

Review

Autonomic nervous system dysfunction in obesity and Prader–Willi syndrome: current evidence and implications for future obesity therapies

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Summary

The autonomic nervous system (ANS) controls essential functions like breathing, heart rate, digestion, body temperature and hormone levels. Evidence suggests that ANS dysfunction is associated with adult and childhood obesity and plays a role in the distribution of total body fat and the development of obesity-related complications in humans. This review summarizes our current understanding of ANS involvement in the pathogenesis of obesity and Prader–Willi syndrome. Available evidence of ANS dysfunction in the control of energy balance is limited and, in some cases, contradictory. Further investigation in this area is warranted in order to better understand the important contributions of the ANS to regulation of body fat, development of obesity and its comorbidities. Results from these studies will guide the development of novel obesity therapeutics targeting specific ANS dysfunction.

Keywords: Autonomic Nervous System (ANS), childhood obesity, Prader–Willi syndrome.

Introduction

Obesity rates remain at epidemic proportions in developed countries (1). Given the serious comorbidities associated with obesity such as cardiovascular disease, insulin resistance and type 2 diabetes, dyslipidemia, non-alcoholic steatohepatitis, cancer, psychiatric problems and early adult mortality, obesity poses a great threat to global health (2). Much research has explored the genetic and environmental factors responsible for the development of obesity, yet few effective treatments exist (3,4). This fact highlights the complexity of the underlying pathogenesis of obesity and underscores the need for further research.

Prader–Willi syndrome (PWS) is a genetic disorder associated with childhood obesity; its incidence approximates 1 : 10 000 (5). In comparison with patients with general obesity, excess total body fat in PWS is associated with increased insulin sensitivity and adiponectin levels, and decreased levels of pro-inflammatory adipokines and visceral fat (6,7). PWS is therefore a unique model to understand the relationship between excess fat and development of metabolic abnormalities and to understand the factors responsible for ‘metabolically healthy obese individuals’.

Evidence suggests that the progression of obesity in children and adults can be linked to dys-regulation between the central nervous system and the autonomic nervous systems

(ANSs), the gastrointestinal tract and the peripheral endocrine system (including fat tissue) (8,9). The ANS controls essential functions including breathing, heart rate (HR), blood pressure, digestion, body temperature and hormone production. This review highlights the changes in the ANS associated with obesity in the paediatric age group and its possible roles in the distribution of body fat and development of obesity-related comorbidities. Changes observed in the ANS among children with obesity are contrasted with those observed in PWS. Differences in the development of the ANS in PWS may underscore the observed differences between PWS and normal obese children and play an important role in the differential expression of obesity-related comorbidities. Further research delineating the ANS manifestations of normal obese children and PWS may help clarify the pathogenic role of the ANS in obesity and lead to new areas of investigation for development of obesity-related therapeutic targets.

Autonomic nervous system regulation of body fat distribution and metabolic profile in obesity

The ANS has many homeostatic functions (reviewed in Table 1), including cardiac regulation, constriction and dilatation of blood vessels, contraction and relaxation of smooth muscle in various organs, visual accommodation, pupillary size, and secretions from exocrine and endocrine glands. The ANS includes the *parasympathetic* and *sympathetic divisions*, as well as a largely self-regulated *enteric*

division of the gastrointestinal tract. Regulation of autonomic function depends upon visceral sensory feedback from visceral sensory neurons which carry information from receptors located in the end organs to the central nervous system through the central autonomic network (CAN). Although the parasympathetic and sympathetic nervous systems have generally opposing actions, both are actively involved in maintaining homeostasis; indeed, it is *the balance of activity* in the two systems (along with the distribution and responsiveness of post-synaptic receptors) that dictates the resultant action in target tissues. The sympathetic system is often referred to as the 'flight or fight' response (increases energy expenditure or 'catabolic state') and the parasympathetic system as 'rest and digest' response (promotes energy storage or 'anabolic state').

Clinical assessment of the ANS in human subjects can involve direct more invasive assessment of nerve activity (microneurography), but more traditionally involves indirect measurements of autonomic activity through non-invasive measurements of cardiovascular and respiratory control systems. HR, blood pressure and respiratory rate are most readily measured in response to specific perturbations (e.g. head-up tilt to 70°). The heart rate variability (HRV) and power spectral analysis are non-invasive and also commonly employed. The power spectra are typically divided into low frequency (LF) and high frequency (HF) providing an indirect measure of sympathetic (LF) to parasympathetic (HF) balance (10) and have prognostic power in the prediction of mortality in congestive heart failure (11). HRV only

Table 1 ANS functions and relative location (rostral to caudal)

Target	Sympathetic	Parasympathetic
Eye	Pupil dilation	Pupil constriction
Lacrimal, submandibular and parotid glands	Relaxation of ciliary muscle (far vision) Weak stimulation of secretion	Constriction of ciliary muscle (near vision) Strong stimulation of secretion
Blood vessels and sweat glands	Vasoconstriction Stimulation of sweat gland secretion	Stimulation of sweat gland secretion
Lungs	Bronchodilation	Bronchoconstriction
Heart	Increased heart rate; positive inotropism	Decreased heart rate; negative inotropism
Blood vessels and sweat glands of the trunk	Vasoconstriction Stimulation of sweat gland secretion	
Esophagus, stomach, small intestine and large intestine	Inhibition of peristalsis (motility) and glandular secretion, increased sphincter activity	Stimulation of peristalsis (motility) and glandular secretion
Liver	Glycogenolysis and gluconeogenesis	
Gallbladder		Contraction and release of bile salts
Pancreas		Secretion of digestive enzymes, insulin, pancreatic polypeptide
Kidney	Inhibition of output	
Bladder	Detrusor relaxation Sphincter contraction	Detrusor contraction Sphincter relaxation
Adrenal medulla	Release of catecholamines into systemic circulation	
Reproductive organs	Stimulation of ejaculation	Stimulation of erection

ANS, autonomic nervous system.

reflects autonomic regulation of the heart; HRV varies significantly with circadian rhythm, age, activity and disease with more complex non-linear fluctuations than originally assumed making interpretation more challenging (12,13). Cerebral blood flow, pupillary response, quantitative sudomotor axon reflex tests (QSARTs), sweat responses, and muscle and skin sympathetic nerve activity are employed less commonly. A battery of ANS tests may provide more complete information about autonomic activity. However, generalization of the findings as representative of whole body activity does not take regional variation into account. For example, cardiovascular systems in the thoracic compartment will respond to different perturbations (e.g. orthostasis) than the stomach (e.g. eating) in the visceral compartment. As such, conclusions drawn from observations using ANS tests in health, obesity and disorders like PWS need to be drawn carefully.

Nonetheless, because the ANS is involved in the regulation of the cardiovascular system, hormonal secretion and energy balance, it is plausible that *altered regulation of either the parasympathetic or sympathetic branches or both may contribute to the development of obesity and related metabolic comorbidities* (Fig. 1) (14–16). For example, low sympathetic activity may predispose to weight gain through

decreased energy expenditure. Transgenic mice lacking β -adrenergic receptors have normal food intake, but lower metabolic rate compared to controls and when placed on a high-fat diet develop severe obesity (17). Similarly, weight gain occurs in some patients taking β -blockers, suggesting that sympathetic hypofunction may precede weight gain in humans (18). Conversely, a decrease in parasympathetic function may be associated with altered regulation of food intake and satiety (19).

The progression of obesity in adults is generally associated with an adaptive increase in sympathetic activity that may contribute to the development of obesity-related complications such as hypertension (12,13,20). However, advancing age is also associated with sympathetic activation and weight gain (21); thus, adult studies of obesity and autonomic dysfunction might not accurately reflect the pathogenic mechanisms operative in children or adolescents due to confounding by effects of advancing age and age-related disease.

In fact, the relative activity of sympathetic and parasympathetic systems in childhood obesity is less clear and study results conflicting. Decreases in both sympathetic and parasympathetic activity have been reported with increasing percentage of body fat, and increasing duration

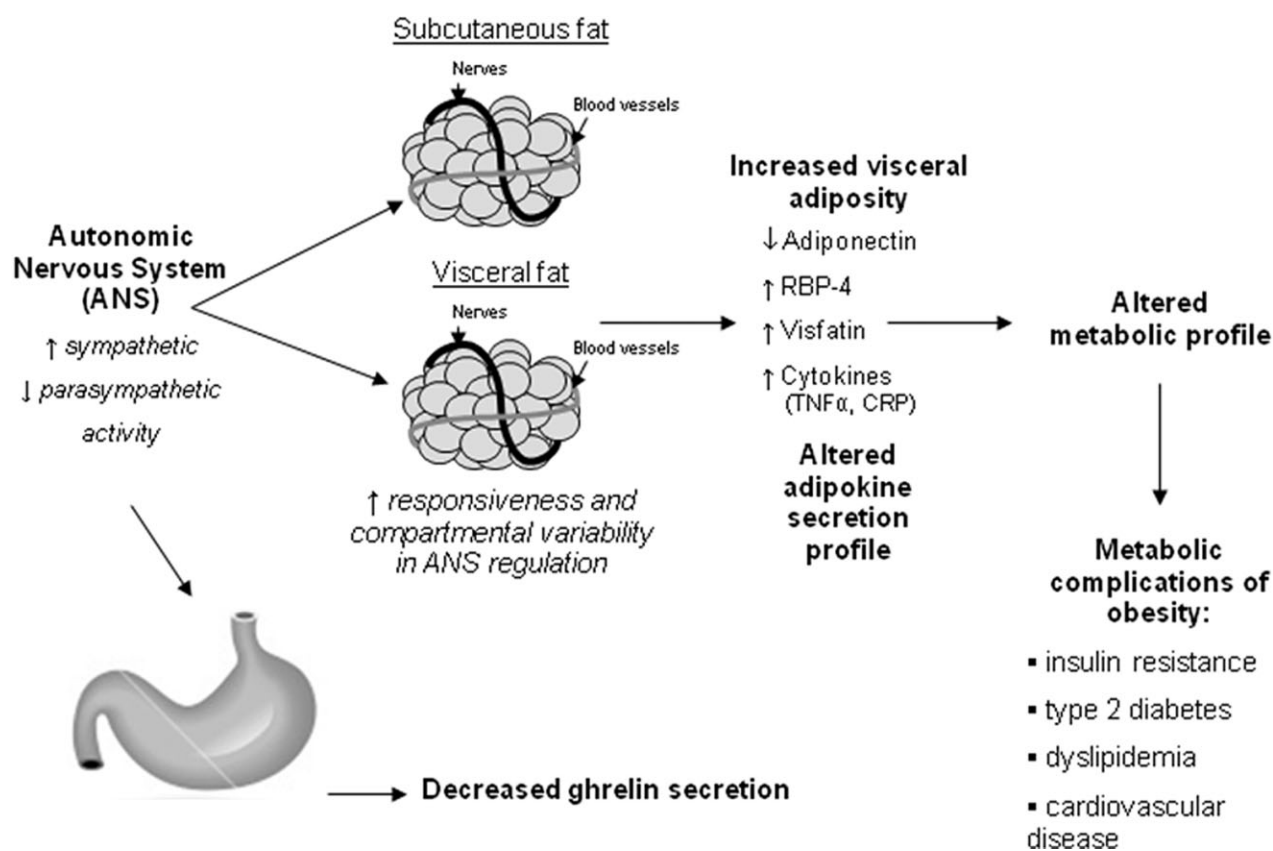


Figure 1 Model of pathophysiology of non-syndromic obesity.

of obesity in childhood (22,23). Others have reported decreased parasympathetic nervous system function with normal sympathetic activity in childhood obesity (24,25). More consistent with findings reported in the adult literature, Rodriguez-Colon *et al.* found a graded association between the degree of obesity and impairment in cardiac autonomic regulation in keeping with reduced parasympathetic modulation and increased sympathetic outflow (26). *The conflicting findings in obesity may be related to the insensitivity and variation in the tests used to assess autonomic function. However, the predominant overall observation in otherwise normal obese individuals appears to be a withdrawal or reduction of parasympathetic cardiovagal activity and a relative increase in sympathetic activity. The association between autonomic dys-regulation and obesity in childhood and adolescence would benefit from further research and the replication of studies already conducted solely in adults.*

Some researchers hypothesize that disrupted ANS circadian function results from lack of precisely timed food intake, which is shifted towards the end of the day and decreased physical activity. This unbalanced ANS circadian function could in theory be linked with the development of metabolic syndrome (visceral obesity, insulin resistance $\pm$ glucose intolerance, atherogenic dyslipidemia, elevated blood pressure, and both a pro-inflammatory and a prothrombotic state) (27) through increased parasympathetic activity in the visceral compartment and increased sympathetic tone in the thoracic compartment (28). A recent study shows that the metabolic syndrome develops in mice lacking the CLOCK gene, a regulator of hypothalamic circadian biologic rhythm controlled by the ANS (29).

Predisposition to type 2 diabetes is also linked to ANS dysfunction as measured by HR and HRV. A study of more than 8000 patients demonstrated a high relative risk for development of type 2 diabetes (independent of body weight) if ANS dysfunction is present (30). The relative risk for developing diabetes was 1.2 (95%, confidence interval 1.0–1.4) for participants with low HRV compared to those with high HRV; participants with a high resting HR had a 60% increased risk for development of diabetes. Another study shows that the amount of visceral fat is most strongly associated with a higher ratio of sympathetic vs. parasympathetic reactivity in HRV assessment in subjects predisposed to type 2 diabetes (31). While both studies suffer from the limitations in conclusions drawn from HRV analysis as discussed above, the metabolic syndrome and type 2 diabetes might result from or lead to imbalances in autonomic regulation, which disturbs the central circadian body clock or alters the distribution of body fat. *The relationship between altered ANS function and metabolic disorders suggests that the ANS is important in the regulation of hormones and other metabolic signals; however, at*

present it is not clear whether ANS dysfunction precedes or results from metabolic dysfunction.

ANS outflow is regulated and integrated by the CAN, which receives neural input from the brainstem and humoral input from circulating hormonal factors and signals to the hypothalamus, amygdala and forebrain (32). Key areas in the hypothalamus, in turn, are important in the regulation of energy balance (33). The arcuate nucleus of the hypothalamus integrates various peripheral endocrine signals such as leptin, insulin, glucose, ghrelin and peptide YY to affect energy balance. Within the arcuate nucleus are two distinct sub-populations of neurons: the first is pro-opiomelanocortin (POMC) neurons which are stimulated by leptin and inhibited by neighbouring agouti-related protein (AgRP)/neuropeptide Y (NPY) neurons; the second are neurons which co-express NPY and AgRP, neuropeptides that stimulate food intake via distinct mechanisms. These NPY/AgRP neurons are inhibited by leptin, insulin and PYY3–36 and stimulated by ghrelin. Leptin, for example, acts to increase excitation of POMC neurons while at the same time inhibiting the NPY/AgRP neurons; thus, the net effect of leptin stimulation is to decrease food intake and increase energy expenditure through its synergistic actions (34). *The hypothalamus, therefore, acts as a coordinator of metabolism and energy balance in humans, using both neurons and hormones to communicate with the body. There is evidence that fat tissue is controlled not only by hormones, but also directly by the ANS. White adipose tissue (WAT) is innervated by the sympathetic and the parasympathetic branches of the ANS (35–37). In WAT, an increase in sympathetic tone leads to decreased proliferation and differentiation, and enhanced apoptosis, thereby decreasing WAT mass. Catecholamines act directly on fat tissue to elicit fat breakdown (36). Parasympathetic input to adipose tissue, on the other hand, increases adipose tissue mass (38).*

WAT releases important hormones and cytokines including leptin, adiponectin, resistin, C-reactive protein and tumour necrosis factor- α (TNF- α); these can act at the level of the hypothalamus to modulate energy balance, satiety and energy expenditure (36,39). The effects of leptin, which increases energy expenditure, are mediated by sympathetic β -adrenergic receptors in the kidneys, adipose tissue, skeletal muscle vasculature and the neural traffic to the adrenal (34,40). Furthermore, the sympathetic nervous system is a key regulator of leptin production (41); acute treatment with catecholamines in humans reduces circulating leptin levels, while pharmacologic sympathetic blockade leads to increases in leptin levels (42). Ghrelin, a hormone produced primarily in the stomach, stimulates appetite and promotes weight gain (43). Ghrelin uses the ANS to exert some of its central actions (44,45), and the sympathetic nervous system to exert its effects on adipocyte cell metabolism (46). The ANS also regulates gastric

ghrelin secretion, and the gastric vagal afferent has been shown to be the major pathway that conveys ghrelin's signals to the brain (47,48). Other key adipocytokines regulated by the sympathetic nervous system include plasminogen activator inhibitor-1 (49), IL-6 (50) and TNF- α (51). *Therefore, the ANS regulates the levels and effects of WAT-derived hormones and adipokines.*

Several lines of evidence demonstrate that the ANS is involved in regulation of WAT cellular metabolism (36,52,53). For example, parasympathetic input to the adipose tissue was shown to directly stimulate glucose and free fatty acid (FFA) uptake and to modulate insulin sensitivity in an anabolic manner (38). Interestingly, intra-abdominal (visceral) and subcutaneous adipose tissues are innervated by different sets of autonomic neurons within the spinal cord and brainstem (38,54). Thus, the ANS could control adipose tissue distribution by (i) the whole body balance of sympathetic and parasympathetic output; and (ii) selective control of output to the particular site of the fat compartment (intra-abdominal vs. subcutaneous). Selective parasympathetic denervation of an intra-abdominal fat pad reduced insulin-dependent uptake of glucose and FFAs in adipose tissue and decreased leptin and resistin mRNA synthesis; these results support the theory that parasympathetic innervation to adipose tissue stimulates growth of adipose tissue (through increased glucose and FFA uptake) and modulates WAT hormone synthesis (38).

These findings suggest that *the ANS could have a major role in the regulation of fat distribution (36), which would have implications for health risks.* For example, imbalanced autonomic outflow to the intra-abdominal compartment might be a factor in diseases with relative excessive visceral adiposity such as the metabolic syndrome, type 2 diabetes and Cushing's syndrome.

Prader–Willi syndrome

PWS affects 1 : 10 000 individuals and is a common genetic cause of childhood obesity (5). PWS is caused by the lack of expression of paternally derived genes on chromosome 15q11-13; the diagnosis is confirmed by DNA methylation genetic studies. Infants with PWS are hypotonic, suck poorly and have difficulty gaining weight. These are followed by rapid onset of severe hyperphagia and weight gain between ages 1 and 5 years resulting in dramatic obesity. In comparison with patients with general obesity, however, excess total body fat in individuals with PWS is associated with increased insulin sensitivity and levels of adiponectin, and decreased levels of pro-inflammatory adipokines and visceral fat (6,7). PWS is therefore a unique model to understand the relationship between excess fat and development of metabolic abnormalities and to understand the factors responsible for 'metabolically healthy obese individuals'.

Understanding the unique 'protective' metabolic profile and reduced visceral fat deposition in PWS is important, and can lead to novel avenues of treatment for childhood obesity in PWS and non-PWS children.

Prader–Willi syndrome is a unique model of obesity to study the relationship between autonomic nervous system function and obesity-related metabolic complications

A number of unique aspects of PWS distinguish this disorder from 'exogenous' childhood obesity. Individuals with PWS demonstrate abnormal partitioning of body fat and lean mass. Whole body magnetic resonance imaging has found PWS adults to have greater overall body fat mass but significantly less visceral adiposity compared to body mass index (BMI)-matched controls (7,55). This altered body composition might protect PWS individuals against metabolic complications of obesity such as insulin resistance, type 2 diabetes and hypertriglyceridemia (7,23). We have also demonstrated higher total and high molecular weight adiponectin concentrations and higher insulin sensitivity in PWS children compared to BMI-matched controls (6).

PWS children also have high fasting and postprandial levels of ghrelin, an orexigenic peptide produced in the stomach. Ghrelin stimulates appetite and promotes weight gain in animal models and in humans when administered at pharmacologic doses. In contrast, total ghrelin levels are suppressed in children and adults with 'exogenous' obesity or with obesity caused by mutations in leptin or the melanocortin-4 receptor (56). These findings have been confirmed by several other groups (57–59). The ratio between acylated and unacylated ghrelin in PWS has not yet been studied, and the mechanisms underlying the hyperghrelinemia of PWS remain unclear at this time. It is possible that increased vagal nerve efferent activity to the gastrointestinal tract in PWS contributes to the higher concentrations of ghrelin seen in this disorder. This theory is supported by emerging evidence that the vagus nerve controls ghrelin secretion. Data in rodents show that vagotomy eliminates the fasting-induced increase in ghrelin (60), and blockade of the vagus nerve via atropine produces reduction in ghrelin levels in humans (61). Patients with bulimia who exhibit increased vagal tone demonstrate increased ghrelin levels (62).

Symptoms of autonomic nervous system dysfunction in Prader–Willi syndrome

Several features in PWS individuals suggest underlying disturbances in autonomic control. PWS subjects exhibit oropharyngeal and bowel dysmotility, abnormal temperature regulation (reduction in core temperature in response to cold stress) (63), altered sleep control (excessive daytime

somnolence, a primary abnormality of the circadian rhythm of rapid eye movement sleep, insensitivity to hypoxia and hypercarbia) (64,65), altered perception of pain, decreased salivation, learning disabilities and poor executive planning (63,66). Interestingly, some of the clinical features of PWS are reminiscent of those manifested by patients with a classic peripheral autonomic disorder called familial dysautonomia (FD) (formerly called Riley–Day syndrome). FD is a genetic autosomal recessive disease caused by mutations in IKBKAP (I κ B kinase complex associated protein) gene on chromosome 9, which affects the development, survival and migration of sensory and autonomic neurons (67). The sympathetic neurons are more affected to a greater degree than parasympathetic neurons in FD. It is postulated that IKBKAP affects catecholamine metabolism and this process is impaired in FD (68).

Current data regarding abnormalities in ANS function in PWS (Table 2). The earliest human study of 14 patients with PWS and eight control subjects reported diminished parasympathetic nervous system function based on findings of higher resting pulse rates, smaller changes in diastolic

blood pressure upon standing, abnormal 30 : 15 RR interval ratios and greater pupillary constriction to pilocarpine (69). The same authors observed no differences in the regulation of cutaneous temperature and blood flow in PWS patients, presumed to be under sympathetic control at rest (70). Another study of 26 PWS patients observed no differences in HR, blood pressure and HRV in the supine position, sitting, during Valsalva and while performing moderate exercise when compared with age and BMI-matched controls (71). Each of these studies is limited by small sample sizes and the predominant use of cardiac autonomic regulation as an indirect measure of ‘systemic’ autonomic activity. Regional variation (e.g. thoracic vs. visceral compartments) was not explored and only one study attempted to examine peripheral sympathetic function in the regulation of cutaneous temperature and blood flow. More direct measures of peripheral sympathetic activity such as the QSART and muscle or skin sympathetic nerve activity were not explored.

Experimental animal models of PWS suggest specific abnormalities in the development of the sympathetic

Table 2 Summary of prior studies evaluating ANS function in PWS subjects

Author	Study design	ANS testing methods	Major findings
DiMario <i>et al.</i> , 1994 (69)	Cross-sectional study in 14 PWS (8F/6M; ages 4–40 years) and 8 controls (4F/4M; ages 5–37 years)	- Electrocardiography and HR and systolic/diastolic mean BPs during orthostatic maneuvers - Pupillary response to pilocarpine - Plasma noradrenaline at rest and after standing	- PWS had higher resting HR - PWS had lower change in diastolic BP after standing ($P < 0.02$) - Pupillary constriction ≥ 2 mm (7 of 14 PWS) ($P < 0.004$) - Abnormal 30 : 15 RR interval ratio (6 of 14 PWS) ($P < 0.03$) - No differences in plasma noreadrenaline between groups - Overall diminished parasympathetic activity in PWS is reported
DiMario <i>et al.</i> , 2002 (70)	Cross-sectional study in 32 PWS subjects compared to 5 controls	Thermal and laser Doppler flow continuous and simultaneous recording of capillary blood flow and temperature over a 10-min interval	No significant difference in regulation of cutaneous temperature and blood flow in PWS
Wade <i>et al.</i> , 2000 (71)	Cross-sectional study in 26 PWS subjects compared to 26 age-, gender- and BMI-matched controls	- BP, HR and respiration recorded: a) supine; b) after transition from supine to standing; c) sitting; d) during Valsalva; e) while performing moderate exercise; and f) during recovery from exercise while seated - Power spectral analysis of heart period variability used to assess cardiac ANS modulation	- No differences in LF and HF cardiac autonomic modulation and in the LF/HF frequency modulation ratio at rest and for any provocations between groups - Significantly higher HR in the control group seen during exercise - Lower SBP seen in the PWS during exercise
Priano <i>et al.</i> , 2009 (73)	Cross-sectional study in 14 adult PWS subjects; 10 obese non-diabetic subjects; 10 age-matched controls	Testing involved: a) motor/sensory nerve conduction velocities (upper and lower limbs); (b) palmar/plantar sympathetic skin response; (c) somatosensory-evoked potentials from upper/lower limbs; (d) quantitative sensory testing	- Electroneurographic examination, sympathetic skin response and somatosensory-evoked potentials were all normal in PWS - In the PWS group, thermal and pain thresholds were significantly higher than in healthy and obese people

ANS, autonomic nervous system; BP, blood pressure; HF, high frequency; HR, heart rate; LW, low frequency; PWS, Prader–Willi syndrome; SBP, systolic blood pressure.

nervous system. Necdin is one of several proteins that are genetically inactivated in PWS and is important in differentiation of sensory neurons. Necdin null mice have diminished formation, migration and survival of the sympathetic superior cervical ganglion neurons (the most rostral of the paravertebral sympathetic ganglions innervating the pupil, lacrimal, salivary glands and cerebral blood vessels) and reduced innervation of target systems (72). Thus, necdin has been shown to mediate the development and survival of autonomic neurons and to play an essential role in the development of the ANS.

PWS patients are generally less sensitive to pain, but the pathogenesis of this trait is poorly understood. Motor and sensory nerve conduction studies are normal, but PWS patients have high thermal and pain thresholds suggestive of impairment in small peripheral pain sensing neurons (73). Necdin null mice also show high thermal pain tolerance which may be related to a reduction in peripheral sensory neurons (74,75). We recently reported that serum brain-derived neurotrophic factor (BDNF) levels in children with PWS are lower than those in obese, age-matched controls (64). Heterozygous *BDNF* knockout mice and humans lacking *BDNF* display hyperphagia, obesity, diminished pain sensitivity and behavioural disturbances that phenotypically resemble the abnormal behaviours of PWS (76–78). BDNF plays a role also in the development and survival of sympathetic autonomic neurons (79,80), and is required for the development of some types of sensory neurons in the dorsal root ganglion (81). BDNF also plays a role in the development of vagal nerve afferents important in gastric function and food intake (82). Common mechanisms involving necdin and BDNF in the development of sensory neurons and both the parasympathetic (particularly vagus nerve afferents) and sympathetic branches of the ANS may explain some of the clinical autonomic dysfunction and pain insensitivity common in PWS.

Conclusion

It will be clinically important to fully characterize the autonomic dysfunction associated with obesity and PWS in the future. Understanding these novel neural factors associated with body fat distribution and metabolic profile in PWS and non-PWS individuals will provide insight into developing treatment strategies for the general childhood obese population. Reduction of intra-abdominal fat may be most important for reducing obesity-associated comorbidities. New techniques are required to assess the site-specific innervations of the ANS. For example, a dominant sympathetic tone in the thorax might co-exist with a dominant parasympathetic tone in the abdomen. Drugs targeting the control of visceral fat deposition or resulting in a more favourable adipokine profile (increased adiponectin) would be prime candidates for treatments of the metabolic syndrome. PWS

offers a unique model of obesity and ANS dysfunction to explore the links between altered ANS activity and development of subsequent obesity and metabolic complications.

Nevertheless, much of the current data on the ANS's contribution to the regulation of body fat distribution, obesity and metabolic complications remain confusing and in some cases contraindicatory. Clearly, more research is needed in this important, complex area to unravel the ANS's novel contribution to obesity.

Conflict of Interest Statement

No conflict of interest was declared.

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