Roles of Beta2- and Beta3-Adrenoceptor Polymorphisms in Hypertension and Metabolic Syndrome

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Received 19 July 2010; Accepted 2 September 2010

Hypertension, diabetes mellitus (especially type 2 diabetes mellitus), metabolic syndrome and obesity are rapidly growing public health problems. Sympathetic nerve activation is observed in obesity, hypertension and diabetes mellitus, which 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 have been mainly mediated via the β2- and β3-adrenergic receptors in humans. Further, β2-adrenoceptors importantly influence vascular reactivity and may regulate blood pressure. Genetic polymorphisms of the β2-adrenoceptor gene have been shown to alter the function of several adrenoceptor subtypes and thus to modify the response to catecholamine. β2-adrenoceptor polymorphisms (Arg16Gly, Gln27Glu, and Thr164Ile) have been studied in relation to hypertension. Genetic variations in the β3-adrenoceptor (i.e. Try64Arg variant) are also associated with both obesity and hypertension. However, the precise relationships of the polymorphisms of β2- and β3-adrenoceptor genes with sympathetic nervous system activity, hypertension, and metabolic syndrome have not been fully clarified. This paper will discuss the current topics involving the influence of the sympathetic nervous system and β2- and β3-adrenoceptor polymorphisms in hypertension and metabolic syndrome.

1. Introduction

Obesity, hypertension, and metabolic syndrome (type 2 diabetes mellitus) are major and growing health problems and are known as high-risk factors for subsequent cardiovascular and renal complications [1–3]. Obesity, hypertension, diabetes, and metabolic syndrome are intimately associated [4–6], and sympathetic nervous activation is frequently observed in those conditions. Thus, sympathetic nerve activation may play a major role in the onset and development of hypertension, obesity, and metabolic syndrome (diabetes mellitus) as well as cardiovascular complications in patients with hypertension, diabetes and obesity [2, 7].

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). The sympathetic nervous system participates in regulating energy balance through thermogenesis [8]. A large part of the sympathetic nervous system-mediated energy expenditure takes place in skeletal muscle, via the coupling of catecholamines with β2-adrenoceptors. Catecholamines are also powerful regulators of lipolysis and act via β1-, β2-, β3- (stimulatory), and α2- (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 [9–13].

Recently, there is evidence that human hypertension and obesity have strong genetic backgrounds [14–16]. Harrap et al. reported that about 46% of the phenotype of systolic blood pressure are determined genetically for hypertension [17, 18]. Masuo et al. [18–22] have reported close relationships between β2- and β3-adrenoceptor polymorphisms
accompanying elevated sympathetic nervous activity, blood pressure elevation (hypertension), weight gain (obesity), and insulin resistance in a series of longitudinal study. Many epidemiological studies on the relationships between \( \beta \)-adrenoceptor polymorphisms, hypertension, obesity, and diabetes (metabolic syndrome) have still been discordant.

This paper will discuss the current topics involving the contribution of the sympathetic nervous system and \( \beta_2 \)- and \( \beta_3 \)-adrenoceptor polymorphisms in the onset and the development of hypertension and metabolic syndrome (type 2 diabetes mellitus).

2. Subtypes of Adrenoceptors (Table 1)

The adrenoceptors (or adrenergic receptors) are a class of G protein-coupled receptors which specifically bind their endogenous ligands, the catecholamines (epinephrine and norepinephrine). Many tissues possess these adrenoceptors, and the binding of an agonist generally elicits a “typical” sympathetic response (i.e., the fight-or-flight response). Table 1 shows the effects of catecholamines bound to adrenoceptors (Table 1) and these effects on sympathetic nervous activity are through \( \alpha \)- and \( \beta \)-adrenergic receptors.

There are several types of adrenergic receptors, but there are two main groups: \( \alpha \)-adrenoceptors (\( \alpha_1 \)- and \( \alpha_2 \)-adrenoceptors) and \( \beta \)-adrenoceptors (\( \beta_1 \)-, \( \beta_2 \)-, and \( \beta_3 \)-adrenoceptors). Table 1 also summarizes the distributions and functions of the \( \alpha_1 \)-, \( \alpha_2 \)-, \( \beta_1 \)-, \( \beta_2 \)-, and \( \beta_3 \)-adrenoceptors [24, 25]. The \( \alpha \)-receptors bind norepinephrine and epinephrine, though norepinephrine has higher affinity. Phenylephrine is a selective agonist of the \( \alpha \)-adrenoceptors (both \( \alpha_1 \)- and \( \alpha_2 \)-receptors), thus phenylephrine is usually used to investigate the \( \alpha \)-adrenoceptors function. \( \beta \)-adrenoceptors are linked to G proteins, which are linked to adenyl cyclase. \( \beta \)-adrenoceptor agonists cause the intracellular elevation of the second messenger cyclic AMP. Downstream effects of cyclic AMP include cyclic AMP dependent protein kinase, which mediates the intracellular events following hormone binding.

3. Sympathetic Nervous Activity and Insulin Resistance in Hypertension (Figure 1)

Insulin resistance in hypertension has been well documented in many epidemiological and clinical studies [8, 26, 27]. Several investigators have reported that chronic insulin administration elevates blood pressure in rats and in humans [28], although insulin also has effects on vasodilation. In addition, many clinical and epidemiological studies have demonstrated the close relationships between sympathetic nerve activity, insulin resistance and hypertension [19, 29–32].

Landsberg and other investigators examined the effect of feeding and starvation on sympathetic nerve activity in the cardiac tissue of animals, noting that feeding raised sympathetic nerve activity, and starvation had the opposite effect [33–35]. Energy intake stimulates hyperinsulinemia and sympathetic nerve activity resulting in blood pressure elevations in a cycle to inhibit thermogenesis. Insulin-mediated sympathetic nerve stimulation in obese subjects is a compensatory mechanism aimed at restoring the energy balance by increasing the metabolic rate [33]. Therefore, hyperinsulinemia and insulin resistance in obese subjects are all part of a response to limit further weight gain via stimulating sympathetic nerve activity and thermogenesis [28].

On the other hand, Julius et al. [36] have hypothesized that increased sympathetic nerve activity in skeletal muscle causes neurogenic vasoconstriction, thereby reducing blood flow to muscle and consequently inducing a state of insulin resistance by lowering glucose delivery and uptake in hypertension and obesity. Both blood pressure elevation and weight gain may reflect a primary increase in sympathetic nervous tone. Masuo et al. [30, 37] supported Julius’s hypothesis. They described that high plasma norepinephrine might predict future blood pressure elevations and weight gain accompanying deterioration in insulin resistance observed in HOMA-IR (homeostasis model assessments of insulin resistance) [30, 37]. Rocchini et al. [38] reported that clonidine prevented insulin resistance in obese dogs over a 6-week period. Their results suggest that sympathetic nerve activity might play a major role in the development of insulin resistance accompanying blood pressure elevations. Valentini et al. [39] reported attenuation of hemodynamic and energy expenditure responses to isoproterenol infusion in hypertensive patients, suggesting that sympathetic nerve activity-induced hypertension may subsequently lead to the development of obesity.

Many epidemiological studies showed close linkages of beta2- and beta3-adrenoceptor polymorphisms with obesity, hypertension, and the metabolic syndrome shown in Tables 2, 3, and 4. Sympathetic nervous activity is related to body weight or blood pressure through \( \beta \)-adrenoceptors. Thus, close linkages between sympathetic nerve activity and insulin resistance might depend on the \( \beta \)-adrenoceptor polymorphisms. Thus, one could speculate that the strong associations between \( \beta \)-adrenoceptor polymorphisms and insulin resistance might provide evidence that heightened sympathetic nerve activity followed by insulin resistance might play a major role in hypertension and obesity, because \( \beta \)-adrenoceptor polymorphisms might relate to insulin resistance through heightened sympathetic nerve activity (Figure 1).

4. Role of \( \beta \)-Adrenoceptor Polymorphisms in Hypertension, Obesity, and Diabetes

The sympathetic nervous system plays an important role in the regulation of energy expenditure and blood pressure regulation. A large part of the sympathetic nervous system-mediated energy expenditure takes place in skeletal muscle, via the coupling of catecholamines with \( \beta_2 \)-adrenoceptors. Catecholamines are also powerful regulators of lipolysis and act via \( \beta_1 \)-, \( \beta_2 \)-, \( \beta_3 \)- (stimulatory), and \( \alpha_2 \)- (inhibitory) adrenoceptor subtypes in adipose tissue, where their role becomes especially important during both exercise and
### Table 1: Comparisons of adrenergic receptor subtypes.

| Receptor type | Agonist potency order | Action sites | Functions |
|---------------|------------------------|--------------|-----------|
| α1-adrenoceptor | norepinephrine ≥ | blood vessels of skin, gastrointestinal, kidney | vasoconstriction |
| | epinephrine ≫ | ureter, uterus, urethral sphincter, bronchioles | smooth muscle contraction, contraction, |
| | isoprenaline | urinary bladder, iris, blood vessels of erectile tissue, heart muscle, salivary gland, adipose tissue, liver sweat glands, kidneys | smooth muscle relaxation, positive inotropic effect, increase in secretion, glycogenolysis and gluconeogenesis, increase in secretion, Na reabsorption |
| α2-adrenoceptor | epinephrine > | pancreas and gastrointestinal tract | inhibition of insulin secretion, induction of glucagon release, and contraction of sphincters |
| | norepinephrine ≫ | gastrointestinal tract | |
| β1-adrenoceptor | isoprenaline > | heart, kidneys (juxtaglomerular cells) | increase cardiac output, increase renin release, and lipolysis |
| | Norepinephrine > | adipose tissue | |
| | Epinephrine | | |
| β2-adrenoceptor | isoprenaline > | Bronchi, urinary sphincter, bladder wall, skeletal muscle, adipose tissue, liver gastrointestinal tract, salivary glands, mast cells, and kidneys (juxtaglomerular cells) | smooth muscle relaxation, smooth muscle relaxation, dilate arteries, glycogenolysis and gluconeogenesis, contract sphincters, thickened secretions, inhibit histamine release, and increase renin release |
| | epinephrine ≫ | | |
| | norepinephrine | | |
| β3-adrenoceptor | isoprenaline > | adipose tissue | enhancement of lipolysis |
| | norepinephrine = epinephrine | | |

**Figure 1:** Potential pathophysiological mechanisms by which obesity may contribute to hypertension (modified figure from [23]). RAAS: renin-angiotensin-aldosterone system; SNS: sympathetic nervous system; OSA: obstructive sleep apnea; BRS, baroreflex sensitivity.
Table 2: Arg16Gly, β2-adrenoceptor polymorphisms: association with hypertension, metabolic syndrome (type 2 diabetes: DM), and obesity.

| Authors                        | Year | Populations     | Subjects                                                                 | Associations with the polymorphism               |
|--------------------------------|------|-----------------|--------------------------------------------------------------------------|--------------------------------------------------|
| Large et al. [40]              | 1997 | Swedish         | 140 Caucasian women with a wide range of obesity                        | Obesity                                          |
| The Quebec Family Study [41]   | 2000 | Canada          | Caucasian men and women                                                  | Obesity, hyperlipidemia                          |
| Hayakawa et al. [42]           | 2000 | Japanese        | 210 Japanese men from a population                                        | No association with obesity                      |
| Jia et al. [43]                | 2000 | USA             | Caucasians (298 hypertensive versus 298 normotensive subjects)           | No association with hypertension                 |
| Xie et al. [44]                | 2000 | USA             | Black and white Americans (including normotensive and hypertensive subjects) | No associations with hypertension                |
| Candy et al. [45]              | 2000 | English         | England Black African men (including 192 hypertensive and 123 normotensive men) | No association with hypertension                 |
| Cockcroft et al. [46]          | 2000 | Caucasian       | 127 young normotensive men                                                | Forearm vascular responses (hypertension)        |
| Meirhaeghe et al. [47]         | 2000 | French          | 1195 middle-aged Caucasian from the urban population                      | Obesity, if subjects carry Gln27Gln              |
| Kato et al. [48]               | 2001 | Japanese        | 842 hypertensive and 633 normotensive subjects                           | BP levels (hypertension) in normotensives         |
| Bengtsson et al. [49]          | 2001 | Swedish         | Hypertensive patients with and without type 2 DM                         | Hypertension in subjects with DM                 |
| The Bogalusa Heart Study [50]  | 2002 | USA             | 1151 Caucasian and Black Africans children (including boys and girls)    | Weight gain in males                             |
| Kim et al. [51]                | 2002 | Korean          | type 2 DM patients                                                       | Obesity, DM, hyperlipidemia                       |
| Chang et al. [52]              | 2002 | Taiwanese       | type 2 DM patients                                                       | Type 2 DM                                        |
| Van Rossum et al. [53]         | 2002 | Dutch           | 286 subjects with a significant weight gain over 7 years including men and women | Weight gain in men, but not in women             |
| The HERITAGE family study [54] | 2003 | Canada          | Sedentary black and white women                                          | Lower fat in obese white women                   |
| Pereira et al. [20]            | 2003 | Brazilian       | 1576 ethnically mixed population (including men and women)               | Systolic BP, BMI                                 |
| The Olivetti heart study [55]  | 2004 | Italian         | 993 middle-aged men regardless of BP levels or BMI                      | No association with obesity or hypertension       |
| Ikarashi et al. [56]           | 2004 | Japanese        | type 2 diabetic patients                                                 | Association with IR                               |
| Tafel et al. [57]              | 2004 | Germany         | extremely obese children                                                 | No association with obesity                       |
| Ellsworth et al. [58]          | 2005 | USA             | Black and white American men and women                                   | BMI (obesity) in only men                         |
| Trombetta et al. [59]          | 2005 | Brazilian       | Brazilian healthy women                                                  | Hypertension (blunted forearm vasodilation response) |
| Masuo et al. [21]              | 2005 | Japanese        | Nonobese, normotensive men                                               | Weight gain, BP elevation, obesity-HT            |
| Masuo et al. [60]              | 2005 | Japanese        | Nonobese, normotensive men                                               | Insulin resistance                               |
| Masuo et al. [61, 62]          | 2006 | Japanese        | Normotensive men (including nonobese and obese men)                      | Weight gain, blunted leptin-sympathetic axis     |
| Kurabayashi et al. [63]         | 2006 | Japanese        | PCOS patients                                                             | Association with high prevalence of PCOS         |
| Gjesing et al. [64]            | 2007 | Dutch           | 7808 white subjects                                                      | No association with hypertension or obesity      |
| Masuo et al. [65]              | 2007 | Japanese        | 219 nonobese, normotensive men                                           | Association with high SNA followed by IR         |

BP: blood pressure; BMI: body mass index; HT: hypertension; DM: diabetes mellitus; IR: insulin resistance; PCOS: polycystic ovary syndrome; SNA: sympathetic nervous activity.
Table 3: Gln27Glu, β2-adrenoceptor polymorphisms: association with hypertension, metabolic syndrome (type 2 diabetes (DM)), and obesity.

| Authors [reference number] | Year | Populations | Subjects | Associations with the polymorphism |
|---------------------------|------|-------------|----------|-----------------------------------|
| Large et al. [40]         | 1997 | Swedish     | Caucasian women with a wide range of obesity | Association with obesity |
| Echwald et al. [66]       | 1998 | Danish      | Caucasian juvenile-onset obese men | No association with obesity |
| Hellström et al. [67]     | 1999 | Swedish     | Caucasian men and women | Association with obesity only in men |
| Kortner et al. [68]       | 1999 | German      | Caucasian with morbid obesity | No association with obesity |
| Xie et al. [44]           | 2000 | USA         | Black and white Americans | No associations with hypertension |
| The Quebec Family Study [41] | 2000 | Canada      | Caucasian men and women | Association with obesity and hyperlipidemia |
| Hayakawa et al. [42]      | 2000 | Japanese    | 210 Japanese men from a population Black African men (including 192 hypertensive and 123 normotensive men) | No association with obesity |
| Candy et al. [45]         | 2000 | England     | 1195 middle-aged Caucasian in the urban population | No association with hypertension |
| Meirhaeghe et al. [47]    | 2000 | French      | 842 hypertensive and 633 normotensive subjects | Association with BP levels (hypertension) in NT |
| Kato et al. [48]          | 2001 | Japanese    | Japanese-Americans | No association with obesity or DM |
| Kawamura et al. [69]      | 2001 | Japanese    | 12 pairs of twins, Caucasians | Association with weight gain (obesity) |
| Ukkola et al. [70]        | 2002 | USA         | Patients with type 2 DM | Association with obesity, DM, and hyperlipidemia |
| Kim et al. [51]           | 2002 | Korean      | 666 Caucasian-based study (including men and women) | Association with obesity only in men |
| Gonzalez-Sanchez et al. [71] | 2003 | Spanish    | Sedentary black and white men | Association with lower fat in obese white men |
| The HERITAGE family study [49] | 2003 | Canada      | 1576 ethnically mixed population (including men and women) | No association with systolic BP or BMI |
| Pereira et al. [20]       | 2003 | Brazilian   | 993 middle-aged men (regardless of BP levels or BMI) | No association with obesity or hypertension |
| The Olivetti heart study [55] | 2004 | Italian    | Extremely obese children | No association with obesity |
| Masuo et al. [21]         | 2005 | Japanese    | Nonobese, normotensive men | Association with BP elevation, but no association with IR |
| Trombetta et al. [59]     | 2005 | Brazilian   | Brazilian healthy women | Association with hypertension (blunted forearm vasodilation response) |
| Kurabayashi et al. [63]   | 2006 | Japanese    | PCOS women | Association with high prevalence of PCOS accompanying IR |
| Gjesing et al. [64]       | 2007 | Dutch       | 7808 white subjects | No association with hypertension or obesity |
| Masuo et al. [65]         | 2007 | Japanese    | 219 nonobese, normotensive men | No association with IR |

BP: blood pressure; BMI: body mass index; DM: diabetes mellitus; NIDDM: noninsulin-dependent diabetes mellitus; IR: insulin resistance; PCOS: polycystic ovary syndrome; NT: normotensive subjects.

Recent studies show that β-adrenoceptors are polymorphic. Single nucleotide polymorphisms might have functional consequences in terms of receptor activity and regulation and hence may contribute to the pathophysiology of hypertension and obesity. On the other hand, there are few studies on the relationships between α-adrenoceptor polymorphisms, hypertension, obesity, and metabolic syndrome.

4.1. β1-Adrenoceptor Polymorphisms. The β1-adrenoceptor is predominantly expressed in cardiac myocytes and adipose
Table 4: Trp64Arg, β3-adrenoceptor polymorphisms: association with hypertension, metabolic syndrome (type2 diabetes (DM)), and obesity.

| Authors [reference number] | Year | Populations     | Subjects                                                                 | Associations with the polymorphism                                                                 |
|---------------------------|------|-----------------|--------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Clement et al. [76]       | 1995 | French          | 185 subjects with morbid obesity and 94 subjects with normal weight     | Increased capacity of weight gain                                                                      |
| Widen et al. [77]         | 1995 | Finns           | 335 subjects including 207 non-DM and 128 patients with NIDDM            | Insulin resistance                                                                                   |
| Walston et al. [78]       | 1995 | Pima Indians    | 360 with DM and 252 without DM                                          | Association with the early onset of DM2                                                                |
| Fujisawa et al. [79]      | 1996 | Japanese        | Patients with NIDDM                                                      | Type 2 DM, weight gain (obesity)                                                                     |
| Silver et al. [80]        | 1996 | Nauruans        | 65 obese subjects with NIDDM                                             | No association with DM2 or IR                                                                        |
| Fujisawa et al. [81]      | 1997 | Japanese        | Essential hypertension patients                                         | No association with IR during hyperinsulinemia euglycemic glucose clamp                               |
| Sakane et al. [82]        | 1997 | Japanese        | 131 obese women versus 218 controls                                     | Association with IR and obesity                                                                      |
| Rissanen et al. [83]      | 1997 | Finns           | 110 with NIDDM, 183 with IR, and 82 controls                            | No association with NIDDM or IR                                                                      |
| McFarlane-Anderson et al. [84] | 1998 | Jamaican        | Population study                                                        | Association with hyperglycemia only in women, but not in men                                         |
| Gracía-Rubi et al. [85]   | 1998 | American        | Postmenopausal women                                                    | Association with IR                                                                                    |
| Janssen et al. [86]       | 1998 | Dutch           | Postmenopausal women                                                    | Association with IR                                                                                    |
| Shiwaku et al. [87]       | 1998 | Japanese        | Moderate overweight men                                                 | No association with obesity                                                                           |
| Ongphiphadhanakul et al. [88] | 1999 | Thais           | 76 men and 135 women                                                    | No association with IR assessed by fasting insulin/glucose ratio                                       |
| Puikkinen et al. [89]     | 1999 | Finns           | 185 untreated non-DM and 119 untreated NIDDM                            | No association with IR or CHD in both non-DM and NIDDM                                               |
| Christiansen et al. [90]  | 1999 | Danish          | 196 dizygotic twins                                                     | Association with lower insulin secreting capacity, Similar distribution between Japanese-America and Japanese-Japanese, Association with IR in subjects with impaired oral glucose tolerance test. |
| Kawamura et al. [69]      | 1999 | Japanese-American | Japanese living in USA versus living in Japan               |                                                                                                      |
| Stangl et al. [91]        | 2001 | German          | 1000 with CHD and 1000 controls                                         | No association with prevalence of CHD or IR                                                           |
| Strazzullo et al. [92] (The Olivetti Prospective Heart Study) | 2001 | Italian         | 979 population study                                                    | No association with IR observed in HOMA-IR                                                           |
| Ishii et al. [93]         | 2001 | Japanese        | 196 young normoglycemic men, 186 old normoglycemic men, and 122 old hyperglycaemic men meta-analysis in 6582 subjects | No association with IR or NIDDM                                                                      |
| Kurokawa et al. [94]      | 2001 | Japanese        | BMI (obesity)                                                            |                                                                                                      |
Table 4: Continued.

| Authors [reference number] | Year | Populations | Subjects | Associations with the polymorphism |
|----------------------------|------|-------------|----------|------------------------------------|
| Ochoa et al. [95]          | 2004 | Spanish     | 185 obese and 185 nonobese children | BMI (obesity) |
| Porto et al. [96]          | 2004 | Argentina   | 121 NT and 54 HT from 934 high school students | Association with central obesity, but no association with IR |
| Tsai et al. [97]           | 2004 | Taiwanese   | 299 pregnant women 1179 | No association with gestational IR |
| Ellsworth et al. [58]      | 2005 | USA         | African-Americans and white-Americans | BMI (obesity) |
| Masuo K., et al. [21]      | 2005 | Japanese    | Nonobese, normotensive men | BP elevation |
| Masuo et al. [62]          | 2006 | Japanese    | 55 obese normotensive men | Weight gain (obesity), BP elevation (hypertension) |
| Højlund et al. [98]        | 2006 | Danish      | 10 male twins | No association between heterozygous for Trp64Arg and IR or NIDDM |
| Tamaki et al. [99]         | 2006 | Japanese    | 1416 population study without HT, DM, or hyperlipidemia | No association with metabolic syndrome |
| Morcillo et al. [100]      | 2008 | Spanish     | 1020 population study | Join association of alleles of -75A and Arg64 with the risk of DM |
| Gjesing et al. [101]       | 2008 | Danish      | 7605 population study | Association with NIDDM and IR, but no association with obesity |
| Dunajska et al. [102]      | 2008 | Polish      | 284 postmenopausal women | No association with metabolic syndrome |

BP: blood pressure; BMI: body mass index; DM: diabetes mellitus; NIDDM: noninsulin-dependent diabetes mellitus; DM2: type 2 diabetes mellitus; IR: insulin resistance.

Table 5: Confounding variables considered to cause the discrepancy of the relationships between β-adrenoceptor polymorphisms and phenotypes of hypertension and metabolic syndrome in obesity.

| Variables [reference number] | Findings in the studies |
|-----------------------------|------------------------|
| Severity of obesity [16, 57, 62, 76, 95] | In lean subjects, β2-AR polymorphisms linked to obesity and obesity-related hypertension, but in obese subjects, β2- and β3-AR polymorphisms relate to obesity and obesity-related hypertension. Morbid obesity is linked with β3-AR polymorphisms, but overweight or mild obesity is not associated with those. |
| Gender differences [71]     | Interaction between β1- and β2-AR polymorphisms with changes in BMI was observed in men only, while in women an interaction between β1- and β3-AR polymorphisms was observed in a longitudinal over a 24-year period large cohort study. |
| Ethnic difference [103, 104] | Distributions of β-AR polymorphisms are different in 8 different ethnic populations. |
| Haplotype [20, 58, 59, 105–107] | Functions expressed of β-AR polymorphisms are different due to the other β-AR polymorphisms. |

AR: adrenoceptor; BMI: body mass index.

Tissue, where its activation leads to increased heart rate and contractility and stimulation of lipolysis, respectively. The two most common β1-adrenoceptor polymorphisms are Ser49Gly and Arg389Gly, with relative allele frequencies of 0.85/0.15 and 0.70/0.30 in the Caucasian population, respectively. The β1-adrenoceptor is a candidate gene for obesity because of its role in catecholamine-mediated energy homeostasis [72, 73]. For example, in obese individuals, the degree of weight loss during a very low calorie diet has been shown to correlate with changes in β1-adrenoceptor protein concentration in adipose tissue [72]. A population cohort of 761 women showed that women carrying the Gly49 genotype had greater increases in BMI over 15 years compared to those with the Ser49 genotype [73]. Conversely, the distribution of the Arg389Gly polymorphism is similar in lean and obese subjects [74] and in a large cohort study including 3981 normotensive and 2518 hypertensive subjects [75]. The factors which might explain the discrepancy of published data are shown in the later section.
4.2. \(\beta_2\)-Adrenoceptor Polymorphisms. The \(\beta_2\)-adrenoceptor is the dominant lipolytic receptor in white human adipose tissue [13] and in skeletal muscle [12]. It also plays an important regulatory role in the peripheral vasculature. Genetic polymorphisms of the \(\beta_2\)-adrenoceptor have been associated with hypertension, obesity, and metabolic syndrome (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 Caucasians 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 downregulation when compared with the Gln27 variant [108]. A number of clinical studies have investigated the impact of these polymorphisms on vascular responsiveness [40, 109]. Gratze et al. [110] found that young normotensive white men homozygous for the Gly16 allele had higher blood pressure and lower peripheral vasodilation after infusion of the \(\beta_2\)-agonist salbutamol. Similar results were obtained by Hoit et al. [111] using the agonist terbutaline. On the other hand, three studies investigating isoprenaline induced increase in the limb blood flow Thus, volunteers homozygous for Gly16 exhibited larger vasodilatory responses than did volunteers homozygous for Arg16 [23]. Conflicting results have also been published with regard to the effects of genetic variants on the sympathetic nervous system modulation of energy expenditure. Bell et al. [112] reported that the response of resting energy expenditure to nonspecific \(\beta\)-adrenoceptor stimulation (with isoproterenol infusion) was not different between the 3 genotypes of Arg16Gly. Stob et al. [41] showed that individuals carrying the Arg16Arg variant of the \(\beta_2\)-adrenoceptor gene have a reduced thermogenic response to selective \(\beta_2\)-adrenoceptor activation.

Associations of \(\beta_2\)-adrenoceptor polymorphisms with hypertension and metabolic syndrome have been reported in many epidemiological studies but results are also discordant (summarised in Tables 2 and 3).

4.3. \(\beta_3\)-Adrenoceptor Polymorphisms. The \(\beta_3\)-adrenoceptor, which is mainly expressed in adipose tissue, differs from the \(\beta_2\)-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 \(\beta_2\)-adrenoceptors and \(\beta_3\)-adrenoceptors. \(\beta_3\)-adrenoceptors stimulate the mobilization of lipids from the white fat cell and increase thermogenesis in brown fat cell. Decreased function of \(\beta_3\)-adrenoceptor in white adipose tissue could slow lipolysis and thereby cause the retention of lipids in fat cells. Slow lipolysis may contribute strongly to visceral obesity in human, and treatment of obese animal models with selective \(\beta_3\)-adrenergic agonists reduces fat stores most effectively [94, 113, 114]. Many epidemiological studies have shown the strong relationships between \(\beta_3\)-adrenoceptor polymorphisms (mainly Trp54Arg), hypertension, metabolic syndrome, and obesity [78, 94, 113–117] (Table 4).

4.4. Confounding Variables Affecting the Relationships of \(\beta\)-Adrenoceptor Polymorphisms with Obesity, Hypertension, and Diabetes (Table 5). Tables 2, 3, 4, and 5 show the discordant contributions of \(\beta\)-adrenoceptor polymorphisms to hypertension, metabolic syndrome (type 2 diabetes), and obesity. Table 5 summarizes factors which might explain the discrepancy of published data. Further, haplotypes of polymorphisms have strong influence on \(\beta\)-adrenoceptor function in each polymorphism [20, 58, 59, 105–107].

5. Conclusions

The role of the sympathetic nervous system \(\beta_2\)- and \(\beta_3\)-adrenoceptor polymorphisms in hypertension, metabolic syndrome (diabetes mellitus), and obesity is discussed through a literature review. Sympathetic nervous system activity and \(\beta\)-adrenoceptor polymorphisms (mainly \(\beta_2\)- and \(\beta_3\)-adrenoceptor polymorphisms) might contribute to the onset and maintenance of hypertension, metabolic syndrome, and obesity; however, the findings have been discordant. Further, few studies have been performed to evaluate the relationship between \(\beta_2\)- and \(\beta_3\)-adrenoceptor polymorphisms and sympathetic nervous system activity in the same study. A better understanding for the relationships of genetic background (polymorphisms) with sympathetic nervous system activity as the cause for hypertension (blood pressure elevation), metabolic syndrome (insulin resistance), and obesity (weight gain) might help for clinical treatment for obesity-related hypertension and metabolic syndrome. In fact, a number of studies have investigated genetic polymorphisms as determinants of cardiovascular response to antihypertensive drug therapy [103, 104]. But further research on gene-drug interactions is necessary. In addition, to clarify the pathogenesis and mechanisms may lead to the prevention of hypertension and metabolic syndrome in obesity.

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