original article

Association of genetic polymorphisms of glutamate decarboxylase 2 and the dopamine D2 receptor with obesity in Taiwanese subjects

Ke-Chang Chen,[a] Yi-Chen Lin,[a] Wen-Chii Chao,[a] Hsieh-Kun Chung,[a] Su-Sheng Chi,[a] Wen-Sheng Liu,[b] Wen-Tung Wu[c]

From the [a]Department of General Surgery, Antai, Tian-Sheng Memorial Hospital, Pingtung, Taiwan, [b]Asia-Pacific Biotech Developing, Inc., Kaohsiung, Taiwan, [c]Department of Biotechnology, Yung-Ta Institute of Technology and Commerce, Pingtung, Taiwan

Correspondence: Wen-Tung Wu · Department of Biotechnology, Yung-Ta Institute of Technology and Commerce, Pingtung, Taiwan · T: +886-8-7233733 ext.529, F: +886-8-7212646 · gerrywu8769@yahoo.com.tw · Accepted: February 2011

Ann Saudi Med 2012; 32(2): 121-126

DOI: 10.5144/0256-4947.2012.121

BACKGROUND AND OBJECTIVES: It has been proposed that glutamate decarboxylase 2 and the dopamine D2 receptor are involved in the brain reward cascade to increase carbohydrate craving and cause eating disorders. We investigated the association between the polymorphisms of the *GAD2* and *DRD2* genes and obesity with a higher body mass index (BMI) in Taiwanese patients.

DESIGN AND SETTING: A retrospective, case-control study at Antai Tian-Sheng Memorial Hospital from 1 January to 31 December 2009.

SUBJECTS AND METHODS: Of 300 subjects enrolled in the study, 132 were obese (BMI≥30 kg/m^2) and 168 controls were not obese (BMI≤24 kg/m^2). The polymorphisms of *GAD2* (+61450 C/A), (+83987 T/A) and *DRD2* (S311C) were characterized, respectively, by polymerase chain reaction-restriction fragment length polymorphism. The genotype and allele frequencies of the polymorphisms in this study were statistically analyzed.

RESULTS: The genotype and allele frequencies of the *GAD2* (+83987 T/A) and *DRD2* (S311C) were significantly different between cases and controls (*P*=.001 for both). The frequencies of TT genotype and T allele of the *GAD2* (+83987 T/A) as well as the frequencies of Ser/Cys genotype and Cys allele of *DRD2* (S311C) were higher in cases compared to controls (*P*=.034 and .036 for both).

CONCLUSIONS: The study demonstrated a statistically significant difference in the frequency of the *GAD2* (+83987 T/A) and *DRD2* (S311C) genes between cases and controls in Taiwanese subjects.

Obesity, an abnormal excessive storage of body fat, has contributed to the gradually increasing list of health complications, such as heart disease, type 2 diabetes, breathing difficulties during sleep, hypertension, dyslipidemia, heart failure, stroke, cancers, and osteoarthritis.[1] The definition of obesity is based on body mass index (BMI), an index of weight-for-height that that is associated with the content of body fat. It is well known that obesity is most commonly caused by a combination of excessive dietary calories, lack of physical activity, and genetic susceptibility. The causes of obesity are debated and studied, but previous studies have suggested that some reasons behind morbid obesity may include a genetic predisposition, endocrine disorders, medications, or psychiatric illness.[2-5]

It has been demonstrated that the glutamate decarboxylase 2 gene (*GAD2*) on the locus of chromosome 10p12 is the candidate gene concerned for craving behavior and weight gain, and is associated with severe human obesity.[6,7] *GAD2* plays a role in catalyzing the production of the γ-aminobutyric acid (GABA) neurotransmitter in neurochemical pathway, and regulates the release of dopamine (DA) in the nucleus accumbens site. DA is known as a pleasure or antistress molecule, and it is involved in the events of the brain reward cascade.[8] Boutin et al[9] showed that the variations of +61450 C/A and +83897 T/A *GAD2* gene were associated with the modulation of food intake and the development of morbid obesity. Conversely, Swarbrick et al[10] found that the *GAD2* gene did not play an important role in severe obesity in three independent case-control studies carried out in Germany, the United States, and Canada.

The dopamine D2 receptor gene (*DRD2*), located on chromosome 11q23, encodes the D2 subtype of the DA receptor, to maintain normal craving behaviors.[11] More recent data has indicated that a lack of D2 receptors caused subjects to have a high risk for multiple addictive, impulsive, and compulsive behaviors, such as alcoholism, glucose binging, sex addiction, and antisocial behaviors.[12] Consistently, an amino acid enkephalinase known as synaptamine potentially induces DA release and stimulates the proliferation of D2 receptors and promotes the attenuation of abnormal behaviors. DA deficiency is usually due to an association with the *DRD2* gene A1 allele and other gene variations involved in the reward cascade. This reduces DA release and/or receptivity and has been described as the reward deficiency syndrome (RDS).[13]

Pharmacological studies have described that cannabinoid and opioid receptor antagonists could potentially attenuate alcohol addiction and help to control alcohol intake and reduce the motivation to consume alcohol.[14] Recently, a novel therapeutic approach was proposed to reduce many harmful craving behaviors by using immunologically compatible substances, through the help of a genetic positioning system map.[15] Individuals with genetic polymorphisms crave substances that will increase DA release at the "reward site" in the mesolimbic region of the brain that helps them feel normal. Neurofeedback was used to exercise the brain to achieve a feeling of well-being through its impact on neurotransmitter rebalancing. It was an attractive method, as it was medication-free and a type of neurophysiologic and self-actualizing treatment for a substance-based, brain-impaired, and self-defeating disorders.[16]

Recent studies have reported the differences in the prevalence of the S311C variances in the *DRD2* gene in different populations.[17,18] For example, the prevalence of the C311 allele was 16% in Pima Indians, 3% in Caucasians, and 2.3% in the Japanese population. The C311 variant of the dopamine D2 receptor has been shown to markedly impair the ability to modulate craving behaviors.[19,20] Additionally, in Pima Indians, the *DRD2* gene was located near a locus known to influence type 2 diabetes, obesity, and energy expenditure. Individuals with a C311-encoding allele have a higher BMI than those homozygous with an S311-encoding allele.[21,22] In this study, we suggest that the *GAD2* and *DRD2* polymorphism is associated with addiction and craving behaviors, and we investigated the association between *GAD2* (+61450 C/A, +83897 T/A) and *DRD2* (S311C) polymorphism and obesity in Taiwanese subjects.

SUBJECTS AND METHODS

Of 300 subjects in the study, there were 168 controls with an average age of 56.8 (13.4) years, including 70% non-obese women (BMI≤24 kg/m^2) and 132 cases with an average age of 48.9 (10.9) years, including 75% obese women (BMI≥30 kg/m^2). The patients were selected from the Antai Tian-Sheng Memorial Hospital in Taiwan from March to October in 2009. Normal body weight was defined as BMI in the range 18.5-24.9 kg/m^2 and obesity was defined as BMI≥30 kg/m^2. All individuals agreed to participate in the study. The study plan was accepted and supported by the Ethical Committee of the Antai Tian-Sheng Memorial Hospital. All specimens were collected and stored at −20°C until DNA extraction.

DNA extraction

Total genomic DNA was extracted with the DNeasy Kit (Qiagen, USA) according to the manufacturer's instructions. The blood was digested with 0.5 mg/mL proteinase K in 400 μL cell-lysis solution for 24 hours at 55°C until the blood was completely lysed. After adding 200 μL absolute ethanol to the lysed sample, the mixture was transferred into the DNeasy mini column and centrifuged for 1 minute at 8000 revolutions per minute (rpm). The DNeasy mini column was washed with 500 μL washing buffer and centrifuged for 1 minute at 8000 rpm. Finally, the DNA was eluted in a clean 1.5-mL microcentrifuge tube. The amount of DNA was measured spectrophotometrically using a spectrophotometer (GeneQuant, GE Healthcare Bio-Sciences AB, Sweden) and stored at −20°C until polymerase chain reaction (PCR) amplification.

Gene polymorphisms

The T/A substitution at position +83897 in the *GAD2* gene was assessed by PCR amplification and the products were submitted to digest. The sequences of PCR primers were 5'-GTG GCA GGC AGC TGA TAG TC-3' (sense) and 5'-CAC CTG TGG GAC AGA CCA TA-3' (antisense) with an expected PCR product size of 242 bp. Amplification was performed by using a Perkin-Elmer 9700 thermal cycler (Applied Biosystems, Foster City, CA) and polypropylene PCR plates no. 170651 (Biozym, Landgraaf, The Netherlands). The amplification conditions consisted of 94°C for 3 minutes, followed by 45 cycles of 94°C for 1 minute, 56°C for 1 minute, and 72°C for 40 seconds. The reaction was terminated by a final elongation at 72°C for 7 minutes. The products were digested with 5 U/μL of AluI at 37°C for 2 hours and formed 146- and 96-bp DNA

products for allele T and an intact fragment of 242-bp DNA products for allele A. The digested products were separated on a 2.5% agarose gel stained with ethidium bromide (0.5 μg/mL), and genotypes were determined by analyzing different bands. The C/A substitution at position +61450 in the *GAD2* gene was genotyped by tetra-primer amplification refractory mutation system (ARMS)-PCR by using 2 primer pairs to amplify, respectively. The primers were as follows: GAD-61450-FiC 5'-ATT CTT ACT GAC AAA GCT GAG TTT ACC C-3' and GAD-61450-Ro 5'-TAT TTA GGT GAA GTG CTT AGA ACT GTG C-3', the 199 bp for detecting the C allele; and GAD-61450-RiA 5'-TCA TGT TCT ATG GCT AGA TGT CTA ATC CT-3' and GAD-61450-Fo 5'-GGC AGC TTC TCT TCT AAA AAG ACA AAT A-3', the 151 bp for detecting the A allele. The S311C variant in *DRD2* was genotyped by amplification of the corresponding DNA fragment according to the PCR method. The 294 bp PCR fragments were digested with Sau961 restriction enzyme (New England Biolabs, United Kingdom). The Ser311 allele has 4 bands of 126, 92, 53, and 23 bp, whereas the Cys311 allele has 3 bands of 149, 92, and 53 bp. Genotyping was checked by two readers who were blinded to the clinical data.

Statistical analysis

Genotype and allele frequencies were compared by analysis of variance (ANOVA) and the χ^2 test for small sample size. The P value, odds ratios, and 95% confidence interval were calculated. A *P* value of less than .05 was significant for all analyses.

RESULTS

Women and men comprised approximately equal proportions of the case and control groups (**Table 1**). Since men and women differ in adiposity, women are more liable to being obese than men. The frequencies of *GAD2* (+83897 T/A) TT, TA, and AA genotypes were 31.8%, 46.3%, and 21.9% in cases and 14.9%, 52.9%, and 26.2% in controls, respectively (**Table 2**). The distribution of *GAD2* (+83897 T/A) genotypes was significantly different in controls and cases (*P*=.001, OR 1.603, 95% CI 1.032-2.489). The frequencies of *DRD2* (Ser311Cys) SS, SC, and CC genotypes were 46.2%, 43.2%, and 10.6% in cases and 60.7%, 32.1%, and 7.2% in controls, respectively. The distribution of *DRD2* (Ser311Cys) genotypes was significantly different in controls and cases (*P*=.001, OR 1.83, 95% CI 1.258-2.6). No association was observed in the polymorphism of the +61450 C/A of *GAD2* gene. The allelic distribution of *GAD2* (+83897 T/A) and *DRD2* (Ser311Cys) polymorphisms between the two groups were statistically significant (*P*=.034 and *P*=.036), respectively.

DISCUSSION

Obesity is a chronic disease that contributes to metabolic complications, including hypertension, cardiovascular disease, type 2 diabetes, and some cancers in both men and women. These complications increase the risk of mortality and morbidity worldwide. Genetic risk factors play an important role in the development of obesity in humans. Rankinen et al[23] described an obesity-related genes map to show putative loci on all chromosomes except Y. A total of 127 candidate genes have been reported, and these gene variations were associated with obesity phenotypes. Among these genes, Blum et al[24] found that low D2 receptor density and *DRD2* gene polymorphisms were associated with risk for relapse of substance abuse, including alcohol dependence, heroin craving, cocaine dependence, methamphetamine abuse, nicotine sensitization, and glucose craving. Moreover, the defect of the *DRD2* gene is associated with RDS, which is a dysfunction in the brain reward cascade involved in abnormal craving behavior. In spite of all the supportive data, few genetic treatments have not been developed to attenuate the abnormal craving behaviors. Blum et al[25] have succeeded in the development of the DNA-customized nutraceutical product, LG839, which is an antiobesity agent, that could increase weight loss, decrease food cravings, prevent weight regain, and also reduce stress. Among the obesity-related genes (LEP, PPAR-γ2, MTHFR, 5-HT2A, and *DRD2* genes), only the *DRD2* genes polymorphism had a significant association with days on treatment.

Table 1. Demographic data of cases and controls.

Group	N	Body mass index (kg/m^2)	Age (years)	Women (%)
Cases	132	38.2 (7.4)	48.9 (10.9)	75
Controls	168	21.5 (2.3)	56.8 (13.4)	70

Values are mean and standard deviation unless otherwise indicated.

Table 2. Genotype and allele distributions among the cases and controls.

		Cases N, (%)	Controls N, (%)	OR (95% CI)	*P*
GAD2 +61450 C/A	Genotype			0.986 (0.707-1.376)	NS
	CC	60 (45.5%)	72 (42.9%)		
	CA	42 (31.8%)	64 (38.1%)		
	AA	30 (22.7%)	32 (19.0%)		
	Allele			0.898 (0.616-1.303)	NS
	C	162 (61.4%)	208 (61.9%)		
	A	102 (38.6%)	128 (38.1%)		
GAD2 +83987 T/A	Genotype			1.603 (1.032-2.489)	.001
	TT	42 (31.8%)	25 (14.9%)		
	TA	61 (46.3%)	89 (52.9%)		
	AA	29 (21.9%)	44 (26.2%)		
	Allele			1.913 (1.621-2.375)	.034
	T	145 (54.9%)	139 (41.3%)		
	A	119 (45.1%)	177 (52.7%)		
DRD2 Ser311Cys	Genotype			1.83 (1.258-2.6)	.001
	Ser/Ser	61 (46.2%)	102 (60.7%)		
	Ser/Cys	57 (43.2%)	54 (32.1%)		
	Cys/Cys	14 (10.6%)	12 (7.2%)		
	Allele			1.6 (1.23-2.2)	.036
	Ser	179 (67.8%)	258 (76.8%)		
	Cys	85 (32.2%)	78 (23.2%)		

OR: Odds ratio, NS: not significant, Ser:serine, Cys: cysteine.

DA is a neurotransmitter in the brain reward pathway that controls feelings of motivation, reward, and behaviors through the interaction with D2 receptor.[26] The central job of the reward pathway is to make us feel better while we are involved in behaviors that are necessary for our survival. These beneficial behaviors include eating, drinking, and sex. Tataranni et al[27] described that the absence of the murine dopamine D2 receptor gene led to the bradykinesia and hypothermia. These findings were the first evidence indicating that a genetic mutation was associated with reduced energy expenditure in humans. The authors suggested that the impact of this mutation on human obesity was small, and that the energy deficit induced was not large enough to significantly influence body weight in this population. Southon et al[28] described that Ser311Cys polymorphisms in the *DRD2* gene are unlikely to be common causes of obesity in the Nauruan and Australian population.

GABA is also a neurotransmitter in the mammalian central nervous system. It plays a major role in enhancing food intake by interacting with neuropeptide Y (NPY).[29] Many other physiologic processes in the brain are also associated with NPY, including the regulation of energy balance, memory, and learning; epilepsy is also associated with NPY. Allen et al[30] discovered the highest levels of NPY immunoreactivity within the paraventricular nucleus of the hypothalamus in the rat brain. With in situ hybridization and immunoassay studies, Hanson et al[31] observed that the NPYergic activity increases the food intake of rats. This was further confirmed by behavioral assays. Additionally, orexigenic studies have proved that exogenous NPY could also enhance feeding behavior, such as a NPY agonist: dexamethasone or N-acetyl (Leu28, Leu31) NPY (24-36).[32,33] Moreover, Dryden et al[34] reported that weight gain was increased by the hypothalamic arcuate nucleus

and the paraventricular nucleus pathway in the fatty Zucker rat, a well-known animal model of obesity and insulin resistance. The results support the association between NPY and obesity.

A recent study investigated a role of positional candidate gene *GAD2*, which encodes for glutamate decarboxylase, in the development of morbid obesity.[7] Previous reports have found 15 variants in a coding and regulating region in patients with type 1 diabetes.[35] In a study reported by Boutin et al,[9] 3 variants -243 A/G, +61450 C/A, and +83897 T/A in *GAD2* were found, and these variants were associated with obesity in the French population. The activity of the promoter variant -243 A/G in *GAD2* was about 6 times higher than that of the wild-type promoter, and it could increase the concentration of GABA and increase dietary intake in the hypothalamus. Additionally, the +61450 C/A and +83897 T/A variants in coding region of *GAD2* have proved the implications of family history of obesity in obese patients. Likewise, 6 *GAD2* sequence variants were genotyped by Choquette et al.[6] The results proved the association between +61450 C/A and +8473 A/C polymorphisms and eating behavior and dietary intake in women. The two variants could significantly increase BMI and body weight. The authors suggested these *GAD2* polymorphisms influence eating behavior and dietary intake, resulting in increased weight gain. In the current study, a significant association was found between +83897 T/A polymorphism and dietary intake. We did not observe any association between the *GAD2* -243 A/G variant and obesity in this study. In the future, we will conduct an adequately powered case-control study to test the association between obesity and the *GAD2* -243 A/G variant in Taiwanese. This case-control study will help in a meta-analysis of the findings of other research performed to study the association between the -243 A/G and obesity.

In conclusion, these experiments suggest that the polymorphisms of *GAD2* (+83897 T/A) and *DRD2* (-243 A/G) are significantly associated with an increased risk of developing obesity. We recognized that the value of this study was limited by a relative small sample and also that only a few variants in each gene were studied. Eventually, if confirmatory studies are done on large populations to assess the significance, these variants may be concluded as factors predisposing an individual to obesity.

Acknowledgments

We thank all individuals who agreed to participate in this study. We thank the Ethics Committee of the Antai Tian-Sheng Memorial Hospital in Donggang, Pingtung, for supporting us to collect samples and carry out genotype analysis, and giving us the Certifiacte of Approval from the Institutional Review Board. Finally, we thank the Asia-Pacific Biotech Developing, Inc. in Kaohsiung for assisting with the steps requiring biotechnological expertise.

REFERENCES

1. Kopelman PG. Obesity as a medical problem. Nature 2000;404:635-43.
2. Eckel RH, Krauss RM. American Heart Association call to action: Obesity as a major risk factor for coronary heart disease. AHA Nutrition Committee. Circulation 1998;97:2099-100.
3. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA 1999;282:1523-9.
4. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Bodymass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 2003;341:1097-105.
5. Hager J, Dina C, Francke S, Dubois S, Houari M, Vatin V, et al. A genome wide scan for human obesity genes reveals a major susceptibility locus on chromosome 10. Nat Genet 1998;20:304-8.
6. Choquette AC, Lemieux S, Tremblay A, Drapeau V, Bouchard C, Vohl MC, et al. GAD2 gene sequence variations are associated with eating behaviors and weight gain in women from the Quebec family study. Physiol Behav 2009;98:505-10.
7. Tiwari HK, Bouchard L, Pe´russe L, Allison DB. Is GAD2 on chromosome 10p12 a potential candidate gene for morbid obesity? Nutr Rev 2005;63:315-9.
8. Blum K, Kozlowski GP. Ethanol and neuromodulator interactions: A cascade model of reward. In: Ollat H, Parvez S, Parvez H, editors. Alcohol and Behavior. Utrecht The Netherlands: VSP Press; 1990. p. 131-49.
9. Boutin P, Dina C, Vasseur F, Dubois S, Corset L, Séron K, et al. GAD2 on Chromosome 10p12 is a candidated gene for human obesity. PLoS Biol 2003;1:361-71.
10. Swarbrick MM, Waldenmaier B, Pennacchio LA, Lind DL, Cavazos MM, Geller F, et al. Lack of support for the association between GAD2 polymorphisms and severe human obesity. PLos Biol 2005;3:1662-71.
11. Eubanks JH, Djabali M, Selleri L, Grandy DK, Civelli O, McElligott DL, et al. Structure and linkage of the D2 dopamine receptor and neural cell adhesion molecule genes on human chromosome 11q23. Genomics 1992;14:1010-8.
12. Blum K, Braveman ER, Holder JM, Lubar JF, Monastra VJ, Miller D, et al. Reward deficiency syndrome: A biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. J Psychoactive Drugs 2000;32:1-112.
13. Blum K, Chen AL, Chen TJ, Braverman ER, Reinking J, Blum SH, et al. Activation instead of blocking mesolimbic dopaminergic reward circuitry is a preferred modality in the long term treatment of reward deficiency syndrome (RDS): A commentary. Theor Biol Med Model 2008;5:24.
14. Colombo G, Serra S, Vacca G, Carai MA, Gessa GL. Endocannabinoid system and alcohol addiction: Pharmacological studies. Pharmacol Biochem Behav 2005;81:369-80.
15. Downs BW, Chen AL, Chen TJ, Waite RL, Braverman ER, Kerner M, et al. Nutrigenomic targeting of carbohydrate craving behavior: Can we manage obesity and aberrant craving behaviors with neurochemical pathway manipulation by Immunological Compatible Substances (nutrients) using a Genetic Positioning System (GPS) Map? Med Hypotheses 2009;73:427-34.
16. Blum K, Giordano J, Morse S, Liu Y, Tan J, Bowirrat A, et al. Genetic Addiction Risk Score (GARS) analysis: Exploratory development of polymorphic risk alleles in polydrug addicted males. Integr Omics Appl Biol 2010;1:1-14.
17. Itokawa M, Arinami T, Futamura N, Hamaguchi H, Toru M. A structural polymorphism of human dopamine D2 receptor, D2 (Ser3113Cys). Biochem Biophys Res Commun 1993;196:1369-75.
18. Cravchik A, Sibley DR, Gejman PV. Functional analysis of the human D2 dopamine receptor missense variants. J Biol Chem 1996;271:26013-7.
19. Blum K, Braverman ER, Wood RC, Gill J, Li C, Chen TJ, et al. Increased prevalence of the Taq I A1 allele of the dopamine receptor gene (DRD2) in obesity with comorbid substance use disorder: A preliminary report. Pharmacogenetics 1996;6:297-305.
20. Comings DE, Gade R, MacMurray JP, Muhleman D, Peters WR. Genetic variants of the human obesity (OB) gene: Association with body mass index in young women, psychiatric symptoms, and interaction with the dopamine D2 receptor (DRD2) gene. Mol Psychiatry 1996;1:325-35.
21. Norman RA, Tataranni PA, Pratley R, Thompson DB, Hanson RL, Prochazka M, et al. Autosomal genomic scan for loci linked to obesity and energy metabolism in Pima Indians. Am J Hum Genet 1998;62:659-68.
22. Jenkinson CP, Hanson R, Cray K, Wiedrich C, Knowler WC, Bogardus C, et al. Association of dopamine D2 receptor polymorphisms Ser-311Cys and Taq1A with obesity or type 2 diabetes mellitus in Pima Indians. Int J Obes Relat Metab Disord 2000;24:1233-8.
23. Rankinen T, Zuberi A, Chagnon YC, Weisnagel SJ, Argyropoulos G, Walts B, et al. The human obesity gene map: The 2005 update. Obesity (Silver Spring) 2006;14:529-644.
24. Blum K, Chen TJ, Downs BW, Bowirrat A, Waite RL, Braverman ER, et al. Neurogenetics of dopaminergic receptor supersensitivity in activation of brain reward circuitry and relapse: Proposing "deprivation-amplification relapse therapy" (DART). Postgrad Med 2009;121:176-96.
25. Blum K, Chen AL, Chen TJ, Rhoades P, Prihoda TJ, Downs BW, et al. LG839: Anti-obesity effects and polymorphic gene correlates of reward deficiency syndrome. Adv Ther 2008;25:894-913.
26. Davis C, Levitan RD, Kaplan AS, Carter J, Reid C, Curtis C, et al. Reward sensitivity and the D2 dopamine receptor gene: A case-control study of binge eating disorder. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:620-8.
27. Tataranni PA, Baier L, Jenkinson C, Harper I, Del Parigi A, Bogardus C. A Ser311Cys mutation in the human dopamine receptor D2 gene is associated with reduced energy expenditure. Diabetes 2001;50:901-4.
28. Southon A, Walder K, Sanigorski AM, Zimmet P, Nicholson GC, Kotowicz MA, et al. The Taq IA and Ser311 Cys polymorphisms in the dopamine D2 receptor gene and obesity. Diabetes Nutr Metab 2003;16:2-6.
29. Colmers WF, El Bahn B. Neuropeptide Y and Epilepsy. Epilepsy Curr 2003;3:53-8.
30. Allen YS, Adrian TE, Allen JM, Tatemoto K, Crow TJ, Bloom SR, et al. Neuropeptide Y distribution in the rat brain. Science 1983;221:877-9.
31. Hanson ES, Dallman MF. Neuropeptide Y (NPY) may integrate responses of hypothalamic feeding systems and the hypothalamo-pituitary-adrenal axis. J Neuroendocrinol 1995;7:273-9.
32. White BD, Dean RG, Edwards GL, Martin RJ. Type ? corticosteroid receptor stimulation increase NPY gene expression in basomedial hypothalamus of rats. Am J Physiol 1994;266:R1523-9.
33. King PJ, Widdowson PS, Doods HN, Williams G. Regulation of neuropeptide Y release by neuropeptide Y receptor ligands and calcium channel antagonists in hypothalamic slices. J Neurochem 1999;73:641-6.
34. Dryden S, Pickavance L, Frankish HM, Williams G. Increased neuropeptide Y secretion in the hypothalamic paraventricular nucleus of obese (fa/fa) Zucker rats. Brain Res 1995;690:185-8.
35. Johnson GC, Payne F, Nutland S, Stevens H, Tuomilehto-Wolf E, Tuomilehto J, et al. A comprehensive, statistically powered analysis of GAD2 in type 1 diabetes. Diabetes 2002;51:2866-70.