30,31} The results of clinical studies have demonstrated that the average Nesfatin-1 level is significantly higher in patients with major depressive disorder than in healthy controls.²³ Similarly, the results of animal studies have indicated that water-avoidance stress, which is a model of acute depression, could increase the plasma Nesfatin-1 levels.²² Consistent with these findings, our results showed

Table 2 Comparison of mean values of plasma Nesfatin-1, corticosterone, TSH, fT3, and fT4 in patient group and control group (mean ± SEM)

Variables	Control group	Patient group	Statistics (t)	P-value	Effect size (Cohen's d)	Power
Nesfatin-1 (ng/mL)	1.25±0.05	1.57±0.04	-3.70	<0.001**	0.85	0.99
Corticosterone (nmol/L)	302.45±14.17	397.44±10.99	-4.88	<0.001**	0.90	1.00
TSH (mIU/L)	2.35±0.18	5.25±0.08	-17.33	<0.001**	2.60	1.00
fT3 (pg/mL)	2.78±0.09	2.77±0.05	0.098	0.922		
fT4 (ng/dL)	1.37±0.07	1.24±0.04	1.391	0.168		

Note: **P<0.001 was considered statistically significant.

Abbreviations: SEM, standard error of the mean; TSH, thyroid-stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine.

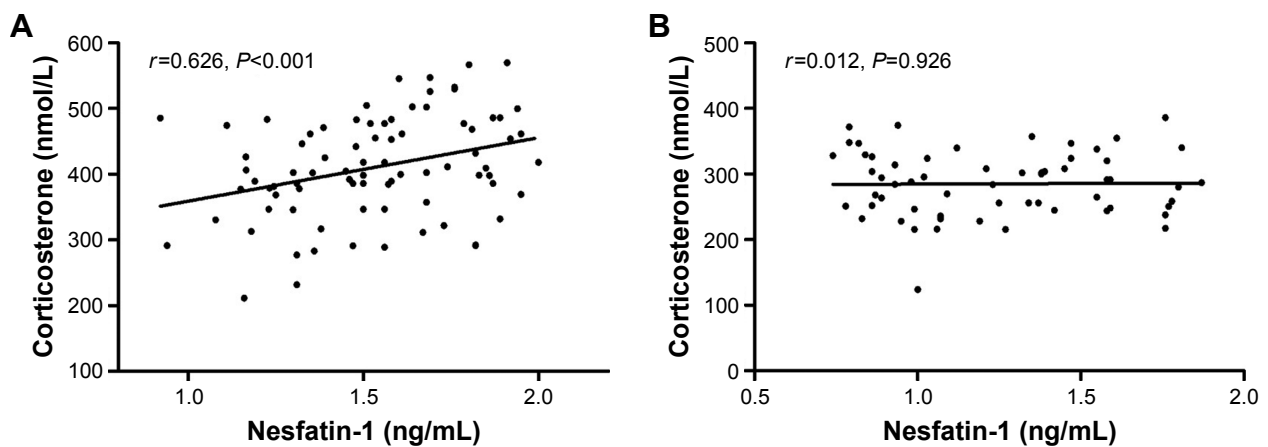


Figure 2 Correlation between plasma Nesfatin-1 and corticosterone concentrations in the patient group (A) and the control group (B).
Note: P -value <0.05 (two-tailed) was considered statistically significant.

that the plasma Nesfatin-1 levels were significantly higher in depressed patients with SCH than in healthy volunteers. Moreover, considering the fact that stress and subsequent HPA axis hyperactivity have been characteristically associated with the pathogenesis of depression,³² plasma corticosterone concentrations were measured in our study. The results showed that the corticosterone concentrations were significantly higher in depressed patients with SCH, providing more data that link the HPA axis to the onset of depression. Additionally, recent studies have indicated that both intraperitoneal and intracerebroventricular administration of Nesfatin-1 can activate the HPA axis and result in depression-like behaviors in rats,^{20,21} suggesting that Nesfatin-1 is involved in the regulation of depression, and the underlying mechanism may relate to the relationship between Nesfatin-1 and hyperactivity of the HPA axis.³³ Interestingly, the results of our study confirmed that plasma

Nesfatin-1 levels were positively correlated with corticosterone levels in depressed patients with SCH. Given that the central administration of Nesfatin-1 infusion has been shown to increase corticotropin-releasing hormone levels in the hypothalamus,³³ it is logical to hypothesize that the dysfunction of the HPA axis in depressed patients with SCH might be due to increased plasma Nesfatin-1 levels.

Recent studies corroborate the suggestion that Nesfatin-1 may have a close relationship with thyroid function. Correlations between Nesfatin-1 and TSH concentrations have been documented in several thyroid disorders.^{25,27} In our study, we found that there was a positive relation between Nesfatin-1 and TSH concentrations in depressed patients with SCH; however, the underlying mechanisms remain unclear. Recent studies have shown that Nesfatin-1 is colocalized with thyrotropin-releasing hormone (TRH) and affects the membrane potential of TRH neurons in the paraventricular

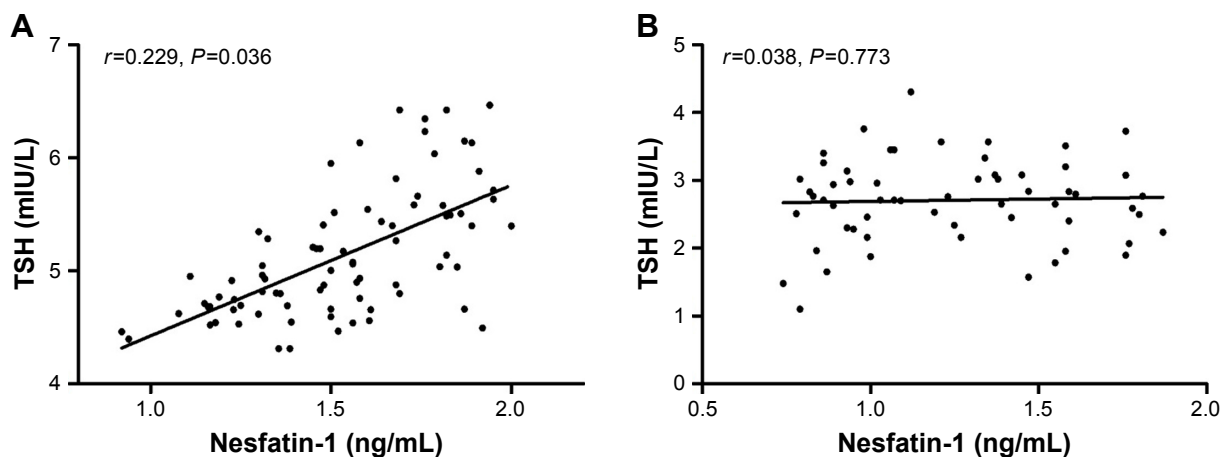


Figure 3 Correlation between plasma Nesfatin-1 and TSH concentrations in the patient group (A) and the control group (B).
Note: P -value <0.05 (two-tailed) was considered statistically significant.
Abbreviation: TSH, thyroid-stimulating hormone.

nucleus,^{34,35} which is known to be involved in the regulation of thyroid function. Moreover, a central Nesfatin-1 infusion has been shown to increase the TRH levels in the paraventricular nucleus of the hypothalamus.³³ In contrast, the central administration of anti-TRH has been shown to attenuate the Nesfatin-1-induced reduction in food intake, suggesting that TRH mediates the anorectic effect of Nesfatin-1 in the hypothalamus.³³ Together with the observation that the plasma level of Nesfatin-1, which crosses the blood–brain barrier without saturation,^{36,37} is correlated with the level of Nesfatin-1 in the cerebrospinal fluid,³⁸ we speculated that the increased plasma Nesfatin-1 levels might regulate thyroid function by adjusting TRH secretion in the hypothalamus, thereby resulting in SCH in depressed patients. Further research is required to explore this hypothesis.

Several limitations in this study should also be acknowledged. First, the study's findings should be interpreted with caution until they have been replicated in larger patient groups as the sample size was small. Second, due to the cross-sectional study design, no causality can be determined. Third, although all of the patients were drug free for at least 2 weeks, we were unable to take into account the probable long-term effects of previous drugs on their plasma Nesfatin-1 levels.

Conclusion

In conclusion, this study is the first to reveal that Nesfatin-1 levels are significantly higher in depressed patients with SCH than in healthy controls, which might be related to dysfunction of the HPA and HPT axes. However, the roles of neuropeptides such as Nesfatin-1 in depression and SCH need to be investigated in further studies.

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Disclosure

The authors report no conflicts of interest in this work.

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