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Reward Deficiency Syndrome in Obesity: A Preliminary Cross-Sectional Trial With a Genotrim Variant

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ABSTRACT

Obesity is the second largest preventable cause of death in the United States. Even though it was classified as a disease in 1985, traditionally, obesity has been treated primarily as a behavioral problem that requires only modifications in diet and exercise. Similar to research on obesity, clinical studies have elucidated the role of biologic and genetic factors in alcoholism and other conditions previously classified as behavioral. These studies showed that behavioral adjustments alone may not address underlying genetic causes. We hypothesize that biologic and genetic factors must be addressed synergistically while behavioral modifications are implemented to adequately treat obese patients. We hypothesize that a predisposition to glucose craving and obesity is due to inadequate dopaminergic activity

1018

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in the reward center of the brain. This defect drives individuals to engage in activities of behavioral excess, which, in turn, enhance brain dopamine function. Consumption of large quantities of alcohol or carbohydrates (carbohydrate bingeing) stimulates production and usage of dopamine within the brain; the term *reward deficiency syndrome (RDS)* may be used to categorize such biologic influences on behavior. We propose that a novel approach to nutritional supplementation may be required to target the role of RDS in obesity. In this regard, GenoTrim™, a DNA-customized nutritional solution, has been developed and is currently under investigation in several clinical studies. Through its mechanism of action, GenoTrim addresses the genetic influence of RDS on obesity. In this cross-sectional study, 24 subjects were studied after they had completed a case report format questionnaire. For this assessment, we used a novel assessment tool—a path analysis. This statistical regression model is used to (1) examine the effectual relationships between various systems within a multisystem matrix, and (2) measure the contributory roles of those relationships in obesity, enabling the development of targeted and effective therapeutic interventions.

Keywords: obesity; genetics; reward deficiency syndrome; nutritional supplementation

INTRODUCTION

Obesity is caused by many single factors and combinations of factors, including genetics and lifestyle habits that impose varying levels of metabolic consequences. What could be classified as "one-size-fits-all" obesity management tactics cannot possibly effectively address the dynamic influence and interdependence of these factors. In this regard, our goal as scientists should be to provide the obese individual with a "tailor-made" solution, rather than a standard protocol. We suggest that treatment must bring together information about genetics, lifestyle, and the influence of genetics on behavior if it is to be effective in the patient with glucose craving and compulsive behaviors associated with obesity. The influence of genetics on behavior cannot be understated, as has been previously shown in various craving behaviors classified as *reward deficiency syndrome (RDS)*. This term is derived from earlier reports that described RDS as a way of elucidating the genetic antecedents of impulsive, addictive, and compulsive disorders under a single rubric.[1-14] We hypothesize that use of a multivariant nutrigenomic index to customize or adjust treatment formulations may result in an improved and novel approach to the diagnosis, stratification, and treatment of obesity by targeting the influence of genes on behavior, or what has been classified as RDS. This multivariant genetic index, or GenoScore™ (a published and patented process of Salugen, Inc., San Diego, Calif), is derived through analysis of genotype and/or phenotype, multiple genetic and/or phenotypic measurements, and the use of complex algorithms; a customized solution is thus delivered. This process gives clinicians the opportunity to provide DNA-customized nutrition through the use of multiple genes involved in RDS; the metabolism, efficacy, and/or toxicity of specific vitamins, minerals, herbal supplements, and homeopathic and other ingredients must be considered as part of their inclusion in the nutritional and/or dietary supplement regimen.

In this regard, we preliminarily tested our hypothesis by developing a novel nutraceutical technology that targets the various pathways involved in obesity.[15] We developed a nutraceutical formula (GenoTrim™; Salugen Inc.) that combines specific nutrients to influence various functions or paths that are affected by dopaminergic activity or RDS, including sleep, mood, energy, stress, and immune and hormonal function. When these paths are considered, a multidisciplinary approach can be pursued that appropriately targets underlying factors that influence obesity. This is the first study in which investigators used path analysis, a statistical regression model that is designed to evaluate the effectual relationships between various systems within a multisystem matrix to measure the contributory roles of those paths to obesity, enabling the development of targeted and effective therapeutic interventions.

METHODS

Participants

A total of 24 individuals completed a survey on which they documented their experience with a GenoTrim formula. Subjects were pooled from a small open-label, cross-sectional, observational trial.

Categorization of Benefits

Benefits reported by study participants were categorized by investigators as follows:

- Stress reduction
- Sleep enhancement
- Increase in energy level
- Generalized well-being
- Reduction in craving behavior (sweets/carbs)
- Improvement in mental focus/memory
- Improvement in blood sugar levels
- Reduction in food consumption
- Loss of inches
- Loss of weight
- Reduction in blood pressure (BP)
- Improvement in workout performance
- Reduction in drug-seeking behavior (ie, alcohol, nicotine, cocaine, marijuana, opiates, etc.)
- Reduction in hyperactivity
- Reduction in cholesterol levels

Path Analysis

A preliminary statistical analysis of qualitative information was performed. Increases (↑) in physiologic condition were coded as 1, decreases (↓) in physiologic condition were coded as –1, and no reported change was coded as 0. Because of the trichotomous nature of the data, Kendall's Tau correlations among responses were calculated. Because these analyses were conducted during the early phases of theory building, statistical significance was set at the .10 alpha level. Correlations were hypothesized in directional form, and 1-tailed tests of significance were used.

RESULTS

Outcome measures and Tau correlations among these measures are presented in Tables 1 and 2. The correlations that appear in Table 2, combined with careful reasoning regarding functional relations among the variables, suggested the path model that appears in Fig 1. Correlations seen on this figure suggest that 2 major paths originate with stress reduction: the first leads from reduction in stress through improved sleep, heightened energy, and positive focus to improved performance; the second passes from reduction in stress through reduced appetite, reduced weight, and decreased inches to well-being. Because of the small sample size and the nature of the scales of measurement used, an actual path analysis was not performed; however, the correlations that emerged and their configuration in the model shown in Fig 1 strongly suggest that further research with enhanced measurement scales and a large sample size would shed light on (1) the direct and indirect functional relationships addressed by novel nutraceutical technology and (2) the key physiologic pathways and responses that are improved by this promising therapy.

Fig 1. Proposed path model of response processes with nutraceutical treatment.

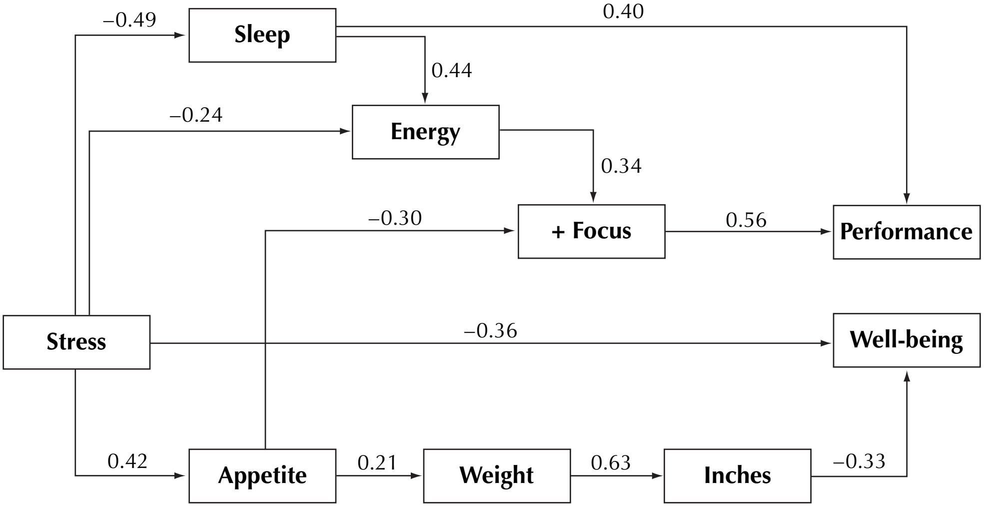


Table 1. Reported Perceived Physiologic Responses to Nutraceutical Formula Variation Intervention

Subject (Time)	Stress	+ Sleep	+ Energy	Well-Being	Craving	+ Focus	Sugar Levels	Appetite	In	Weight	BP	Perf	% Fat	Chol	Net Change, lb
001 (5 M)	NR	NR	NR	↑	NR	NR	NR	NR	↓	↑	NR	NR	UK	NR	↑3
002 (3 M)	↓	NR	NR	↑	NR	NR	NR	NR	↓	↓	NR	NR	UK	NR	↓16
003 (2 W)	NR	NR	NR	↑	↓	NR	NR	↓	↓	↓	NR	NR	UK	NR	UK
004 (3 W)	↓	NR	NR	↑	↓	NR	NR	↓	NR	↓	NR	NR	UK	NR	↓7
005 (6 W)	↓	↑	↑	↑	↓	NR	NR	↓	↓	↓	NR	NR	UK	NR	↓26
006 (2 M)	NR	NR	↑	↑	NR	NR	NR	NR	↓	↓	NR	↑	UK	NR	↓20
007 (3 W)	↓	NR	↑	↑	↓	NR	NR	↓	↓	↓	NR	NR	UK	NR	↓5
008 (3 M)	↓	↑	↑	↑	NR	↑	NR	↓	↓	↓	NR	↑	UK	↓	↓55
009 (8 D)	↓	NR	NR	↑	↓	NR	NR	↓	NR	NR	NR	NR	UK	NR	UK
010 (3 M)	↓	↑	↑	↑	↓	↑	NR	↓	↓	↓	NR	↑	UK	NR	UK
011 (12 M)	↓	↑	↑	↑	↓	NR	NR	↓	UK	UK	NR	NR	UK	NR	UK
012 (4 M)	↓	↑	↑	↑	↓	↑	NR	↓	↓	↓	NR	NR	UK	NR	UK
013 (UK)	↓	NR	↑	↑	↓	NR	NR	↓	UK	UK	NR	NR	UK	NR	UK
014 (6 M)	↓	NR	NR	↑	↓	NR	NR	↓	↓	↓	NR	NR	UK	NR	UK
015 (2 M)	NR	NR	NR	↑	↓	↑	NR	↓	↓	↓	NR	NR	UK	NR	↓15
016 (4 M)	↓	↑	↑	↑	NR	NR	NR	NR	UK	UK	NR	NR	UK	NR	UK
017 (1 M)	↓	↑	↑	↑	↓	↑	NR	↓	↓	↓	NR	↑	↓	NR	↓10
018 (3 M)	↓	↑	↑	↑	↓	↑	NR	↓	UK	UK	NR	↑	UK	NR	UK
019 (5 M)	↓	↑	NR	↑	↓	NR	↓	↓	↓	↓	↓	NR	↓	NR	↓26
020 (6 M)	↓	↑	NR	↑	↓	NR	NR	↓	↓	↓	NR	NR	UK	NR	↓15
021 (1 M)	NR	NR	↑	↑	↓	NR	NR	↓	↓	↓	NR	NR	UK	NR	↓6
022 (UK)	↓	NR	↑	↑	↓	NR	NR	↓	↓	↓	↓	NR	↓	↓	↓70
023 (6 W)	NR	NR	NR	NR	NR	NR	NR	NR	UK	↓	NR	NR	UK	NR	↓10
024 (1 M)	↓	NR	NR	↑	↓	NR	NR	↓	↓	↓	NR	NR	UK	NR	↓8

NR=not reported; UK=unknown; In=inches; Chol=cholesterol; Perf=performance; D=d; W=wk; M=mo; ↑=increased; ↓=decreased.

Table 2. Correlation (Kendall's Tau) Matrix of Outcome Measures

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Stress	1.00														
2. Sleep	–.49	1.00													
3. Energy	–.24	.44	1.00												
4. Well-being	–.36	.18	.23	1.00											
5. Craving	.33	–.10	–.05	–.36	1.00										
6. Positive focus	–.11	.49	.34	.12	–.11	1.00									
7. Sugar level	.12	–.25	.23	–.04	.12	.12	1.00								
8. Appetite	.42	–.23	–.15	–.41	.89	–.30	.11	1.00							
9. Inches	–.16	.02	.04	–.33	.05	–.16	.13	.12	1.00						
10. Weight	–.06	.07	.03	.12	.22	–.12	.12	.21	.63	1.00					
11. BP	.17	–.05	.03	–.06	.17	.17	.69	.16	.19	.17	1.00				
12. Performance	–.06	.40	.47	.11	.18	.56	.11	–.01	–.10	–.07	.16	1.00			
13. Fat	.17	–.05	–.28	–.06	–.17	–.17	–.06	.16	.19	.17	.46	–.22	1.00		
14. Cholesterol	.17	–.05	–.28	–.06	–.17	–.17	–.06	.16	.19	.17	.46	–.22	1.00	1.00	
15. Net weight change	–.03	.10	.01	.17	.04	.07	.17	.05	.34	.72	.25	–.03	.25	.25	1.00

Coefficients above .27 are statistically significant beyond the 0.10 level (1-tailed test).

Examination of Fig 1 reveals a number of very interesting correlations (negative and positive): stress is negatively correlated with sleep (r=–0.49)—when stress is high, sleep is low; stress is positively correlated with appetite (r=0.42)—when stress is high, appetite is high; stress is negatively correlated with energy (r=–0.24)—when stress is high, energy is low; sleep is positively correlated with energy (r=0.44)—when sleep is high, energy is high; stress is negatively correlated with well-being (r=–0.36)—when stress is high, well-being is low; sleep is positively correlated with performance (r=0.40)—when sleep is high, performance is high; appetite is negatively correlated with focus (r=–0.30)—when appetite is high, focus is low; appetite is positively correlated with weight (r=0.21)—when appetite is high, weight is high; and, finally, weight is positively correlated with inches (r=0.63)—when weight is high, the measurement in inches is high as well.

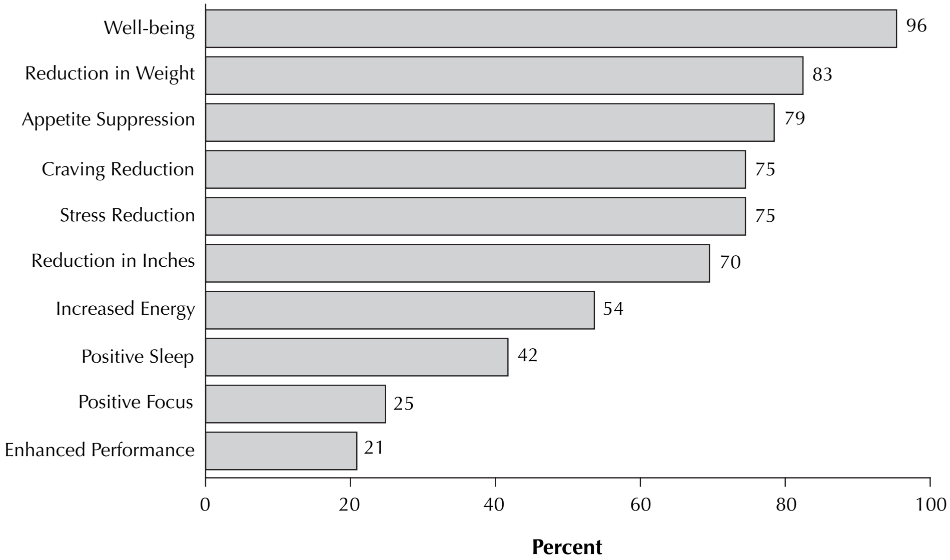
DISCUSSION

Findings from this open-label, cross-sectional study revealed a number of beneficial effects of the GenoTrim formula. The duration of benefit ranged from 8 days to 12 months. It is interesting to note that after only 8 days of use, subjects experienced a reduction in stress, enhanced well-being, a decrease in sugar cravings, and a reduction in appetite. Although 1 individual experienced an increase in body weight (3 lb over 5 mo), 83% of subjects achieved weight reduction by the time the study ended. Of 24 individuals who responded, 96% reported a greater feeling of well-being, 83% achieved weight reduction, 79% reported a significant suppression of appetite, 75% described a reduced craving for sugar, 75% reported a reduction in stress, 70% achieved loss of inches, 54% reported increased energy, 42% described positive sleep patterns, 25% related an enhanced focus, and 21% reported enhanced performance. Of 24 respondents, 13 (54%) measured the pounds actually lost. Notwithstanding other factors such as exercise and better eating habits, average loss of scale weight was 17.15 lb. Of 24 respondents, 5 (20%) measured inches lost; on average, subjects lost 10.7 inches. Only 1 respondent measured actual percentage of body fat and lost 3% over a 1-month period after treatment with GenoTrim. In a very small number of patients, other reported features included reductions in sugar level (0.42%), BP (0.83%), and cholesterol (0.83%) (Fig 2).

CONCLUSION

Reported here are 2 positive path analysis correlations: (1) stress reduction leading to improved sleep, enhanced energy, and improved focus and performance; (2) stress reduction leading to reduced appetite, loss of unwanted weight, decreased body inches, and enhanced well-being. Because of the preliminary nature of this study, we remain optimistic but cautious. However, due to the inherent limitations of "one-size-fits-all" protocols in addressing the idiosyncratic nature of clinical practice, existing weight loss tactics for the most part have failed to provide successful means of achieving sustainable healthy body composition and fat loss. Emerging technologies that customize the nutritional/nutraceutical needs of an individual on the basis of genetic traits merit further investigation. It is common knowledge that factors such as exercise or extreme exertion, disease, drug intake, and poor diet alter nutritional needs. Along this line, research has shown that genetic polymorphisms

Fig 2. Summary of benefits associated with nutraceutical treament.*



*Reported as percentage.

may alter nutritional needs for maintaining healthy homeostasis. This is particularly true in persons with RDS who exhibit polymorphisms that predispose to aberrant pleasure seeking (and addictive) behavior, excessive cravings and obesity, and related syndrome X disorders.[16]

Products of nutraceutical technology, such as GenoTrim, through a novel formula and method, safely and naturally induce effective body recomposition and achieve healthy weight management objectives. They are designed to fill extraordinary nutritional needs created by certain genetic predispositions. Potassium and calcium salts of (–)hydroxycitric acid have been shown to effectively blunt the conversion of excess carbohydrate into fat, promote fat oxidation, enhance serotonin release and availability in the brain, promote healthy blood lipid levels, improve the success of weight management efforts, and induce gene expression of serotonin, leptin, and other genes. Passionflower has demonstrated stress reduction benefits that may lead to cortisol-lowering effects, thereby reducing the accumulation of excess abdominal fat. A novel oxygen-coordinated chromium nicotinate has been shown to improve insulin sensitivity, enhance fat loss, and promote lean muscle–sparing benefits in overweight individuals.[17]

Significant evidence substantiates the role of RDS as a new therapeutic target in the treatment and prevention of obesity. Moreover, this study and others have established the role of catecholaminergic pathways in aberrant substance seeking behavior, in particular, cravings for carbohydrates.[4] The genetic basis for generalized craving behavior has been the subject of intense investigation. Growing evidence supports the augmentation of precursor amino acid therapy and enkephalinase and catechol-O-methyltransferase inhibition, leading to enhanced levels of the neurotransmitters serotonin, enkephalin, γ-aminobutyric acid, and dopamine/norepinephrine.[18-20] Use of genetically guided combinations of amino acids, SuperCitrimax™ (InterHealth Nutraceuticals, Benicia, Calif), passionflower, and a proprietary oxygen-coordinated chromium nicotinate, such as that used in GenoTrim, has been evaluated in an open-label trial. On the basis of a number of case reports, it seems possible that this unique combination of ingredients may have generalized antistress and anticraving effects, resulting in inhibition of carbohydrate bingeing and inducing fat loss and enhanced body image/composition.[21-25]

These hypothesis-generating data underscore the need for further study of the role of dopamine and RDS as a therapeutic target for obesity treatment. In addition, the work of Volkow's group on D2 receptor density describes the use of positron emission tomography to detect low D2 receptors in obese humans.[12] Evidence cited here shows a relationship between body type and D2 receptors. Other studies show the relationship of dopamine receptors to hyperphagia, body mass index, and carbohydrate bingeing. Evidence also shows associations with the D2 A1 allele, as well as with the leptin receptor gene and other neurotransmitter genes (eg, serotonin, acetylcholine [which has links to dopaminergic fibers in the mesolimbic system]), and with carbohydrate bingeing, obesity, body mass index, and energy expenditure.[26-39]

In essence, similar to pharmaceutical analogs, neuronutrient amino acid–based compositions may cause synthesis of the brain reward neurotransmitters such as serotonin and catecholamines. Through its effects on natural opioids via inhibition of γ-aminobutyric acid, this type of composition may cause a significant release of dopamine at the nucleus accumbens.[40] This constant release of possibly therapeutic amounts of dopamine (antistress substance) occupies dopamine D2 receptors, especially in carriers of the A1 allele (low D2 receptors and high glucose craving); over time (possibly 6–8 wk), this may cause RNA transcription, leading to a proliferation of D2 receptors, thereby reducing the craving for carbohydrates.[41]

GenoTrim is a manifestation of this process. It was test launched in The Netherlands in early 2006. More than 1000 Dutch subjects who identified themselves as overweight are currently taking the product.[42] This product, through a multivariate genetic analysis of 5 genes, seeks to address the genetic factors that influence weight: a serotonin receptor gene (5-HT2a –1438 A>G), which influences appetite control; a PPAR-γ (Pro[12]Ala) polymorphism, which affects fat cell creation and metabolism; a leptin OB gene, which alters obesity risk; the MTHFR C677T polymorphism, which changes folate (vitamin B_9) metabolism and homocysteine levels; and the dopamine D2 receptor Taq 1 allele, which reduces sugar and carbohydrate cravings. On the basis of a genetic profile derived from this in-depth genetic analysis, a DNA-customized formula was derived to address the genetic predisposition of the subjects in the belief that this was a major contributing factor underlying their weight problems associated with RDS. Ongoing analysis of the findings of this large study will seek to provide further evidence that this approach may be viable.

This is the first time that the components of this nutraceutical formula have been combined at clinically tested doses to promote successful and sustainable loss of fat and improvement in body composition. Although a number of important pathways may be related to unwarranted weight gain, weight and obesity may be mutually exclusive. Path analysis suggests that these same pathways are interdependent, resulting in a net enhancement of body composition. Future studies should explore the use of nutraceutical formula variations after path analysis in obese patients.

REFERENCES

1. Blum K, Sheridan PJ, Wood RC, et al. The D2 dopamine receptor gene as a predictor of impulsive-addictive-compulsive behavior: Bayes' theorem. *J R Soc Med.* 1996;89:396-400.
2. Blum K, Cull JG, Comings ED. Biogenetics of reward deficiency syndrome. *Am Sci.* 1996;84: 132-145.
3. Blum K, Kozlowski GP. Ethanol and neuromodulator interactions: a cascade model of reward. In: Ollat H, Parvez S, Parvez H, eds. *Alcohol and Behavior.* Utrecht, Netherlands: VSP Press; 1990:131-149.
4. Blum K, Braverman ER. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive and compulsive behaviors. *J Psychoactive Drugs.* 2000; 32:1-100.
5. Bowirrat A, Oscar-Berman M. Relationship between dopaminergic neurotransmission, alcoholism, and reward deficiency syndrome. *Am J Med Genet.* 2005;132:29-37.
6. Reuter J, Raedler R, Rose M, Hand I, Glascher J, Buchel C. Pathological gambling is linked to reduced activation of the mesolimbic reward system. *Nat Neurosci.* 2005;8:147-148.
7. Noble EP, Blum K, Ritchie T, Montgomery A, Sheridan P. Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics. *Arch Gen Psychiatry.* 1991;48:648-654.
8. Breese GR, Criswell HE, Mueller RA. Evidence that lack of brain dopamine during development can increase the susceptibility for aggression and self-injurious behavior by influencing D1-dopamine receptor function. *Prog Neuropsychopharmacol Biol Psychiatry.* 1990;14(suppl): s65-s80.
9. Comings DE, Gade R, Wu S, et al. Studies of the potential role of the dopamine D1 receptor gene in addictive behaviors. *Mol Psychiatry.* 1997;2:44-56.
10. Comings DE, Blum K. Reward deficiency syndrome: genetic aspects of behavioral disorders. *Prog Brain Res.* 2000;126:325-341.
11. Chen TJH, Blum K, Mathews D, et al. Are dopaminergic genes involved in a predisposition to pathological aggression? Hypothesizing the importance of "super normal controls" in psychiatric genetic research of complex behavioral disorders. *Med Hypotheses.* 2005;65:703-707.
12. Wang G-J, Volkow ND, Logan J, et al. Brain dopamine and obesity. *Lancet.* 2001;357:354-357.
13. Spitz MR, Detry MA, Pillow P, et al. Variant alleles of the D2 dopamine receptor gene and obesity. *Nutr Res.* 2000;20:371-380.
14. Fang YJ, Thomas GN, Xu ZL, Fang JQ, Critchley JA, Tomlinson B. An affected pedigree member analysis of linkage between the dopamine D2 receptor gene TaqI polymorphism and obesity and hypertension. *Int J Cardiol.* 2005;102:111-116.
15. Blum K, Meshkin B, Downs BW. DNA based customized nutraceutical "gene therapy" utilizing a genoscore: a hypothesized paradigm shift of a novel approach to the diagnosis, stratification, prognosis and treatment of inflammatory process in the human. *Med Hypotheses.* 2006;66: 1008-1018.
16. Comings DE, Blum K. Reward deficiency syndrome (RDS): genetic aspects of behavior disorders and validation. *Neurotoxicol Res.*, in press.
17. Downs BW, Bagchi M, Subbaraju GV, Shara MA, Preuss HG, Bagchi D. Bioefficacy of a novel calcium-potassium salt of (–)-hydroxycitric acid. *Mutat Res.* 2005;579:149-162.
18. Blum K, Wallace JE, Trachtenberg MC. Enkephalinase inhibition: regulation of ethanol intake in genetically predisposed mice. *Alcohol.* 1987;4:449-456.

19. Blum K, Trachtenberg MC, Elliott CE, et al. Enkephalinase inhibition and precursor amino acid loading improves inpatient treatment of alcohol and poly drug abusers: double-blind placebo-controlled study of the nutritional adjunct SAAVE. *Alcohol.* 1988;5:481-493.

20. Blum K, Briggs AH, Trachtenberg MC. Ethanol ingestive behavior as a function of central neurotransmission [Review]. *Experientia.* 1989;45:444-452.

21. Adler CM, Elman I, Weisenfeld N, Kestler L, Pickar D, Breier A. Effects of acute metabolic stress on striatal dopamine release in healthy volunteers. *Neuropsychopharmacology.* 2000;22:545-550.

22. Akhondzadeh S, Naghavi HR, Vazirian M, et al. Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. *J Clin Pharmacol Ther.* 2001;26:63-67.

23. Chen TJ, Blum K, Payte JT, et al. Narcotic antagonists in drug dependence: pilot study showing enhancement of compliance with SYN-10, amino-acid precursors and enkephalinase inhibition therapy. *Med Hypotheses.* 2004;63:538-548.

24. Milner JD, Irie K, Wurtman RJ. Effect of phenylalanine on the release of endogenous dopamine from rat striatal slices. *J Neurochem.* 1986;47:1444-1448.

25. Bagchi SP, Smith TM. Synaptosomal dopamine from phenylalanine in brain: effects of some dopaminergic agents. *Res Commun Chem Pathol Pharmacol.* 1979;26:447-458.

26. Levin BE. Glucosensing neurons do more than just sense glucose. *Int J Obes Relat Metab Disord.* 2001;(suppl 5):S68-S72.

27. Koshimura K, Tanaka J, Murakami Y, Kato Y. Effect of high concentration of glucose on dopamine release from pheochromocytoma-12 cells. *Metabolism.* 2003;52:922-926.

28. Bello NT, Sweigart KL, Lakoski JM, Norgren R, Hajnal A. Restricted feeding with scheduled sucrose access results in an upregulation of the rat dopamine transporter. *Am J Physiol Regul Integr Comp Physiol.* 2003;284:R1260-R1268.

29. Conti G, Blandini F, Tassorelli C, et al. Intrastriatal injection of D1 or D2 dopamine agonists affects glucose utilization in both the direct and indirect pathways of the rat basal ganglia. *Neurosci Lett.* 2001;309:161-164.

30. Cincotta AH, Tozza E, Scislowski PW. Bromocryptine/SKF38393 treatment ameliorates obesity and associated metabolic dysfunctions in obese (ob/ob) mice. *Life Sci.* 1997;61:951-956.

31. Umhau JC, Petrulis SG, Diaz R, Rawlings R, George DT. Blood glucose is correlated with cerebrospinal fluid neurotransmitter metabolites. *Neuroendocrinology*. 2003;78:339-343.

32. Colantuoni C, Rada P, McCarthy J, et al. Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. *Obes Res.* 2002;10:478-488.

33. Kogan HA, Marsden CA, Fone CF. DR4004, a putative 5-HT7 receptor antagonist, also has functional activity at the dopamine D2 receptor. *Eur J Pharmacol.* 2002;449:105-111.

34. Hajnal A, Szekely M, Galosi R, Lenard L. Accumbens cholinergic interneurons play a role in the regulation of body weight and metabolism. *Physiol Behav.* 2000;70:95-103.

35. Trugman JM, James CL. D1 dopamine agonist and antagonist effects on regional cerebral glucose utilization in rats with intact dopaminergic innervation. *Brain Res.* 1993;607:270-274.

36. Shiroyama K, Moriwaki K, Yuge O. The direct effect of dopamine on glucose release from primary cultured rat hepatocytes. *In Vivo.* 1998;12:527-529.

37. Hamilton ME, Freeman AS. Diet and chronic haloperidol effects on rat midbrain dopamine neurons. *Synapse.* 2004;53:1-5.

38. Collaku A, Rankinen T, Rice T, et al. A genome-wide linkage scan for dietary energy and nutrient intakes: the health, risk factors, exercise training, and genetics (HERITAGE) family study. *Am J Clin Nutr.* 2004;79:881-886.

39. Balcioglu A, Wurtman RJ. Sibutramine, a serotonin uptake inhibitor, increases dopamine concentrations in rat striatal and hypothalamic extracellular fluid. *Neuropharmacology.* 2000;39:2352-2359.

40. Di Chiara G. Nucleus accumbens shell and core dopamine: differential role in behavior and addiction. *Behav Res.* 2002;137:75-114.

41. Blum K, Chen TJH, Meshkin B, et al. Manipulation of catechol–O methyl transferase (COMT) activity to influence the attenuation of substance seeking behavior, a subtype of Reward Deficiency Syndrome (RDS), is dependent upon gene polymorphisms. A hypothesis. *Med Hypotheses.*, in press.

42. Blum K, Chen TJH, Meshkin B, et al. Genotrim™, a DNA-customized nutrigenomic product, targets genetic factors of obesity: Hypothesizing a dopamine-glucose correlation demonstrating reward deficiency syndrome (RDS). *Med Hypotheses.*, in press.