Modulation of Blood Pressure and Obesity With the Dopamine D2 Receptor Gene TaqI Polymorphism

G. Neil Thomas, Brian Tomlinson, Julian A.J.H. Critchley

Abstract—Pharmacological data suggest that obesity and blood pressure (BP) may be modulated through the dopamine D2 receptor (DD2R), which may represent an underlying mechanism that links these conditions. A TaqI polymorphism near the DD2R gene has been associated with indices of obesity in white populations. We compared anthropometric and fasting plasma biochemical parameters between 209 nondiabetic hypertensive and 174 gender-matched normotensive Chinese subjects. The hypertensives had increased dyslipidemia, increased fasting plasma glucose concentrations, and a greater degree of obesity. The A1 and A2 alleles of the DD2R gene TaqI polymorphism were identified with a polymerase chain reaction–based restriction fragment length polymorphism protocol. The A1 allele frequency was decreased in the hypertensives (42.0%) compared with the control subjects (52.0%, P=0.006), and genotype frequencies were different (P=0.05) between the 2 groups. In the combined population (n=383), systolic, diastolic, and mean arterial BPs were 6, 5, and 6 mm Hg lower, respectively, in subjects with the A1A1 genotype relative to the A2A2 genotype (all P<0.05), whereas skinfold thickness was increased at the iliac (P<0.001) and triceps (P<0.03) sites but not at the biceps or subscapular sites. Furthermore, this DD2R gene polymorphism was shown to be a significant independent predictor of diastolic BP and iliac and triceps skinfold thicknesses (all P<0.03). These contrasting associations of the DD2R TaqI polymorphism A1 allele with lower BP but increased markers of “gynoidal” or peripheral subcutaneous obesity (iliac and triceps skinfold thicknesses) in our Chinese population may provide some insight into the underlying relationship between BP and body fat distribution, but the exact nature of this link remains to be determined. (Hypertension. 2000;36:177-182.)

Key Words: body mass index ■ race ■ dopamine ■ receptors, dopamine ■ genetics ■ hypertension, obesity

The positive relationship between increased body weight indices and hypertension is strongly supported by data gathered from epidemiological studies in many ethnic groups.1–3 Twin and adoption studies have shown that genetic factors influence body fat percentages over the entire range of adiposity.4–6 Hypertension alone6,7 or in combination with obesity8 also exhibits a high degree of heritability, which is associated more with genetic factors rather than the shared familial environment.4,8 The close relationship between these parameters has suggested a common underlying pathogenesis.6,9

Pharmacological data suggest that the dopamine D2 receptor (DD2R) can modulate both blood pressure and obesity. The DD2R belongs to the D2-like (D2 to D4) family of dopamine receptors. The remaining dopamine receptors, of the 5 currently identified, fall into the D1-like (D1 and D5) family.10,11 The DD2R has been localized to the cerebral medulla, kidneys, and systemic arteries.10,11 Dopamine has both central and peripheral neurotransmitter roles, and the stimulation of the DD2R has been shown to inhibit sympathetic neuronal norepinephrine release.12 Dopamine also acts as an intrarenal natriuretic hormone through the D1 receptor and, to a lesser extent, the DD2R.10,12,13

The central dopaminergic reward pathway appears to be involved in the reinforcing effect received by the brain after a pleasurable experience, including the use of some “recreational” drugs.14,15 The drugs that stimulate this pathway include alcohol17 and nicotine,18 and they have a positive reinforcing action that leads to addiction. Food has also been proposed to be such a reinforcing agent.14,16 Stimulation of this pathway may reduce the effectiveness of satiety factors, thus promoting overeating and leading to obesity.14 DD2R antagonistic neuroleptic drugs lead to weight gain,19,20 whereas amphetamine-like drugs, which release dopamine, promote weight loss.21 The DD2R gene exhibits polymorphic variants, and some, including Ser311Cys and Pro310Ser, are functional in modifying the receptor activity.22–25 Several DD2R gene polymorphisms, including the TaqI polymorphism located ≈10 kb away from the gene,25 have been associated with several psychiatric disorders related to stimulation of the reward pathway, including substance abuse.23,24 Polymorphisms in the receptor gene have also been associ-
ated with obesity-related parameters such as body weight and adult-onset obesity and dietary carbohydrate preference.

In populations with a previously low prevalence of cardiovascular risk factors, such as in Hong Kong, the effects of genetic factors may be particularly evident in the determination of which individuals develop disorders such as obesity, hypertension, and type 2 diabetes mellitus. There has been a rapid increase in the prevalence of these disorders and associated comorbidities in populations who undergoing modernization in contrast to equivalent ethnic groups in less developed rural localities, such as mainland China. It is therefore important to identify risk factors that may predispose to the development of these disorders. Although there is evidence to support the association of the DD2R TaqI polymorphism with obesity-related parameters in whites, the relationship of this polymorphism with blood pressure remains to be determined. In the present study, we attempted to determine the relationship of the DD2R gene TaqI polymorphism with both blood pressure and anthropometric parameters in a population of 383 nondiabetic Chinese subjects.

Methods

The study protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All 383 unrelated subjects gave written informed consent. The hypertensive and normotensive subjects were of Han Chinese origin, without any known ancestors of other ethnic origin, and were living in the Hong Kong Special Administrative Region of China at the time of the study. They were drawn from the catchment area of the Prince of Wales Hospital, which is a typical socioeconomic representation of first- or second-generation migrants from Southern China who are currently living in a Westernized environment.

Subjects were defined as hypertensive if after 5 minutes of rest, the seated systolic blood pressure (SBP) was ≥140 mm Hg, the diastolic blood pressure (DBP) was ≥90 mm Hg, or both, with the Dinamap 8100 sphygmomanometer (Critikon Inc) on at least 2 occasions while off antihypertensive treatment (after a 4-week washout period). A mean of 3 readings taken 1 minute apart was used. No subjects had a history of significant renal, hepatic, or cardiac disease. The 209 hypertensive subjects were consecutively recruited, if they gave consent, from the medical outpatient clinics at the Prince of Wales Hospital. Seated blood pressure and anthropometric and plasma biochemical parameters were measured after an overnight fast. The anthropometric parameters required to calculate the body mass index (BMI) and waist-to-hip ratio (WHR) parameters were measured. Skinfold thickness measurements were taken at the triceps, biceps, iliac crest, and subscapular sites with digital calipers (Skyindex electronic body fat calculator system; Caldwell Justiss) and used to derive percent body fat in a subset of 273 subjects. One hundred seventy-four normotensive (SBP <140 mm Hg, DBP <90 mm Hg) nondiabetic (fasting plasma glucose [FPG] <6.0 mmol/L) control subjects were recruited from hospital staff and their friends. No subjects had a history of alcoholism or of any form of drug abuse, and none had been previously diagnosed or treated as hypertensive.

Subjects with an impaired fasting glucose and diabetes were diagnosed on the basis of FPG levels. An FPG level of <6.0 mmol/L was considered normal, an FPG level of 6.0 to 7.0 mmol/L was considered an impaired fasting glucose level, and an FPG level of ≥7.0 mmol/L was considered to be indicative of diabetes mellitus. Subjects with previously known diabetes or with an FPG level of ≥6.0 mmol/L were excluded from the study. General obesity was defined as a BMI (weight [kg]/height [m]^2) of ≥25.0 or ≥27.0 kg/m^2, and central obesity was defined as a WHR of ≥0.85 or ≥0.90 in women and men, respectively. Subjects were classified as having dyslipidemia if either the fasting plasma total cholesterol level was ≥6.2 mmol/L or between 5.2 and 6.2 mmol/L with a total cholesterol-to-HDL cholesterol ratio of ≥5.0 or if the fasting plasma triglyceride level was ≥2.3 mmol/L. The DD2R gene TaqI polymorphism was determined in all subjects with a polymerase chain reaction–based restriction fragment length polymorphism protocol, similar to that previously described by Grandy et al.

Data from normally distributed parameters are presented as mean ± SD, whereas parameters with a skewed distribution were logarithmically (base 10) transformed and are presented as geometric mean values with 95% CIs of the mean. The χ^2 test was used to identify any differences in the genotype or allele distribution of the DD2R TaqI polymorphism between the normotensive and hypertensive populations and to assess for deviations from the Hardy-Weinberg equilibrium for each cohort. Differences in the levels of anthropometric and biochemical parameters between the genotypes were assessed with the Student’s t test. Statcalc (EpiInfo version 5.0, 1990) was used for the χ^2 analyses, whereas Statistics Package for the Social Sciences (SPSS version 7.5.1, 1996; SPSS Inc) was used for the remaining statistical procedures.

To examine the contribution of the gene in the modulation of blood pressure, a stepwise multiple regression analysis was also used to determine important independent predictors of SBP and DBP. The variables included in the analyses were linearly related to the dependent variables. P > 0.1 was used as the level of rejection from the model. The genotype was coded 0, 1, and 2 for the A1 homozygotes, the heterozygotes, and the A2 homozygotes, and male and female were coded 0 and 1, respectively. Also included in the analysis were age and BMI. The appropriateness of the regression models was judged with the Durbin-Watson statistic (test for serial correlation of adjacent error terms) and partial plots of the residuals. The tolerance and variance inflation factors were taken as measures of colinearity, with low tolerance and high variance inflation factors being signs of collinearity that indicate a variable should not be included in the model. A similar approach was used to determine the independent relationship of the DD2R genotype with the iliac and triceps skinfold thicknesses (SFTs), with age, gender, and DD2R genotype included in the analyses.

Results

The demographic, anthropometric, and biochemical characteristics of the hypertensive and control subjects are shown in Table 1. Subjects in the hypertensive group had a gender distribution similar to that of the normotensives (male 44.9% versus 40.7%, P = NS) but were older. The subjects with hypertension had more adverse fasting lipid profiles (elevated total and LDL cholesterol and triglyceride levels and reduced HDL cholesterol level) and glucose levels (all P < 0.01) than the control subjects. Furthermore, the majority of anthropometric markers of obesity were greater in the hypertensive subjects (all P < 0.01). However, iliac and triceps SFTs were similar in the 2 groups.

The genotype distributions of the 2 groups were in accordance with the Hardy-Weinberg equilibrium. The genotype and allele frequencies differed significantly between the control and hypertensive populations (between the 3 genotypes, χ^2 = 7.8, P = 0.05; between the A1A1 and A2A2 genotypes, χ^2 = 7.4, P = 0.008; between the allele frequencies, χ^2 = 7.5, P = 0.003, Table 1). An increase (P = 0.003) in the A2 allele frequency was seen in the hypertensive (58.0%) compared with the gender-matched normotensive (48.0%) population. There was no relationship between the DD2R polymorphism and gender.

Because blood pressure is a continuous rather than a dichotomous variable, the relationship between the genotypes
and blood pressure was also examined in the combined population of hypertensives and normotensives (Table 2). Subjects with the homozygous A2 genotype had higher DBP (P<0.03), SBP (P=0.04), and mean arterial pressure (P<0.03) than subjects homozygous for the A1 allele (Table 2). There was a mean reduction of 6 mm Hg for SBP, 5 mm Hg for DBP, and 6 mm Hg for mean arterial pressure in subjects with the A1A1 compared with those who carried the A2 genotype. There was a consistent stepwise relationship for each blood pressure parameter across the A1A1, A1A2, and A2A2 genotype groups. Furthermore, there was a possible relationship with DBP between the genotypes with 1-way ANOVA (P=0.057, Table 2).

Table 3 shows the results of the multiple regression analyses to determine the predictors of SBP and DBP in the combined population of hypertensives and normotensives. The DD2R gene polymorphism was shown to be a significant independent predictor of DBP [DBP=(0.22 · age)+(1.5 · BMI)-(1.6 · gender)+(3.2 · DD2R genotype)+33.7; P=0.023 for the DD2R genotype, Table 3]. Furthermore, the DD2R polymorphism showed a close relationship with SBP [SBP=(0.51 · age)+(2.2 · BMI)+(3.2 · DD2R genotype)+51.6; P=0.055 for the DD2R genotype, Table 3], although this did not quite reach significance.

When the 383 subjects were grouped according to the presence or absence of obesity as defined with BMI and WHR (Table 1), there was no difference in the prevalence of the DD2R genotypes between the obese and nonobese groups. The prevalence of the A1A1, A1A2, and A2A2 genotypes was 20.7%, 50.0%, and 29.3% for the nonobese subjects and 20.6%, 52.7%, and 26.7% for the obese subjects.

Despite a lack of association between the DD2R polymorphism and general obesity, in a subset of 273 subjects for whom the SFT-derived percentage body fat was determined, the iliac and triceps SFTs were increased in the subjects who carried the A1 allele compared with those who carried the A2 allele (Table 2). Furthermore, there was a significant relationship between the genotypes and both iliac and triceps
Factors for SBP and DBP and Iliac and Triceps SFTs

TABLE 3. Multiple Regression Analyses of the Predictive DD2R gene

The findings of our study support the hypothesis that the DD2R genotype was an independent predictor of both iliocal SFT [iliac SFT = (0.14 \cdot gender) - (0.06 \cdot DD2R genotype) + 1.20; \( P = 0.001 \) for DD2R genotype] and triiceps SFT [triceps SFT = (0.19 \cdot gender) - (0.03 \cdot DD2R genotype) + 0.98; \( P = 0.029 \) for DD2R genotype]. For the relationship between the DD2R genotype and iliocal and triiceps SFTs, only the genotype, age, and gender were included in the regression analyses (Table 3). Age was not an independent predictor of either anthropometric measure.

Discussion

The findings of our study support the hypothesis that the DD2R gene TaqI polymorphism modulates blood pressure and fat deposition in specific regions rather than obesity per se. The DD2R genotype and allele frequencies differed between the gender-matched hypertensive and normotensive groups, with the DD2R A2 allele being associated with elevated blood pressure and decreased SFT at the iliocal and triiceps sites. Because the control group was relatively young, we cannot exclude the possibility that these subjects might subsequently become hypertensive. However, this would tend to reduce the apparent effects of the DD2R genotype and allele frequencies. In addition, when we investigated blood pressure as a continuous variable with the use of multiple regression analyses, the DD2R genotype was an independent predictor of both SBP and DBP and of fat deposition at the iliocal and triiceps sites in the total population even after the adjustment of each variable for age and gender. There are several possible mechanisms by which the DD2R may be involved with blood pressure regulation. In the kidney, costimulation of the DD2R and DD1R has a synergistic action to reduce proximal tubule Na\(^+\),K\(^-\)-ATPase activity and thus sodium reabsorption and, hence, to reduce blood pressure.\(^{10,35,36}\) This dopamine-induced natriuresis is impaired in several animal models of hypertension.\(^{37}\)

Major dopaminergic systems are present within the brain.\(^{11,38}\) As part of the centrally acting baroreceptor reflex pathway, the DD2R in the brain can modulate blood pressure.\(^{38}\) Studies in sodium- and potassium-equilibrated hypertensive and normotensive whites reported that treatment with the dopamine D2 agonist bromocriptine significantly reduced mean arterial pressure and prolactin levels in the hypertensive subjects but not in the normotensive subjects.\(^{39,40}\) The greater effect of bromocriptine on the plasma norepinephrine response to posture and of bromocriptine on prolactin levels in the hypertensives suggested decreased central dopaminergic activity in the maintenance of hypertension.\(^{40}\)

In hypertension, the sympathetic nervous system is often hyperactive.\(^{41}\) Bromocriptine has been shown to reduce plasma norepinephrine levels in whites, which suggests the involvement of the dopaminergic system.\(^{39}\) Negative feedback systems should modulate this hyperactivity through the stimulation of presynaptic \(\alpha_2\)-adrenergic and DD2 receptors.\(^{12,42}\) In the spontaneously hypertensive rat (SHR), the

### TABLE 2. Blood Pressure (n=383) and Anthropometric (n=273) Parameters Significantly Related to the Dopamine \(D_2\) Receptor TaqI Polymorphism Genotypes in the Hypertensive and Normotensive Subjects Combined

<table>
<thead>
<tr>
<th>Parameters</th>
<th>A1A1</th>
<th>A1A2</th>
<th>A2A2</th>
<th>A1A1 vs A2A2</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>83</td>
<td>190</td>
<td>110</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>77±15</td>
<td>79±15</td>
<td>82±16</td>
<td>0.028</td>
<td>0.057</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>130±22</td>
<td>131±23</td>
<td>136±23</td>
<td>0.050</td>
<td>NS</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>112±19</td>
<td>114±19</td>
<td>118±19</td>
<td>0.033</td>
<td>0.059</td>
</tr>
<tr>
<td>n</td>
<td>60</td>
<td>135</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iliac SFT, mm</td>
<td>19.6 (17.3–21.8)</td>
<td>15.4 (14.1–16.2)</td>
<td>14.4 (12.9–16.2)</td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>Triceps SFT, mm</td>
<td>11.8 (10.4–13.4)</td>
<td>11.2 (10.5–12.2)</td>
<td>9.7 (8.6–11.0)</td>
<td>0.033</td>
<td>0.039</td>
</tr>
<tr>
<td>Subscapular SFT, mm</td>
<td>16.2 (14.8–17.8)</td>
<td>15.5 (14.8–16.6)</td>
<td>15.3 (14.1–16.6)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Biceps SFT, mm</td>
<td>4.7 (3.8–5.9)</td>
<td>4.8 (4.2–5.5)</td>
<td>5.3 (4.6–6.2)</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

In hypertension, the sympathetic nervous system is often hyperactive.\(^{41}\) Bromocriptine has been shown to reduce plasma norepinephrine levels in whites, which suggests the involvement of the dopaminergic system.\(^{39}\) Negative feedback systems should modulate this hyperactivity through the stimulation of presynaptic \(\alpha_2\)-adrenergic and DD2 receptors.\(^{12,42}\) In the spontaneously hypertensive rat (SHR), the
α₁-adrenoceptor response is normal. However, the ability of dopamine to stimulate the DD2R and hence inhibit the release of norepinephrine has been shown to be impaired, leading to increased norepinephrine-mediated vasoconstriction. Furthermore, the replacement of a section of chromosome 8 from the SHR that carries the DD2R gene with that from the normotensive Brown-Norway rat reduced blood pressure. Further studies are required to determine through which site the DD2R polymorphism might modulate blood pressure regulation.

Although on an individual basis, the functional consequences of the DD2R mutation may not modify the physician’s approach to antihypertensive intervention, on a population level, the significant changes in blood pressure levels are important. A review of 14 nonconfounded randomized trials of antihypertensive drugs revealed that during a 5-year treatment period, a mean reduction of 5 to 6 mm Hg in DBP was associated with ≈35% to 40% less stroke and ≈20% to 25% less coronary heart disease. The Eastern Stroke and Coronary Heart Disease Collaboration investigated the relationship between blood pressure and stroke in 13 cohorts composed of 124,774 Oriental subjects. This study suggests that the 5 mm Hg difference in DBP we found between the A1A1 and A2A2 genotypes is associated with a 44% lower risk of stroke in the A1A1 group, which suggests that the DD2R polymorphism may contribute substantially to the morbidity and mortality rates in our Oriental population. However, as we have suggested with regard to the ACE gene polymorphism and coronary heart disease, in populations with a high prevalence of lifestyle risk factors, these factors may overwhelm small genetic effects such as those seen with the DD2R polymorphism.

The relationship of the genotypes with the iliac and triceps SFTs supports previous studies in white subjects that reported significant relationships between the DD2R gene and gynoid obesity-related parameters. Gynoid fat distribution has been associated with a lower risk of cardiovascular disease than when the fat deposition distribution is androital. It appears that the association of fat deposition with cardiovascular disease risk factors is not directly related to overall obesity; rather, the distribution of the fat depots is important. Because there was no relationship between these sites and blood pressure, the associations of the A2 allele with both elevated blood pressure and decreased fat deposition at the iliac and triceps SFTs are not conflicting. In a previous study of Chinese siblings discordant for hypertension, we showed that these sites are not associated with hypertension. The lack of a relationship between the DD2R polymorphism and gender and gender-matched hypertensive and normotensive groups suggests that the relationship between the polymorphism and gynoid fat distribution is unlikely to be confounded by gender. The results of the previous studies proposed that the DD2R receptor polymorphism modulated obesity by influencing the dopaminergic reward pathway. The consumption of food is essential for survival; the feeling of pleasure and satisfaction after the provision of nutrients strongly reinforces the action. Stimulation of this pathway may reduce the effectiveness of satiety factors, thus promoting overeating and leading to obesity. However, we found that the receptor polymorphism was not associated with obesity per se but rather with regionalized body fat deposition. The method of modulation by DD2R of fat metabolism and distribution at specific sites and the interrelationship with blood pressure remain to be determined. The A1 allele of the TaqI polymorphism, localized in a region 3’ to the coding region, has been associated with reduced dopaminergic function; although the findings are not consistent, it is more likely to be in linkage disequilibrium with a functional mutation within the promoter or coding region of the receptor gene.

The DD2R TaqI polymorphism A2 allele was associated with significantly higher blood pressures yet lower iliac SFTs in this population of non-diabetic Hong Kong Chinese subjects. The DD2R gene therefore may be one of the genes that underlies the close relationship between obesity and blood pressure. It may have a significant impact on cardiovascular disease morbidity and mortality rates. Further investigations are required to determine the mechanism by which this receptor is capable of modulating blood pressure and obesity parameters in this population and whether these interesting findings are applicable to other ethnic groups.

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References


38. Comish JL, van den Buse M. Stimulation of the rat mesolimbic dopaminergic system produces a pressor response which is mediated by dopamine D1 and D2 receptor activation and the release of vasopressin. Brain Res. 1995;701:28–38.


49. Laruelle M, Gelernter J, Innis RB. D2 receptors binding potential is not associated with the degree of expression of the dopamine receptor Taq1 B RFLP. J Pharmacol Exp Ther. 1999;290:1133–1139.


54. Conte-Alonso M, Gelernter J, Innis RB. D2 receptors binding potential is not associated with the degree of expression of the dopamine receptor Taq1 B RFLP. J Pharmacol Exp Ther. 1999;290:1133–1139.
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