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SYSTEMATIC REVIEW

Physiology and Biochemistry

The interplay between the adrenergic system and obesity: a systematic review

Beatriz Araújo [1,2], Fernanda Leite [1,3,4] and Laura Ribeiro [1,3]✉

BACKGROUND: Obesity is an increasingly alarming public health problem. Emerging evidence suggests that a dysregulation of sympathetic nervous system activity, particularly related to the adrenergic system, can play a role in the pathophysiology of obesity.
OBJECTIVE: This systematic review explores the complex interplay between the adrenergic system and obesity.
METHODS: PubMed, Web of Science and Scopus were searched until June 2023 using the following Boolean expression: (obese OR obesity) AND (adrenaline OR noradrenaline OR epinephrine OR norepinephrine). No time frame or other filters were set. Observational or interventional studies reporting plasma or urinary adrenaline and/or noradrenaline concentrations in adults with obesity were included.
RESULTS: Among the 8680 studies, 35 met the eligibility criteria, comprising a total of 2588 subjects from which 1617 with general obesity or abdominal obesity. Despite some heterogeneity across studies, the evidence suggests a hyperadrenergic state in subjects with obesity, characterized by higher noradrenaline and lower adrenaline plasmatic concentrations, coupled with a blunted response to sympathetic stimuli, compared with their lean counterparts. Additionally, the adrenergic overdrive seems to be more pronounced when subjects with obesity are also diagnosed with obesity-associated comorbidities, except for hypertension. Abdominal fat weight loss interventions have a positive effect not only on reducing baseline noradrenaline levels, but also on restoring the impaired sympathetic response observed in subjects with obesity.
CONCLUSION: Overall, this systematic review highlights the complex interplay between catecholamines and obesity. It synthesizes current evidence and identifies key research gaps, thus providing valuable insights to guide future biomedical research and clinical practice.

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INTRODUCTION

Obesity, defined by the World Health Organization (WHO) as an "abnormal or excessive fat accumulation that may impair health", characterized by a body mass index (BMI) greater than 30 kg/m^2 [1], is an increasingly alarming global public health challenge that has reached epidemic proportions [2, 3]. It is now recognized as one of the leading causes of poor health worldwide [4]. Ranked as the fourth highest cause of death, following high blood pressure, dietary and tobacco use [5], overweight and obesity affect nearly one in three children's and almost 60% of adults, resulting in more than 1.2 million deaths across the WHO European Region every year [6].

Globally, obesity, particularly abdominal obesity, and its determinants, are significant risk factors for the development of noncommunicable diseases associated with increased mortality, such as cardiovascular diseases [7], type 2 diabetes [8], certain types of cancers [9] and infertility [10–12]. Additionally, excessive fat accumulation can lead to various health problems, including psychosocial problems [13], obstructive sleep apnea (OSA) [14], and osteoarthritis [15]. Identifying the underlying factors contributing to obesity development and progression is a critical step toward its early detection and diagnosis [16]. While the traditional view primarily attributes obesity to excessive energy storage rather than energy expenditure [17, 18], obesity is currently recognized as a multifactorial disease [19]. Although the observed associations with health outcomes may be partly due to the effects of enlarged fat cells and to the increased secretion of proinflammatory cytokines [20], there is a growing consensus that alterations in the sympathetic nervous system (SNS) activity can play a role in the pathophysiology of obesity [21–24]. Furthermore, a complex triangular relationship seems to exist between adipocytes, the SNS and immune cells [25, 26].

The SNS plays an essential role in the regulation of metabolic and cardiovascular homeostasis [22].

[1]Department of Public Health and Forensic Sciences, and Medical Education, Medical Education Unit, Faculty of Medicine of the University of Porto, Porto, Portugal. [2]Department of Biomedicine, Unit of Pharmacology and Therapeutics, Faculty of Medicine of the University of Porto, Porto, Portugal. [3]I3S-Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal. [4]Department of Clinical Haematology, Hospital de Santo António (HSA), Centro Hospitalar Universitário do Porto, Porto, Portugal.
✉email: lribeiro@med.up.pt

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Central to this regulation are the catecholamines (CAs)—adrenaline (AD), mainly produced and secreted by the adrenal medulla, and noradrenaline (NA), its biosynthetic precursor and the principal neurotransmitter of the SNS [27–30]. Their effects are mediated through the activation of adrenergic receptors (adrenoceptors), classified into α (α_1, α_2) and β (β_1, β_2, β_3) subtypes [31]. AD activates both α- and β-adrenoceptors, while NA primarily stimulates α-adrenoceptors and, to a smaller extent, β_1-adrenoceptors [28]. These receptors are differentially distributed across tissues with β_1-adrenoceptors primarily located in the heart, β_2 in bronchial and vascular smooth muscle, and β_3 predominantly in adipose tissue, where they regulate lipolysis [30, 32]. In humans, CAs regulate lipid metabolism by stimulating or inhibiting lipolysis, respectively, through β- and α_2-adrenoceptors [33], Additionally, CAs modulate lipogenesis, thermogenesis and the secretion of adipocyte-derived hormones that control whole-body energy homeostasis [34] thereby positioning them as key players in obesity pathophysiology.

This systematic review aims to explore the complex interplay between the adrenergic system and obesity. We specifically aim to (1) determine whether subjects with obesity exhibit an adrenergic overdrive, assessed through plasmatic and/or urinary AD and NA concentrations; (2) explore this phenomenon in the presence or absence of obesity-associated comorbidities; and (3) investigate whether stress, exercise, glucose intake and weight loss (induced by diet, exercise or surgery) modulate the adrenergic system.

METHODOLOGY

Study protocol

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [35] and is registered in the Open Science Framework (OSF): https://doi.org/10.17605/OSF.IO/6RFU2. The PRISMA statement checklist is provided as Supplementary File 1.

Information sources and search strategy

The search was performed on the 22nd of June 2023 in PubMed, Web of Science and Scopus using the following Boolean expression: (obese OR obesity) AND (adrenaline OR noradrenaline OR epinephrine OR norepinephrine). No time frame or other filters were set.

Eligibility criteria

Studies were eligible according to the following inclusion and exclusion criteria following the PICOS tool [36]:

- P (population)—Subjects with general obesity (classified as BMI ≥ 30.0 kg/m^2 [37, 38]) or abdominal obesity [classified as WC ≥ 80 cm in women and ≥94 cm in men [38–41] or WC ≥ 88 cm in women and ≥102 cm in men [42]].
- I (Interventions/exposure)—with or without intervention (e.g., weight loss programs, or other interventions except pharmacological-based interventions).
- C (Comparator)—with the comparator/control group regarding anthropometric characteristics or other variables such as obesity-associated comorbidities, sex, or others.
- (outcomes)—adrenergic response markers (plasmatic or urinary AD and/or NA concentration).
- S (Study design)—quantitative studies.

Duplicate articles, reviews, meta-analyses, systematic reviews, letters, abstracts-only, single-case studies, books, conference papers and articles lacking access to the full text despite attempts to contact the authors were not included. Studies with no clear definition of the obesity cutoff criteria and those evaluating pharmacological-based interventions were also excluded. Articles were not excluded based on language or country where the intervention took place to avoid bias.

Selection process and data collection process

After identifying records in databases and excluding duplicates, the screening process was conducted by two independent reviewers. First, studies were screened based on the title, and second, they were screened based on the abstract. During the eligibility phase, both reviewers screened the full-text reports to determine whether they met the inclusion criteria. Disagreements were resolved through discussion and consensus among all three authors. The reviewers were not blinded to the journal title or study authors. Finally, the eligible studies were summarized in two tables, including information on authors, publication year, first author affiliation country, study design, main sample characteristics, obesity cutoff criteria, intervention (if applicable), main outcomes, comparator and main results. Tables 1 and 2 summarize the characteristics of the observational and experimental/interventional studies, respectively. The articles are summarized in more detail in Supplementary File 2.

Quality assessment/study risk of bias assessment

The included studies were subjected to a quality assessment by two independent reviewers using The Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields [43]. Journal impact factor and quartile were also included—Supplementary File 2.

Data management

Studies were categorized as observational or interventional/experimental, and interventions were briefly described. The baseline characteristics of the study subjects were described, and comparisons between study groups were performed as follows:

(a) *Within-subject comparisons* focused on differences related to:
  (i) Timing: comparing data before and after the intervention
  (ii) Type of intervention: when different interventions were compared

(b) *Between-subject comparisons* focused on differences related to:
  (i) BMI categories
  (ii) WC categories
  (iii) Obesity-associated comorbidities
  (iv) Other variables (sex, ethnicity, chronotype, genotype, etc.)

The outcomes were analyzed with a focus on adrenergic markers, specifically urinary or plasmatic AD or NA concentrations. When justified, other markers related to the sympathetic nervous activity, including muscle sympathetic nerve activity (MSNA), skin sympathetic nerve activity (SSNA), NA clearance and NA spillover, were included in the analysis.

The results were described and simplified as higher or increased, lower or decreased, or similar based on statistical significance as follows: non-significant; $p < 0.05$; $p < 0.01$ and $p < 0.001$.

RESULTS

Search, study selection and quality assessment

Figure 1 summarizes the selection process. The 35 included articles were published between 1987 and 2022. The quality ratings of the studies ranged from 0.63 to 0.95, with a mean score of 0.88. The lower scores were due to a poor description of the subject selection method, sampling appropriateness and lack of confounding assessment (Supplementary File 3).

Tables 1. Characteristics of the observational studies evaluating the adrenergic system in subjects with obesity.

Ref.	Country	Study design	Sample size; health characteristics; sex (% F); BMI (kg/m^2); WC (cm)	Obesity criteria	Main outcomes	Comparator	Results
[32]	Spain	Cross-sectional	$n = 742$ with chronic HF with Ob ($n = 247$) 70 ± 10 yr; 54% F 35 ± 3 kg/m^2 without Ob ($n = 495$) 73 ± 11 yr; 38% F 25 ± 3 kg/m^2	BMI ≥ 30 kg/m^2	Plasma NA (pg/ml)	Between groups (a) Regarding BMI (with vs. without Ob)	NA < Ob vs. non-Ob with chronic HF (**lower, $p < 0.001$**).
[56]	Brazil	Cross-sectional	$n = 53$ with Ob with OSA ($n = 33$) 39.60 ± 1.48 yr; 39% F 34.39 ± 0.51 kg/m^2; 107.08 ± 1.42 cm without OSA ($n = 20$) 32.50 ± 2.09 yr; 75% F 34.51 ± 0.66 kg/m^2; 104.99 ± 2.02 cm	BMI > 30 kg/m^2 and <40 kg/m^2	Plasma AD (pg/mL) Plasma NA (pg/mL)	Between groups (a) regarding Ob associated comorbidities (with vs. without OSA)	AD = in Ob with OSA vs. Ob without OSA (**NS; $p = 0.18$**). NA > in Ob with OSA vs. Ob without OSA (**higher, $p = 0.02$**). After adjustment for age, sex, BMI, WC, alcohol intake, physical activity, and urinary sodium excretion, this difference was no longer significant.
[42]	Iraq	Cross-sectional	$n = 64$ with PCOS 24.53 ± 4.07 yr; 100% F with Ob ($n = 32$) without Ob ($n = 32$) $n = 40$ without PCOS 25.53 ± 4.78 yr; 100% F With Ob ($n = 20$) Without Ob ($n = 20$)	BMI ≥ 30 kg/m^2	Plasma AD (pg/ml)	Between groups (a) regarding Ob associated comorbidities (with PCOS vs. without PCOS) (b) regarding position (standing vs. lying)	AD > in both Ob and PCOS vs. in Ob without PCOS (**higher $p < 0.001$**). AD > at lying but not at standing position in subjects with PCOS without Ob vs. subjects without both Ob and PCOS (**higher, $p < 0.001$**).
[58]	Italy	Cross-sectional	$n = 66$ L without OSA ($n = 20$) 45.2 ± 1.5 yr; 10% F 23.4 ± 0.5 kg/m^2 L with OSA ($n = 14$); 44.5 ± 1.9 yr; 14% F 23.8 ± 0.7 kg/m^2 with Ob and without OSA ($n = 13$) 47.7 ± 2.5 yr; 23% F 3.2 ± 0.7 kg/m^2 With both Ob and OSA ($n = 19$) 48.1 ± 1.9 yr; 10% F 33.0 ± 0.6 kg/m^2	BMI > 30 kg/m^2, peripheral Ob: WHR < 0.85 for women and <0.95 for men visceral Ob: WHR > 0.85 for women and >0.95 for men	Plasma NA (pg/mL) Other outcomes: MSNA (bursts/min) SSNA (bursts/min)	Between groups: (a) Regarding BMI (Ob vs. lean) (b) Regarding Ob associated comorbidities (with OSA vs. without OSA)	NA > in Ob **vs.** lean both with and without OSA (**higher, $p < 0.01$**). NA > in both Ob and OSA vs. Ob without OSA (**higher, $p < 0.05$**). Other results: MSNA > in lean with OSA vs. lean without OSA MSNA > in Ob with OSA vs. lean without OSA SSNA = in lean and Ob with or without OSA. MSNA was positively related to WHR.
[49]	Italy	Cross-sectional	$n = 120$ with Ob with MetS ($n = 49$) 42.7 ± 6.5 yr; 71% F 38.5 ± 6.2 kg/m^2; 114.4 ± 11.7 cm without MetS ($n = 71$) 39.2 ± 6.7 yr; 80% F 38.5 ± 6.4 kg/m^2; 113.3 ± 14.1 cm	BMI range: 30–55 55 kg/m^2	24 h-urinary AD (ug/24 h) 24 h-urinary NA (ug/24 h)	Between groups: (a) Regarding Ob associated comorbidities (with MetS vs. without MetS)	AD = in Ob with MetS vs. without MetS (**NS; $p = 0.313$**) Urinary NA > in Ob with MetS vs. without MetS (**higher; $p < 0.001$**).
[45]	USA	Cross-sectional	$n = 119$ with Ob reporting sleep less than 6.5 h per night Morning chronotype ($n = 80$) 41.7 ± 65.9 yr; 76% F 38.2 ± 66.3 kg/m^2; 113.0 ± 613.6 cm Evening chronotype ($n = 39$) 38.6 ± 67.8 yr; 80% F 39.1 ± 66.6 kg/m^2; 114.7 ± 611.5 cm	BMI range: 30–55 55 kg/m^2	24 h-urinary AD (ug/24 h) 24 h-urinary NA (ug/24 h)	Between groups: (a) regarding other variables (with morning chronotype vs. with evening chronotype)	Urinary AD > in evening chronotype vs. morning chronotype (**higher; $p < 0.05$**). Urinary NA = in evening chronotype vs. morning chronotype (**NS; $p = 0.052$**).

Table 1. continued

Ref.	Country	Study design	Sample size; health characteristics; sex (% F); BMI (kg/m²); WC (cm)	Obesity criteria	Main outcomes	Comparator	Results
[50]	USA	Cross-sectional	$n = 126$ with Ob Men ($n = 30$) 40.7 ± 7.3 yr 36.7 ± 6.1 kg/m²; 118.1 ± 14.1 cm Women ($n = 96$) 40.5 ± 6.8 yr 39.2 ± 6.5 kg/m²; 112.5 ± 12.4 cm	BMI range: 30–55 55 kg/m²	24 -urinary A (ug/24 h) 24 h-urinary NA (ug/24 h)	Between groups: (a) regarding other variables—sex (men vs. women)	Urinary NA and AD > in Ob men vs. Ob women reporting sleep less than 6.5 h per night (**higher; $p = 0.004$**)
[38]	Italy	Cross-sectional	$n = 54$ untreated with MetS ($n = 16$) 49.4 ± 2.8 yr; 19% F 32.4 ± 1.0 kg/m²; 104.3 ± 1.5 cm with essential HT ($n = 12$) 48.2 ± 2.3 yr; 17% F 25.1 ± 0.7 kg/m²; 94.2 ± 1.5 cm with Ob ($n = 12$) 46.3 ± 2.6 yr; 25% F 38.7 ± 1.2 kg/m²; 109.1 ± 1.7 cm Lean healthy NT controls ($n = 14$) 46.1 ± 2.2 yr; 29% F 24.3 ± 0.8 kg/m²; 93.8 ± 1.4 cm	BMI > 30 kg/m² and WC > 102 in men and WC > 88 cm in women.	Plasma NA (pg/mL) Other outcomes: MSNA (bursts/min) SSNA (bursts/min)	Between groups: (a) Regarding BMI (with Ob vs. lean) (b) Regarding Ob associated comorbidities (with MetS and with HT)	NA = in Ob vs. lean-NT (**NS**). NA > in MetS vs. lean-NT (**higher, $p < 0.05$**). Other outcomes: MSNA > in Ob vs. lean ($p > 0.01$). MSNA > in HT and MetS vs. lean without HT and MetS ($p < 0.05$ and $p < 0.01$, respectively). SSNA = between groups.
[35]	USA	Cross-sectional	$n = 43$; 100% F Black with Ob ($n = 6$) 48.2 ± 7.4 yr 36.5 ± 3.0 kg/m²;119.7 ± 20.6 cm Black with N/Ow ($n = 6$) 48.7 ± 6.9 yr 25.3 ± 2.9 kg/m²; 90.6 ± 11.0 cm White with Ob ($n = 12$) 46.3 ± 7.3 yr 35.8 ± 5.1 kg/m²; 117.7 ± 14.7 cm White with N/Ow ($n = 8$) 47.1 ± 8.8 yr 27.6 ± 1.7 kg/m²; 96.0 ± 6.0 cm	BMI > 30 kg/m²	Plasma NA (pg/mL) Note: a blood sample as taken 120 min after the subjects finished eating the standardized meal	Between groups: (a) regarding BMI (with Ob vs. with N/Ow) (b) regarding other variables—ethnic (white vs. black)	NA = N/Ow in both ethnics' vs. Ob (**NS**) NA = in back vs. white (**NS**)
[46]	Italy	Cross-sectional	$n = 97$; 100% M; 51–61 yr Healthy control ($n = 14$) 23.9 ± 1.0 kg/m² Lean with HT ($n = 13$) 24.0 ± 0.9 kg/m² with Ob NT ($n = 15$) 32.5 ± 1.2 kg/m² Lean NT with congestive HF ($n = 14$) 23.7 ± 0.8 kg/m² Lean with HT and congestive HF ($N = 14$) 24.0 ± 0.9 kg/m² with Ob and congestive HF ($N = 14$) 32.8 ± 1.3 kg/m² With Ob, HT and congestive HF ($N = 13$) 33.0 ± 1.2 kg/m²	BMI > 30 kg/m²	Plasma NA (pg/mL) Other outcomes: MSNA (bursts/min)	Between groups: (a) regarding BMI (with Ob vs. lean) (b) regarding Ob associated comorbidities (HT and congestive HF)	NA = in Ob vs. lean (**NS**) NA > in congestive HF (**higher; $p < 0.01$**) and was significantly more pronounced and maximal when Ob and HT were concomitantly associated with HF ($p < 0.01$) Other results: MSNA > in Ob, HT, and congestive HF vs. healthy lean (**$p < 0.01$**) and was significantly more pronounced and maximal when Ob and HT were concomitantly associated with congestive HF (**$p < 0.01$**)

Table 1. continued

Ref.	Country	Study design	Sample size; health characteristics; sex (% F); BMI (kg/m^2); WC (cm)	Obesity criteria	Main outcomes	Comparator	Results
[37]	Italy	Cross-sectional	$n = 41$ with both Ob and HT ($n = 14$) 30.9 ± 5.2 yr; 57,1% F 35.5 ± 4.3 kg/m^2 With Ob ($n = 27$) 30.3 ± 5.4 yr; 55,6% F 34.6 ± 5.9 kg/m^2 Lean without HT (N = 20) 31 ± 4.9 yr; 50% F 22.2 ± 2.1 kg/m^2	BMI > 30 kg/m^2	Plasma AD (pg/mL) Plasma NA (pg/mL)	Between groups: (a) regarding BMI (with Ob vs. lean) (b) regarding Ob associated comorbidities (HT)	NA > in Ob (with HT and without HT) vs. lean (higher, $p < 0.05$) AD = between the three groups (NS) NA = (similar) between Ob-NT and Ob-HT (NS)
[48]	Germany	Cross-sectional	$n = 67$; 100% F with both Ob and HT ($n = 33$) 53 ± 10 yr 33 ± 3.4 kg/m^2 with Ob and Borderline-HT ($n = 9$) 49 ± 11 yr 33.3 ± 2.8 kg/m^2 with Ob without HT ($n = 25$) 47 ± 9 yr 34.1 ± 3.3 kg/m^2	BMI > 30 kg/m^2	Plasma AD (pg/mL) Plasma NA (pg/mL)	Between groups: (a) regarding Ob associated comorbidities (HT)	AD and NA = in Ob-HT vs. Ob without HT (**NS**)

Bold values represent statistically significant.

Ob obesity, *BMI* body mass index, *WC* waist circumference, *yr* years, *F* females, *NA* noradrenaline, *AD* adrenaline, *HF* heart failure, *OSA* obstructive sleep apnea, *PCOS* polycystic ovary syndrome, *WHR* waist-to-height ratio, *MetS* metabolic syndrome, *HT* hypertension, *NT* normotension, *MSNA* muscle sympathetic nerve activity, *SSNA* skin sympathetic nerve activity, *N/Ow* normal weight/overweight.

Studies and subjects' characteristics

Overall, 12 studies were observational (all cross-sectional) and 23 were experimental. The included studies involved a total of 2588 subjects, of which 1617 (63%) had obesity/abdominal obesity. Most of the studies involved both males and females (60%). The sample sizes ranged from six males with obesity [44] to 742 subjects with chronic heart failure (HF), among whom 247 (33%) with obesity [45]. Among the subjects with obesity/abdominal obesity, the mean ± SD for age and BMI ranged from 21.73 ± 0.47 years [46] to 70 ± 10 years [45] and from 30.3 ± 0.7 kg/m^2 [47] to 45 ± 4 kg/m^2 [48], respectively. The highest assessed WC average was 119.7 ± 20.6 cm [49]. In terms of disease characteristics, 18 studies (51%) included subjects with obesity-associated comorbidities (Table 3), and one of the studies included subjects with obesity with two distinct genotypes [50].

In most studies ($n = 66\%$), participants were either not taking any medication or had discontinued their medication prior to the study [47, 51–54]. Some studies did not specify participants' medication use [46, 50, 55–59]. In a few studies, participants were under pharmacological treatment, including loop diuretics [45, 60], antihypertensives [45, 61–65], cardiac glycosides and antiplatelet/anticoagulant therapy [45]. Additionally, some participants were using oral contraceptives [63, 64, 66], psychiatric, antidiabetic, anti-inflammatory, statins and corticosteroids [63, 64].

Regarding interventions, the individuals were subjected to stress, exercise, glucose intake and weight loss programs (induced by diet, exercise or surgery), as summarized in Table 3. In terms of adrenergic response markers, most of the studies (86%) assessed plasma CAs, while urinary CAs were analyzed in five studies. Notably, none of the studies simultaneously evaluated the plasma and urinary concentrations of AD and NA. However, a small number of studies have also examined other clinical parameters related to the SNS, including muscle sympathetic nerve activity (MSNA) (14%), skin sympathetic nerve activity (SSNA) (6%), NA clearance (9%) and NA spillover (9%).

Methodology wise, plasmatic and urinary CAs were predominantly assessed by high-performance liquid chromatography, with some exceptions in which CAs were assessed via radioenzymatic assays [55, 67], radioimmunoassays [65, 68], enzyme-linked immunosorbent assays [46, 54, 69–71], and high-resolution liquid chromatography [45]. One study did not specify the method used [56]. CAs were generally assessed under fasting, except in some studies where they were measured after a light breakfast with overnight abstinence from alcohol, smoking, and coffee [49, 52, 72]. Additionally, some studies did not specify the sampling conditions [45, 56, 57, 60].

With respect to comparators, some studies have conducted multiple analysis. AD and/or NA plasmatic or urinary concentrations were compared between (i) subjects with and without obesity (17 studies, 49%), (ii) subjects with obesity, with versus without obesity-associated comorbidities (12 studies, 34%) and (iii) subjects with obesity before and after an intervention or after different types of interventions (23 studies, 66%). A subset of studies ($n = 8$; 23%) also compared AD and/or NA plasmatic or urinary concentrations in relation to additional variables, such as sex [64], chronotype (morning vs. evening type) [59], insulin sensitivity (sensitive vs. resistant) [47, 58], ethnicity (black vs. white) [49], response to induced hypoglycemia [48], genotype (ADRB2 Glu27Glu vs. Gln27Gln) [50] and response to OGTT (in the feeding or fasting state) [73].

Differences in adrenergic system

In subjects with obesity versus those without obesity. There is a significant variability in plasma AD and NA concentrations across studies. Among the 17 studies comparing subjects with and without obesity, five (29.4%) reported significantly higher circulating concentrations of NA in subjects with obesity than in those without obesity [$p < 0.001$ [74, 75]; $p < 0.01$ [72, 76]; $p < 0.05$

Table 2. Characteristics of the experimental/interventional studies evaluating the adrenergic system in subjects with obesity.

Ref	Country	Study design	Baseline subjects' characteristics	Criteria	Intervention	Main outcomes	Comparator	Results
[63]	Australia	Randomized, control study 12 months follow-up	$n = 42$ with both Ob and OSA 49.4 ± 9.4 yr; 26% F 37.2 ± 5.6 kg/m^2; 116.6 ± 13.6 cm	BMI > 30 kg/m^2	**DIET:** 2-month VLED (very low energy diet) (450–800 kcal/day) followed by randomization to a 10-month weight loss maintenance diet (Low Glycemic Index High-Protein or the Australian Guide to Healthy Eating diet.	Daytime urinary AD (nmol) Daytime urinary NA (nmol) Night-time urinary AD (nmol) Night-time urinary NA (nmol)	Withing group 1) Before vs. after (2 and 12 months)	Day-time urinary NA < after 2 months weight loss (**decrease;** $\boldsymbol{p < 0.05}$). Night-time urinary NA = after 2 months weight loss (**NS**) Night-time urinary AD > after 2 months weight loss (**increase;** $\boldsymbol{p < 0.05}$). Day-time urinary AD = after 2 months weight loss (**NS**) Urinary catecholamines = after 12 months weight loss (**NS**) Urinary catecholamines did not show a correlation with weight loss.
[52]	Germany	Uncontrolled experimental study (one group pretest vs. posttest intervention) 8 weeks follow-up	$n = 26$ healthy subjects with Ob 29.2 ± 1.01 yr; 54% F 36.34 ± 0.96 kg/m^2	BMI > 30 kg/m^2	**DIET:** Weight loss program via replacement of meals by a commercial diet drink for 2 weeks (with a follow-up 6 weeks thereafter).	Plasma AD (nmol/L) Plasma NA (nmol/L)	Within group: 1) Before vs. after (14 days and 6 weeks of the diet)	AD = before vs. after 14 days (**NS**). AD > after 6 weeks (**increase;** $\boldsymbol{p < 0.05}$). NA > before vs. after 14 days (**decrease;** $\boldsymbol{p < 0.05}$) NA = before vs. after 6 weeks (**NS**).
[62]	Canada	Nonrandomized controlled experimental study 6 weeks follow-up	$n = 37$ <u>with Ob ($n = 19$)</u> 22.9 ± 8.4 yr; 36,8% F 33.4 ± 1.4 kg/m^2 <u>with NW ($n = 18$)</u> 23.2 ± 4.4 yr; 38,9% F 23.3 ± 1.2 kg/m^2	BMI > 30 kg/m^2	**EXERCISE:** 6-week SET (supramaximal exercise training) 3 sessions per week for 6 weeks	Plasma AD (nmol/L) Plasma NA (nmol/L)	Withing group a) Before vs. after 6 weeks Between groups b) Regarding BMI (with Ob vs. with NW)	AD and NA > after vs. before 6-week SET weight loss program (**decrease; both** $p < 0.01$) AD and NA > Ob vs. Nw (**higher; both** $\boldsymbol{p < 0.01}$).
[55]	Turkey	Prospective, randomized, parallel exercise group 12 weeks follow-up	$n = 51$ with MetS 25–65 yr; 100% F <u>high-intensity exercise (HIE) ($n = 20$)</u> 32.90 (30.32–35.15) kg/m^2 108.0 (105–116) cm <u>moderate-intensity exercise (MIE) ($n = 20$)</u> 32.85 (29.19–38.62) kg/m^2 117.0 (100–127) cm	Abdominal Ob defined as WC >88 cm in women and >102 cm in men	**EXERCISE:** 12-week exercise program: HIE group exercised 20 min a day, 3 days a week at %70 VO2 max MIE and ECE PEDO groups exercised 5 days a week, 30 min a day at %50 VO2max	Serum AD (ng/L) Serum NA (ng/L)	Withing group a) Before vs. after 12 weeks	Anthropometric measurements < at 12th week vs. baseline (decrease; all groups $p < 0.017$). AD and NA = after 12 weeks of HIE and MIE vs. baseline (**NS**) AD and NA = after 12 weeks of ECE PEDO vs. baseline (**NS**)

Table 2. continued

Ref	Country	Study design	Baseline subjects' characteristics	Criteria	Intervention	Main outcomes	Comparator	Results
			moderate-intensity pedometer (ECE PEDO) ($n=20$) 32.9 (28.01—38.10) kg/m^2 114.0 (104–120) cm					
[31]	USA	Randomized, crossover study	$n=15$ with Ob 21.73 ± 0.47 yr; 100% M 34.25 ± 1.17 kg/m^2	BMI > 30 kg/m^2	**EXERCISE:** single bout of cycling exercise at lower (LI) and higher intensities (HI) in random order LI: 50% of maximal heart rate HI: 80% of maximal heart rate	Plasma AD (pg/mL) Plasma NA (pg/mL)	Within group a) Before vs. immediately postexercise vs. 1 h postexercise b) types of exercise (HI vs. LI exercise)	AD and NA = before vs. immediately postexercise vs. 1 h postexercise (**NS**) AD and NA = HI vs. LI exercise (**NS**)
[53]	USA	Controlled experimental study (pre vs. post intervention)	$n=15$; 100% M Lean ($n=5$) 31 ± 3 yr 21 ± 1 (18–23) kg/m^2 With Ow ($n=5$) 37 ± 4 yr 27 ± 1 (26–29) kg/m^2 With Ob ($n=5$) 38 ± 2 yr 34 ± 1 (30–37) kg/m^2	BMI > 30 kg/m^2	**EXERCISE:** Aerobic exercise	Plasma AD (pg/mL) Plasma NA (pg/mL) measured at rest and after 90 min of exercise	Withing group: a) regarding intervention (before vs. after) Between groups: b) regarding BMI (Lean vs. with Ow vs. with Ob)	AD > in Ob vs. lean after 90 min of exercise (**higher; $p<0.05$**). NA = in Ob vs. lean after 90 min of exercise (**NS**) AD = in Ob vs. lean at baseline (**NS**). NA = in Ob vs. lean at baseline (**NS; $p=0.10$**).
[64]	France	Randomized, crossover study	$n=6$ 100% M 30.7 ± 2.8 yr 31.8 ± 1 kg/m^2	BMI range: 30–34.5 kg/m^2	**EXERCISE:** Moderate exercise (60 min) at 50% of VO2 max.	Plasma AD (ng/mL) Plasma NA (ng/mL)	Withing group: a) regarding the intervention (before vs. after exercise)	AD and NA > during the exercise period (**increase; $p<0.05$**). AD and NA = During postexercise recovery vs. resting session (**NS**).
[36]	Spain	Controlled experimental study (pre vs. post intervention)	$n=15$ with Ob; 100% F with Glu27Glu genotype ($n=8$) 43 ± 5 yr 31.7 ± 0.9 kg/m^2; 94.19 ± 2.9 cm with Gln27Gln genotype ($n=7$) 43 ± 5 yr 33.9 ± 1.3 kg/m^2; 97.5 ± 3.3 cm	BMI > 30 kg/m^2	**EXERCISE:** Rest or submaximal exercise (treadmill for 60 min at a constant speed that elicited 30–35% of their individual VO2max)	Plasma AD (ng/mL) Plasma NA (ng/mL)	Within group: a) regarding intervention (at rest; during submaximal exercise-60 min; and after 60 min of recovery) Between groups: b) regarding other variables – genotype (Ob with ADRB2 Glu27Glu vs. Gln27Gln)	AD = in Glu27Gln vs. Glu27Glu group at both baseline and at 60 min of recovery after exercise (**NS**). NA > at 60 min of exercise in both groups (**increase; both $p<0.01$**). NA concentrations decreased to basal values during the recovery. Although no statistical differences were found between groups in plasma catecholamines, NA tended to be higher in the Glu27Glu group

Table 2. continued

Ref	Country	Study design	Baseline subjects' characteristics	Criteria	Intervention	Main outcomes	Comparator	Results
								(ANOVA for group, $p = 0.090$).
[65]	USA	Nonrandomized controlled study (pre vs. post intervention)	$n = 14$; 100% M Lean ($n = 7$) 34.4 ± 3.3 yr 23.7 ± 0.7 kg/m^2 with Ob ($n = 7$) 39.3 ± 3.2 yr 33.7 ± 1.1 kg/m^2	BMI ≥ 30 kg/m^2	**EXERCISE:** 60 min of moderately intense cycle ergometry exercise	Plasma NA (nM)	Withing group: a) regarding intervention (at rest vs. during exercise - at 30 and 60 min of exercise) Between groups: b) regarding BMI (lean vs. with Ob)	NA = in Ob vs. lean at rest (**NS**). NA > during exercise in both groups (increase). NA > in Ob vs. lean during exercise both at 30 min and 60 min (**higher; both $p < 0.05$**).
[41]	USA	Nonrandomized controlled study	$n = 197$ With both Ob and HT ($n = 55$) 46 ± 2 yr; 14.5% F 32.5 ± 0.3 kg/m^2 Lean with HT ($n = 66$) 45 ± 2 yr; 13.6% F 24.3 ± 0.2 kg/m^2 With Ob ($n = 21$) 45 ± 2 yr old; 14.3% F 31.8 ± 0.6 kg/m^2 Lean ($n = 55$) 45 ± 2 yr; 18.2% F 23.9 ± 0.2 kg/m^2	BMI > 30 kg/m^2	**EXERCISE:** 10 min treadmill exercise—physical stress	Plasma AD (ng/mL) Plasma NA (ng/mL)	Withing group: a) regarding intervention (during exercise) Between groups: a) regarding BMI (with Ob vs. lean) b) regarding Ob associated comorbidities (HT)	E and NA = at rest between the 4 groups (**NS**) NA < in Ob vs. lean subjects during exercise (**lower; $p < 0.01$**) NA = in HT and NT subjects during exercise (**NS**)
[39]	Australia	Randomized Controlled Trial	$n = 59$ men and postmenopausal women with central Ob and MetS; WL group ($n = 20$) 55 ± 1 yr; 40% F 32.2 ± 0.9 kg/m^2; 106.5 ± 1.9 cm WL + EX group ($n = 20$) 54 ± 1 yr; 40% F 31.8 ± 0.8 kg/m^2; 105.1 ± 2.2 cm Control ($n = 19$) 55 ± 1 yr; 42% F 33.0 ± 0.8 kg/m^2; 109.4 ± 2.5 cm	Central Ob (WC > 102 cm in men and >88 cm in women)	**DIET + EXERCISE:** 12 weeks—weight loss by caloric restriction alone (WL) or weight loss by combined caloric restriction and aerobic exercise (WL + EX)	Plasma NA (ng/mL) Other outcomes: NE clearance (L/min) NE spillover (ng/min) MSNA (bursts per min)	Within group: a) before and after intervention Between groups: b) regarding intervention type (WL vs. WL + EX vs. no treatment-control)	NA < after both WL and WL + EX treatment vs. baseline (**decreased; $p < 0.001$ and $p < 0.05$**, respectively). NA < after both WL and WL + EX treatment vs. control group (**decreased; $p < 0.01$**). Differences between the WL and WL + EX group were not significant. Other outcomes: NA spillover rates and MSNA < after both WL and WL + EX treatment. NA clearance = after both WL and WL + EX treatment.
[33]	Australia	Controlled nonrandomized study (pre vs. post	$n = 34$ with central Ob and MetS Insulin sensitive ($n = 15$)	Central Ob (WC > 102 cm in men and >88 cm in women)	**DIET + EXERCISE:** 12-week weight loss program—hypocaloric	Plasma NA (ng/mL) Other outcomes:	Within group: a) before and after intervention Between groups:	Body weight and WC < after the 12 weeks (**decreased; both $p < 0.001$**).

Table 2. continued

Ref	Country	Study design	Baseline subjects' characteristics	Criteria	Intervention	Main outcomes	Comparator	Results
		intervention) 3-months follow-up	54 ± 1 yr; 27% F 30.3 ± 0.7 kg/m^2; 104.2 ± 2.0 cm Insulin resistant ($n = 19$) 55 ± 1 yr; 47% F 32.7 ± 0.9 kg/m^2; 107.0 ± 2.5 cm		diet (600 kcal/day) with or without exercise	NA clearance (L/min) NA spillover (ng/min)	b) regarding other variables (Insulin sensitive vs. Insulin resistant groups)	NA < after intervention (**decreased;** $p < 0.001$). NA response to 75 g OGTT < after intervention (**lower;** $p < 0.001$). NA = insulin resistance vs. insulin sensitive at baseline (**NS**). Other results: NA spillover < after intervention (**decreased;** $p < 0.001$). NA clearance = after intervention (**NS**) NA spillover in response to glucose > after weight loss (**increased;** $p < 0.001$).
[54]	Germany	Controlled nonrandomized study (pre vs. post intervention) 4 weeks follow-up	$n = 40$ with Ob diet ($n = 20$) 43 ± 8 yr; 50% F 36 ± 3 kg/m^2 diet + exercise ($n = 20$) 44 ± 4 yr; 50% F 34 ± 4 kg/m^2	BMI range 30–45 kg/m^2	**DIET + EXERCISE:** 4 weeks - 300 kcal/day (25–30% CH; 35–40% fat; 35–40% protein) alone or in combination with exercise on a bicycle ergometer.	Plasma AD (nmol/L) Plasma NA (nmol/L)	Within group: a) regarding intervention (before vs. during; at rest vs. during work) Between groups: b) Intervention type (diet vs. diet + exercise)	AD and NA < after 4 weeks in both groups at rest (by 45 and 74%, respectively) NA > in diet + exercise group vs. diet groups during exercise (higher). At maximal work plasma AD and NA concentrations decreased after diet and increased after diet + exercise.
[44]	Australia	Controlled nonrandomized study (pre vs. post intervention) 2 h follow-up	$n = 31$ with central Ob and MetS Insulin resistant ($n = 19$) 55 ± 1 yr; 47% F 32.2 ± 1.1 kg/m^2; 108.6 ± 2.9 cm Insulin sensitive ($n = 12$) 56 ± 1 yr; 42% F 31.7 ± 0.9 kg/m^2; 107.2 ± 2.7 cm	Central Ob (WC > 102 cm in men and >88 cm in women)	**GLUCOSE:** OGTT (2 h)	Plasma NA (ng/mL) Other AS outcomes: NE clearance (L/min) NE spillover (ng/min) MSNA (bursts per min)	Within group: a) before vs. after (30, 60, 90 and 120 min) intervention Between groups: b) regarding other variables (Insulin sensitive vs. Insulin resistant groups) c) regarding intervention (after OGTT)	NA = in both groups at baseline (NS) Other results: NA clearance and MSNA > in insulin resistance vs. insulin sensitive group at baseline (**higher;** $p < 0.01$ **and** $p = 0.05$, respectively). NA spillover = in insulin resistance vs. insulin sensitive group at baseline (**NS;** $p = 0.11$). MSNA > in insulin resistance vs. insulin sensitive group at 60, 90, and 120 min after

Table 2. continued

Ref	Country	Study design	Baseline subjects' characteristics	Criteria	Intervention	Main outcomes	Comparator	Results
								glucose ingestion, (**increased; all** $p \leq$ **0.001**). NA spillover > insulin sensitive at 30 min after glucose ingestion vs. baseline (**increased;** $p <$ **0.01**). The response was blunted and delayed, reaching statistical significance only at 120 min in subjects with insulin resistance.
[61]	Italy	Controlled nonrandomized study (pre vs. post intervention)	$n = 69$; 100% F with Ob ($n = 24$) 38.3 ± 1.8 yr 37.9 ± 1.1 kg/m^2 with both Ob and HT ($n = 25$) 37.7 ± 1.9 yr 39.4 ± 1.3 kg/m^2 Healthy control ($n = 20$) 38.3 ± 1.2 yr 23.1 ± 0.4 kg/m^2	BMI > 30 kg/m^2	**GLUCOSE:** OGTT (75 g)	Plasma NA (ng/mL)	Within group: c) regarding intervention (fasting vs. during OGTT) Between groups: a) regarding BMI (with Ob vs. control) b) regarding Ob associated comorbidities (HT)	NA > in all groups during OGTT (increased) NA > in Ob vs. control during OGTT (higher; $p <$ **0.001**) NA > in Ob with HT vs. Ob without HT during OGTT (higher; $p <$ **0.05**) NA > in Ob vs. control during fasting (higher; $p <$ **0.001**) NA > in Ob with HT vs. Ob without HT during fasting (higher; $p <$ **0.05**)
[60]	Italy	Controlled nonrandomized study (pre vs. post intervention)	$n = 46$ with Ob ($n = 19$) 31.6% F 22.1 ± 0.73 kg/m^2; 107.5 ± 3.5 cm With both Ob and HT ($n = 15$) 60% F 38.8 ± 1.8 kg/m^2; 113.6 ± 4.0 cm Healthy control ($n = 12$) 66.7% F 22.1 ± 0.73 kg/m^2; 74.6 ± 3.72 cm	BMI > 30 kg/m^2	**GLUCOSE:** OGTT (75-g)	Plasma NA (ng/mL)	Within group: c) regarding intervention (fasting vs. during OGTT) Between groups: a) regarding BMI (with Ob vs. control) b) regarding Ob associated comorbidities (HT)	NE > in all groups during OGTT (increased) NE > in Ob vs. control during OGTT (higher; $p <$ **0.001**) NE > in Ob with HT vs. Ob without HT 60 min after OGTT (higher; $p <$ **0.001**) NE > in Ob vs. control during fasting (higher; $p <$ **0.001**) NE > in Ob with HT vs. Ob without HT during fasting (higher; $p <$ **0.05**)
[59]	USA	Controlled nonrandomized study (pre vs. post intervention)	$n = 97$ NW ($n = 33$) 33 ± 1 yr; 58% F 22.4 ± 0.3 kg/m^2;	BMI > 30 kg/m^2	**GLUCOSE:** OGTT (2 h)	Plasma AD (nmol/mL) Plasma NA (nmol/mL)	Within group: c) regarding intervention (before vs. after) Between groups	AD > males vs. females irrespective of BMI (**higher**). NA = males vs.

Table 2. continued

Ref	Country	Study design	Baseline subjects' characteristics	Criteria	Intervention	Main outcomes	Comparator	Results
			83.1 ± 1.3 cm Ow ($n = 28$) 32 ± 1 yr; 46% F 27.6 ± 0.2 kg/m^2; 95.9 ± 1.3 cm Ob (n = 36) 35.6 ± 1 yr; 72% F 111.1 ± 2.7 kg/m^2; 0.91 ± 0.02 cm				a) regarding BMI (with NW vs. with OW vs. with Ob), b) regarding sex c) regarding fasting/ feeding state	females. Sex difference disappeared after adjustment for %BF. AD < in Ob vs. NW (**lower; $p = 0.018$**). NA = between the BMI groups (**NS**). Suppression of AD secretion in response to carbohydrate ingestion was significantly blunted in subjects with Ow and Ob vs. with NW (**$p = 0.045$**).
[51]	Spain	Uncontrolled experimental study (pre vs. post intervention) 12 months follow-up	$n = 37$ with both Ob and HT 52 ± 8 yr; 76% F 45 ± 5 kg/m^2 129 ± 11 cm	(BMI) > 40 kg/m^2 or 35-40 kg/m^2 with major obesity-associated comorbidities	**SURGERY:** Bariatric surgery	Plasma NA (pg/mL)	Within group a) Before vs. after (4- and 12-months postoperation)	NA < after BS (**decreased; $p < 0.05$**).
[34]	Sweden	Uncontrolled experimental study (pre vs. post intervention) 12 months follow-up	$n = 8$; 40 yr; 87.5% F Before weight loss 45 ± 4 kg/m^2; 116 ± 4 cm After weight loss 30.7 ± 2.7 kg/m^2; 102 ± 10 cm	BMI > 40 kg/m^2	**SURGERY:** Bariatric surgery and 32% Weight loss	Plasma AD (nmol/mL) Plasma NA (nmol/mL)	Within group: a) regarding intervention (before vs. after) b) regarding other variables - counterregulatory responses to insulin-induced hypoglycemia and of cognitive function before and after	AD = after interventions (NS). NA = significant before intervention (NS, $p = 0.20$). AD and NA > during insulin-induced hypoglycemia before intervention (both $p < 0.05$).
[47]	Sweden	Controlled nonrandomized study (pre vs. post intervention) 1-year follow-up	$n = 84$; 39–60 yr; 46.4% F With Ob - referred to operation ($n = 28$) 38.6 ± 3.7 kg/m^2 With Ob - dietary (control) ($n = 24$) 38.9 ± 5.4 kg/m^2 Lean ($n = 28$) 24.7 ± 2.3 kg/m^2	With Ob - BMI range: 31 to 52 kg/m^2 Without Ob: BMI range 17–27 kg/m^2	**SURGERY:** gastroplasty or Dietary recommendations	24 h-Urinary NA (nmol/ 24 h)	Within group: a) Regarding Intervention type (Operation vs. diet) Between groups: b) regarding BMI (with Ob vs. without Ob)	NA > in Ob vs. lean at baseline (**higher; $p < 0.01$**). NA > in subjects submitted to diet vs. submitted to operation 1 yr after interventions (**$p = 0.047$**). Subjects submitted to diet did not lose weight (112 ± 14 vs. 116 ± 9) while those submitted to surgery did (116 ± 14 vs. 84 ± 9).
[57]	USA	Controlled nonrandomized study (pre vs. post intervention)	$n = 22$ healthy subjects 100% M with Ob ($n = 12$)	BMI > 30 kg/m^2 and BF > 30%	**STRESS:** After 45 min of rest, subjects were exposed to 20 min of acute stress (5 cycles of	Plasma NA (pg/mL)	Withing group a) Before vs. after stress exposure (20 min and 1 h after recovery)	NA > immediately post stress vs. at baseline (higher; **$p < 0.001$**).

Table 2. continued

Ref	Country	Study design	Baseline subjects' characteristics	Criteria	Intervention	Main outcomes	Comparator	Results
			26.6 ± 2.1 yr 39.0 ± 1.6 kg/m^2 with NW (n = 10) 23.8 ± 1.0 yr 21.3 ± 0.6 kg/m^2		the computer-based color-word task (2 min) and the mental arithmetic task (2 min)) while they sat in a semi recumbent position		Between groups b) Regarding BMI (with Ob vs. with NW)	NA = in NW and Ob groups (**NS**).
[43]	Germany	Nonrandomized Crossover study	n = 20; 100% M With Ob (n = 10) 25.6 ± 1.6 yr 36.0 ± 1.6 kg/m^2 With NW (n = 10) 22.7 ± 1.1 yr 22.8 ± 0.6 kg/m^2	BMI > 30 kg/m^2	**STRESS:** Each subject participated in two sessions (stress intervention and nonstress control session) with an interval of 7 to 14 days between these two sessions.	Plasma AD (pg/mL) Plasma NA (pg/mL)	Within groups a) before vs. after and stress intervention vs. nonstress control session Between groups Regarding BMI (with Ob vs. with NW)	AD and NA > after social stress in both groups (**increased; all $p < 0.05$**). Subjects with obesity showed a higher hormonal response to psychosocial stress (**$p < 0.05$ and $p < 0.01$**, respectively, in NW group vs. **$p < 0.01$ and $p < 0.001$**, respectively in Ob group)
[40]	Slovakia	Controlled nonrandomized study (pre vs. post intervention)	n = 45; 100% M with both Ob and HT (n = 10) 28 ± 4 yr 34.4 ± 3.6 kg/m^2, 109 ± 8 cm with Ob (n = 14) 27 ± 5 yr 34.0 ± 3.9 kg/m^2, 111 ± 8 cm with HT (n = 8) 23 ± 3 yr 23.4 ± 2.4 kg/m^2; 85 ± 9 cm Control (n = 13) 23 ± 5 yr 22.0 ± 1.8 kg/m^2; 83 ± 6 cm	BMI ≥ 30 kg/m^2	**STRESS:** Mental stress test (the Stroop test)	Plasma AD (pg/mL) Plasma NA (pg/mL)	Withing group: a) before vs. after intervention (mental stress test) b) regarding BMI (with Ob vs. lean) Between groups: a) Regarding Ob associated comorbidities (HT)	AD > in HT groups compared to those without HT at baseline as well as during the mental stress tests (**higher; both $p < 0.01$**). AD and NA = in Ob vs. lean (**NS**). NA = in both Ob with HT vs. the other 3 groups **(NS)**

Bold values represent statistically significant.

Ob obesity, *BMI* body mass index, *WC* waist circumference, *yr* years, *F* females, *NA* noradrenaline, *AD* adrenaline, *HF* heart failure, *OSA* obstructive sleep apnea, *PCOS* polycystic ovary syndrome, WHR waist-to-height ratio; *MetS* metabolic syndrome, *HT* hypertension, *NT* normotension, *MSNA* muscle sympathetic nerve activity, *SSNA* skin sympathetic nerve activity, *NW* normal weight, *Ow* overweight.

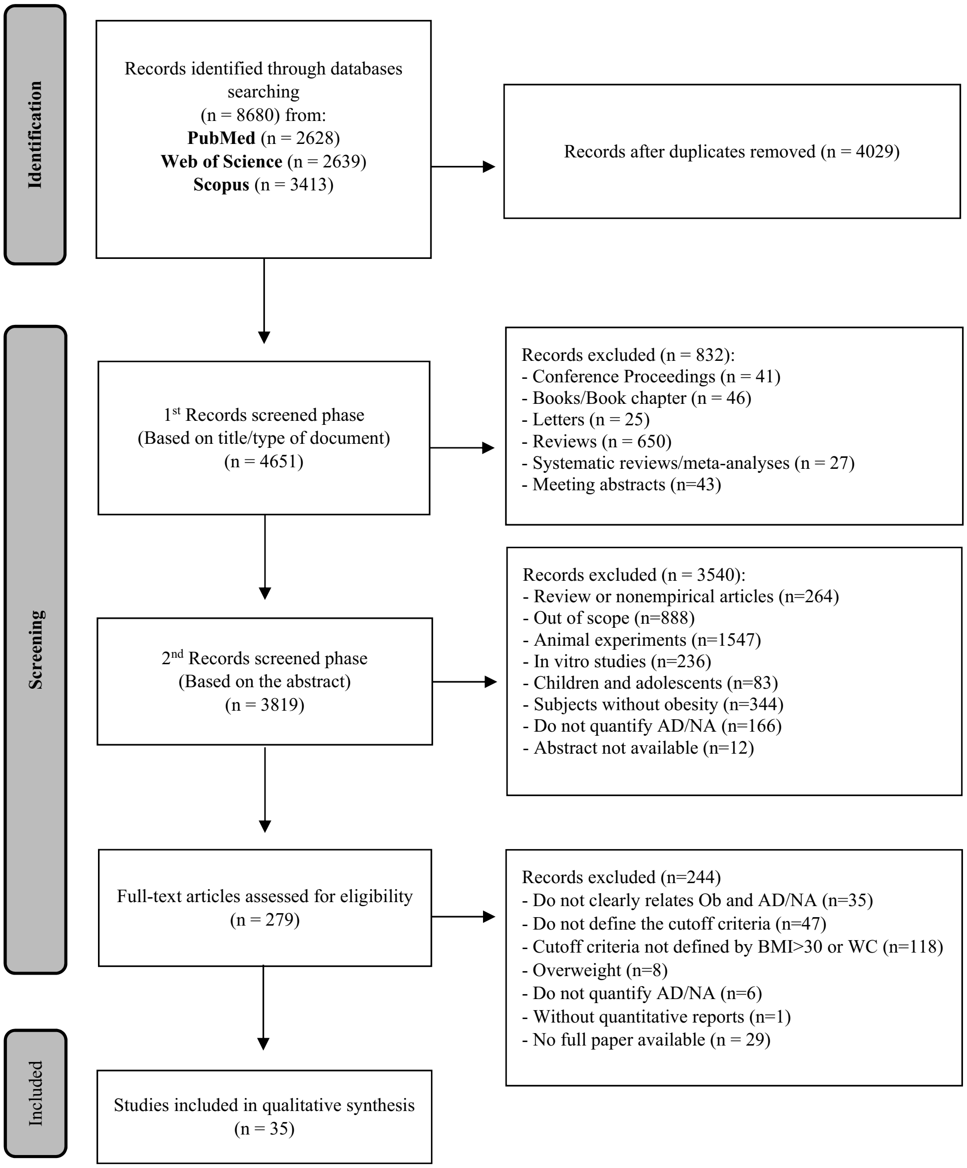

Fig. 1 Literature review flow diagram, adapted from Page et al. [35].

[51]]. One study revealed significantly lower concentrations of NA ($p < 0.001$) in subjects with obesity compared to those without obesity, both groups with chronic HF [45]. In addition, 24-h urinary NA excretion rates were also significantly higher in subjects with obesity compared to lean ($p < 0.01$) [61]. However, more than half of these studies (59%) reported no statistically significant differences between groups.

With respect to AD, assessed in seven of these studies, a subset ($n = 3/7$) reported significantly lower concentrations in subjects with obesity at rest than in their normal weight counterparts ($p < 0.05$) [73] as well as after physical exercise, compared with their lean counterparts [$p < 0.01$ [55] and $p < 0.05$ [67]], even when plasma AD concentrations were similar [55, 67] under resting conditions. In contrast, one study [76] reported significantly higher concentrations of AD in subjects with obesity compared to those with normal weight ($p < 0.01$), while three studies [51, 54, 57] reported similar concentrations under resting conditions.

In subjects with obesity regarding obesity-associated comorbidities. Compared with their counterparts with obesity and without OSA, subjects with OSA presented significantly higher NA concentrations [$p = 0.02$ [70] and $p < 0.05$ [72]]. However, after adjustment for potential confounding factors such as age, sex, BMI, WC, alcohol intake, physical activity, and urinary sodium excretion, this difference was no longer significant ($p = 0.15$) [70]. In addition, no significant differences were found in plasma AD ($p = 0.18$) [70]. However, MSNA values were significantly higher in subjects with OSA than in those without OSA, and MSNA was positively associated with WHR ($p < 0.01$) in a multivariate analysis conducted on subjects with and without obesity, with and without OSA. However, the SSNA values remained similar among the four groups [72].

Similarly, compared with their counterparts with obesity without this syndrome, subjects with metabolic syndrome (MetS) also presented significantly higher NA concentrations ($p < 0.001$) and non-significant AD concentrations ($p = 0.313$) [63]. However, according to Grassi et al., although plasma NA values were significantly higher in patients with MetS ($p < 0.05$), this trend was not observed in those with obesity or hypertension (HT) alone, despite a concomitant and marked increase in MSNA observed in all these clinical conditions [52].

Compared with their counterparts without the syndrome,

Table 3. Summary of the main study features.

	n	(%)
First author affiliation		
Italy	7	20.0
Germany	4	11.4
Australia	4	11.4
Spain	3	8.6
Sweden	2	5.7
Brazil	1	2.9
Iraq	1	2.9
Canada	1	2.9
Turkey	1	2.9
France	1	2.9
Slovakia	1	2.9
Journal quartile		
Q1	14	40.0
Q2	13	37.1
Q3	4	11.4
Q4	4	11.4
Studies by sex		
Males	8	22.9
Females	6	17.1
Both	21	60.0
Obesity characterized by		
BMI	29	82.9
WC	4	11.4
Both	2	5.7
Obesity associated comorbidities	18	51.4
HT	7	20.0
MetS	4	11.4
OSA	2	5.7
PCOS	1	2.9
chronic HF	1	2.9
MetS and OSA	1	2.9
HT and congestive HF	1	2.9
Interventions		
Exercise	8	34.8
Induces tests	3	13.0
Oral glucose tolerance tests	4	17.4
Weight loss program induced by diet	2	8.7
Weight loss program induced by diet and exercise	3	13.0
Weight loss induced by surgery	3	13.0
Main outcomes		
Both plasma AD and NA concentrations	16	45.7
Only plasma NA concentrations	13	37.1
Only plasma AD concentrations	1	2.9
Urinary AD and NA concentrations	4	11.4
Only urinary NA concentrations	1	2.9
MSNA	5	14.3
SSNA	2	5.7
NA clearance	3	8.6
NA spillover	3	8.6

HT hypertension, *MetS* metabolic syndrome, *OSA* obstructive sleep apnea, *PCOS* polycystic ovary syndrome, *HF* heart failure, *MSNA* muscle sympathetic nerve activity, *SSNA* skin sympathetic nerve activity.

subjects with polycystic ovary syndrome (PCOS) presented significantly higher AD concentrations, both in the lying and standing positions (both $p < 0.001$). Moreover, the plasma AD concentration in the lying position was higher in subjects with PCOS when compared to the control group ($p < 0.001$) and both BMI and WHR were positively correlated with the plasma AD concentration (both $p < 0.05$). Overall, this evidence suggests a chronic elevation in sympathetic activity in subjects with PCOS [56].

On the one hand, subjects with congestive HF presented significantly higher NA concentrations and MSNA values than did their counterparts without congestive HF (both $p < 0.01$). Furthermore, compared with a healthy group, MSNA significantly increased in the groups of subjects with obesity, HT, and congestive HF. In addition, this increase was particularly pronounced and reached its maximum when obesity and HT cooccurred in the presence of congestive HF ($p < 0.01$) [60]. On the other hand, significantly lower NA concentrations were observed in subjects with obesity and chronic HF compared to subjects without obesity. Additionally, BMI and obesity were significantly associated with lower NA concentrations ($p < 0.001$) [45].

Studies with subjects with both obesity and HT ($n = 6$) have yielded controversial results. Some ($n = 2$) reported significantly higher NA concentrations in subjects with both obesity and HT than in normotensive subjects with obesity, both under fasting ($p < 0.05$) [75] and during OGTT conditions ($p < 0.001$) [74]. Conversely, other studies reported similar AD and NA concentrations [51, 55, 62] in subjects with HT compared with their normotensive counterparts. In addition, one study [54] reported significantly higher plasma AD levels in subjects with both obesity and HT ($p < 0.01$), highlighting the significant impact of HT on baseline plasma AD ($F = 8.345$, $p = 0.006$) but not on NA concentrations.

In subjects with obesity before and after intervention

Adrenergic response to dietary interventions: When the impact of diet-induced weight loss across five studies that implemented different dietary intervention types was examined, it was evident that both circulating and urinary NA concentrations consistently decreased across studies, at rest, after weight loss [$p < 0.05$ [68, 77]; $p < 0.001$ [47, 53, 66]], regardless of the dietary regimen. In addition, MNSA and plasma resting NA spillover rates significantly decrease in subjects with abdominal obesity after weight loss treatment, whereas no changes in NA plasma clearance were noted [47, 53]. Moreover, the concentration of NA decreased with weight loss but remained stable during follow-up ($p = 0.012$) [66], indicating that this decrease was induced by weight loss. However, findings regarding AD concentrations, assessed in four of these studies, are less conclusive. On the one hand, a significant increase in the daily urinary AD concentration in subjects with obesity was identified after a 2-month period of a very low-energy diet (450–800 kcal/day), followed by 10 months of a weight loss maintenance diet ($p < 0.05$) [77]. However, Altree et al. [77] did not find a correlation between urinary CAs and weight loss. On the other hand, evidence also suggests a slight decrease in AD concentrations after 2 weeks on a commercial diet, followed by a significant increase 6 weeks later during the follow-up period ($p < 0.05$) [66]. In addition, AD concentrations also seem to decrease after 4 weeks of underfeeding at 300 kcal/day ($p < 0.05$) [68].

Adrenergic response to exercise. When the impact of exercise on the adrenergic response was examined, two types of analyses were performed: (1) CAs response during exercise in subjects with obesity in comparison to their lean counterparts as well as across different types of exercise and (2) CAs response at rest in subjects with obesity after weight loss induced by exercise.

Overall, there is evidence suggesting a significant increase in AD [$p < 0.05$ [78]] and NA [$p < 0.05$ [78, 79]; $p < 0.01$ [50]] concentrations during exercise in both subjects with and without obesity [$p < 0.05$ [79]], regardless of the exercise type. Furthermore, evidence points to similar [67] and higher NA concentrations in subjects with obesity compared to their lean counterparts ($p < 0.05$), even when both groups present similar NA concentrations at rest [79]. Conversely, there is also evidence suggesting significantly lower AD concentrations in subjects with obesity compared with their lean counterparts after 90 min of exercise ($p < 0.05$) [67]. In addition, changes in plasma NA concentrations during a 10 min treadmill test were significantly higher in lean subjects than in subjects with obesity ($p < 0.01$) [55].

Regarding different types of exercise, evidence shows a significant increase in AD and NA after 90 min of aerobic exercise [67] as well as after 60 min of moderate exercise (50%VO2 max) [78]. In contrast, no statistically significant changes were found in the levels of CAs when exercise intensity and time were compared in a study involving 15 males with obesity submitted to a single bout of cycling exercise at both lower and higher intensities [46].

With respect to the CA response at rest, after weight loss induced by exercise, evidence suggests a decrease in AD and NA concentrations after a 6-week weight loss program, promoted by 3 sessions per week of supramaximal exercise training, both in subjects with obesity and in their normal weight counterparts (both $p < 0.01$) [76]. In contrast, no statistically significant changes were found in AD or NA after a 12-week weight loss exercise program in either the high- or moderate-intensity groups, although the anthropometric measurements were significantly lower at week 12 than at baseline in all groups (all $p < 0.017$)[69].

Adrenergic response to a combination of diet and exercise: When assessing the impact of weight loss programs that incorporate dietary modifications and exercise, evidence indicates a significant decrease in NA concentrations after weight loss [$p < 0.01$ [47] and $p < 0.05$ [53]. In addition, NA spillover rates were significantly lower after weight loss intervention with both diet plus exercise, whereas no changes in NA plasma clearance were recorded [53]. Additionally, Wirth et al. [68] revealed a decrease in both AD and NA plasma concentrations after 4 weeks in both the diet restriction and the diet restriction plus exercise groups ($p < 0.05$). Specifically, AD at rest declined by 45% in the diet restriction group and by 74% in the diet restriction plus exercise group [68].

Adrenergic response to weight loss surgery: With respect to surgical interventions, specifically bariatric surgery, there were no significant differences in AD or NA concentrations in subjects with obesity after bariatric surgery, with a 32% weight reduction [48]. However, NA concentrations were significantly lower in a group of subjects with both obesity and HT at both 4 and 12 months after bariatric surgery ($p < 0.05$) [65]. In addition, the NA excretion rate (nmol/24 h) significantly decreased ($p < 0.01$) in subjects with obesity 1 year after gastroplasty (Karason et al. [61]). Karason et al. [61] also reported that, after 1 year, the NA excretion rate was significantly higher in those who followed a dietary intervention than in those who underwent surgery ($p = 0.047$). However, the weight of the subjects in the dietary group increased during the intervention, whereas those who underwent surgery decreased their weight [61].

Adrenergic response to stress: Compared with their baseline values, subjects with obesity presented a significant increase in plasma NA concentrations under stressful conditions ($p < 0.001$). However, no significant difference was found between groups when comparing subjects with obesity with their normal weight counterparts. However, the percent change in NA (pre- vs. post-stress) was correlated with BF% ($r = 0.614$, $p = 0.044$) and BMI ($r = 0.733$, $p = 0.010$) in the group of subjects with obesity [71]. In addition, one session of social stress also induced a significant increase in plasma AD and NA concentrations in both subjects with obesity and overweight, however, subjects with obesity showed a higher hormonal response to psychosocial stress (AD, $p < 0.05$; NA, $p < 0.01$ in subjects with overweight vs. AD, $p < 0.01$; NA, $p < 0.001$ in subjects with obesity) [57]. Under mental stress, both AD and NA concentrations increased significantly in both groups of subjects with and without obesity (both $p < 0.001$), with subjects with HT showing heightened adrenergic responses to stress, suggesting enhanced sympathetic activation in response to mental stress in young untreated patients in the early stage of HT compared with healthy controls without any influence of obesity (both $p < 0.05$) [54].

Adrenergic response to the oral glucose tolerance test: The evidence indicates a significant increase in the NA concentration after oral glucose loading with subjects with obesity showing a significantly higher increase compared with their lean counterparts ($p < 0.001$) [74, 75], as well as in subjects with both obesity and HT compared with their normotensive counterparts [$p < 0.05$ [75] and $p < 0.001$ [74]]. In addition, a group of subjects with obesity had lower plasma concentrations of AD than their normal-weight counterparts did in response to glucose ($p = 0.018$), whereas NA concentrations did not significantly differ between groups. Suppression of AD secretion in response to carbohydrate ingestion was significantly blunted in overweight and obesity compared to subjects compared with normal weight subjects, indicating that most of the variance in basal AD was related to whole BF%, since fasting plasma AD concentrations were inversely correlated with BF% ($r = -0.437$; $p = 0.001$) [73]. After glucose loading, the sympathetic response, assessed by MSNA, was also blunted and delayed in a group of subjects with both obesity and insulin resistance compared with their insulin-sensitive counterparts, even when endogenous NA concentrations were similar in both the insulin-resistant and insulin-sensitive groups at baseline, which indicated that central adiposity was associated with a blunted MSNA response [58].

Effects of other variables, such as sex, ethnicity, genotype, insulin resistance and chronotype, on the adrenergic system

With respect to chronotype, subjects with both obesity and OSA, with an evening chronotype who reported sleeping less than 6.5 h per night, presented significantly higher concentrations of 24-h urinary AD ($p < 0.05$) and slightly, albeit no significantly, higher concentrations of 24-h urinary NA (NS; $p = 0.052$) than their morning chronotype counterparts did [59]. In addition, moving from morningness to eveningness scores was associated with an increase in BMI and neck circumference [59]. Moreover, sex-specific distinctions were observed within this context, since the levels of both urinary CAs were significantly higher in men with obesity than in women (both $p = 0.004$) [64]. Furthermore, the plasma concentration of AD was significantly in males than in females, irrespectively of BMI ($p = 0.001$); however, this sex difference disappeared after adjustment for body fat percentage (BF%), whereas no sex-related differences were found in NA concentrations [73].

With respect to ethnicity, differences were not found in NA concentrations between black and white females with obesity [49]. In addition, differences were not found in the CAs concentrations between the ADRB2-Glu27Glu genotype and the ADRB2-Gln27Gln genotype [50].

Both males and females with abdominal obesity and insulin resistance presented NA concentrations similar to those of their insulin-sensitive counterparts [47, 58]. However, MNSA and NA clearance were significantly higher in the insulin-resistant groups ($p < 0.05$), whereas the NA spillover rate was slightly higher, albeit not significantly different, in the insulin-resistant groups (NS; $p = 0.11$), as similar NA concentrations were detected in both groups [58].

DISCUSSION

Summary and reflection of the main results

In this systematic review, our primary aim was to identify differences in the adrenergic system between subjects with and without obesity. Additionally, we sought to explore these differences while considering obesity-associated comorbidities and possible modulators of the adrenergic system.

Overall, our review revealed heterogeneous results regarding neurotransmitter concentrations in adults with obesity. Most studies reported similar (10/17) or higher (6/17) plasmatic or urinary NA levels in individuals with obesity than in their counterparts without obesity, both at rest and during exercise. In contrast, studies on AD levels have shown similar (3/7) or lower (3/7) concentrations in individuals with obesity.

A meta-analysis (2019), which included approximately 1400 subjects, also revealed heterogeneous results regarding sympathoadrenal activity in human obesity when it was assessed via plasmatic or urinary NA assays [80]. Across more than 40 studies [80], NA plasma levels in subjects with obesity were reported to be lower, similar, or higher than those without obesity, suggesting that SNS activity does not significantly differ between subjects with and without obesity. However, studies have also reported lower plasma AD concentrations, both at rest and in response to stimuli such as physical activity [81], in agreement with our review. More recently, with a cross-sectional approach, Reimann et al. [73] described a lower fasting concentration of venous plasma metanephrine, a metabolite of AD, in individuals with obesity, suggesting not only lower AD secretion but also potentially lower AD storage, possibly linked to adrenal medullary dysfunction.

In a mouse model, overnutrition was shown to increase plasma NA levels leading to insulin resistance, adipose tissue dysfunction and hepatic steatosis [82]. The authors have shown that this metabolic dysfunction was due to lipolysis-induced free fatty acids release into the bloodstream, which can then accumulate in non-adipose tissues and disrupt insulin signaling [82].

The introduction of microneurography to assess MSNA in peripheral nerves provides more consistent findings than plasma CAs measurements. Recent meta-analyses demonstrate pronounced sympathetic overactivity in subjects with obesity [80] and MetS [83], even without concomitant comorbidities. Additionally, hyperinsulinemia appears to contribute to sympathetic activation independently of other metabolic factors [84].

Therefore, discrepancies in NA and AD levels across studies likely result from a combination of biological heterogeneity and methodological differences. In agreement with some authors [81], differences in baseline CAs levels and their responsiveness to physiological stimuli may be partially explained by individual variability in body composition, fat distribution, diet, sex, age, presence or absence of comorbidities, insulin sensitivity, and physical activity level. Our review highlights the role of body composition, particularly fat degree and distribution, in these discrepancies, with significant associations between CAs concentrations and anthropometric measurements. Higher NA concentrations correlate positively with both BF% and WHR, while AD concentrations display an inverse relationship with BF% [73], suggesting a potential link between these hormonal changes and obesity-related factors. Furthermore, the degree of sympathetic responsiveness was inversely related to measures of central adiposity [47]. Although the exact mechanisms by which central obesity triggers increased sympathetic activity are not fully understood, SNS activity associates more strongly with visceral than subcutaneous fat mass [53, 80, 83, 84]. Hence, visceral adiposity may be more relevant than traditional anthropometric measures such as body weight, BMI, WC, lean body mass, and subcutaneous fat [63]. In this context, differences in adiposity may also account for hormonal differences in AD between men and women [73]. In addition, our review highlighted a potential increase in adrenergic system activity in subjects with obesity and with an evening chronotype [59] or with insulin resistance. Besides, it is well known that aging is associated with progressive changes in body composition, including an increase in total fat mass, redistribution of fat from the subcutaneous to the visceral compartment, and a reduction in lean body mass [85, 86]. Moreover, CAs-induced lipolysis decreases with age, favoring adiposity and insulin resistance [87]. However, no conclusions can be drawn within the scope of this review, as it was not possible to examine data according to age.

Despite the limited number of studies, evidence suggests higher NA concentrations in subjects with OSA, MetS and congestive HF. In contrast, similar AD concentrations in subjects with OSA and MetS and higher AD concentrations in subjects with PCOS were found. However, the underlying reasons for this heightened adrenergic system activity remain unexplained. In addition, there are still conflicting views regarding whether subjects with HT exhibit abnormal adrenergic system activity based on plasma or urine CAs concentrations, in agreement with the ongoing debate outlined in prior reviews [88, 89]. Interestingly, when obesity and HT are both present in the same patient, the degree of sympathetic activation is higher than that in those with either condition alone [60, 90]. In addition, recently, SNS overactivity has been firmly established in the pathogenesis, maintenance and progression of HT [91]. Additionally, divergent findings across studies may be explained by the regional differences in SNS activity, which are inadequately captured by systemic CAs measurements [52]. Microneurography techniques have demonstrated that SNS responses vary between target organs and vascular beds, allowing localized overactivity despite unchanged plasma or urinary CAs levels. Therefore, measuring regional NA release is essential to capture organ-specific sympathetic tone and better understand selective activation patterns in different conditions [92].

Furthermore, beyond their release, the sympathetic tone regulation involves CAs transport and degradation mechanisms that may be also altered in obesity. The upregulation of extraneuronal CAs transport—primarily mediated by organic cation transporters (OCTs)—accelerates CAs metabolism, contributing to diminished lipolysis and adipose tissue dysfunction [87]. OCT3, expressed in adipocyte cell membranes, plays a key role in regulating β-adrenoceptors signaling by actively removing NA from the local microenvironment, thereby reducing extracellular concentrations and attenuating β-AR/cAMP/PKA signaling pathways [93].

Furthermore, both the variable expression of β and α_2 receptors in adipose tissue and the different CAs affinity for these receptors can lead to distinct metabolic responses to these hormones [94]. Moreover, the mechanisms underlying CAs resistance in adipocytes appear to involve β3-adrenergic receptor downregulation, although this process remains incompletely understood [95]. These biological factors, combined with technical variations in sampling protocols, timing, and handling procedures across studies, likely contribute to the observed inconsistencies in the literature regarding AD and NA levels in obesity.

In this review, we also aimed to understand how the adrenergic system responds in subjects with obesity when exposed to different stimuli, including stress, exercise, glucose intake and weight loss (induced by diet, exercise, or surgery). Overall, despite differences between studies, consistent patterns have emerged. Collectively, evidence suggests that stress can lead to significant adrenergic responses characterized by increased AD and NA concentrations [54, 57, 71]. In the case of obesity, while NA responses to stress may be similar to those in subjects with normal weight, there is evidence of a correlation between the NA response and obesity-related factors (BMI and BF%) [71]. In addition, subjects with obesity exhibit a diminished and delayed response to sympathetic stimuli, specifically glucose intake (both at rest and during exercise), compared with their lean counterparts. The reduced sensitivity of adrenergic receptors caused by obesity could further contribute to this phenomenon [96]. Furthermore, compared with their insulin-sensitive counterparts, with obesity, insulin-resistant subjects with MetS presented reduced NA spillover and delayed MSNA responses to oral glucose [47]. Reimann et al. [73] revealed that the AD response to oral glucose was diminished in subjects with increased BMI. Furthermore, BF% is a significant predictor of fasting AD concentrations and a determinant of sex differences in adrenal medullary function [73]. In terms of exercise, our results agree with a prior review reporting a significant increase in CAs concentrations in both subjects with and without obesity, regardless of the exercise type [96]. However, Zouhal et al. [96] reported that these concentrations remained lower in subjects with obesity compared to their counterparts without obesity in response to submaximal or maximal exercise. In contrast, our review presents conflicting results, as we found studies reporting similar [67] higher [67, 79] and lower [55] increases in NA concentrations in subjects with obesity than in their lean counterparts. Moreover, our review highlights that weight loss, particularly abdominal fat loss interventions, whether induced by diet, exercise or surgery, exerts a positive effect not only on reducing baseline adrenergic system activity, particularly NA concentrations, but also on restoring the impaired sympathetic response observed in subjects with obesity [47]. This effect also results in significant improvements in MetS components, including blood pressure; fasting plasma glucose, triglyceride, and high-density lipoprotein cholesterol levels; and insulin sensitivity [53]. Additionally, a decrease in WHR and abdominal fat mass was strongly associated with lower whole-body NA spillover, and changes in body weight, total body and trunk fat, and plasma leptin concentration were the main predictors of changes in MSNA. Therefore, the impact of weight loss on SNS might be dependent mainly on the degree of weight reduction [53].

Reflection on the interplay between obesity and the adrenergic system

Obesity appears to be linked to alterations in CAs release, reuptake, and responsiveness [71, 97–100]. However, the pathophysiological mechanisms involving adrenergic system overactivity and obesity need further elucidation. Additionally, the debate persists as to whether SNS activation is the cause or consequence of obesity. On the one hand, there is evidence indicating that chronic increased sympathetic activity can contribute to central obesity, hyperinsulinemia and elevated adipokine levels [101], creating a vicious cycle that may contribute to the development of conditions such as HT, MetS, and cardiovascular and kidney diseases [89]. Some reviews also support these connections, emphasizing that elevated baseline sympathetic activity, which is mainly determined by plasma NA concentrations, could predispose individuals to the development of obesity-related HT. In addition, it is also linked to future weight gain, higher blood pressure and elevated insulin levels [102, 103]. Furthermore, Lansdown and Rees [104] highlighted an association between common features of PCOS, such as central obesity, hyperinsulinemia and OSA, and chronic sympathetic overactivity, suggesting a role in its pathogenesis [104]. Moreover, blunted sympathetic responsiveness to stimuli such as an oral glucose load has been shown to be related to increased central adiposity [103]. On the other hand, there is also evidence indicating that obesity, impaired baroreflex sensitivity, hyperinsulinemia, and high levels of adipokines, such as leptin, may contribute to increased sympathetic nerve activity in metabolic abnormalities [104]. Furthermore, weight loss is associated with substantial improvements in glucose control, the plasma lipid profile, blood pressure, and reductions in leptin concentrations, suggesting a complex interplay between CAs and adiposity-related factors [53, 105].

In line with existing evidence, our review underscores the importance of adipose tissue, particularly visceral adipose tissue, in the interplay between the adrenergic system and obesity, regardless of whether sympathetic activation contributes to weight gain or results from obesity. First, CAs induce adipose tissue lipolysis [26, 106], and the desensitization of adrenergic receptors, caused by sympathetic activation, may contribute to weight gain [53, 107]. Furthermore, chronic sympathetic overactivity can potentially disrupt CAs signaling in fat tissue, leading to reduced metabolism and increased insulin resistance [104, 108, 109]. Second, dysregulated adipokine production and secretion from visceral fat, with a permissive role of leptin, can also trigger sympathetic activation [89]. Increased adiposity, along with elevated circulating leptin or changes in other products of visceral fat, may contribute to obesity-related sympathetic activation [110]. Third, there is evidence of an interaction between SNS activation and inflammatory pathways in adipose tissue. The presence of macrophages, which are more prevalent in adipose tissue from subjects with obesity, can lead to increased levels of proinflammatory factors such as tumor necrosis factor-α and interleukin-6 [103, 111]. Furthermore, recent findings indicate that macrophages [112] and adipocytes [113] are able to produce, secrete and respond to CAs, suggesting their role as key signaling molecules in the regulation of immune–metabolic crosstalk within adipose tissue [114].

Strengths and limitations of the review

This systematic review is not the first to identify differences in the adrenergic system in subjects with obesity; however, to the best of our knowledge, it is the first to consider the variability of factors inherent to obesity that may be related to these differences.

This systematic review has several limitations. The limited number of included studies, coupled with the inherent heterogeneity in experimental designs and baseline clinical conditions among subjects, challenges the establishment of direct comparisons among studies. In addition, indirect markers such as plasmatic or urinary AD or NA concentrations do not reflect regional differences in sympathetic nerve activity and are influenced by clearance, metabolism and uptake from the circulating blood [99]. In addition, the lack of a uniform cutoff for obesity across studies could introduce a potential source of bias since the definitions of obesity based on BMI and/or WC conducted to the exclusion of numerous studies during the screening phase. Thus, achieving consensus regarding the most accurate measure for characterizing obesity is crucial. A more comprehensive and careful characterization of subjects with obesity considering the presence of overt metabolic and cardiovascular diseases would be crucial in the scope of the review. Additionally, only a few studies have considered the potential impact of body fat distribution on subjects' differences in adrenergic system behavior. In this context, metrics such as BF%, WHR, WC and distinctions between visceral and subcutaneous body fat distributions could offer valuable insights into the relationship between the adrenergic system and obesity. An accurate assessment of the relationship between each of these components and neurohormonal activation could yield more valuable insights. Finally, the cross-sectional nature of most studies does not allow the establishment of causality.

Further studies

Future studies should focus on adrenergic system differences in terms of BF% and fat (visceral and subcutaneous) distributions. In addition, exploring variations in sympathetic nerve activity by specifically targeting visceral fat cells, also known for releasing CAs, could offer valuable insights into the distinctions between subjects with and without obesity. Additionally, further research should focus on determining the conditions and mechanisms linking adiposity to heightened sympathetic activity, as well as those associated with lower sympathetic activity. These findings could help to identify appropriate targets for better prevention and treatment of obesity. Additionally, to increase the reproducibility of plasmatic NA concentrations as a reflective measure of sympathetic activity, conducting assays on multiple robust samples and subsequently averaging the obtained data could be employed in further studies. Furthermore, prospective studies focusing on a large and wide population coupled with longer follow-up periods would address knowledge gaps in understanding the possible bidirectional relationship between obesity and the adrenergic system.

CONCLUSIONS

In summary, this systematic review highlights the complex interplay between CAs, obesity and, especially, adiposity-related factors. The evidence suggests a hyperadrenergic state in subjects with obesity coupled with a blunted response to sympathetic stimuli compared with their lean counterparts. Additionally, adrenergic overdrive seems to be potentiated when subjects with obesity are also diagnosed with obesity-associated comorbidities such as MetS, OSA, PCOS and congestive HF, whereas the results from studies involving subjects with both obesity and HT are less conclusive. The difference in those hormonal responses may be attributed to variations in body composition, since an intriguing association emerged between hormonal concentrations and BMI and BF%. In addition, abdominal visceral fat appears to be an important depot linking obesity and the SNS. The activation of the SNS appears to be regionally specific. Weight loss programs, whether induced by diet, exercise or surgery, exert a positive effect not only by reducing baseline adrenergic system activity, particularly NA concentrations, but also by restoring the impaired sympathetic response observed in subjects with obesity. Further studies are still needed to understand whether these differences are the cause or consequence of obesity. Moreover, there is a crucial need to explore the specific relationship between the adrenergic system and adipose tissue. Addressing this gap in research can advance our understanding of the mechanisms behind dysfunction in the adrenergic system related to obesity, leading to more effective and personalized approaches to address obesity and its associated complications.

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AUTHOR CONTRIBUTIONS

BA: conceptualization, methodology, analysis and writing of the original draft of the paper. FL: analysis and revised the final draft of the paper. LR: conceptualization, analysis, supervision and revised the final draft of the paper. All authors contributed and approved the final paper.

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COMPETING INTERESTS

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Correspondence and requests for materials should be addressed to Laura Ribeiro.