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The autonomic nervous system in anorexia nervosa — an implication for the fat tissue

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Abstract: Eating disorders are a heterogeneous group of diseases affecting mainly young people in developed countries. Among them, anorexia nervosa (AN) is the one with the highest mortality, up to five times higher compared to healthy individuals. The etiology of this medical condition is complex and still uncertain. However, disturbances of the autonomic nervous system (ANS) and increased lipolysis resulting in a decrease of the adipose tissue volume are common findings among AN patients. Since ANS is directly connected to adipocyte tissue, thus significantly affecting the body's metabolic homeostasis, we suspect that this relationship may be a potential pathophysiological underpinning for the development of AN.
In this narrative review, we have analyzed scientific reports on ANS activity in AN considering different phases of the disease in humans as well as animal models. Due to the different effects of the disease itself on the ANS as well as specific variations within animal models, the common feature seems to be dysregulation of its function without the identification of one universal pattern. Nonetheless, higher norepinephrine concentrations have been reported in adipocyte tissue, suggesting local dominance of the sympathetic nervous system. Further studies should explore in depth the modulation of sympathetic in adipose tissue factor and help answer key questions that arise during this brief narrative review.

Keywords: anorexia nervosa, eating disorders, autonomic nervous system, heart rate variability, adipose tissue.

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Introduction

Among the global medical problems affecting modern societies, one of the most significant issues is the increasing prevalence of obesity and its associated health complications, for the treatment of which the world's health systems are dedicating

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enormous resources [1]. On the other hand, numerous young people are affected by eating disorders. The DSM-V specifies several disease entities in this group, such as anorexia nervosa, bulimia nervosa, binge-eating disorder, and avoidant/restrictive food intake disorder [2]. In this review, we aim to delve deeper into the etiopathogenesis of anorexia nervosa.

Anorexia nervosa (AN) is clinically characterized by a restriction of energy intake leading to significantly low weight, fear of weight gain, and disturbances in self-evaluation. The occurrence of anorexia nervosa varies with age and sex and predominantly affects young women. Its lifetime prevalence ranges from 0.8–6.3% for women and 0.1–0.3% for men [3]. The treatment of AN remains a therapeutic challenge, requiring a multidisciplinary approach that includes adequate nutrition, psychotherapy, and the treatment of comorbidities [4]. Even with proper treatment, AN increases mortality in comparison to age- and sex-matched individuals, with rates up to five times higher than in the general population, especially in the group receiving inpatient treatment with lower adherence rates [5].

The etiology of this medical condition is complex and still uncertain. Some authors have suggested early trauma and psychological maladjustment as the major predictive factors for AN [6]. Patients with AN often have co-occurring psychiatric disorders, mainly involving depressive disorders, anxiety disorders, or those associated with obsessive-compulsive behavior [7]. In addition to numerous psychological factors, genetic predisposition, and neurohormonal alterations appear to be closely linked to the development of the disease. One example is reduced levels of norepinephrine and dopamine in the central nervous system, suggesting abnormalities in the reward system [8]. Moreover, endocrine dysfunctions, including the hypothalamic-pituitary-adrenal, hypothalamic-pituitary-thyroid, and hypothalamic-pituitary-gonadal axes, as well as dysregulation of the autonomic nervous system (ANS), are commonly observed as the disease progresses. The ANS function is multifactorial, affecting the central nervous system (CNS), the aforementioned hormonal axes, and metabolic homeostasis through its effect on adipocyte tissue. We suspect that ANS could be the link connecting neurological and metabolic factors involved in AN development, which still requires further investigation. The pattern of disturbances in the ANS function varies at different stages of the disease, including acute, chronic, and recovery phases.

Adipose tissue is a heterogeneous structure in mammals' bodies. White adipose tissue (WAT) primarily serves as energy storage, while brown adipose tissue (BAT) is primarily responsible for heat production through non-shivering thermogenesis. Yet, these cells exhibit plasticity and can, under certain circumstances, transform from one type into the other in processes called browning and whitening.

The ANS directly regulates the different types of adipose tissue (white and brown) through nine different adrenoreceptor subtypes, modulating the synthesis and storage

of triglycerides (lipogenesis), the breakdown of stored triglycerides (lipolysis), thermogenesis (heat production), glucose metabolism, and the secretion of adipocyte-derived hormones that control whole-body energy homeostasis [9]. Sympathetic activation in adipose tissue is responsible for enhancing basic metabolic processes such as lipolysis and glycogenolysis. What is more, the activation of beta receptors promotes heat production by brown adipose tissue and triggers browning of white adipose tissue. In AN, deregulated ANS activity can affect adipose tissue function, promoting further lipolysis and facilitating weight loss by increasing WAT browning [10].

This narrative review aims to summarize current research on the role of ANS disturbances in the pathogenesis of AN, taking into account the autonomic innervation of adipose tissue in both human and animal models of this eating disorder.

The Adipose Tissue

White adipose tissue

White adipose tissue, apart from stromal vascular fraction (non-adipocyte cell types such as macrophages, fibroblasts, or endothelial cells), consists of spherical cells that contain a single lipid droplet located centrally and a relatively low quantity of peripherally distributed mitochondria. Such construction highlights the main function of WAT, which is energy storage. The central lipid droplet is a composition of triglycerides and glycerol [11]. These cells derive from progenitor cells without myogenic factor (Myf5) and they develop through processes of hypertrophy and hyperplasia, which is particularly evident during a high-fat diet [12]. Another property of WAT is the ability to produce adipokines (such as leptin, adiponectin, or resistin), in response to physiological stimuli, with a regulatory role in energy intake and storage [13]. In humans, the main distribution sites of WAT are subcutaneous, visceral, and bone marrow depots, while in rats, epididymal (eWAT), subcutaneous (scWAT), inguinal, and peritoneal.

Brown adipose tissue

Initially, the existence of BAT as a thermogenic structure was confirmed in small mammals and human newborns. Nowadays, it has also been identified in adults although in smaller quantities, located mainly in the cervical, supraclavicular, axillary, paraspinal, mediastinal, and abdominal areas, of which the supraclavicular region is the most common location of active BAT visualized using 18F-FDG-PET/CT — the gold standard for BAT detection [14–16]. In rodents, however, the structures containing the largest amounts of brown adipocyte tissue are the interscapular (iBAT) and perirenal areas (pBAT).

Unlike WAT, the origin of BAT cells are Myf5 positive progenitor cells similar to muscle cells [17]. BAT is a structure consisting of cells that, like WAT cells, can store energy, but in numerous multilocular fat droplets and with a number of mitochondria that is much higher than in WAT. The latter is related to its unique characteristics, the expression of a specific protein, the uncoupling protein-1 (UCP-1), and the process of non-shivering thermogenesis. UCP-1 allows the proton gradient across the inner mitochondrial membrane to dissipate during standard mitochondrial respiration, resulting in the inefficiency of the ATP formation in oxidative phosphorylation. As a result of this process, the heat is generated [11].

Brite adipose tissue

The brite or beige adipose tissue is sometimes called "brown-in-white" adipose tissue. This simple descriptive name is very accurate if we take a closer look at the issue of its development and architecture. The brite cells' origin and localization are similar to the WAT cells, derived from Myf5 positive progenitor cells and typically located in the subcutaneous tissue. This has also its basis in differentiation from WAT cells under the influence of certain stimuli, described below. However, the morphology (mitochondrial density, UCP-1 presence, multilocular fat droplets) and function of beige tissue (lipolysis and thermogenesis) are closer to BAT cells [18–19].

Plasticity of the adipose tissue

Under certain circumstances, WAT can mimic the function of BAT. The most common and best-described situation is exposure to low temperatures, which requires the body to adapt through increased thermogenic activity. During cold exposure, scientists observed increased BAT activity — increased UCP1 concentration, and thus increased heat production provided by the concomitant transformation of WAT into BAT. The entire process is modulated by SNS activity and is called "browning". In this way, a portion of WAT cells, derived from Myf5-negative progenitor cells, exhibit properties of BAT cells (UCP-1 expression and thermogenesis), which are called brown-white or white-beige cells. This process was described both in humans and in animal models [20].

Cold exposure is not the only trigger of WAT "browning". The same transformation has been provoked by specific nutrition, such as capsaicin or menthol, substances that mimic cold exposure and SNS activation. Many dietary supplements enhance this process, like seathorn buck or ashwagandha, but this is beyond the scope of this review. Other conditions that promote browning are exercise and fasting [21]. BAT activation and WAT browning are still one of the most promising ways to combat obesity, so many pharmacological agents are known to trigger this process: mirabegol, FGF 21, BMP 7, irisin, thyroid hormones or direct SNS agonists [22].

Exploring the Relationship Between the Autonomic Nervous System and Adipose Tissue

As we have already mentioned, ANS influences the activity of the adipocyte tissue through various receptors. The presence and function of the adrenoreceptors vary depending on the type of adipose tissue and is different in humans and rodents [9].

In rodent WAT, both visceral and subcutaneous, there is an expression of β1, β2, and β3 receptors, but no evidence of any α-receptors [23]. Activation of these receptors is responsible for controlling the metabolic function with the turnover of fatty acids and glycerol through the processes of lipolysis and lipogenesis. Although other hormonal stimuli may also play a role in lipolysis, sympathetic innervation is the central control point for lipolytic activity in WAT [24, 25]. The effects of hormones such as leptin also depend on the activity of the sympathetic nervous system. Noteworthy are the differences between receptor subtypes within which β3 receptor is mainly responsible for modulating metabolic functions, while β1 receptor is responsible for increased preadipocyte proliferation. Human WAT does not express high levels of β3 receptor activity, however, the lipolytic function is still activated by other β adrenoreceptors. Moreover, while in rodents the α-receptors function was not significant, in humans they act in an anti-lipolytic manner [26].

The rodent BAT shows a greater diversity of adrenoreceptors than WAT. In addition to β receptors, α-receptors are present as well. The uncoupling function and the lipolysis of the BAT cells, as well as glucose re-uptake, are predominantly mediated by β receptors, mainly β3 [9]. The latter function is what we call the activity of BAT commonly assessed in imaging tests. Among the key functions mediated by adrenoreceptors, importantly, is also adipocyte differentiation. No significant differences are observed in human BAT, so lipolysis, uncoupling, and higher glucose uptake are mediated by the same receptors in both humans and rodents.

The beige adipose tissue also expresses a unique constellation of adrenoreceptors [9]. However, the effects are similar to those observed in BAT — activation of the β3 receptors causes uncoupling with heat production [19].

Finally, the effect and concentration of catecholamines representing the activation of the sympathetic component of the ANS may differ between specific adipose tissue compartments nevertheless activity through adrenoreceptors may have an impact on all adipose tissue functions.

Techniques for Assessing The Autonomic Nervous System

A number of different research methods are available for assessing the autonomic nervous system in humans as well as in animal models. The most popular of these are based on non-invasive measurements of cardiovascular parameters. From resting

heart rate (HR) or blood pressure (BP) values to their dynamic changes during specialized tests included in the Ewing battery (e.g., the Valsalva maneuver, respiratory sinus arrhythmia, or the tilt/stand-up test), these parameters can show disturbances or predominance of specific branches of the autonomic nervous system. Other options for assessing ANS activity include baroreceptor sensitivity and function. However, in both clinical and scientific practice, HR or BP variability is more commonly used [27].

Methods for more direct assessment of sympathetic activity include the concentration of catecholamines in body fluids or directly in adipose tissue [28]. The range of biochemical tests also includes measurement of alpha-amylase (α-1,4-α-D-glucan-4-glucanohydrolase) levels in saliva, an enzyme that has been reported as a useful marker of sympathetic activation [29].

Understanding Autonomic Nervous System Function in Anorexia Nervosa

Heart rate

Analysis of heart rate is inevitably linked to a baseline assessment of ANS activity. Simple HR monitoring can estimate the predominance of the ANS branch [30]. The most commonly observed deviation in AN studies, the authors noted, was a decrease in baseline HR compared to healthy control subjects [31–33]. However, Platisa *et al.* showed in a small number of patients that this is observed only in the acute course of the disease, and in chronic AN the heart rate is higher than in healthy controls [34]. A decrease in basal HR may suggest parasympathetic predominance, but not every patient with AN has incompetent chronotropism [35].

A decrease in resting HR is among the very early manifestations of AN [36, 37]. Moreover, during the refeeding process of AN patients, along with weight gain, HR normalization is not only the first symptom but also a predictor of successful therapy [38, 39]. Normalization of chronotropism and higher baseline HR values reduce the risk of cardiovascular events [35].

Heart rate variability

Heart rate variability is the most common way to non-invasively assess ANS. Typically, frequency domain analysis is used for short measurement periods. In this way, it is possible to estimate the overall activation of the ANS using the total power of the spectrum (TP). Parasympathetic activation is represented by the power of the high-frequency oscillations (HF), and the predominance of a specific ANS component can be distinguished using the ratio of the power in the low-frequency range (LF) to HF.

Generally, if the LF/HF >1 the sympathetic activation is predominant. The exact relationship of LF and very low-frequency (VLF) bands with ANS activity is not clearly defined [40]. The LF band is often associated with both sympathetic and parasympathetic activity, making its interpretation more complicated.

In a short recording of frequency domain HRV analysis, most authors found that patients with AN exhibited an overall increase in TP during rest compared to healthy controls [36, 41]. However, Lachish *et al.* came up with opposite results, showing higher TP in the control group [42]. Almost all authors recorded increased HF in the AN group and a low LF/HF ratio, suggesting a predominance of the parasympathetic nervous system [36, 43, 44]. Galetta *et al.* confirmed these differences when comparing AN patients to healthy control groups with similar body mass index (BMI) [45]. However, isolated LF measurement varied significantly between studies.

HRV measurements during mental stressors were also performed. The responses to stressful tasks (Adult Attachment Projective) in the AN group differed from those in the healthy control group as reported by Lonigro *et al.*, but with no clear pattern. Usually, HF was higher in the AN group in response to consecutive images. However, the tendency in both groups was to decrease from the basal level of HF, which was statistically higher in the AN group [31]. Het *et al.* conducted a similar mental stress test (Trier Social Stress Test) with corresponding results, although their test group included patients with other eating disorders [46].

The time domain HRV is the preferred technique in longer recording periods, preferably in 24-hour recordings. In such readings, the standard deviation of all normal-to-normal intervals (SDNN), corresponding to TP, and the square root of the mean of the sum of the squares of differences between adjacent normal-to-normal intervals (RMSDNN), representing HF, are analyzed [40]. The results obtained in the 24-hour Holter examination of AN patients are consistent with the frequency domain analysis. The majority of authors noticed increased SDNN and RMSDNN, suggesting increased HRV activity with parasympathetic predominance [33, 45, 47]. However, Melanson *et al.* reported the opposite result, although their study was performed on a very small group (6 AN patients, 10 healthy controls) [48].

HRV changes showed no significant differences after treatment in groups of AN patients [37, 39, 42]. However, none of these scientific reports demonstrated the typical differences mentioned earlier, such as increased TP, lowered LF, or low LF/HF ratio. Yoshida *et al.* observed that in weight-restored patients, there was a tendency for LF to rise and HF to decline during daytime, while nighttime measurements showed no significant alterations [49].

Blood pressure variability and baroreceptors

Blood pressure variability (BPV) refers to the constant changes in BP over time, influenced by various internal and environmental mechanisms that work to maintain an individual's baseline blood pressure. Short-term fluctuations in blood pressure, influenced by the ANS, are known as very short variability and are typically measured over brief periods. An increase in blood pressure variability is often observed in response to heightened central sympathetic drive [50]. Baroreflex sensitivity and orthostatic tests are additional methods used to assess the effectiveness of the sympathetic nervous system.

BPV is not commonly used to assess ANS function in cases of AN. In such instances, studies have reported similar results, including a decrease in low-frequency (LF) components in blood pressure variability. These effects have been observed at rest [37, 41, 51] and during orthostatic tests [52] and they persist even during the weight restoration phase [37].

Despite lower heart rate (HR) and indications of parasympathetic drive, previous publications often noted increased baroreceptor sensitivity [41, 51]. However, in the latest publication by Jenkins *et al.*, there were no significant differences in baroreceptor function compared to healthy controls. The only notable difference was a lower tilt mean slope between the weight-restored AN group and the healthy control group [53].

Orthostatic tests uncovered a diminished sympathetic reaction, which would typically be accompanied by an increase in HR in the group with AN [48, 54]. This blunted sympathetic response was evident in the lower LF while in the supine position compared to the healthy control group [54]. In passive examinations on a tilt-up table, a similar lower increase in HR was observed in the AN group [37]. This effect was easily reversed during the weight regain period [55].

Biochemical analysis

Salivary alpha-amylase [29] and plasma catecholamines [28] levels are used as non-invasive biomarkers of the sympathetic nervous system. In a study by, no difference in salivary alpha-amylase levels were found in the group of acute phase AN patients [56]. On the other hand, Monteleone *et al.* reported that AN patients exhibited reduced levels of the salivary alpha-amylase, a significant decrease in its overall diurnal secretion, and a dysregulated secretory pattern [57]. A similar tendency was shown in response to stress, with lower response in salivary alpha-amylase in AN. The difference was abolished during the refeeding phase [46]. Measurements of catecholamines, such as adrenaline, norepinephrine, and a metabolite of noradrenaline — 3,4-dihydroxyphenylglycol, were performed in female AN patients both at rest and during exercise. At rest, Jenkins *et al.* showed no difference in catecholamines in the AN group during acute phase and

weight restoration in comparison with healthy control participants [37]. Bartak *et al.* also reported that basal and exercise-stimulated plasma norepinephrine levels were indifferent in AN patients and healthy controls [58]. Yet, during exercise, plasma norepinephrine concentration were significantly lower in female AN patients [60].

In adipose tissues, norepinephrine (NE) is the main lipolytic agent, whereas epinephrine has only a slight effect at physiologic concentrations [61]. Despite the discrepancies in the levels of catecholamines in the plasma, their levels in human subcutaneous adipose tissue were reported to be consistent. Basal adipocyte tissue NE concentrations were increased in AN patients in comparison with the controls. The effect was more pronounced after local administration of NE reuptake inhibitor, maprotiline, or during exercise. Increased levels of NE were noted in the subcutaneous adipocyte tissue, i.e. WAT [58, 59].

Autonomic Nervous System in Animal Models of Anorexia Nervosa

An activity-based rodent model of anorexia (ABA), also known as exercise-induced anorexia or food restriction-induced hyperactivity, is the most commonly used animal model of AN, and variations in the experimental protocol enable to mimic different phases of AN [61]. The model reproduces the core features of AN, namely food restriction, hyperactivity, and social distress (due to the isolation of rodents in individual cages) [62]. However, the HRV analysis did not show the typical changes observed in clinical studies, including bradycardia, increased TP of HRV, and parasympathetic domination. On the contrary, the SDNN was lower than in the control group, suggesting a sympathetic activation in ABA rats [62].

What is more, fasting in rodents was associated with an increased sympathetic activation in the WAT but not BAT depots areas [63, 64]. Under such circumstances, an increased browning of WAT and activation of BAT thermogenesis would be expected [65, 66]. Yet, Fraga *et al.* confirmed browning of the WAT but did not confirmed higher activation of the BAT in ABA rats. What is more, an increased temperature should reverse hyperactivity, weight loss, and hypoleptinemia [67]. Interestingly, Okita *et al.* reported that long-term caloric restriction in rats activated mitochondrial energy metabolism and fatty acid biosynthesis in WAT, with no effect on BAT, however, WAT and BAT cooperate to use energy effectively [68]. Corrales *et al.* reported that prolonged caloric restriction promoted browning of subcutaneous WAT and prevented the whitening of BAT due to aging [69]. Gutierez *et al.* hypothesized that impaired thermoregulation should be a major cause of hyperactivity, suggesting activation of compensatory mechanisms of thermal homeostasis such as BAT activation [70, 71].

Results of the assessment of ANS activity in animal models in comparison to AN patients are presented in Table 1.

Table 1. The comparison of the activity of the autonomic nervous system in animal models of anorexia nervosa and human disease. The table takes into account different phases of the disease. ? — no data, NS — non-significant, the arrows are compared to the control.

	Autonomic Nervous System in different phases of anorexia nervosa			
	Disease/Model	Acute Phase	Chronic Phase	Refeeding
Heart rate	Human	↓	↓/↑	NS
	Animal model	NS	?	?
HRV frequency domain	Human	Parasympathetic drive		NS
	Animal model	NS	?	?
HRV time domain	Human	Parasympathetic drive	NS	NS
	Animal model	Sympathetic drive	?	?
Plasma NE	Human	↓ /NS	?	NS
	Animal model	NS	?	?
Adipose tissue NE	Human	↑	?	?
	Animal model	↑ in white adipose tissue (starvation)	?	?

Discussion

AN patients clearly present with disturbances in the function of the autonomic nervous system. The acute phase of this eating disorder is characterized by bradycardia, an overall increase in the TP of HRV, with the predominant activation of the parasympathetic branch of ANS and decreased sympathetic tone during exercise or orthostatic tests, as it was discussed above**.** The most frequent cause of death among severe AN patients is cardiovascular [72], and it could be partly explained by reported resting bradycardia and chronotropic incompetence [35]. Still, the available clinical data remains inconclusive. On the other hand, an activity-based rodent model of AN, which mimics the acute phase of the disorder, was associated with a shift towards sympathetic dominance of the ANS [62]. Surprisingly, the autonomic nervous system activity during the re-feeding period of AN has been a neglected area of research. Recently, Jenkins et al. synthesized the evidence of the basal ANS function in individuals with a current diagnosis of AN and those with a previous diagnosis who had achieved weight restoration, as compared to controls [73]. Unfortunately, the statistical analysis could not be performed due to the significant heterogeneity of the available clinical data.

The ANS homeostasis is inevitably influenced by numerous factors, including pharmacotherapy. AN mainly affects young patients but the diagnosis of other psy-

chiatric conditions, such as anxiety or depression, may co-occur, demanding adequate pharmacological treatment [4]. Accordingly, either selective serotonin reuptake inhibitors (SSRI) or serotonin–norepinephrine reuptake inhibitors (SNRI) are frequently used for the treatment, however previously, tricyclic antidepressants, with obvious antimuscarinic effects, were commonly prescribed [74]. The effect of SNRI and SSRI on the ANS activity remains debatable and inconclusive [74–76]. Recently, olanzapine, a second-generation antipsychotic agent, was also included into the treatment of AN [4]. Olanzapine is a potent antagonist of the muscarinic M3 receptor and thus, influences HRV records (with lower LF, HF, and TP) [75]. Yet, not all of the abovementioned studies with the assessment of the ANS activity among AN patients thoroughly discussed the influence of the prescribed pharmacotherapy.

An increased sympathetic drive in the adipose tissue may depend on many factors: hyperactivity, starvation, or/and direct dysregulation of the ANS. Smith *et al.* stated that hypothermia and hyperactivity (HyAc) are central to AN pathophysiology. The lowered basal metabolic rate caused by food restriction could lower the core body temperature and reduce peripheral circulation. As a result, transient receptor potential melastatin 8 (TRPM8) channels could be activated, leading to sympathetic activation and hyperactivity [77]. In animal models, Gutierrez *et al.* observed that the hyperactivity of rodents in animal AN models may be an adaptive behavioral response to compensate for hypothermia [70]. While hypothermia is a factor that induces WAT browning and enhances BAT activity in animal models [20, 67], evidence from clinical studies of AN remains still limited and incomplete [78].

The crosstalk between the ANS and adipose tissue is complex both in health and AN. Hyperactivity and starvation are known to be associated with significantly lower levels of leptin, and the effect is enhanced in the presence of both factors [79]. It was demonstrated in animal models that levels of the circulating leptin should correlate with hyperactivity, and an increase in the circulating leptin level decreased hyperactivity in rodents [71, 80]. The use of nonselective β blocker (propranolol) in fasting rodents increased leptin levels [79, 81]. Adipokine dysregulation, with a decrease in leptin levels, is also evident in AN patients [82]. Thus, leptin levels should be also taken into consideration in the context of the ANS activity assessment among AN patients. The crosstalk between autonomic activity, leptin, and adipose tissue, which is beyond the scope of this review, was already summarized [79, 83–85].

The etiopathogenesis of AN is complex and heterogeneous, and the role of the autonomic innervation of the adipose tissue, especially after refeeding, is poorly understood. Thus, there is a need to address refeeding period and chronic phase of AN in animal models to improve understanding of this eating disorder and the quality of long-term patient care.

Key questions to consider in future research

(1) Are beta-blockers safe in patients diagnosed with anorexia nervosa in the acute phase and during the weight restoration?
(2) Could a reduced sympathetic nervous activity in adipose tissue inhibit weight loss in patients with anorexia nervosa by limiting the browning of WAT?
(3) How does the autonomic nervous system activity influence the course of the chronic and weight restoration phases of AN in animal models?

Conflict of interest

None declared.

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