

Review Article

Relationships of Adrenoceptor Polymorphisms with Obesity

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Obesity, hypertension, and type 2 diabetes are rapidly growing public health problems. Heightened sympathetic nerve activity is a well-established observation in obesity, hypertension, and type 2 diabetes. Human obesity, hypertension, and diabetes have strong genetic as well as environmental determinants. Reduced energy expenditure and resting metabolic rate are predictive of weight gain, and the sympathetic nervous system participates in regulating energy balance through thermogenesis. The thermogenic effects of catecholamines in obesity are mainly mediated via the β_2 , and β_3 -adrenergic receptors in humans. Further, β_2 -adrenoceptors importantly influence vascular reactivity and may regulate blood pressure. β -adrenoceptor polymorphisms have also been associated with adrenoceptor desensitization, increased adiposity, insulin resistance, and enhanced sympathetic nervous activity. Many epidemiological studies have shown strong relationships between adrenoceptor polymorphisms and obesity, but the observations have been discordant. This paper will discuss the current topics involving the influence of the sympathetic nervous system and β_2 - and β_3 -adrenoceptor polymorphisms in obesity.

1. Introduction

Obesity is a major and growing health problem. Importantly, the presence of increased adiposity is associated with elevated risk of development of cardiovascular and renal complications [1–4]. Obesity is frequently associated with hypertension, diabetes, and metabolic syndrome [5–7], and sympathetic nervous activation is frequently observed in those conditions [8]. Thus, sympathetic nerve activation may play a major role in the onset and development of obesity, hypertension, and the development of the metabolic syndrome as well as controlling to the cardiovascular complications evident in patients with hypertension, diabetes, and obesity [2, 4, 9].

The sympathetic nervous system plays an important role in the regulation of energy expenditure. Reduced energy expenditure and resting metabolic rate are predictive of weight gain (obesity). Furthermore, blunted sympathetic nervous responses to energy intake have been observed in obese subjects with the metabolic syndrome and insulin resistance [10, 11]. The sympathetic nervous system participates in regulating energy balance through thermogen-

esis [12]. Recently, the important relationships of brown adipose tissue for energy expenditure [13–15] were argued, however a large part of the sympathetic nervous system-mediated energy expenditure takes place in skeletal muscle, via the coupling of catecholamines with β_2 -adrenoceptors. Catecholamines are also powerful regulators of lipolysis and act via β_1 -, β_2 -, β_3 -(stimulatory), and α_2 -(inhibitory) adrenoceptor subtypes in adipose tissue, where their role becomes especially important during both exercise and energy restriction, when increased need for fat as a fuel exists. Thus, β -adrenoceptors play important roles in energy expenditure and control body weight [16–20].

Recent evidence indicates that human obesity indeed has a genetic component with [21–23] several epidemiological and clinical studies indicating a strong linkage between β -adrenoceptor polymorphisms and obesity or weight gain [24, 25]. Furthermore, heightened sympathetic nervous system activity associated with β_2 - and β_3 -adrenoceptor polymorphisms predicts subsequent weight gain and blood pressure elevation in originally nonobese subjects [11, 24], and rebound weight gain after significant weight loss in obese subjects [26]. β_2 -adrenoceptor polymorphisms are related to

the onset of insulin resistance [27] and blunted responses of sympathetic nerve activity to acute hyperinsulinemia [10, 11, 27–29]. These findings show that the genetic background, especially β 2- and β 3-adrenoceptor polymorphisms, are associated with sympathetic nervous system activation, and are important in the pathogenesis of obesity-related hypertension and insulin resistance. Many investigations regarding the relationships between β -adrenoceptor polymorphisms and obesity have been analysed; however, the results are discordant [30–32].

2. Role of the Sympathetic Nervous System in Obesity

Many epidemiological and clinical studies have demonstrated a close relationship between sympathetic nervous activation and insulin levels in obesity [33–37]. Several longitudinal studies have examined the effect of body weight changes (weight loss or weight gain) on sympathetic nervous system activity and insulin sensitivity (fasting plasma insulin levels and HOMA-IR). Elevated activity of the sympathetic nervous system and increased insulin levels during weight gain [16, 24, 26, 38, 39] and reductions of sympathetic nerve activity and insulin levels during weight loss [40–45] have been observed. In obese normotensive subjects, a reduction in body weight induced exerts a marked reduction in sympathetic activity owing to central sympathoinhibition due to the consequences of an increased insulin sensitivity and a restoration of the baroreflex [45]. These studies have clearly shown heightened sympathetic nerve activity and insulin resistance are closely linked to weight gain and the onset and maintenance of obesity.

Landsberg et al. [46–48] and Julius et al. [49] have proposed hypotheses to explain the mechanism linking the sympathetic nervous system and insulin resistance in obesity. The former proposes that hyperinsulinemia and insulin resistance in obese subjects are all part of a response to limit further weight gain via stimulating sympathetic nervous activity and thermogenesis [50], and the latter indicates that sympathoexcitation in the skeletal muscle vascular bed cause neurogenic vasoconstriction and reduction in blood flow to muscle and consequently induces a state of insulin resistance by lowering glucose delivery and uptake in hypertension and obesity. Masuo et al. in a series of longitudinal studies observed that heightened sympathetic activity was the prime mover for future weight gain in originally nonobese, normotensive subjects, and that insulin resistance was more an ancillary factor [24, 51, 52]. In investigations examining the effect of weight loss, reductions in plasma norepinephrine followed by reductions in HOMA-IR as a marker of insulin resistance were significantly greater in subjects experiencing significant weight loss compared to those without significant weight loss [26, 40, 43]. These observations provide some support for the hypothesis of Julius and colleagues.

Valentini et al. [53] reported attenuation of hemodynamic and energy expenditure responses to isoproterenol infusion in hypertensive patients. Their findings that a generalized decrease of β -adrenergic responsiveness in hyper-

tension supports the hypothesis that heightened sympathetic nerve activity, through downregulation of β -adrenoceptor-mediated thermogenesis, may facilitate the development of obesity in hypertension. Their results suggested that sympathetic nerve activity-induced hypertension may subsequently lead to the development of obesity.

3. Role of β -Adrenoceptor Polymorphisms in Obesity

The sympathetic nervous system plays an important role in the regulation of energy expenditure. A large part of the sympathetic nervous system-mediated energy expenditure takes place in skeletal muscle, via the coupling of catecholamines with β 2-adrenoceptors [54]. Catecholamines are also powerful regulators of lipolysis and act via β 1-, β 2-, β 3- (stimulatory) and α 2- (inhibitory) adrenoceptor subtypes in adipose tissue, where their role becomes especially important during both exercise and energy restriction, when increased need for fat as a fuel exists. Stimulation of β -adrenergic receptors by the sympathetic nervous system is a significant physiological modulator of pre- and postprandial energy expenditure [18–20] and total daily energy expenditure [16, 17, 50]. The subtypes of adrenoceptors on lipid and glucose metabolisms are summarized as following; α 1-adrenoceptors, glycogenolysis and gluconeogenesis in adipose tissue and liver; α 2-adrenoceptors, induction of glucagon release from pancreas; β 1-adrenoceptors, lipolysis in adipose tissue; β 2-adrenoceptors, glycogenolysis and gluconeogenesis in adipose tissue and liver; β 3-adrenoceptors, lipolysis on adipose tissue.

Recent studies show that β -adrenoceptors are polymorphic with single nucleotide polymorphisms exerting functional consequences in terms of receptor activity and regulation and hence perhaps may contributing to the pathophysiology of obesity and hypertension [24, 25, 55–59]. On the other hand, there are few studies on the relationships between α -adrenoceptor polymorphisms and obesity.

3.1. β 1-Adrenoceptor Polymorphisms (Table 1). The β 1-adrenoceptor is predominantly expressed in cardiac myocytes and adipose tissue, where its activation leads to increased heart rate and contractility and stimulation of lipolysis, respectively. The β 1-adrenoceptor is a candidate gene for obesity because of its role in catecholamine-mediated energy homeostasis. In obese individuals, the degree of weight loss during a very low calorie diet has been shown to correlate with changes in β 1-adrenoceptor protein concentration in adipose tissue [65]. The two most common β 1-adrenoceptor polymorphisms are Ser49Gly and Arg389Gly, with relative allele frequencies of 0.85/0.15 and 0.70/0.30 in Caucasian population, respectively. An investigation involving a population cohort of 761 women indicated that women carrying the Gly49 genotype had greater elevation in BMI over 15 years compared to those with the Ser49 genotype [62]. Again, in Caucasian women ($n = 931$), Dionne et al. [60] observed that the Gly389Arg, β 1-adrenoceptor variant exhibited a strong relationships

TABLE 1: Summary of studies showing associations between on β 1-adrenoceptor polymorphisms and obesity.

Authors (reference)	Year	Population	Subjects	Findings
Dionne et al. [60]	2002	Caucasian	931 women	Arg allele of Arg389Gly was associated with obesity (greater body weight and BMI due to greater fat mass).
Tafel et al. [61]	2004	German	Children and adolescents	The distributions of Ser49Gly and Arg389Gly were not different between lean and obese adolescents.
Linné et al. [62]	2005	Scandinavian	761 women	The combination of Gly49-Gly389 (Ser49Gly + Arg389Gly) was associated with long term of 15 years weight gain and the incidence of adult-onset overweight in women, but no effect of Arg389Gly alone on obesity.
Gjesing et al. [63]	2007	Danish-Caucasians	7,677	Arg389Gly polymorphism was not related with obesity, but minor influence on BP.
Nonen et al. [64]	2008	Japanese	188 type 2 diabetic patients	Ser49Gly, but not Arg389Gly, was associated with obesity.

BP: blood pressure.

with obesity. Conversely, Gjesing and colleagues found that the distribution of the Arg389Gly polymorphism was similar in lean and obese subjects, suggesting that it has no important influence on human obesity [63, 66]. Although earlier small case-control studies demonstrated an increase in the risk of hypertension in Arg389 homozygotes [67, 68], a recently published study comprising 3981 normotensive and 2,518 hypertensive patients failed to replicate this association [63] (summarised in Table 1). Arner [67] reviewed that Arg389Gly polymorphism in the β 1-adrenoceptor, which alters receptor function in transfected cell lines, and concluded that the SNP has no effect on lipolysis in human fat cells and is not associated with obesity.

3.2. β 2-Adrenoceptor Polymorphisms (Table 2). The β 2-adrenoceptor is the dominant lipolytic receptor in white human adipose tissue [20, 55, 56] and in skeletal muscle [19, 57]. Gln16Glu and an Arg164Ile variation in the β 2-adrenoceptor cause marked variations in the lipolytic sensitivity of this receptor in human adipocytes. Multiple β 2-adrenoceptor polymorphisms including haplotypes, markedly influence β 2-receptor function- and catecholamine-induced lipolysis in fat cells [76]. These haplotypes may be important genetic factors behind impaired lipolysis in obesity [25].

The β 2-adrenoceptor also plays an important regulatory role in the peripheral vasculature. Genetic polymorphisms of the β 2-adrenoceptor have been associated with obesity, hypertension, and diabetes mellitus. The most common polymorphisms are Arg16Gly, with an allele frequency of 0.40/0.60 and Gln27Glu, with an allele frequency of 0.55/0.45 in the Caucasian population. The Thr164Ile polymorphism is rare, occurring in only 3 to 5% of the general (Caucasian) population.

Studies of agonist stimulation in cultured cells demonstrate that Gly16 receptors have a greater reduction in numbers or enhanced downregulation when compared with

Arg16, whereas the Glu27 receptor is resistant to down regulation when compared with the Gln27 variant [77]. A number of clinical studies have investigated the impact of these polymorphisms on vascular responsiveness [55, 78]. Gratze et al. [79] found that young normotensive white men homozygous for the Gly16 allele had higher blood pressure and lower peripheral vasodilation after infusion of the β 2-agonist salbutamol. Similar results were obtained by Hoit et al. [80] using the agonist terbutaline. On the other hand, volunteers homozygous for Gly16 exhibited larger vasodilatory responses than did volunteers homozygous for Arg16 [81]. Conflicting results have also been published with regards to the effects of genetic variants on the sympathetic nervous system modulation of energy expenditure. Bell et al. [82] reported that the response of resting energy expenditure to nonspecific β -adrenoceptor stimulation (with isoproterenol infusion) was not different between the 3 genotypes of Arg16Gly. Stob et al. [70] showed that individuals carrying the Arg16Arg variant of the β 2-adrenoceptor gene have a reduced thermogenic response to selective β 2-adrenoceptor activation.

Associations of β 2-adrenoceptor polymorphisms with obesity have been reported in many epidemiological studies but results are also discordant (summarised in Table 2).

3.3. β 3-Adrenoceptor Polymorphisms (Table 3). The β 3-adrenoceptor, which is mainly expressed in adipose tissue, differs from the β 2-adrenoceptor in two ways: it has a lower affinity for catecholamines, and it resists desensitisation (i.e., downregulation). These characteristic differences might lead to the different effects of catecholamine on β 2-adrenoceptors and β 3-adrenoceptors. β 3-adrenoceptors stimulates the mobilization of lipids from the white adipose tissue and increases thermogenesis in brown adipose tissue. Cypess et al. and other investigators demonstrated that potential roles of β 3-adrenoceptor polymorphism (Trp64Arg) associated with potential role of uncoupling protein (UCP)

TABLE 2: Summary of studies showing associations between β 2-adrenoceptor polymorphisms and obesity.

Authors [reference]	Year	Population	Subjects	Findings
Large et al. [55]	1997	Swedish	Caucasian women with wide range of obesity	Gln27Glu polymorphism was associated with obesity.
Echwald et al. [58]	1998	Danes	Caucasian juvenile-onset obese men	No association between Gln27Glu and obesity.
Hellström et al. [59]	1999	Swedish	Swedish-Caucasian men and women	Gln27Glu polymorphism was associated with obesity only in women, but not in men.
Kortner et al. [69]	1999	German	Caucasian with morbid obesity	Gln27Glu polymorphism was not associated with obesity.
The Quebec Family Study [70]	2000	Canadian	Caucasian men and women	Gln27Glu polymorphism was associated with obesity and hyperlipidemia.
Ukkola et al. [56]	2001	USA	12 pairs of twins, Caucasians	Gln27Glu polymorphism was associated with weight gain (obesity).
Meirhaeghe et al. [71]	2000	French	1,195 subjects	Subjects carrying Gln27 homozygous had an increased risk of obesity in men, but not in women. Further, men with Gln27 homozygous carried in addition the Arg16 allele, had more significant increase in body weight, BMI and waist-to-hip ratio (central obesity).
The HERITAGE family study [72]	2003	Canada	Sedentary black and white men	Gln27Glu polymorphism was associated with lower fat in obese white men.
Pereira et al. [25]	2003	Brazilian	1,576 individuals randomly selected	Subjects carrying Gln27 homozygous had higher risk of obesity, whereas those with Gly27 homozygous had increased risk of hypertension.
Jiao et al. [73]	2005	Scandinavian	1,354 women and 421 men	Common haplotypes of ADRB2 polymorphisms had recessive effects against excess body fat only in women, but not in men.
Masuo et al. [26]	2005	Japanese	154 overweight/obese men	Gly16 allele was related to obesity and rebound weight gain in weight-loss study.
Masuo et al. [24, 27]	2005	Japanese	160 nonobese, normotensive men	Gly16 allele was related to future weight gain, BP elevation and insulin resistance in originally nonobese, normotensive men.
Masuo et al. [28]	2006	Japanese	329 normotensive men with a wide range of BMI	Gly16 and Glu27 alleles were related to obesity through blunted-leptin-mediated sympathetic activity.
Kawaguchi et al. [29]	2006	Japanese	55 overweight/obese men	Gly16 allele was related to further weight gain in obese subjects.
Petrone et al. [74]	2006	European	642 overweight/obese subjects	The haplotype of 5'LC-Cys(19)Arg(16)Gln(27) was related to additional weight gain with increases of triglycerides and LDL-cholesterol.
Gjesing et al. [75]	2009	Danes	6,514 adults	No consistent effect of ADRB2 haplotypes on obesity and quantitative traits of body fatness.

ADRB2: β 2-adrenoceptors; BP: blood pressure.

polymorphisms and brown adipose tissue in thermogenesis and resultant body weight in humans [13–15]. Decreased function of β 3-adrenoceptor in white adipose tissue could slow lipolysis and thereby cause the retention of lipids in adipocytes. Slow lipolysis may contribute strongly to visceral obesity in human, and treatment of obese animal models with selective β 3-adrenergic agonists reduces fat

stores effectively [88–90]. Hoffstedt et al. [91] compared adrenergic regulation of lipolysis between omental and subcutaneous adipocytes from 15 obese and 14 nonobese men. In their study, catecholamine-induced lipolysis was markedly increased in omental adipocytes as compared to subcutaneous adipocytes in obese male subjects mainly due to an increase in β 3-adrenoceptor function of visceral fat,

TABLE 3: Summary of studies showing associations between β 3-adrenoceptor polymorphisms and obesity.

Authors [reference]	Year	Population	Subjects	Findings
Clement et al. [83]	1995	French	Patients with morbid obesity	Subjects carrying β 3-ADR polymorphisms has an increased capacity to gain weight.
Sakane et al. [84]	1997	Japanese	61 obese women with type 2 diabetes	The Arg64 allele of Trp64Arg may predict difficulty in losing body weight, lowering waist-to-hip ratio, and improving glycemic control and insulin resistance in obese patients with type 2 diabetes.
Umekawa et al. [85]	1999	Japanese	18 omental fat samples obtained during total hysterectomy	Trp64Arg polymorphism was associated with lower lipolytic activities.
Endo et al. [86]	2000	Japanese	553 Japanese schoolchildren (291 boys and 262 girls)	Trp64Arg polymorphism might be a genetic risk factor for obesity in Japanese children.
Oizumi et al. [87]	2001	Japanese	1,685 (935 women and 750 men)	Arg64/Arg64, but not Trp64/Arg64, of the β -adrenergic receptor polymorphism was associated with both obesity and type 2 diabetes in a large Japanese cohort.
Masuo et al. [24]	2005	Japanese	160 nonobese, normotensive men	Trp64Arg polymorphism was related to BP elevations, but not to weight gain in originally nonobese subjects.
Kawaguchi et al. [29]	2006	Japanese	55 overweight/obese men	Trp64Arg polymorphism was related to further weight gain in originally obese subjects.
Gjesing et al. [63]	2007	Danish-Caucasians	7,605	Trp64Arg polymorphism did not confer an increased risk of obesity among Danes, although the variant is associated with type 2 diabetes and quantitative traits related to type 2 diabetes.

TABLE 4: Confounding variables considered to cause the discrepancy of the relationships between β -adrenoceptor polymorphisms and phenotypes of obesity, hypertension, and diabetes.

Variables [reference number]	Findings in the studies
Severity of obesity [23, 28, 29]	In lean subjects, β 2-AR polymorphisms linked to obesity and obesity-related hypertension, but in obese subjects β 2- and β 3-AR Polymorphisms related to obesity and obesity-related hypertension. Morbid obesity was linked with β 3-AR polymorphisms, but Overweight or mild obesity was not associated with those.
Gender differences [71, 73]	Interaction between β 1- and β 2-AR polymorphisms with changes in BMI was observed in men only, while in women an interaction between β 1- and β 3-AR polymorphisms was observed in a longitudinal over a 24-year period large cohort study.
Ethnic difference [30]	Distributions of β -AR polymorphisms are different in 8 different ethnic population.
Haplotype [25, 73, 74, 76, 86, 93–97]	Functions expressed of β -AR polymorphisms are different due to the other β -AR polymorphisms.

AR: adrenoceptor; BMI: body mass index.

in combination with a smaller increase in β 1-adrenoceptor function [91]. Recently, Eriksson et al. [76] observed that Trp64Arg polymorphism in the β 3-receptor, which associates with obesity, is accompanied by changes in lipolytic sensitivity of the receptor in human adipocytes. Many epidemiological studies have shown the strong relationships between β 3-adrenoceptor polymorphisms (mainly Trp54Arg), obesity, metabolic syndrome, and hypertension [87–92] (Table 3).

3.4. *Confounding Variables Affecting the Relationships of β -Adrenoceptor Polymorphisms with Obesity, Hypertension and Diabetes (Table 4).* Tables 1–3 show the discordant contributions of β -adrenoceptor polymorphisms to obesity. Table 4 summarizes factors which might explain the discrepancy of published data. Importantly, haplotypes of polymorphisms have strong influence on β -adrenoceptor function in each polymorphism [25, 73, 86, 93–97].

4. Sympathetic Nervous System Activity and β 2- and β 3-Adrenoceptor Polymorphisms in Obesity

Many studies have examined the associations of the β 2- or β 3-adrenoceptor polymorphisms with obesity and blood pressure as mentioned above. A series of studies conducted by Masuo et al. have included measurements of sympathetic nervous system activity [24, 26]. In a longitudinal study over 5 years, originally nonobese, normotensive subjects carrying the Gly16 allele of Arg16Gly, the combination of β 2-adrenoceptor polymorphisms and high plasma norepinephrine levels on entry were linked to weight gain and blood pressure elevations in addition to weight gain-induced blood pressure elevations [24]. In a weight loss study over a 24-month period, the β 2-adrenoceptor the Gly16 allele of Arg16Gly was associated with resistance to long term significant weight loss, and the Glu27 allele was linked to resistance to short-term weight loss [26]. Nonobese normotensive men carrying the Gly16 allele of Arg16Gly had a higher frequency of insulin resistance, as indicated by elevation in the homeostasis model assessment for insulin resistance (HOMA) index. This deterioration in insulin resistance is generally observed in obesity and hypertension [27, 36, 44, 98]. These studies provide strong evidence for the linkage between β 2-adrenoceptor polymorphisms, heightened sympathetic nervous system activity, obesity, hypertension, and the development of insulin resistance.

5. Elevated Sympathetic Nervous Activity in Obesity Is a Risk Factor for Cardiovascular Complications and Renal Complications

The increased risk of cardiovascular complications in obesity, especially associated with hypertension or type 2 diabetes, has been attributed to a variety of mechanisms, including dyslipidemia, coagulation abnormalities, endothelial dysfunction, chronic sympathetic nerve activation, and repeated occurrence of excessive hyperinsulinemia [99–102]. Sympathetic nerve hyperactivity leads to arterial blood pressure elevation [103–105], triggers arterial damage, and results in cardiovascular events. Recent studies and reviews reported that sympathetic nerve stimulation contributes to the progression of renal disease [106, 107]. Norepinephrine infusion into the renal artery in dogs produced a reversible ischemic model of acute renal failure [108]. Another study demonstrated renal protection by β -adrenergic receptor blockade in a nephrectomized rat without any BP changes [109]. Plasma norepinephrine and heightened sympathetic nerve activity may predict mortality and incident cardiovascular events including renal injury in large cohort longitudinal studies [110] and clinical studies [111, 112]. Renal injury also predicts the development of cardiovascular disease [105, 106, 110, 111]. There is consistent evidence that elevated sympathetic nervous activity predicts mortality in cardiovascular disease such as in patients with heart failure [111] and end-stage renal disease [112, 113]. Given

these observations and the recent demonstration of the effectiveness of catheter based sympathetic renal denervation for the treatment of refractory hypertension [114, 115], it may be of importance to aim antihypertensive treatments or anti-diabetic treatment not only at the reduction of raised blood pressure or blood glucose but also at the excessive sympathetic activation that may underpin these effects.

6. Conclusions

Established and emerging data emphasises the importance of the sympathetic nervous system in obesity and obesity-related illness. Sympathetic nervous system activity and β -adrenoceptor polymorphisms (mainly β 2- and β 3-adrenoceptor polymorphisms) may contribute to the onset and maintenance of obesity; however, the findings have been discordant. A better understanding of the pathogenesis of obesity, including an understanding of adrenoceptor polymorphisms and their impact on sympathetic nervous activity might help in the prevention of obesity and the pharmacological treatment of obesity-related illness including hypertension and insulin resistance.

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