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Mechanism of Acupuncture in Treating Obesity: Advances and Prospects

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Abstract: Obesity is a common metabolic syndrome that causes a significant burden on individuals and society. Conventional therapies include lifestyle interventions, bariatric surgery, and pharmacological therapies, which are not effective and have a high risk of adverse events. Acupuncture is an effective alternative for obesity, it modulates the hypothalamus, sympathetic activity and parasympathetic activity, obesity-related hormones (leptin, ghrelin, insulin, and CCK), the brain-gut axis, inflammatory status, adipose tissue browning, muscle blood flow, hypoxia, and reactive oxygen species (ROS) to influence metabolism, eating behavior, motivation, cognition, and the reward system. However, hypothalamic regulation by acupuncture should be further demonstrated in human studies using novel techniques, such as functional MRI (fMRI), positron emission tomography (PET), electroencephalogram (EEG), and magnetoencephalography (MEG). Moreover, a longer follow-up phase of clinical trials is required to detect the long-term effects of acupuncture. Also, future studies should investigate the optimal acupuncture therapeutic option for obesity. This review aims to consolidate the recent improvements in the mechanism

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of acupuncture for obesity as well as discuss the future research prospects and potential of acupuncture for obesity.

Keywords: Obesity; Acupuncture; Electroacupuncture; Mechanism.

Introduction

Obesity is a common metabolic syndrome due to the energy imbalance between intake and consumption, leading to excessive body fat accumulation. The WHO defines obesity as BMI $\geq$ 30kg/m^2 (Whitlock *et al.*, 2009). The prevalence of obesity (BMI $\geq$ 30kg/m^2) increased from 3.2% to 10.8% in male adults and from 6.4% to 14.9% in female adults between 1975 and 2014 (Collaboration, 2016). It also forecasts that the overweight will be 38% of worldwide adults if the number continues rising at the same rate until 2030 (Kelly *et al.*, 2008).

The mechanisms of obesity include habits and customs, genetic predisposition, and social environment. The elevated levels of free fatty acids, inflammatory cytokines, and lipid intermediates in non-adipose tissues, as well as chronic overactivity of the sympathetic nervous system, are present in some patients with obesity, which account in part for multiple pathophysiological processes, such as cardiovascular diseases, metabolic diseases, musculoskeletal diseases, and gynecological diseases. Besides, the hypothalamus regulates food intake and energy expenditure by inhibiting or exciting circulating neuropeptide hormones (Blüher, 2019).

Conventional therapies for obesity include lifestyle interventions (such as dietary restriction and physical exercise), bariatric surgery, and drug treatment (Heymsfield and Wadden, 2017). However, lifestyle intervention is limited for elderly patients, and it's easy to regain weight after suspension (Heymsfield and Wadden, 2017). Bariatric surgery and drug treatment are associated with multiple side effects, such as malnutrition and gastrointestinal symptoms (Kalarchian *et al.*, 2014). Therefore, conventional therapies are limited to all patients with obesity, and we need to find alternative therapies that provide extra treatment strategies for different patients, such as acupuncture.

Acupuncture is an important part of traditional Chinese medicine that shows high effectiveness in various diseases with few side effects. Also, acupuncture is recognized by both WHO and the National Institute of Health (NIH) as one of the most popular complementary therapies in the world (Belivani *et al.*, 2013). By inserting needles into specific acupoints and using different acupuncture manipulation methods, the Deqi sensation (a compositional sensation of soreness, numbness, heaviness, and distention) is produced to achieve an ideal therapeutic effect. The most common acupuncture techniques used to treat obesity include manual acupuncture, electroacupuncture (EA), and catgut embedding. Previous studies have demonstrated that manual acupuncture is effective for weight loss (Fang *et al.*, 2017), while EA and catgut embedding present better properties in strengthening the Deqi sensation and improving the effect. EA transforms different electrical stimulation to acupoints by adjusting the frequency, waveform, intensity, and detention time (Kang *et al.*, 2022a; 2022b). Catgut embedding embeds absorbable thread into acupoints to produce long-lasting stimulation (Hong *et al.*, 2020).

The mechanisms of acupuncture in treating obesity are intricate and need further exploration. So far, more and more animal studies and clinical trials have been conducted and demonstrate the underlying mechanisms that are associated with the nervous system, hormones, brain-gut axis, inflammatory factors, adipose tissues, etc., eventually increasing energy expenditure and/or reducing energy intake. This paper aims to condense the advances in mechanism of acupuncture for obesity and discuss the prospects of treating obesity with acupuncture (Table 1).

Regulation of the Central Nervous System

Adipose tissue reflects the accumulation of energy, and the central nervous system (CNS) plays an important role in energy homeostasis by integrating and responding to various signals from peripheral nerves and related hormones (Kang *et al.*, 2022a; 2022b). The hypothalamus is the center of food intake and energy metabolism in the CNS, and it affects feeding by integrating neural signals that come from the brainstem or even higher cortical centers and peripheral humoral signals that influence energy expenditure and food intake, ultimately achieving the goal of weight control (Wang *et al.*, 2021b). Moreover, there are extensive appetite circuits between the hypothalamus and brainstem, especially the nucleus of the tractus solitaries (NTS) (Singh *et al.*, 2022). Acupuncture can effectively regulate the hypothalamus feeding center and related neuropeptides, as well as nuclei of the brainstem, which inhibit the sense of hunger while stimulating the sense of satiety (Ji *et al.*, 2013), eventually reducing weight (Fig. 1).

Hypothalamic Nuclei and Related Neuropeptides

Hypothalamus is divided into several interconnected nuclei, mainly including the arcuate nucleus (ARC), ventromedial hypothalamic nucleus (VMH), dorsomedial hypothalamic nucleus (DMH), paraventricular nucleus (PVN), and lateral hypothalamic area (LHA). These nuclei form complex networks to collectively modulate appetite by the connection of neuropeptide Y (NPY)/agouti gene-related protein (AgRP) neurons and pro-opiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons, which are projected from the ARC and have opposite functions in the regulation of appetite. Fu *et al.* suggested that EA treatment could reverse the abnormal expressions of obesity-related genes in the hypothalamus to achieve weight loss (Fu *et al.*, 2017). Besides, Yao *et al.* found that EA may reduce weight by modulating the expression of autophagy-related components in the hypothalamus, which is lower in obese mice and higher when it's undernourished (Yao *et al.*, 2022). These findings demonstrate the regulation of acupuncture in hypothalamus, and it's worth further exploring potential mechanisms for weight loss.

Arcuate Nucleus

The ARC is in the mediobasal hypothalamus, adjoins the third ventricle, and lies close to the median eminence. The ARC mainly consists of two distinct neuronal populations

Table 1. Mechanisms of Acupuncture in Treating Obesity

Mechanism		Model	Intervention Type	Comparison	Acupoints	Frequency (Duration)	Effects	Reference
Hypothalamic nuclei and related neuropeptides		SD rats	Manual acupuncture with EA	Blank control	Zusanli (ST36) Neiting (ST44)	Once per day (12 days)	1. Reduce excitation of LHA 2. Increase frequency of electric activity in VMH	Zhao *et al.* (2001)
		Wistar rats	EA	Blank control	Zusanli (ST36) Neiting (ST44)	Once per day (14 days)	1. Decrease serum leptin and INS levels 2. Increase hypothalamic leptin and INS levels and OB-R gene expression	Yang *et al.* (2007)
		Stat5NKO mice	EA	Blank control	Zusanli (ST36) Neiting (ST44)	6 times per week (4 wks)	Reverse the abnormal expressions of obesity-related genes in the hypothalamus	Fu *et al.* (2017)
		Wistar rats	EA	Sham EA Blank control	Zhongwan (RN12) Tianshu (ST25) Zusanli (ST36) Sanyinjiao (SP6)	5 times per week (4 wks)	Modulate the expression of autophagy-related components in the hypothalamus	Yao *et al.* (2022)
	ARC	SD rats	EA	Orlistat group-Blank control	Zusanli (ST36) Quchi (LI11)	Once per day (28 days)	Inhibit the expressions of AgRP and NPY	Liu *et al.* (2016)
		Rats	EA	Blank control	Tianshu (ST25) Zhongwan (RN12) Sanyinjiao (SP6) Zusanli (ST36)	5 times per week (30 days)	1. Regulate the appetite-related neuropeptides via the hypothalamic TSC1 promoter demethylation 2. Inhibit the activity of mTORC1 signaling pathway	Leng *et al.* (2018)

Table 1. (*Continued*)

Mechanism	Model	Intervention Type	Comparison	Acupoints	Frequency (Duration)	Effects	Reference
	Wistar rats	EA	Blank control	Zhongwan (RN12) Zusanli (ST36) Guanyuan (RN4) Fenglong (ST40)	3 times per week (8 wks)	1. Upregulate the protein and gene expressions of POMC 2. Downregulate protein and gene expressions of AgRP in the hypothalamus	Ren *et al.* (2020)
	SD rats	EA	Blank control	Zusanli (ST36) Sanyinjiao (SP6)	7 times per week (2 wks)	Stimulate α-MSH expression and release	Fei *et al.* (2011)
	Rats	EA	Sham EA Blank control	Zusanli (ST36) Zhongwan (CV12) Guanyuan (CV4) Fenglong (ST40)	Once every other day (8 wks)	Upregulate the SIRT1 and POMC expression of hypothalamus	Huang *et al.* (2019a)
	Wistar rats	EA	Blank control Sham operation group Agonist group	Zusanli (ST36) Guanyuan (CV4) Zhongwan (CV12) Fenglong (ST40)	Once every other day (7 wks)	1. Upregulate protein expression of hypothalamic SIRT1 2. Downregulate the acetylation level of FOXO1 in the hypothalamic arcuate nucleus 3. Decrease gene expression of NPY and increase that of POMC	Shu *et al.* (2020)
	Sprague–Dawley rats	EA	Restraint group-Blank control	Zusanli (ST36) Sanyinjiao (SP6)	3 times per week (4 wks)	Upregulate the expression of CART peptide in the arcuate nucleus	Tian *et al.* (2005)
VMH	SD rats	EA	Blank control	Zusanli (ST36) Neiting (ST44)	Once per day (12 days)	1. Elevate the level of dopamine 2. Decrease the level of 5-HT	Liu *et al.* (2000)

Table 1. (*Continued*)

Mechanism		Model	Intervention Type	Comparison	Acupoints	Frequency (Duration)	Effects	Reference
	PVN	SD rats	EA	Blank control	Zusanli (ST36) Neiting (ST44)	Once per day (14 days)	Reduce the frequency of spontaneous discharges of nerve cells in the PVN	Liu *et al.* (2003)
		SD rats	EA	Blank control	Zhongwan (RN12) Weishu (BL21)	Once per day (7 days)	1. Regulate gastric motility 2. Relate to the PVN-DVC-vagus-gastric neural pathway	Wang *et al.* (2015)
	LHA	SD rats	EA	Blank control	Zusanli (ST36) Neiting (ST44)	Once per day (12 days)	1. Reduce the level of NA in LHA 2. Increase the 5-HT and activity of ATPase	Liu *et al.* (2000)
		Rabbits	EA	EA + proprano-lol/phentol-amine	Zusanli (ST36) Neiting (ST44)	Once	Inhibit gastric hyperfunction caused by excitation of the LHA	Ma *et al.* (1994)
Brainstem		Obese prone rats Obese resistant rats	EA	Sham EA	Zusanli (ST36)	Once per day (7 days)	1. Increase POMC production in the NTS/HN 2. Induce expression of TRPV1-nNOS in the ST36 3. The NTS/gracile nucleus is involved in the signal transduction of EA's pathways	Ji *et al.* (2013)
		SD rats	EA	Blank control	Zusanli (ST36) Tianshu (ST25)	Once	1. 2 Hz EA treatment at ST36 shows the strongest excitatory effect 2. 100 Hz EA treatment at ST25 shows the strongest inhibitory effect on the NTS	Fang *et al.* (2017)

Table 1. (*Continued*)

Mechanism	Model	Intervention Type	Comparison	Acupoints	Frequency (Duration)	Effects	Reference
	SD rats	EA	Blank control	Zusanil (ST36) Neiting (ST44)	Once per day (12 days)	1. Increase the 5-HT level and 5-HT/5-HIAA ratio 2. Decrease the contents of Trp and 5-HIAA	Wei *et al.* (2003)
ANS	Wistar rats	EA	Blank control	Daju (ST27) Shuidao (ST28) Guilai (ST29) Sanyinjiao (SP6) Yinlingquan (SP9)	Once	Increase whole-body glucose uptake by activation of the sympathetic and partly the parasympathetic nervous systems	Benrick *et al.* (2017)
	SD rats	EA	Blank control	Zusanli (ST36)	Once per day (8 wks)	1. Enhance vagal activity 2. Promote ACh release and activated α7nAChRs in the MWAT 3. Inhibit pro-inflammatory cytokine production	Jie *et al.* (2018)
	SD rats	EA	Sham EA	Zusanli (ST36)	Once per day (1 wk)	1. Delay gastric emptying and increase small intestinal transit 2. Increase fasting plasma level of glucagon-like peptide-1 and peptide YY 3. Increase sympathetic activity and reduce vagal activity	Liu *et al.* (2015)

Table 1. (*Continued*)

Mechanism		Model	Intervention Type	Comparison	Acupoints	Frequency (Duration)	Effects	Reference
		Human	AA	Sham AA	Hunger point Stomach point Lung point Sanjiao point	Once per week (4 wks)	1. Cause sympathomimetic effects for the reduction in body weight temporarily 2. Increase basal metabolic rate and decrease appetite	Shen *et al.* (2009)
Hormone	Leptin	SD rats	EA	Blank control	Tianshu (ST25) Guanyuan (CV4) Zusanli (ST36) Sanyinjiao (SP6)	Once per day (21 days)	Inhibit the production of leptin	Li *et al.* (2021b)
		Wistar rats	EA	Blank control	Zhongwan (CV12) Guanyuan (CV4) Zusanli (ST36) Fenglong (ST40)	Every other day (8 wks)	1. Decrease the level of leptin protein in small intestine and hypothalamus 2. Increase the level of leptin receptor protein	Tian *et al.* (2021)
		Human	Catgut embedding	Sham catgut embedding	Tianshu (ST25) Zhongwan (CV12) Ganshu (BL18) Shuidao (ST28) Guilai (St29) Pishu (BL20) Danshu (BL19) Weishu (BL21) Dachangshu (BL25) Sanjiaoshu (BL22) Daimai (GB26)	Once per 2 weeks (12 wks)	1. Decrease level of serum leptin 2. Inhibit the expression of pro-inflammatory factors	Wan *et al.* (2022)

Table 1. (*Continued*)

Mechanism		Model	Intervention Type	Comparison	Acupoints	Frequency (Duration)	Effects	Reference
	Ghrelin	Human	Acupuncture	Sham acupuncture	Hegu (LI4) Shenmen (HT7) Zusanli (ST36) Neiting (ST44) Sanyinjiao (SP6)	Twice per week (5 wks)	Increase plasma ghrelin level	Güçel *et al.* (2012)
		Human	AA	Sham AA	Hunger point Shenmen point Stomach point Endocrine point	Twice per week (6 wks)	1. Increase ghrelin level 2. Decrease leptin level	Hsu *et al.* (2009)
	Insulin	Human	EA with intradermal needling	EA	Tianshu (ST25) Daheng (SP15) Zusanli (ST36) Shangjuxu (ST37) Quchi (LI11) Pishu (BL20) Weishu (BL21)	3 times per week (3 months)	1. Improve IR 2. Inhibit lymphangiogenesis 3. Promote lymphatic endothelial permeability	Xia *et al.* (2022a)
		Human	EA	Lifestyle control	Zhongwan (CV12) Quchi (LI11) Shuifen (CV9) Huaroumen (ST24) Daheng (SP15) Guanyuan (CV4) Qihai (CV6)	3 times per week (12 wks)	Alleviate IR	Dong *et al.* (2020)
		Wistar rats	EA	Blank control	Zhongwan (CV12) Guanyuan (CV4) Zusanli (ST36) Fenglong (ST40)	3 times per week (8 wks)	1. Reduce the inflammatory response 2. Improve peripheral insulin sensitivity by inhibiting	Lu *et al.* (2022)

Table 1. (*Continued*)

Mechanism	Model	Intervention Type	Comparison	Acupoints	Frequency (Duration)	Effects	Reference
						the TLR4/NF-κB pathway in liver tissues	
	Wistar rats	EA	Blank control Sham EA	Zhongwan (CV12) Guanyuan (CV4) Zusanli (ST36) Fenglong (ST40)	Once every other day (8 wks)	1. Increase contents of glucose of IPGTT and IPITT, serum INS, CRP, IL-6 and TNF-α, expression levels of IL-6, TNF-α, IL-1β and MCP-1 proteins and mRNAs and CD68 protein 2. Reverse decreased levels of GIR and IL-10 protein and mRNA	Huang *et al.* (2019b)
CCK	Wistar rats	EA	Blank control Sham EA	Fenglong (ST40) Zhongwan (CV12) Guanyuan (CV4) Zusanli (ST36)	Once every other day (8 wks)	1. Increase serum level of INS 2. Decrease GIR, serum CCK level, c-fos expression in AP and NTS	Song *et al.* (2020)
	Wistar rats	EA	Blank control	Guanyuan (CV4) Zhongwan (CV12) Tianshu (ST25) Zusanli (ST36) Fenglong (ST40)	3 times per week (8 wks)	Regulate intestinal motility, food intake, and secretion of LEP and CCK	Wang *et al.* (2020)
Gut microbiota	SD rats	EA	Blank control	Daimai (GB26)	3 times per week (8 wks)	1. Modify the composition of gut microbiota 2. Decrease Firmicutes/Bacteroidetes ratio and increase Prevotella _9 abundance	Wang *et al.* (2019)
	C57BL/6 mice	EA	Blank control	Tianshu (ST25) Guanyuan (CV4)	Once per day (21/28 days)	Promote the diversity of gut microbiota	Dou *et al.* (2020)

Table 1. (*Continued*)

Mechanism	Model	Intervention Type	Comparison	Acupoints	Frequency (Duration)	Effects	Reference
				Zusanli (ST36) Sanyinjiao (SP6)			
	Wistar rats	EA	Blank control	Zusanli (ST36)	Once per day (3 days)	1. Increase protein expression of occludin and permeability of the intestinal barrier 2. Reduce serum D-lactate levels	Zhang *et al.* (2018)
	SD rats	EA	Blank control	Zusanli (ST36)	Low-frequency EA group: Once per day (1 day) High-frequency EA group: 4 times per day (1 day)	1. Improve intestinal injury index 2. Protect intestinal mucosal immune barrier	Zhu *et al.* (2015)
	C57BL/6J mice	EA	Blank control	Tianshu (ST25) Zusanli (ST36) Guanyuan (RN4) Zhongwan (RN12)	Once per day (3/7/14/21 days)	1. Promote intestinal defensins 2. Rescue dysbiotic cecal microbiota 3. Reduce lipid absorption in a synergistic mode	Xia *et al.* (2022b)
Inflammation	Wistar rats	EA	Blank control Resveratrol group	Zusanli (ST36) Fenglong (ST40) Zhongji (CV3) Guanyuan (CV4)	3 times per week (9 wks)	Decrease pro-inflammatory type of macrophage-macrophage-1 in WAT	Luo *et al.* (2018)
	C57BL/6J miice	EA	Blank control	Tianshu (ST25) Guanyuan (CV4)		Modulate inflammatory response and macrophage	Wang *et al.* (2021a)

Table 1. (*Continued*)

Mechanism	Model	Intervention Type	Comparison	Acupoints	Frequency (Duration)	Effects	Reference
				Zusanli (ST36) Sanyinjiao (SP6)	Once per day (7/14/21/28 days)	polarization in obese adipose tissues	
	C57BL/6 mice	Catgut embedding	Blank control	Zusanli (ST36) Fenglong (ST40)	Once per 10 days (40 days)	1. Decrease M1 labeled iNOS and pro-inflammatory cytokines IL-6, MCP-1, TNF-α 2. Upregulate M2 macrophage labeled arginase-1 (Arg-1)	Li *et al.* (2021a)
	WKY rats	Warm needling acupuncture	Manual acupuncture	Zusanli (ST36)	Once per day (10 days)	1. Reduce the systolic pressure 2. Reduce the inflammatory factors (MMP-9, IL-6, TNF-α)	Shenbo *et al.* (2019)
Adipose tissue	C56BL/6 mice	EA	Blank control	Zusanli (ST36) Neiting (ST44)	6 times per week (4 wks)	Promote adipose tissue plasticity via activating sympathetic nerves	Lu *et al.* (2019)
	SD rats	EA	Blank control	Tianshu (ST25)	6 times per week (4 wks)	1. Remodel WAT to BAT through inducing SIRT-1 dependent PPARγ deacetylation 2. Regulate PGC-1α-TFAM-UCP1 pathway to induce mitochondrial biogenesis	Tang *et al.* (2020)
	Wistar rats	EA	Blank control	Guanyuan (CV4) Zhongwan (CV12) Zusanli (ST36) Fenglong (ST40)	3 times per week (8 wks)	1. Upregulate the protein expression of SIRT1 in WAT 2. Activate Wnt/β-catenin pathway	Wang *et al.* (2021c)

Table 1. (*Continued*)

Mechanism		Model	Intervention Type	Comparison	Acupoints	Frequency (Duration)	Effects	Reference
							3. Inhibit the expression of PPARγ of downstream lipogenic gene	
Others	SO	Human	EA	Oral essential amino acids	Binao (LI14) Quchi (LI11) Biguan (ST31) Liangqiu (ST34)	Once every 3 days (12 wks)	1. Decrease BFP 2. Increase ASM/H2 3. Increase muscle mass	Zhou *et al.* (2018)
	Hypoxia	C57BL/6J mice	EA	Blank control	Zusanli (ST36)	3 times per week (1/2 wks)	Modulate HIF-1α-dependent pathways and inflammatory response in obese adipose tissues	Wen *et al.* (2015)
	ROS	C57BL/6 mice	Acupuncture	Blank control Sham acupuncture	Guanyuan (CV4) Zusanli (ST36) Yishu (EXB3)	Once per day (8 wks)	1. Regulate oxidative stress and inhibit apoptosis in liver	Zhang *et al.* (2020)

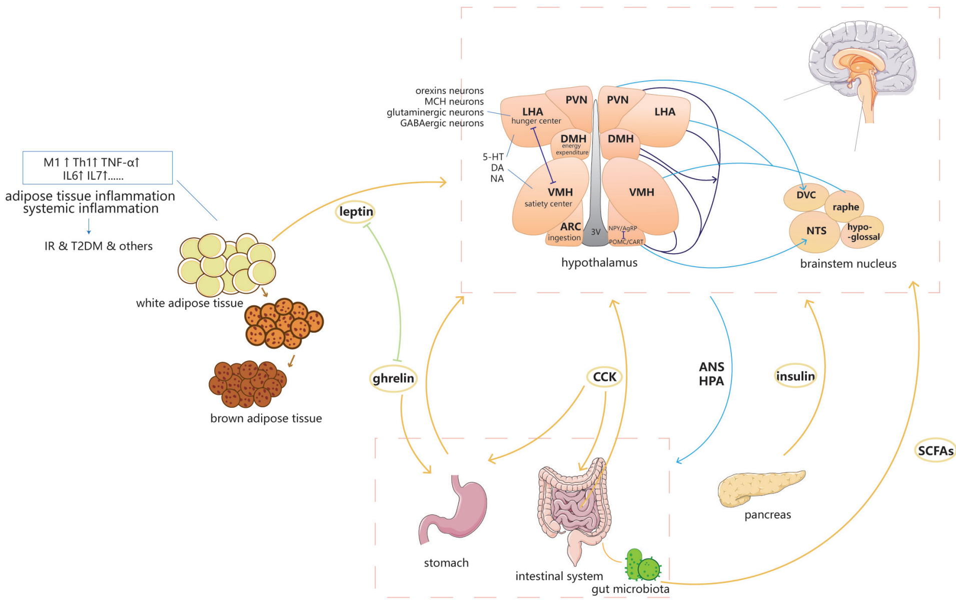

Figure 1. This figure illustrates the main regulation of energy homeostasis by the CNS, and the interplay between the CNS and the peripheral system. ANS: autonomic nervous system; ARC: arcuate nucleus; CCK: cholecystokinin; DMH: dorsomedial hypothalamic nucleus; DVC: dorsal vagal complex; HPA: hypothalamic-pituitary-adrenal; IL-6: interleukin-6; IL-7: interleukin-7; IR: insulin resistance; LHA: lateral hypothalamic area; M1: macrophage-1; M2: macrophage-2; NTS: nucleus of the tractus solitaries; PVN: paraventricular nucleus; SCFAs: short-chain fatty acids; TNF-α: tumor necrosis factor-α; T2MD: type-2 diabetes; VMH: ventromedial hypothalamic nucleus.

releasing opposite neuropeptides to regulate appetite. One releases NPY and AgRP to promote appetite and stimulate food intake, and another expresses POMC and CART to inhibit appetite and reduce food intake (Vohra *et al.*, 2022). Several studies have suggested that acupuncture can reduce weight by regulating both NPY/AgRP and POMC/CART.

Regulation of NPY/AgRP Neurons

The NPY neurons are mainly distributed in ARC and DMH, and the axons of the nerve fibers are primarily projected in the PVN and LHA. NPY is a pivotal neuropeptide to promote food intake and belongs to the pancreatic polypeptide family and abundantly exists in the neurons of both the central and peripheral nervous systems. A study has reported that the level of NPY decreases during high-fat feeding (Hassan *et al.*, 2019). Different from NPY, AgRP is uniquely expressed in the ARC and co-expressed with most NPY neurons. AgRP antagonizes the secmelanocortin-3 and melanocortin-4 receptors (MC3R and MC4R) to induce intense hunger and subsequent food intake. Thus, the NPY/AgRP neurons work together to enhance appetite and food intake (Wang *et al.*, 2021b). EA can reduce weight by inhibiting the expressions of AgRP and NPY and improve insulin resistance (IR) (Liu *et al.*, 2016).

Furthermore, a study has demonstrated that EA can regulate appetite-related neuropeptides via hypothalamic TSC1 promoter demethylation and inhibition of the activity of mTORC1 signaling pathway. The methylation of TSC1 gene promoter and expression of mTORC1, *NPY*, and AgRP genes increased while POMC decreased in the hypothalamus of obese mice. However, after EA treatment, the mice had significantly decreased methylation of the *TSC1* gene promoter, mRNA, and protein of the mTORC1 and the expression of NPY and *AgRP* genes, and significantly increased the POMC level (Leng *et al.*, 2018). Ren *et al.* also reported that EA can upregulate the protein and gene expressions of POMC and downregulate the protein and gene expressions of AgRP in the hypothalamus, thus significantly reducing the desire for food intake in obese rats (Ren *et al.*, 2020). In addition, Y1 receptor (Y1R) is the key NPY receptor that is related to appetite, and the peripheral selective antagonist of Y1R can suppress food-related obesity (Yan *et al.*, 2021). However, the acupuncture study about Y1R is limited, which could be a potential research area in the future study.

Regulation of POMC/CART Neurons

The POMC neurons are mainly located in the ARC and brainstem and are projected onto other nuclei to constitute the neural circuits. POMC is a neuropeptide that inhibits feeding and is also an important part of the central melanoprotein pathway by cleaving to produce α-melanocyte stimulating hormone (α-MSH) to inhibit food intake (Ju *et al.*, 2022). Selective destruction of POMC in the ARC can increase food intake, reduce energy expenditure, and lead to obesity-related metabolic and endocrine disorders. Like AgRP, CART neurons are co-expressed with POMC in the ARC and are abundant in the ARC and PVN. CART is considered a major anorexigenic peptide related to reward, reinforcement, endocrine regulation, and stress. CART-knockout mice showed an increase in body weight, while the intracerebroventricular administration of CART inhibited food intake and weight gain (Liu *et al.*, 2022). Briefly, the POMC and CART neurons work together to control appetite. EA can upregulate the protein and gene expressions of POMC, and a study has reported that EA significantly inhibited food intake and weight gain via stimulating α-MSH expression and release (Fei *et al.*, 2011).

Moreover, another study has proven that EA increased Sirtuin 1 (SIRT1) and POMC expression, which reduced body weight, food intake, and metabolism in obese rats. SIRT1 is a deacetylase that contributes to obesity when overexpressed in POMC neurons (Liu *et al.*, 2021). Similarly, Shu *et al.* (2020) revealed that EA enhanced the expression of hypothalamic SIRT1 and inhibited the acetylation level of FoxO1 (forkhead box protein O1, a kind of downstream substrate of SIRT1 (Sasaki *et al.*, 2014)) in the ARC, leading to a decreased expression of NPY and an increased expression of POMC. Besides, the level of CART peptide decreased in the hypothalamus in diet-induced obesity (DIO) rats, while it increased after treatment with EA, resulting in less food intake (Tian *et al.*, 2005).

Ventromedial Hypothalamic Nucleus

The VMH, known as the "satiety center", mainly receives projections from NPY/AgRP and POMC neurons from the ARC and then projects its axons to other hypothalamus nuclei and the brainstem. The VMH plays a vital role in energy metabolism and food intake and is antagonistic to the LHA. Studies have suggested that lesions of the VMH can lead to hyperphagia and obesity, while the electrical stimulation of VMH results in decreased food intake (Iovino *et al.*, 2022). Liu *et al.* found that the frequency of spontaneous discharges of neurons in the VMH was lowered significantly in the obese rats, but this was higher than the control group after EA treatment at ST36 and ST44 (Liu *et al.*, 2000). This research further demonstrated that after EA treatment, the level of dopamine (DA) elevated, while that of 5-hydroxytryptamine (5-HT) decreased. In obese patients, a low level of DA is found in the brain, which is associated with impaired peripheral insulin sensitivity and β-cell function (Kullmann *et al.*, 2020). Interestingly, 5-HT is known as an anorexigenic factor, and medications increasing 5-HT bioavailability are effective in D'Agostino *et al.* (2018). The potential mechanism could involve the reduced DA concentration and increased 5-HT concentration inhibiting the function of VMH, meaning other orexigenic nuclei are relatively active and EA helps enhance the excitability of VMH.

Dorsomedial Hypothalamic Nucleus

The DMH, located on the dorsal side of the VMH, receives projections from the NPY/AgRP neurons and links to other hypothalamus nuclei. The DMH is also named the "energy expenditure center" (Rønnekleiv *et al.*, 2022) because the activation of DMH improves energy expenditure, which is also how DMH regulates body temperature. Several studies have found that DMH neurons are related to appetite and emotion by inhibiting food intake, and lesions of the DMH can disrupt the diurnal feeding pattern and result in obesity (Maejima *et al.*, 2021). However, there is limited evidence about how acupuncture modulates the DMH, and existing studies are not only antique, but all involved in the process of acupuncture analgesia (Huang *et al.*, 1995). Additional mechanisms in future studies remain to be further explored to explain the role of the DMH in improving obesity by acupuncture treatment.

Paraventricular Nucleus

The PVN is located on the top of the hypothalamus and the side of the third ventricle, constituting pivotal second-order neurons downstream of the ARC. It mainly integrates the projections of the AgRP/NPY from the ARC and is also sensitive to many appetite-related neuropeptides. A study has suggested that triggering the glucose-excited neurons in the PVN increases food intake in rats (Wang *et al.*, 2018). Liu *et al.* reported that acupuncture can reduce the frequency of spontaneous discharges of nerve cells in the PVN to reduce food intake (Liu *et al.*, 2003). Besides, the PVN serves as a central nucleus for modulating gastrointestinal activities by the PVN-dorsal vagal complex (DVC)-vagus-gastric neural pathway. Wang *et al.* proved that the EA signals at RN12 and BL21 can gather in the PVN via destroying the PVN and detecting its c-fos (identified as a sign of active neurons), which suggests that EA might regulate gastric motility through the PVN-DVC-vagus-gastric neural pathway (Wang *et al.*, 2015). In addition, the expression of brain-derived neurotrophic factor (BDNF) in the PVN suppresses food intake and regulates heat production to help keep energy balance (An *et al.*, 2020), but more studies are required to elucidate the relationship between acupuncture and BDNF.

Lateral Hypothalamic Area

The LHA, known as the "feeding center" or "hunger center", is the main neuromodulator in triggering ingestion. The LHA contains various orexigenic neurons, such as orexins, melanin-concentrating hormone (MCH), and GABAergic and glutaminergic neurons. The lesion of the LHA reduces appetite and weight, while activation of the LHA causes hyperphagia and obesity (Marino *et al.*, 2020). Acupuncture can reduce the excitability of the LHA, inhibit hyperphagia, and regulate the activity of 5-HT, the catecholamine neurotransmitter, and ATPase activity in the LHA, eventually leading to weight loss. This animal study has also demonstrated that acupuncture reduced the level of noradrenaline (NA) in the LHA and increased the activity of 5-HT and ATPase, resulting in weight loss (Zhicheng *et al.*, 2000). Besides, another study has reported that EA treatment significantly inhibits gastric hyperactivity by triggering the LHA in rabbits (Ma *et al.*, 1994).

Brainstem

The brainstem also plays a key role in integrating signals from the peripheral to CNSs and regulating energy metabolism (Su *et al.*, 2022). The NTS is an important part of hypothalamus and the brainstem in appetite regulation. The NTS receives peripheral circulation and vagal afferents from the gastrointestinal tract signals, and meanwhile contains many POMC neurons related to energy homeostasis. The raphe nuclei participate in food intake as well. The raphe nuclei are the central serotonergic neurons that mainly originate from the raphe nucleus and innervate the hypothalamus including the LHA and VMH. Ji *et al.* revealed that EA treatment at ST36 upregulated POMC production in the NTS and hypoglossal nucleus (HN) regions to prevent food intake and enhance weight loss (Ji *et al.*, 2013).

Interestingly, a study has suggested that different EA frequencies and different acupoint combinations lead to different effects on the NTS. 2Hz EA treatment at ST36 showed the strongest excitatory effect, while 100Hz EA treatment at ST25 showed the strongest inhibitory effect on the NTS neurons in normal rats (Fang *et al.*, 2017). Besides, in obese rats, 5-HT content and the 5-HT/5HIAA ratio decreased, while the 5-HT precursor Trp and metabolite 5-HIAA levels increased in the raphe nuclei. Possibly, the dysfunction of raphe nuclei affects the LHA and VMH through 5-HT neurons and then participates in food intake (Su *et al.*, 2022). Wei *et al.* found that the 5-HT content, 5-HT/5HIAA ratio, and metabolic rate of 5-HT in the raphe nuclei significantly increased after acupuncture, leading to weight loss in obese rats (Wei *et al.*, 2003). The parabrachial nucleus, ventral tegmental area, and locus ceruleus in the brainstem are also closely related to energy balance and obesity (Su *et al.*, 2022), which needs further exploration due to the limited evidence related to acupuncture at present.

Modulation of Autonomic Nervous System

The autonomic nervous system (ANS) is divided into sympathetic activity and parasympathetic activity, which play significant roles in energy balance. Obesity is associated with perturbations of the ANS, leading to the imbalance of sympathetic activity and parasympathetic activity (Russo *et al.*, 2021). However, acupuncture bi regulates the dysfunction of the ANS and improves neurological function. A clinical study has explored the underlying mechanism of a single bout of low-frequency EA immediately increasing whole-body glucose uptake in overweight and obese women, and demonstrated that this effect was associated with the activation of the sympathetic and partly the parasympathetic nervous systems, but was not related to the opioid receptor system (Benrick *et al.*, 2017). Stimulation of the vagal nerve increases energy expenditure and reduces Body Mass Index (BMI). An animal study found that EA reduced weight as well as the inflammatory status of DIO rats through enhancing vagal activity. The vagal activity stimulated the release of acetylcholine, leading to the promotion of 7-sub-type nicotinic acetylcholine cholinergic receptors which inhibits the release of some pro-inflammatory cytokines (Jie *et al.*, 2018).

Controversial results arose in another animal study that found that in DIO rats, EA promoted sympathetic activity and decreased vagal activity, while the food intake and weight of DIO rats were both reportedly reduced. The underlying mechanisms include gastrointestinal motility and hormones related to autonomic pathways (Liu *et al.*, 2015). The two opposite findings require further investigation into how EA exerts different effects on the ANS in DIO rats. In addition, auricular acupuncture (AA) is a systematic approach to treat obesity since it is inexpensive and easily accessible. The mechanism of AA is associated with the ANS, and it has been proven in a clinical study that four-week stimulation of AA significantly reduced body weight by sympathomimetic effects that temporarily enhanced basal metabolic rate and inhibited appetite (Shen *et al.*, 2009).

Relation of Hormone

Leptin

Leptin is a molecule which is primarily secreted by adipose tissue and plays a crucial role in regulating metabolism and energy homeostasis. Leptin acts mainly in the brain to regulate neuroendocrine function (mainly reproductive) and only secondarily in the periphery but circulates at levels proportional to the percentage of fat mass in the body (Perakakis *et al.*, 2021). Like diabetes, there are two forms of leptin disturbance in obese patients. Type 1 obesity is considered as leptin deficiency with low levels of plasma leptin and leptin sensitivity, and reacts positively to leptin treatment. However, type 2 obesity is defined as obesity associated with elevated plasma leptin levels and leptin resistance, which is blunt to leptin treatment. Type 2 obesity presents more often in human beings, the level of plasma leptin is significantly increased and is highly associated with adipose tissue mass (Friedman, 2019).

Both animal and clinical studies have demonstrated the effect of acupuncture in modulating plasma leptin levels, especially for type 2 obesity, and acupuncture significantly ameliorates the elevated plasma leptin levels and reduces leptin resistance, eventually leading to weight loss. An animal study applied 21 sessions of acupuncture treatment on obese Sprague-Dawley (SD) rats and evaluated weight and serum leptin levels. It was found that acupuncture can boost metabolism and reduce weight by inhibiting the production of leptin (Li *et al.*, 2021b). The same results were found in another animal study, whereas the study also assessed the level of leptin receptors. After an eight-week EA treatment, the levels of leptin protein in small intestine and hypothalamus were significantly downregulated and the leptin receptor protein levels were significantly upregulated, which indicates the effect of acupuncture in improving leptin resistance (Tian *et al.*, 2021). Besides, 144 individuals with common obesity were randomly assigned into a catgut embedding group and sham group. After 12 weeks of treatment, individuals in the catgut embedding group presented a decreased level of serum leptin without severe adverse events (Wan *et al.*, 2022).

Ghrelin

Ghrelin is a gastric hormone that has the opposite physiological functions to leptin. Ghrelin is also called “the hunger hormone” due to its response to fasting situations, the ghrelin receptor is triggered in the brain to initiate appetite (Ouerghi *et al.*, 2021). Also, ghrelin differentially affects food intake behavior via vagal afferent neurons compared with brain signaling pathways. The activation of brain signaling pathways leads to increased meal size but has no effect on meal frequency, whereas through the vagal afferent neuron pathway, meal frequency increases but the cumulative intake is unaltered (Davis *et al.*, 2020). Although an increase in ghrelin causes excessive appetite and weight gain, obese patients have decreased plasma ghrelin levels, which increase in response to weight loss as a compensatory mechanism (Liu *et al.*, 2015). Acupuncture can partly restore ghrelin impairment. Funda *et al.* (Güçel *et al.*, 2012) performed 10-session manual acupuncture on obese women and suggested an increase in plasma ghrelin levels and a decrease in BMI in subjects who received acupuncture treatment. Besides, AA can significantly enhance ghrelin levels in obese women (Hsu *et al.*, 2009). However, studies related to ghrelin, acupuncture, and obesity are limited, requiring further investigation.

Insulin

Insulin, an anabolic hormone secreted by the β cells of the pancreas, favors energy storage in the condition of energy surplus (Mittendorfer *et al.*, 2022). Upon lipid metabolism, insulin works as a far-sparing hormone that increases lipogenesis and decreases lipolysis and lipid oxidation. Moreover, insulin improves glucose uptake and glycogen synthesis, while inhibiting gluconeogenesis through the PI3K/Akt pathway (Huang *et al.*, 2020). The modest rise of fasting insulin levels will substantially affect energy metabolism; thus, insulin dysregulation promotes fat storage, eventually leading to obesity. Indeed, several data support that decreasing insulin levels reverse DIO (Page *et al.*, 2018). Of note, growing evidence suggests that acupuncture can reduce insulin levels to lose weight.

A clinical study has demonstrated that EA reduced body weight and fasting insulin (FINS) levels and improved the insulin resistance index (HOMA-IR) in simple obese patients. The combination of EA and intradermal needling further promoted fasting insulin and IR, which is associated with inhibition of lymphangiogenesis and an increase of lymphatic endothelial permeability (Xia *et al.*, 2022a). Similarly, Dong *et al.* reported that EA combined with lifestyle control effectively alleviated hepatic fat status and IR (Dong *et al.*, 2020). The improvement of IR after acupuncture treatment may be related to the Toll-like receptor 4/nuclear factor kappa B (TLR4/NF-κB) inflammatory pathway in liver, which has been confirmed in several animal studies (Lu *et al.*, 2022). Compared with the model group, the serum level of FINS and HOMA-IR, tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) were decreased, and the protein expressions of TLR4, IκB kinase β (IKKβ), phosphorylated IKKβ (p-IKKβ), NF-κB p65, and TNF-α in liver tissues were also downregulated in the EA group (Lu *et al.*, 2022).

Cholecystokinin

Cholecystokinin (CCK) originates from the I cell found through the gastrointestinal tract and concentrates in the duodenum and jejunum (Steinert *et al.*, 2017). CCK has been known to be a key satiety signal and exerts inhibitory effects on food intake, which is associated with increasing intestinal motility and a decreasing gastric emptying rate (Tacad *et al.*, 2022). A previous study has found that the infusion of exogenous CCK in humans significantly reduced food intake and increased satiety immediately after the infusion (Lieverse *et al.*, 1994). A similar situation was found after being treated with EA. Song *et al.* demonstrated that the mechanism of EA in reducing appetite, body weight, and facilitating insulin sensitivity links to the enhancement of CCK (Song *et al.*, 2020). Another study further illuminated that the increase of CCK induced by EA was irrelevant to different acupuncture point selections, and both abdominal acupuncture points (ST25, CV4 and CV12) and lower limb acupoints (ST36 and ST40) could significantly stimulate the expression of serum CCK (Wang *et al.*, 2020). Nevertheless, whether EA has a long-term effect on enhancing CCK levels needs further investigation, since several studies have reported that CCK infusion failed to have long-lasting effects on food intake and satiety (Murphy *et al.*, 2006). Thus, the long-term effect of EA may compensate for such deficiency.

Brain-Gut Axis

The brain-gut-microbiome (BGM) axis has emerged as a pivotal regulator of energy metabolism, and the bidirectional signal from the axis has been associated with the development of obesity. The signal from the brain contributes to many gastrointestinal processes, such as motility and transit, and intestinal permeability through ANS and the hypothalamic-pituitary-adrenal (HPA) axis (Aron-Wisnewsky *et al.*, 2021). Conversely, the gut microbiota reflects through hundreds of metabolites, and short-chain fatty acids (SCFAs) are the main metabolite of microbial fermentation of dietary fiber, mediating the brain through immune, endocrine, and vagal pathways (Canfora *et al.*, 2019). The perturbations of the BGM system may lead to hedonic-driven eating behavior (cravings and overeating), and less energy expenditure, disturbing energy metabolism and eventually causing weight gain (Li *et al.*, 2022). Brain levels, including the CNS, ANS, and related hormones, have been discussed above. It is believed that acupuncture also regulates the gut level to reduce weight. Previous studies used 16S rRNA gene sequencing combined with high-performance liquid chromatography-mass spectrometry (HPLC-MS) metabolic profiling to figure out the effect of EA in changing gut microbiota for obese individuals. A total of 10 mainly disturbed bacterial genera and 11 metabolites were recognized, which recovered to normal levels after being treated with EA (Si *et al.*, 2022). Besides, the Firmicutes/Bacteroidetes ratio is associated with the increased risk of obesity. Acupuncture can significantly decrease Firmicutes abundance and enhance Bacteroidetes abundance, lowering the Firmicutes/Bacteroidetes ratio. At the genus level, acupuncture elevated the proportion of Prevotella 9 in abdominal obese rats (Wang *et al.*, 2019). Except for rescuing dysbiotic gut microbiota, acupuncture, particularly EA, is able to regulate the damaged enteric neurvous system (Dou *et al.*, 2020), promote the intestinal mucosal barrier (Zhang *et al.*, 2018), strengthen sIgA contents, adjust the subtypes of intestinal T lymphocytes (Zhu *et al.*, 2015), and upregulate multiple mucosal innate immunity-related alpha-defensin genes (Xia *et al.*, 2022b), thus leading to an anti-obesity effect.

Impact of Inflammatory Factors

There are two forms of adipocyte change during excessive energy storage which undergo hypertrophy and hyperplasia. The hyperplastic potential of visceral adipocytes is limited; thus, with the enlargement of visceral adipocytes, these cells become inadequately vascularized and hypoxic, resulting in cell stress, apoptosis, immune cell infiltration, increased secretion of inflammatory cytokines (such as IL-6 and TNF-α), and decreased secretion of anti-inflammatory cytokines, such as adiponectin (Eley *et al.*, 2021). Additionally, the innate immune system and adaptive immune system play critical roles in adipose tissue inflammation and low-degree systemic inflammation in obese humans and mice, which is associated with infiltrating and tissue-resident macrophages (Ying *et al.*, 2020) and increased CD4+ and CD8+ T cells in visceral adipose tissue, respectively (Yang *et al.*, 2010). As discussed previously, obesity is highly regulated by gut microbiota, which also contributes to enhancing interferon-g (T helper (Th)-1 immunity) and IL-17 (T helper (Th)-17 responses), leading to adipogenesis and systemic inflammation (Henao-Mejia *et al.*, 2012). The inflammatory status of obese patients increases the risk of obesity-related complications, especially IR and type 2 diabetes. However, anti-inflammatory interventions, such as anti-TNF-α antibodies, statins, glucocorticoids, and IL-1β receptor antagonists fail to improve insulin sensitivity and overall metabolic function, and even worsen the situation in obese humans (Zhu *et al.*, 2018).

Noteworthily, acupuncture shows a better effect in promoting insulin sensitivity through attenuating inflammation in obese patients. Luo *et al.* introduced that the pro-inflammatory type of macrophage- macrophage-1 (M1) was significantly elevated in white adipose tissue (WAT) of obese rats; after EA treatment, M1 showed a great decrease, leading to an anti-inflammatory effect (Luo *et al.*, 2018). EA can not only improve obesity, hyperlipidemia, and IR but, also regulates metainflammation, which is associated with the modulation of SIRT1 expression and histone deacetylation in WAT. Similar results were found in another animal study that EA on “ST25”, “CV4”, “ST36”, and “SP6” stimulated the polarization of M2 and the expression of IL-4 and IL-10, as well as inhibited the levels of leptin, chemerin, and TNF-α, eventually alleviating the inflammatory response. Meanwhile, EA limits adipocyte enlargement and facilitates small adipocytes (Wang *et al.*, 2021a). Apart from EA, catgut embedding also plays a role in weight control by regulating the macrophage polarization of the mRNA expression of M1 labeled inducible nitric oxide synthase (iNOS). The pro-inflammatory cytokines IL-6, monocyte chemoattractant protein-1 (MCP-1), and TNF-α were decreased while that of M2 macrophage labeled arginase-1 (Arg-1) was upregulated (Li *et al.*, 2021a). A text mining study has confirmed that acupuncture can adjust the expression of IL-6 through the TLR4/NF-κB pathway by analyzing the GO, KEGG, and PPI networks of the genes, thereby attenuating inflammation and improving obesity (Du *et al.*, 2022). In addition, warm needling therapy has also been found to effectively decrease serum levels of IL-6 and TNF-α (Shenbo *et al.*, 2019).

Regulation of Adipose Tissue

There are two types of adipose tissue which have distinct functions. WAT has a major role in energy storage to free the human body from constantly seeking food, as well as the release of hormones and adipokines to regulate metabolism. Thus, WAT is more involved with obesity-related IR and inflammation. Brown adipose tissue (BAT) primarily consumes glucose and triglycerides and functions as a thermogenic organ (van Baak *et al.*, 2019). With the development of obesity, BAT depots decrease whereas WAT depots expand in order to store excess energy (Marcelin *et al.*, 2022). The increased depots of WAT generate a low-grade inflammatory state, resulting in the recruit of macrophages, CD8+ T cells, IL-17-producing CD4+ T cells, natural killer cells, and neutrophils (Grant *et al.*, 2015), which exacerbates the obese situation and increases the risk of obesity-related complications. In addition to white and brown, beige adipocytes display the capacity to dissipate energy through heat production. Beige adipocytes have features of both white and brown adipocytes and can be transformed from white-like to brown-like functions under cold and adrenergic stimulation (Cypess, 2022). The transition of beige and browning of WAT are essential to weight loss, which can be achieved by acupuncture therapy.

Lu *et al.* demonstrated that four-week EA treatment not only restored the obese phenotype but promoted WAT and BAT plasticity, which is associated with the induction of UCP1 and PRDM16 expression (Lu *et al.*, 2019). UCP1 is a BAT-specific gene marker and PRDM16 is related to the BAT gene program as well as mitochondrial biogenesis and uncoupled cellular respiration; thus, the elevation of UCP1 and PRDM16 expression enhances WAT lipolysis and decreases adipocyte sizes. Meanwhile, the beige gene markers, such as PGC-1α, TMEM26, and TBX1, are greatly induced in WAT by EA, thus increasing energy expenditure and reducing body weight. The regulation of UCP1, PRDM16, and PGC-1α has been explored in several studies, and the relevant signaling pathways have been verified. An animal study has found that the modulation of EA in WAT browning is associated with SIRT1 dependent peroxisome proliferators-activated receptor γ (PPAR-γ) deacetylation and the further interaction of PPAR-γ with PRDM16, eventually uncoupling respiration. Furthermore, EA can stimulate the phosphorylation of AMP-activated kinase (AMPK), then activate mitochondrial biogenesis through the PGC-1α — mitochondrial transcription factor A (TFAM) — UCP1 pathway (Tang *et al.*, 2020). Besides, EA inhibits lipid production through the SIRT1-Wnt/β-catenin-PPAR-γ pathway. The increased protein expression of SIRT1 in WAT triggers Wnt/β-catenin, then inhibits the downstream lipogenic gene PPAR-γ expression (Wang *et al.*, 2021c).

Others

Sarcopenia obesity (SO) is defined as high adiposity coupled with low muscle mass and generally happens in elderly people. The synergistic function of abnormal fat accumulation and muscle loss increases the risk of metabolic dysfunction and physical disability in elderly people compared with either sarcopenia or obesity alone (Guan *et al.*, 2022). Although SO usually occurs in adults aged 65 and older and causes unfavorable outcomes and mortality in cancer patients (Ji *et al.*, 2022), similar results were found in younger patients with SO. A 24-year follow-up cohort has observed SO is clinically effective as a predictor of all-cause mortality (Sanada *et al.*, 2018). EA significantly decreases body fat percentage while increasing appendicular skeletal muscle index, thus alleviating SO (Zhou *et al.*, 2018). A possible mechanism of increasing muscle mass is related to the enhancement of muscle blood flow (MBF) (Shinbara *et al.*, 2013), which is caused by the increased level of nitric oxide and prostaglandins after acupuncture treatment (Shinbara *et al.*, 2015). The elevated circulation attenuates hypoxia in muscle, thus stimulating muscle growth and the mitigation of atrophy.

In obesity, hypoxia caused by adipose tissue vascularization can lead to adipose tissue dysfunction, moving the tissue toward a pro-inflammatory condition. Hypoxia inducible factor-1α (HIF-1α) is a maker to detect the adipose tissue hypoxia of obese patients. Hypoxia-induced HIF-1α also triggers macrophage infiltration and inflammation (Gunton, 2020). In obese mice, the protein level of HIF-1α was increased, while after seven iterations of EA treatment, the expression of the hypoxia-related genes vascular endothelial growth factor A (VEGFA); glucose transporter type 1, Slc2al; and glutathione peroxidase 1, GPX1 significantly decreased. The inhibited HIF-1α signaling mainly co-localizes with the presence of F4/80+ macrophages, which indicates that EA stimulation attenuates adipose tissue hypoxia with a concomitant decreased adipose tissue macrophage content (Wen *et al.*, 2015).

Increased reactive oxygen species (ROS) factor is another factor that causes damage to proteins, lipids, and nucleic acids in obesity. Simultaneously, anti-oxidants such as superoxide dismutases (SOD) are decreased with ROS production, which is strongly associated with inflammation and apoptosis. Acupuncture at CV 4, ST 36, and EX-B3 can increase the activity of liver SOD and expression of Bcl-2, whereas inhibiting the level of liver malondialdehyde (MDA) and Bax. Thus, acupuncture plays an important role in improving obesity and obesity-related hepatic disorders by modulating oxidative stress and suppressing apoptosis in the liver (Zhang *et al.*, 2020).

Discussion and Prospects

Findings in our study show that acupuncture is involved in several mechanisms of obesity, and it modulates the hypothalamus, sympathetic activity and parasympathetic activity, obesity-related hormones (leptin, ghrelin, insulin, and CCK), brain-gut axis, inflammatory status, adipose tissue browning, MBF, hypoxia, and ROS to influence metabolism, eating behavior, motivation, cognition, and the reward system (Fig. 2). Moreover, acupuncture is a safe, affordable, and easily available therapy. Physical activity and a restricted diet are unpleasant for many obese patients since the brain signals stimulate food intake, and most obese patients will surrender in a short time. Acupuncture regulates the hypothalamus and related neurotransmitters to reduce hunger and enhance satiety, which helps obese patients defeat the temptation of food. Medications like naltrexone-bupropion, phentermine–topiramate, GLP-1 receptor agonists, and orlistat have increased adverse events leading to drug discontinuation (Shi *et al.*, 2022). However, acupuncture has no harm to the gastrointestinal system; on the contrary, acupuncture may improve gastrointestinal function (Wang *et al.*, 2020) by modulating the PVN, NTS, ANS, CCK, and BGM. Bariatric surgery is more expensive and has many limitations (such as obesity level, age, and complications) with a higher risk of infection, malnutrition, and psychological problems compared with acupuncture. Acupuncture can be applied to any level of obesity (mild, moderate, or severe), and both adolescents and adults are able to have acupuncture treatment. Although acupuncture has certain side effects such as hemorrhage, rash, and infection, the occurrence is much less than in bariatric surgery (Kassir *et al.*, 2016; Zhong *et al.*, 2020).

Nevertheless, hypothalamic regulation by acupuncture has been demonstrated most in animal studies. The locations of acupoints and the areas covered by the acupoints in animals are different from humans, while acupoints selection and stimulation are crucial for achieving therapeutic effects. Therefore, it's necessary to carry out clinical trials to detect the effect of acupuncture in regulating the CNS with novel techniques such as functional MRI (fMRI), positron emission tomography (PET), electroencephalogram (EEG), and magnetoencephalography (MEG) (Scherer *et al.*, 2021). fMRI is used to investigate blood

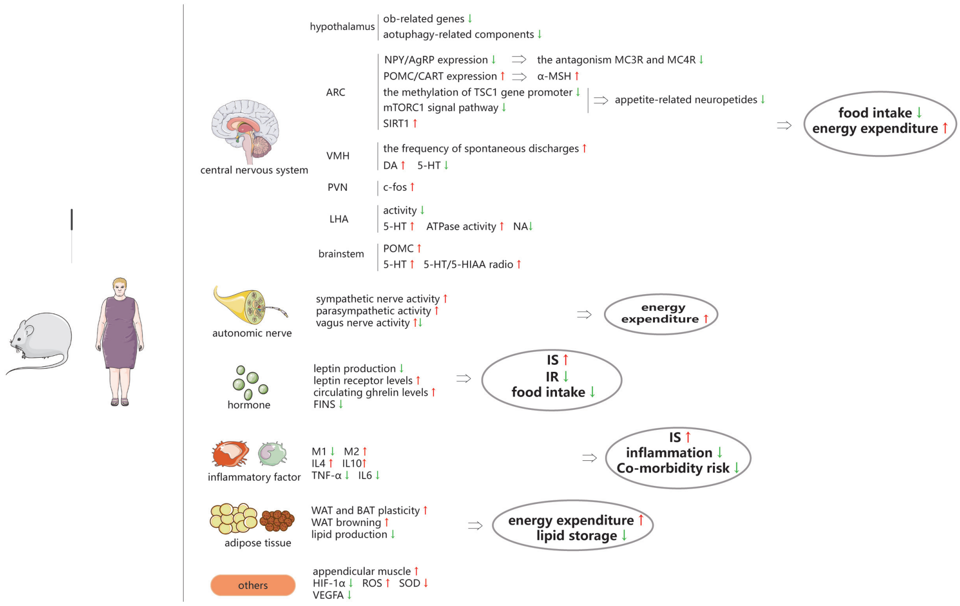

Figure 2. This figure illustrates the main mechanism of acupuncture in regulating obesity. AgRP: agouti gene-related protein; α-MSH: α-melanocyte stimulating hormone; ARC: arcuate nucleus; BAT: brown adipose tissue; CART: cocaine- and amphetamine-regulated transcript; DA: dopamine; FINS: fasting insulin; HIF: hypoxia inducible factor; IL-4: interleukin-4; IL-6: interleukin-4; IL-10: interleukin-10; IR: insulin resistance; IS: insulin sensitivity; LHA: lateral hypothalamic area; MC3R: M1: ecmelanocortin-3 receptors; MC4R: melanocortin-4 receptors; macrophage-1; M2: macrophage-2; NA: noradrenaline; NPY: neuropeptide Y; POMC: pro-opiomelanocortin; PVN: paraventricular nucleus; ROS: reactive oxygen species; SCFAs: short-chain fatty acids; SIRT1: sirtuin1; SOD: superoxide dismutases; TNF-α: tumor necrosis factor-α; VEGFA: vascular endothelial growth factor A; VMH: ventromedial hypothalamic nucleus; WAT: white adipose tissue; 5-HT: 5-hydroxytryptamine; 5-HIAA: 5-hydroxyindoleacetic acid.

flow related to neural activity (Simon *et al.*, 2020), and PET measures directly the synthesis and receptor binding of specific neurotransmitters, like DA. Meanwhile, PET can be combined with MRI to detect specific neurotransmitters at a higher resolution (Scherer *et al.*, 2021). EEG and MEG are non-invasive approaches for investigating the electric activity of simultaneously activated neurons directly with high temporal resolution (Scherer *et al.*, 2021). With the assistance of brain technologies, the change in the CNS after acupuncture in obese patients will be directly reflected. In addition to using novel techniques to detect the effects of acupuncture on the CNS, it is useful to collect biological samples and analyze multi-omics data, such as proteomics, metabolomics, lipidomics, immunomics, phenomics, microbiomics, and brain connectomics, in order to better understand how acupuncture affects obesity. Moreover, machine learning techniques for data analysis can provide information about brain regions of interest to unravel the action mechanisms of acupuncture in the BGM axis.

Additionally, we both agree that losing weight is a consistent battle for obese patients, and many patients regain weight after a short slack. However, several studies have proven that acupuncture has long-term effects (Dai *et al.*, 2022; Murphy *et al.*, 2006), the follow-up phase in most clinical trials is not long enough, and participants in those trials took other methods to control weight during follow-up phase. Therefore, studies with long follow-up phases are required before we hastily claim that acupuncture has long-term effects. Besides, there are various types of acupuncture techniques, such as manual acupuncture, EA, AA, warm acupuncture, and catgut embedding, which are all effective for obesity.

However, which technique is the best choice for obesity often confuses acupuncturists, and the potential mechanisms are likely distinct, which hinders the clinical application. Our study found that most of the studies focus on EA, which affects the hypothalamic nuclei and related neuropeptides, brainstem, ANS, hormones, gut microbiota, inflammation, and adipose tissue. Manual acupuncture has an impact on hypothalamic nuclei (LHA and VMH) and ghrelin, AA mainly regulates ANS, catgut embedding modulates leptin and inflammation, and warm needling is involved in inflammation. Thus, future studies should investigate the effect and underlying mechanisms of different acupuncture techniques to provide optimal acupuncture therapeutic options for obesity.

Acupuncture has a dose-effect property in that the number of acupoints, selection of acupoints, treatment frequency, and treatment duration are associated with the efficacy. There are limited studies exploring the dose-effect property of acupuncture, which leads to inconsistency of the protocol of acupuncture study. Therefore, it is necessary to detect the dose-effect property of acupuncture to optimize acupuncture protocols for obesity treatment as well as better understand the mechanisms.

In conclusion, as an economical and safe alternative, acupuncture could be applied to obese patients to reduce weight. Acupuncture exerts beneficial effects via regulating the CNS, ANS, hormones, brain-gut axis, inflammation, adipose tissue, MBF, hypoxia, and ROS.

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References

An, J.J., C.E. Kinney, J.W. Tan, G.Y. Liao, E.J. Kremer and B. Xu. TrkB-expressing paraventricular hypothalamic neurons suppress appetite through multiple neurocircuits. *Nat. Commun.* 11: 1729, 2020.

Aron-Wisnewsky, J., M.V. Warmbrunn, M. Nieuwdorp and K. Clément. Metabolism and metabolic disorders and the microbiome: The intestinal microbiota associated with obesity, lipid metabolism, and metabolic health-pathophysiology and therapeutic strategies. *Gastroenterology* 160: 573–599, 2021.

Belivani, M., C. Dimitroula, N. Katsiki, M. Apostolopoulou, M. Cummings and A.I. Hatzitolios. Acupuncture in the treatment of obesity: A narrative review of the literature. *Acupunct. Med.* 31: 88–97, 2013.

Benrick, A., M. Kokosar, M. Hu, M. Larsson, M. Maliqueo, R.R. Marcondes, M. Soligo, V. Protto, E. Jerlhag, A. Sazonova, C.J. Behre, K. Højlund, P. Thorén and E. Stener-Victorin. Autonomic nervous system activation mediates the increase in whole-body glucose uptake in response to electroacupuncture. *FASEB J.* 31: 3288–3297, 2017.

Blüher, M. Obesity: Global epidemiology and pathogenesis. *Nat. Rev. Endocrinol.* 15: 288–298, 2019.

Canfora, E.E., R.C.R. Meex, K. Venema and E.E. Blaak. Gut microbial metabolites in obesity, NAFLD and T2DM. *Nat. Rev. Endocrinol.* 15: 261–273, 2019.

Collaboration, N.R.F. Trends in adult body-mass index in 200 countries from 1975 to 2014: A pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet* 387: 1377–1396, 2016.

Cypess, A.M. Reassessing human adipose tissue. *N. Engl. J. Med.* 386: 768–779, 2022.

D'Agostino, G., D. Lyons, C. Cristiano, M. Lettieri, C. Olarte-Sanchez, L.K. Burke, M. Greenwald-Yarnell, C. Cansell, B. Doslikova, T. Georgescu, P.B. Martinez de Morentin, Jr. M.G. Myers, J.J. Rochford and L.K. Heisler. Nucleus of the solitary tract serotonin 5-HT(2C) receptors modulate food intake. *Cell Metab.* 28: 619–630, 2018.

Dai, L., M. Wang, K.P. Zhang, L. Wang, H.M. Zheng, C.B. Li, W.J. Zhou, S.G. Zhou and G. Ji. Modified acupuncture therapy, long-term acupoint stimulation versus sham control for weight control: A multicenter, randomized controlled trial. *Front. Endocrinol. (Lausanne)* 13: 952373, 2022.

Davis, E.A., H.S. Wald, A.N. Suarez, J. Zubcevic, C.M. Liu, A.M. Cortella, A.K. Kamitakahara, J.W. Polson, M. Arnold, H.J. Grill, G. de Lartigue and S.E. Kanoski. Ghrelin signaling affects feeding behavior, metabolism, and memory through the vagus nerve. *Curr. Biol.* 30: 4510–4518, 2020.

Dong, C., C.R. Zhang, B.Y. Xue, W.F. Miu, N.Y. Fang, K. Li, Z.J. Ou and Y.Q. Xu. Electro-acupuncture combined with lifestyle control on obese nonalcoholic fatty liver disease: A randomized controlled trial. *Zhongguo Zhen Jiu* 40: 129–134, 2020.

Dou, D., Q.Q. Chen, Z.Q. Zhong, X.W. Xia and W.J. Ding. Regulating the enteric nervous system against obesity in mice by electroacupuncture. *Neuroimmunomodulation* 27: 48–57, 2020.

Du, Y., L. He, X. Ye, S. Chen, G. Li, Y. Yu, E. Ye, Y. Huang, Y. Zhou, W. Zhang and C. Yang. To explore the molecular mechanism of acupuncture alleviating inflammation and treating obesity based on text mining. *Biomed. Res. Int.* 2022: 3133096, 2022.

Eley, V.A., M. Thuzar, S. Navarro, B.R. Dodd and A.A. van Zundert. Obesity, metabolic syndrome, and inflammation: An update for anaesthetists caring for patients with obesity. *Anaesth. Crit. Care Pain Med.* 40: 100947, 2021.

Fang, J.F., J.Y. Du, X.M. Shao, J.Q. Fang and Z. Liu. Effect of electroacupuncture on the NTS is modulated primarily by acupuncture point selection and stimulation frequency in normal rats. *BMC Complement. Altern. Med.* 17: 182, 2017.

Fang, S., M. Wang, Y. Zheng, S. Zhou and G. Ji. Acupuncture and lifestyle modification treatment for obesity: A meta-analysis. *Am. J. Chin. Med.* 45: 239–254, 2017.

Fei, W., D.R. Tian, P. Tso and J.S. Han. Arcuate nucleus of hypothalamus is involved in mediating the satiety effect of electroacupuncture in obese rats. *Peptides* 32: 2394–2399, 2011.

Friedman, J.M., Leptin and the endocrine control of energy balance. *Nat. Metab.* 1: 754–764, 2019.

Fu, S.P., H. Hong, S.F. Lu, C.J. Hu, H.X. Xu, Q. Li, M.L. Yu, C. Ou, J.Z. Meng, T.L. Wang, L. Hennighausen and B.M. Zhu. Genome-wide regulation of electro-acupuncture on the neural Stat5-loss-induced obese mice. *PLoS One* 12: e0181948, 2017.

Grant, R.W. and V.D. Dixit. Adipose tissue as an immunological organ. *Obesity (Silver Spring)* 23: 512–518, 2015.

Guan, L., T. Li, X. Wang, K. Yu, R. Xiao and Y. Xi. Predictive roles of basal metabolic rate and body water distribution in sarcopenia and sarcopenic obesity: The link to carbohydrates. *Nutrients* 14: 3911, 2022.

Güçel, F., B. Bahar, C. Demirtas, S. Mit and C. Cevik. Influence of acupuncture on leptin, ghrelin, insulin and cholecystokinin in obese women: A randomised, sham-controlled preliminary trial. *Acupunct. Med.* 30: 203–207, 2012.

Gunton, J.E. Hypoxia-inducible factors and diabetes. *J. Clin. Invest.* 130: 5063–5073, 2020.

Hassan, A.M., G. Mancano, K. Kashofer, E.E. Fröhlich, A. Matak, R. Mayerhofer, F. Reichmann, M. Olivares, A.M. Neyrinck, N.M. Delzenne, S.P. Claus and P. Holzer. High-fat diet induces depression-like behaviour in mice associated with changes in microbiome, neuropeptide Y, and brain metabolome. *Nutr. Neurosci.* 22: 877–893, 2019.

Henao-Mejia, J., E. Elinav, C. Jin, L. Hao, W.Z. Mehal, T. Strowig, C.A. Thaiss, A.L. Kau, S.C. Eisenbarth, M.J. Jurczak, J.P. Camporez, G.I. Shulman, J.I. Gordon, H.M. Hoffman and R.A. Flavell. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. *Nature* 482: 179–185, 2012.

Heymsfield, S.B. and T.A. Wadden. Mechanisms, pathophysiology, and management of obesity. *N. Engl. J. Med.* 376: 254–266, 2017.

Hong, P., Y. Gao, Q. Wang, X. Qiu and Q. Chen. The effectiveness of acupoint catgut embedding in hyperlipidemia with obesity: Protocol for a systematic review and meta-analysis. *Medicine (Baltimore)* 99: e20342, 2020.

Hsu, C.H., C.J. Wang, K.C. Hwang, T.Y. Lee, P. Chou and H.H. Chang. The effect of auricular acupuncture in obese women: A randomized controlled trial. *J. Womens Health (Larchmt)* 18: 813–818, 2009.

Huang, Q., R. Chen, L. Chen, F.X. Liang, W.J. He, M. Peng and L. Li. Electroacupuncture reduces obesity by improving metabolism and up-regulating expression of hypothalamic Sirtuin 1 and proopiomelanocortin in obese rats. *Zhen Ci Yan Jiu.* 44: 270–275, 2019a.

Huang, Q., Y.J. Song, Z.M. Yu, J.F. Ren, F.X. Liang, R. Chen and F. Xu. Electroacupuncture improves inflammatory reaction and insulin sensitivity in insulin-resistant obese rats. *Zhen Ci Yan Jiu.* 44: 898–905, 2019b.

Huang, Z., L. Huang, M.J. Waters and C. Chen. Insulin and growth hormone balance: Implications for obesity. *Trends Endocrinol. Metab.* 31: 642–654, 2020.

Huang, Z., Z. Tong and W. Sun. Effect of electroacupuncture on the discharges of pain-sensitive neurons in the hypothalamic dorsomedial nucleus of rats. *Zhen Ci Yan Jiu* 20: 20–23, 1995.

Iovino, M., T. Messana, G. Lisco, F. Mariano, V.A. Giagulli, E. Guastamacchia, G. De Pergola and V. Triggiani. Neuroendocrine modulation of food intake and eating behavior. *Endocr. Metab. Immune Disord. Drug Targets* 22: 1252–1262, 2022.

Ji, B., J. Hu and S. Ma. Effects of electroacupuncture Zusanli (ST36) on food intake and expression of POMC and TRPV1 through afferents-medulla pathway in obese prone rats. *Peptides* 40: 188–194, 2013.

Ji, W., X. Liu, K. Zheng, P. Liu, Y. Zhao, J. Lu, L. Zhao, T. Liang, J. Cui and W. Li. Thresholds of visceral fat area and percent of body fat to define sarcopenic obesity and its clinical consequences in Chinese cancer patients. *Clin. Nutr.* 41: 737–745, 2022.

Jie, X., X. Li, J.Q. Song, D. Wang and J.H. Wang. Anti-inflammatory and autonomic effects of electroacupuncture in a rat model of diet-induced obesity. *Acupunct. Med.* 36: 103–109, 2018.

Ju, M.X., P.H. Fang and Z.W. Zhang. The role of hypothalamic neuropeptides in the central nervous system regulation of energy metabolism. *China J. Mod. Med.* 32: 45–50, 2022.

Kalarchian, M.A., M.D. Marcus, A.P. Courcoulas, Y. Cheng and M.D. Levine. Self-report of gastrointestinal side effects after bariatric surgery. *Surg. Obes. Relat. Dis.* 10: 1202–1207, 2014.

Kang, H., M. Lai, Y. Yao, B. Wang, X. Su and Y. Cheng. Novel insights into the important role of leptin in modulating the pathological development of fibrotic-related diseases. *Curr. Mol. Med.* 23: 1066–1076, 2022a.

Kang, J., K.W. Kim, Y. Seo, M.Y. Song and W.S. Chung. Effects of electroacupuncture for obesity: A protocol for systematic review and meta-analysis. *Medicine (Baltimore)* 101: e29018, 2022b.

Kassir, R., T. Debs, P. Blanc, J. Gugenheim, I. Ben Amor, C. Boutet and O. Tiffet. Complications of bariatric surgery: Presentation and emergency management. *Int. J. Surg.* 27: 77–81, 2016.

Kelly, T., W. Yang, C.S. Chen, K. Reynolds and J. He. Global burden of obesity in 2005 and projections to 2030. *Int. J. Obes. (Lond.)* 32: 1431–1437, 2008.

Kullmann, S., A. Kleinridders, D.M. Small, A. Fritsche, H.U. Häring, H. Preissl and M. Heni. Central nervous pathways of insulin action in the control of metabolism and food intake. *Lancet Diabetes Endocrinol.* 8: 524–534, 2020.

Leng, J., F. Xiong, J. Yao, X. Dai, Y. Luo, M. Hu, L. Zhang and Y. Li. Electroacupuncture reduces weight in diet-induced obese rats via hypothalamic Tsc1 promoter demethylation and inhibition of the activity of mTORC1 signaling pathway. *Evid. Based Complementary Altern. Med.* 2018: 3039783, 2018.

Li, L.L., J.Q. Hu, S.Y. Zhang and Y.H. Xie. Effect of acupoint thread-embedding on macrophage polarization of epididymis adipose tissue in obese mice. *Zhongguo Zhen Jiu* 41: 177–182, 2021a.

Li, D., Y. Li, S. Yang, J. Lu, X. Jin and M. Wu. Diet-gut microbiota-epigenetics in metabolic diseases: From mechanisms to therapeutics. *Biomed. Pharmacother.* 153: 113290, 2022.

Li, X., Z. Wu, Y. Chen, R. Cai and Z. Wang. Effect of acupuncture on simple obesity and serum levels of prostaglandin E and leptin in Sprague-Dawley rats. *Comput. Math. Methods Med.* 2021: 6730274, 2021b.

Lieverse, R.J., J.B. Jansen, A.M. Masclee and C.B. Lamers. Satiety effects of cholecystokinin in humans. *Gastroenterology* 106: 1451–1454, 1994.

Liu, S.C., Q. Fu, Q. Peng and Z.Z. Hu. Research progress on the role and mechanism of CART peptide in central nervous system. *J. Nanchang Univ. (Med. Sci.)* 62: 76–80, 2022.

Liu, X., J. He, F. Y. Qu, Z. Liu, Q.Y. Pu, S.T. Guo, J. Du and P.F. Jiang. Effects of electroacupuncture on insulin resistance and hypothalamic agouti gene-related protein and neuropeptite Y in obesity rats. *Chin. J. Inf. Tradit. Chin. Med.* 23: 57–60, 2016.

Liu, J., H. Jin, R.D. Foreman, Y. Lei, X. Xu, S. Li, J. Yin and J.D. Chen. Chronic electrical stimulation at acupoints reduces body weight and improves blood glucose in obese rats via autonomic pathway. *Obes. Surg.* 25: 1209–1216, 2015.

Liu, Z.C., F.M. Sun, J. Su, M. Zhao, M.H. Zhua, Y.Z. Wang, Q.L. Wei, J. Li and Y. Gu. Action of acupuncture on ventromedial nucleus of hypothalamus in the rat of obesity. *J. Tradit. Chin. Med.* 01: 25–26, 2000.

Liu, Z.C., F.M. Sun, M. Zhao, Z. Sun, Z.C. Zhang, C.Y. Hong, M.H. Hong, X.R. Xiang and Q.L. Wei. Effect of acupuncture on paraventricular nucleus in obese rats. *Chinese Archiv. Trad. Chinese Med.* 07: 1031–1033+1059, 2003.

Liu, X. and H. Zheng. Modulation of Sirt1 and FoxO1 on hypothalamic leptin-mediated sympathetic activation and inflammation in diet-induced obese rats. *J. Am. Heart Assoc.* 10: e020667, 2021.

Lu, S.F., Y.X. Tang, T. Zhang, S.P. Fu, H. Hong, Y. Cheng, H.X. Xu, X.Y. Jing, M.L. Yu and B.M. Zhu. Electroacupuncture reduces body weight by regulating fat browning-related proteins of adipose tissue in HFD-induced obese mice. *Front. Psychiatry* 10: 353, 2019.

Lu, W., S. Wu, J. Li, Y.Y. Wang, Y.D. Zhou and F.X. Liang. Mechanisms of electroacupuncture in improving obesity-induced insulin resistance via TLR4/NF-κB inflammatory pathway in liver. *Zhen Ci Yan Jiu* 47: 504–509, 2022.

Luo, D., L. Liu, F.X. Liang, Z.M. Yu and R. Chen. Electroacupuncture: A feasible Sirt1 promoter which modulates metainflammation in diet-induced obesity rats. *Evid. Based Complementary Altern. Med.* 2018: 5302049, 2018.

Ma, C. and Z. Liu. Regulative effects of electroacupuncture on gastric hyperfunction induced by electrostimulation of the lateral hypothalamus area of rabbits. *Zhen Ci Yan Jiu* 19: 42–46, 1994.

Maejima, Y., S. Yokota, M. Shimizu, S. Horita, D. Kobayashi, A. Hazama and K. Shimomura. The deletion of glucagon-like peptide-1 receptors expressing neurons in the dorsomedial hypothalamic nucleus disrupts the diurnal feeding pattern and induces hyperphagia and obesity. *Nutr. Metab. (Lond)* 18: 58, 2021.

Marcelin, G., E.L. Gautier and K. Clément. Adipose tissue fibrosis in obesity: Etiology and challenges. *Annu. Rev. Physiol.* 84: 135–155, 2022.

Marino, R.A.M., R.A. McDevitt, S.C. Gantz, H. Shen, M. Pignatelli, W. Xin, R.A. Wise and A. Bonci. Control of food approach and eating by a GABAergic projection from lateral hypothalamus to dorsal pons. *Proc. Natl. Acad. Sci. USA* 117: 8611–8615, 2020.

Mittendorfer, B., B.W. Patterson, G.I. Smith, M. Yoshino and S. Klein. β Cell function and plasma insulin clearance in people with obesity and different glycemic status. *J. Clin. Invest.* 132: e154068, 2022.

Murphy, K.G. and S.R. Bloom. Gut hormones and the regulation of energy homeostasis. *Nature* 444: 854–859, 2006.

Ouerghi, N., M. Feki, N.L. Bragazzi, B. Knechtle, L. Hill, P.T. Nikolaidis and A. Bouassida. Ghrelin response to acute and chronic exercise: Insights and implications from a systematic review of the literature. *Sports Med.* 51: 2389–2410, 2021.

Page, M.M., S. Skovsø, H. Cen, A.P. Chiu, D.A. Dionne, D.F. Hutchinson, G.E. Lim, M. Szabat, S. Flibotte, S. Sinha, C. Nislow, B. Rodrigues and J.D. Johnson. Reducing insulin via conditional partial gene ablation in adults reverses diet-induced weight gain. *FASEB J.* 32: 1196–1206, 2018.

Perakakis, N., O.M. Farr and C.S. Mantzoros. Leptin in leanness and obesity: JACC state-of-the-art review. *J. Am. Coll. Cardiol.* 77: 745–760, 2021.

Ren, J.F., R. Chen, Q. Huang, M. Peng, L. Li, Y.J. Song, L. Chen, J. Li, S. Wu and F.X. Liang. Electro-acupuncture on POMC, AgRP protein and gene expressions in hypothalamus of obese rats. *Chin. Arch. Tradit. Chin. Med.* 38: 75–79, 2020.

Rønnekleiv, O.K., J. Qiu and M.J. Kelly. Hypothalamic kisspeptin neurons and the control of homeostasis. *Endocrinology* 163: bqab253, 2022.

Russo, B., M. Menduni, P. Borboni, F. Picconi and S. Frontoni. Autonomic nervous system in obesity and insulin-resistance-the complex interplay between leptin and central nervous system. *Int. J. Mol. Sci.* 22: 5187, 2021.

Sanada, K., R. Chen, B. Willcox, T. Ohara, A. Wen, C. Takenaka and K. Masaki. Association of sarcopenic obesity predicted by anthropometric measurements and 24-y all-cause mortality in elderly men: The Kuakini Honolulu Heart Program. *Nutrition* 46: 97–102, 2018.

Sasaki, T., O. Kikuchi, M. Shimpuku, V.Y. Susanti, H. Yokota-Hashimoto, R. Taguchi, N. Shibusawa, T. Sato, L. Tang, K. Amano, T. Kitazumi, M. Kuroko, Y. Fujita, J. Maruyama, Y.S. Lee, M. Kobayashi, T. Nakagawa, Y. Minokoshi, A. Harada, M. Yamada and T. Kitamura. Hypothalamic SIRT1 prevents age-associated weight gain by improving leptin sensitivity in mice. *Diabetologia* 57: 819–831, 2014.

Scherer, T., K. Sakamoto and C. Buettner. Brain insulin signalling in metabolic homeostasis and disease. *Nat. Rev. Endocrinol.* 17: 468–483, 2021.

Shen, E.Y., C.L. Hsieh, Y.H. Chang and J.G. Lin. Observation of sympathomimetic effect of ear acupuncture stimulation for body weight reduction. *Am. J. Chin. Med.* 37: 1023–1030, 2009.

Shenbo, J., L. Mingzhu, W. Xiaotong and Z. Lide. MMP-9, IL-6, TNF-α — Analysis of changes of warm needing therapy in rats with spontaneously hypertension. *Lishizhen Med. Materia Med. Res.* 30: 2787–2789, 2019.

Shi, Q., Y. Wang, Q. Hao, P.O. Vandvik, G. Guyatt, J. Li, Z. Chen, S. Xu, Y. Shen, L. Ge, F. Sun, L. Li, J. Yu, K. Nong, X. Zou, S. Zhu, C. Wang, S. Zhang, Z. Qiao, Z. Jian, Y. Li, X. Zhang, K. Chen, F. Qu, Y. Wu, Y. He, H. Tian and S. Li. Pharmacotherapy for adults with overweight and obesity: A systematic review and network meta-analysis of randomised controlled trials. *Lancet* 399: 259–269, 2022.

Shinbara, H., M. Okubo, K. Kimura, K. Mizunuma and E. Sumiya. Participation of calcitonin gene related peptide released via axon reflex in the local increase in muscle blood flow following manual acupuncture. *Acupunct. Med.* 31: 81–87, 2013.

Shinbara, H., M. Okubo, K. Kimura, K. Mizunuma and E. Sumiya. Contributions of nitric oxide and prostaglandins to the local increase in muscle blood flow following manual acupuncture in rats. *Acupunct. Med.* 33: 65–71, 2015.

Shu, Q., L. Chen, S. Wu, J. Li, J. Liu, L. Xiao, R. Chen and F. Liang. Acupuncture targeting SIRT1 in the hypothalamic arcuate nucleus can improve obesity in high-fat-diet-induced rats with insulin resistance via an anorectic effect. *Obes. Facts* 13: 40–57, 2020.

Si, Y.C., C.C. Ren, E.W. Zhang, Z.X. Kang, X.Y. Mo, Q.Q. Li and B. Chen. Integrative analysis of the gut microbiota and metabolome in obese mice with electroacupuncture by 16S rRNA gene sequencing and HPLC-MS-based metabolic profiling. *Am. J. Chin. Med.* 50: 673–690, 2022.

Simon, J.J., M.A. Stopyra, E. Mönning, S. Sailer, N. Lavandier, L.P. Kihm, M. Bendszus, H. Preissl, W. Herzog and H.C. Friederich. Neuroimaging of hypothalamic mechanisms related to glucose metabolism in anorexia nervosa and obesity. *J. Clin. Invest.* 130: 4094–4103, 2020.

Singh, I., L. Wang, B. Xia, J. Liu, A. Tahiri, A. El Ouaamari, M.B. Wheeler and Z.P. Pang. Activation of arcuate nucleus glucagon-like peptide-1 receptor-expressing neurons suppresses food intake. *Cell Biosci.* 12: 178, 2022.

Song, A.Q., Y.P. Zhang, M. Yao and F.X. Liang. Effect of electroacupuncture of "biaoben acupoint combination" on central sensitivity of cholecystokinin in obese rats with insulin resistance. *Zhongguo Zhen Jiu* 40: 969–975, 2020.

Steinert, R.E., C. Feinle-Bisset, L. Asarian, M. Horowitz, C. Beglinger and N. Geary. Ghrelin, CCK, GLP-1, and PYY(3-36): Secretory controls and physiological roles in eating and glycemia in health, obesity, and after RYGB. *Physiol. Rev.* 97: 411–463, 2017.

Su, Z.J., B.W. Wang, J.R. Liu, Z. Sun, H. Wang, W. Shen and R.M. Zheng. Brainstem and limbic system regulate metabolism and energy balance. *Prog. Physiol. Sci.* 53: 321–328, 2022.

Tacad, D.K.M., A.P. Tovar, C.E. Richardson, W.F. Horn, G.P. Krishnan, N.L. Keim and S. Krishnan. Satiety associated with calorie restriction and time-restricted feeding: Peripheral hormones. *Adv. Nutr.* 13: 792–820, 2022.

Tang, Q., M. Lu, B. Xu, Y. Wang, S. Lu, Z. Yu, X. Jing and J. Yuan. Electroacupuncture regulates inguinal white adipose tissue browning by promoting sirtuin-1-dependent PPARγ deacetylation and mitochondrial biogenesis. *Front. Endocrinol. (Lausanne)* 11: 607113, 2020.

Tian, D.R., X.D. Li, F. Wang, D.B. Niu, Q.H. He, Y.S. Li, J.K. Chang, J. Yang and J.S. Han. Up-regulation of the expression of cocaine and amphetamine-regulated transcript peptide by electroacupuncture in the arcuate nucleus of diet-induced obese rats. *Neurosci. Lett.* 383: 17–21, 2005.

Tian, X.H., A.Q. Song, F.X. Liang and Y. Wang. Effect of electroacupuncture on leptin in energy-regulated signaling of obese rats with insulin resistance. *Zhen Ci Yan Jiu* 46: 39–44, 2021.

van Baak, M.A. and E.C.M. Mariman. Mechanisms of weight regain after weight loss — The role of adipose tissue. *Nat. Rev. Endocrinol.* 15: 274–287, 2019.

Vohra, M.S., K. Benchoula, C.J. Serpell and W.E. Hwa. AgRP/NPY and POMC neurons in the arcuate nucleus and their potential role in treatment of obesity. *Eur. J. Pharmacol.* 915: 174611, 2022.

Wan, H., S.X. Yan, Z. Yan, S.W. Zhang, X. Wang and M. Zhao. Simple obesity of stomach heat and damp obstruction treated with acupoint thread embedding therapy: A randomized controlled trial. *Zhongguo Zhen Jiu* 42: 137–142, 2022.

Wang, H.F., L. Chen, Y. Xie, X.F. Wang, K. Yang, Y. Ning, J.Y. He and W.J. Ding. Electroacupuncture facilitates M2 macrophage polarization and its potential role in the regulation of inflammatory response. *Biomed. Pharmacother.* 140: 111655, 2021a.

Wang, L., C.C. Yu, J. Li, Q. Tian and Y.J. Du. Mechanism of action of acupuncture in obesity: A perspective from the hypothalamus. *Front. Endocrinol. (Lausanne)* 12: 632324, 2021b.

Wang, Y.Y., F.X. Liang, W. Lu, Y.D. Zhou, X.X. Huang and S.R. Yang. Mechanism of electroacupuncture for regulation of lipid production and improvement in obesity by mediating Wnt/β-catenin pathway through activating SIRT1. *Zhongguo Zhen Jiu* 41: 774–780, 2021c.

Wang, Y.Y., F.X. Liang, L. Chen, W. Lu, Y.D. Zhou, X.X. Huang and S.R. Yang. Electroacupuncture improves obesity by lowering gastrointestinal motility, blood lipids and expression of intestinal leptin and cholecystokinin in obese rats. *Zhen Ci Yan Jiu* 45: 875–881, 2020.

Wang, H., W.J. Liu, G.M. Shen, M.T. Zhang, S. Huang and Y. He. Neural mechanism of gastric motility regulation by electroacupuncture at RN12 and BL21: A paraventricular hypothalamic nucleus-dorsal vagal complex-vagus nerve-gastric channel pathway. *World J. Gastroenterol.* 21: 13480–13489, 2015.

Wang, C., X. Luan, F.F. Guo, R.X. Sun and L. Xu. Effect of hypothalamic PVN exogenous orexin-A on food intake in obese rats and regulation by NPY receptor signaling pathway. *Chin. J. Pathophysiol.* 34: 1162–1169, 2018.

Wang, H., Q. Wang, C. Liang, M. Su, X. Wang, H. Li, H. Hu and H. Fang. Acupuncture regulating gut microbiota in abdominal obese rats induced by high-fat diet. *Evid. Based Complementary Altern. Med.* 2019: 4958294, 2019.

Wei, Q. and Z. Liu. Effects of acupuncture on monoamine neurotransmitters in raphe nuclei in obese rats. *J. Tradit. Chin. Med.* 23: 147–150, 2003.

Wen, C.K. and T.Y. Lee. Electroacupuncture prevents white adipose tissue inflammation through modulation of hypoxia-inducible factors-1α-dependent pathway in obese mice. *BMC Complement. Altern. Med.* 15: 452, 2015.

Whitlock, G., S. Lewington, P. Sherliker, R. Clarke, J. Emberson, J. Halsey, N. Qizilbash, R. Collins and R. Peto. Body-mass index and cause-specific mortality in 900000 adults: collaborative analyses of 57 prospective studies. *Lancet* 373: 1083–1096, 2009.

Xia, M.H., Z. Yu, D.H. Liu, H.Y. Ji and B. Xu. Effect of electroacupuncture combined with intradermal needling on simple obesity and serum intestinal lymphatic function-related factors. *Zhongguo Zhen Jiu* 42: 966–970, 2022a.

Xia, X., Y. Xie, Y. Gong, M. Zhan, Y. He, X. Liang, Y. Jin, Y. Yang and W. Ding. Electroacupuncture promoted intestinal defensins and rescued the dysbiotic cecal microbiota of high-fat diet-induced obese mice. *Life Sci.* 309: 120961, 2022b.

Yan, C., T. Zeng, K. Lee, M. Nobis, K. Loh, L. Gou, Z. Xia, Z. Gao, M. Bensellam, W. Hughes, J. Lau, L. Zhang, C.K. Ip, R. Enriquez, H. Gao, Q.P. Wang, Q. Wu, J.J. Haigh, D.R. Laybutt, P. Timpson, H. Herzog and Y.C. Shi. Peripheral-specific Y1 receptor antagonism increases thermogenesis and protects against diet-induced obesity. *Nat. Commun.* 12: 2622, 2021.

Yang, C.Z., Y. Ma, Y.L. Xu, Y. Wang, Y. Wang and D.W. Zhang. Influence of acupuncture on serum leptin level and hypothalamic leptin receptor expression in simple obesity rats. *Zhen Ci Yan Jiu.* 06: 384–388, 2007.

Yang, H., Y.H. Youm, B. Vandanmagsar, A. Ravussin, J.M. Gimble, F. Greenway, J.M. Stephens, R.L. Mynatt and V.D. Dixit. Obesity increases the production of proinflammatory mediators from adipose tissue T cells and compromises TCR repertoire diversity: Implications for systemic inflammation and insulin resistance. *J. Immunol.* 185: 1836–1845, 2010.

Yao, J., X. Yan, X. Xiao, X. You, Y. Li, Y. Yang, W. Zhang and Y. Li. Electroacupuncture induces weight loss by regulating tuberous sclerosis complex 1-mammalian target of rapamycin methylation and hypothalamic autophagy in high-fat diet-induced obese rats. *Front. Pharmacol.* 13: 1015784, 2022.

Ying, W., W. Fu, Y.S. Lee and J.M. Olefsky. The role of macrophages in obesity-associated islet inflammation and β-cell abnormalities. *Nat. Rev. Endocrinol.* 16: 81–90, 2020.

Zhang, S.Y., L.L. Li, X. Hu and H.T. Tang. Effect of acupuncture on oxidative stress and apoptosis-related proteins in obese mice induced by high-fat diet. *Zhongguo Zhen Jiu* 40: 983–988, 2020.

Zhang, Z., Y. Shi, D. Cai, S. Jin, C. Zhu, Y. Shen, W. Feng, R. Jiang and L. Wang. Effect of electroacupuncture at ST36 on the intestinal mucosal mechanical barrier and expression of occludin in a rat model of sepsis. *Acupunct. Med.* 36: 333–338, 2018.

Zhicheng, L., S. Fengmin and H. Yan. Effect of acupuncture on monoamines and adenosine triphosphatase activity in lateral hypothaiamic area of obese rats. *Chin. J. Integr. Med.* 6: 257, 2000.

Zhong, Y.M., X.C. Luo, Y. Chen, D.L. Lai, W.T. Lu, Y.N. Shang, L.L. Zhang and H.Y. Zhou. Acupuncture versus sham acupuncture for simple obesity: A systematic review and meta-analysis. *Postgrad. Med. J.* 96: 221–227, 2020.

Zhou, X., B. Xing, G. He, X. Lyu and Y. Zeng. The effects of electrical acupuncture and essential amino acid supplementation on sarcopenic obesity in male older adults: A randomized control study. *Obes. Facts* 11: 327–334, 2018.

Zhu, Q. and P.E. Scherer. Immunologic and endocrine functions of adipose tissue: Implications for kidney disease. *Nat. Rev. Nephrol.* 14: 105–120, 2018.

Zhu, M.F., X. Xing, S. Lei, J.N. Wu, L.C. Wang, L.Q. Huang and R.L. Jiang. Electroacupuncture at bilateral zusanli points (ST36) protects intestinal mucosal immune barrier in sepsis. *Evid. Based Complementary Altern. Med.* 2015: 639412, 2015.

Zhao, M., J.H. Yuan, J. Li and X.R. Xiang. Effect of acupuncture on feeding center of hypothalamus in experimental fat rats. *Zhongguo Zhen Jiu.* 05: 49–51, 2001.