Neurogenetic Impairments of Brain Reward Circuitry Links to Reward Deficiency Syndrome (RDS): Potential Nutrigenomic Induced Dopaminergic Activation

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Introduction

There has been over half a century of dedicated and rigorous scientific research on the brain’s mesolimbic system, a critical site for experiences of well-being. These investigations have provided insight into the addictive brain and the neurogenetic mechanisms involved in the quest for happiness. This part of the brain is a reward center where chemical messengers including serotonin, enkephalin, γ-aminobutyric acid (GABA), dopamine (DA), acetylcholine (ACH) and many second messenger proteins work in concert to provide a net release of DA at the nucleus accumbens (NAc). The idea that the synthesis, vesicular storage, metabolism, receptor formation, and catabolism of neurotransmitters are controlled by genes is well understood [1-3]. Polyomorphic variants of these genes have certain variations that can disrupt the neurochemical events that culminate in neuronal release of DA. A breakdown in the cascade “The Brain Reward Cascade” [4] of these neuronal events will eventually lead to DA dysfunction. Two prominent functions of the DA molecule are the experience of pleasure (reward) and the reduction of stress. DA dysfunction then can result in a deficiency in reward and a predisposition to substance-seeking in an attempt to ameliorate hypodopaminergic function [5].

Neurogenetic considerations

Certainly, Homo sapiens have a biological predisposition to drink, eat, reproduce, and desire pleasurable experiences. The mechanisms involved in reward from these natural processes may be impaired due to polyomorph genetic antecedents provoked by epigenetic, environmental factors that can result in multiple impulsive, compulsive, and addictive behaviors. From the many genes known to predispose individuals to excessive cravings and result in SUD, some of the most prominent are the following polymorphisms: the serotonergic 2A receptor (5-HTT2a); serotonergic transporter (5HTTLPR.); DA D1 receptor (DRD1); DA D2 receptor (DRD2); DA D3 receptor (DRD3); DA D4 receptor (DRD4); DA transporter (DAT1); and the catechol-O-methyltransferase (COMT), monoamine-oxidase (MOA); Mu-opiate receptor (MOR); GABA –B, genes [6-8] (Table 1 GARS). Individuals are predisposed to self-medicate with any substance or behavior that will activate DA release. This can occur if they possess, for example, an increased rate of mitochondrial DA breakdown, due to having high MOA activity or an increased rate of synaptic DA breakdown due to having high catabolic genotype of the COMT gene. However, slower breakdown of DA due to polymorphisms in both the MOA and or COMT may lead to hyperactivity as seen in Attention Deficit Hyperactivity Disorder (ADHD).
An association, between common genetic variants of the DAD2 receptor gene (DRD2) polymorphisms [9,10] and other reward genes [6-8] (hypodopaminergic function) and impulsive, compulsive, and addictive behaviors has been identified [6,7,11]. Thus the term Reward Deficiency Syndrome (RDS), first coined in our laboratory, in 1995, was designated to cover all conditions genetically associated with hypodopaminergic function [8].

Most addictions, including alcohol, opiates, psychostimulants (cocaine, methamphetamine), nicotine, glucose, gambling, sex addiction, excessive spending, and even uncontrolled internet gaming are associated with the release of DA in the mesocorticolimbic system or reward pathway of the brain [4,5,12-14] figure 1. While activation of this dopaminergic system results in feelings of reward and pleasure [15-17] reduced activity (hypodopaminergic functioning) can trigger drug-seeking behavior [18-22]. Mechanisms of hypodopaminergic functioning including reduced DA receptor density, blunted response to DA, or enhanced DA catabolism in the reward pathway, can be induced by variant alleles or defined polymorphisms [23]. Cessations of chronic drug use also can generate a hypodopaminergic state that prompts drug-seeking behaviors in an attempt to address the unwanted withdrawal-induced state [24].

Dopaminergic mechanisms

While a feeling of wellbeing can be produced by acute use of psychoactive substances, sustained and prolonged abuse results in tolerance and discomfort [25]. For example, opioid desensitization/tolerance mechanisms have focused on adaptations that occur on the level of the mu-opioid receptor (MOR) itself. These include opioid receptor phosphorylation [26]. Recent research has revealed augmented isoform-specific synthesis of adenylyl cyclase and their phosphorylation as well as augmented phosphorylation of the G(beta) subunit of G(betagamma). The effect of these changes is to shift mu-opioid receptor-coupled signaling from predominantly G(i alpha) inhibitory to (G(i)-derived) G(betagamma) stimulatory adenylyl cyclase signaling [26]. Polymorphisms related to MOR have been associated with excessive drug (ethanol) seeking behavior that interacts with dopaminergic pathways in the NAc [27].

Moreover, excessive cravings caused by carrying the DRD2 A1 allelic genotype, a deficit in DA receptors, are compounded by consequential drug seeking behavior. Conversely, normal densities of DA receptors result in low craving behaviors [19]. Reduction of craving to prevent or treat SUD could result from proliferation of DAD2 receptors in genetically predisposed individuals [28,29] and those with hypodopaminergic function secondary to stress or the toxic effects of the abused substances [30]. Boundy et al. [31,32] have shown, in vitro, that constant stimulation of the DA receptor system with low doses of a D2 agonist results in significant proliferation of D2 receptors, in spite of genetic antecedents [33]. Messenger RNA expression causes proliferation of D2 receptors induced by negative feedback mechanisms, in the mesolimbic system signaled by gentle chronic D2 receptor stimulation [31,32]. This neuro-molecular finding serves as the basis for naturally inducing DA release, to produce the same induction of D2-directed mRNA and thus proliferation of D2 receptors in humans and a resultant attenuation of craving behavior [34,35]. This has been proven with work showing a form of gene therapy [36]. In nonhuman animals DNA-directed overexpression of the DRD2 receptors induces a significant reduction in both alcohol and cocaine craving induced behavior [37-39].

Our most recent findings, derived from a small unpublished pilot study showing a clear difference between placebo and KB220Z™ in terms of BOLD activation of the dopaminergic pathways of the caudate-accumbens area are encouraging. Moreover, we also observed, an attenuation of the hyperactivity in the putamen of abstinent heroin-dependent subjects. The experiment will continue, by adding additional heroin-dependent subjects, until statistical power is sufficient for demonstrating significant results. We did, however, observe statistically significant results (P <.05) in three important brain regions of interest (ROI) when we evaluated placebo compared to the KB220Z™ treatment group in 10 subjects at rest. Currently, albeit knowing that

| Dopamine D1 Receptor Gene | Dopamine D2 Receptor Gene | Dopamine D3 Receptor Gene | Dopamine D4 Receptor Gene | Dopamine Transporter Gene | Serotonin 2A Receptor Gene | Serotonin Transporter Gene | Mu-opiate Receptor Gene | GABA – B2, Receptor Gene | PENK Gene | Mono-Amine – Oxidase A Gene | Catecholamine –Methyl-Transferase Gene | Cytochrome P450 Gene |
|---------------------------|--------------------------|--------------------------|--------------------------|--------------------------|---------------------------|--------------------------|------------------------|------------------------|----------------|-----------------------------|--------------------------|----------------|

Table 1: Proposed Genetic Addiction Risk Score (GARS).
there is a lower D2R availability in the putamen of abstinent heroin dependent subjects, we do not understand the mechanism by which KB220Z™ administration (post one–hour) induced an attenuation of this hypo state. This will be the subject of future investigation and it may involve abnormal white matter synapses.

In ongoing research, we will explore the role of KB220Z compared to placebo, both its impact on white matter and on cue-induced craving behavior. This additional experiment is crucial since the structure and function of white matter synapses has become increasingly important in disease. While vesicular neurotransmitter release is the province of gray matter, synaptic style release of glutamate occurs deep in white matter. As white matter becomes increasingly well-recognized as a substrate for disease, dysregulation of white matter synaptic transmission will play a role a number of impulsive/compulsive/addictive RDS behaviors [34,35].

Interestingly, current cocaine-dependent users show reductions in white matter integrity, especially in connections to cortical regions associated with cognitive control that have been associated with inhibitory dysfunction [40]. In a diffusion tensor imaging study, by Bell, et al. [40] former cocaine dependant groups with different durations of abstinence were observed to show white matter fractional anisotropy differences bilaterally in the inferior longitudinal fasciculus, right anterior thalamic radiation, right ventral postero lateral nucleus of the thalamus, left superior corona radiata, superior longitudinal fasciculus bilaterally, right cingulum and the white matter of the right precentral gyrus [40]. The findings suggested that specific white matter abnormalities discriminate as a function of abstinence duration and therefore, might represent brain changes that mark recovery from addiction. Similar findings have been found in heroin –dependent subjects from research in Liu’s group [41,42]. They found that fractional anisotropy was significantly decreased in specific brain regions of heroin-dependent patients (P<0.001 uncorrected) including the frontal gyrus, the parietal lobe, the insula, and the corpus callosum. Thus, micro structural abnormality is present in the white matter of several specific brain regions of heroin-dependent patients.

Based on the current literature and our pilot findings discussed herein, we are poised to further evaluate the effectiveness of KB220Z on micro structural disruption of white matter in heroin addicts revealed by diffusion tensor imaging. Certainly, a combination of findings that includes BOLD activation of dopaminergic pathways in the caudate-accumbens; attenuation of abnormal hyperactivity of the putamen in heroin-dependent subjects and a potential reduction of micro structural white matter abnormalities by KB220Z should ultimately support its utilization as a novel safe DA agonist for prevention, tertiary treatment and relapse attenuation in RDS victims, especially carriers of reward gene polymorphisms. Currently there are many clinical trials showing significant benefits of KB220Z and variants over four decades of research (Table 2).

Conclusions

While it is true that Homo sapiens in evolutionary terms are changing very slowly, it is also true that certain genetic traits such as genes that regulate pleasure-seeking may be the exception [34,35]. At this juncture, we do not know whether the DRD2 A1 allele is an older gene allele or if it is newer than the DRD2 A2 allele. Understanding this will help clarify the nature of the relationship humans have with pleasure-seeking and perhaps how it benefits our survival. Certainly carriers of the DRD2 A1 allele are more aggressive than carriers of the DRD2 A2 allele [43].

The initial work of Blum, et al. [4] and others including brain imaging studies [44] that have helped clarify addiction mechanisms also have helped to amend the public’s view of drug addiction. Public opinion has moved from the idea that addiction is a moral problem, to an understanding that genetic predisposition and pathological physical changes that occur during active addiction make it extremely difficult for addicts to give up their substance abuse. We must reflect on the question of how we address the legality, of the natural pursuit of pleasure.

Hypodopaminergic function stimulates cravings, which in turn affects attention to goals and maintenance of cognitive control needed for overriding compulsions to use drugs and the ability to make action plans and then monitor action [45]. With drug use there is a steady influx of DA, but it becomes the sole focus of the addict’s attention. The central goal, is obtaining more drugs. They are motivated by their craving for drugs, even though the drugs have long stopped providing pleasure. Victims of SUD are caught in a spiral of physical brain changes and the psychological consequences of those changes that lead to further physical and psychological changes and consequences.

For approximately one-third of Americans, DA is a key genetically induced deficient neurotransmitter resulting in aberrant craving behavior and excessive pleasure seeking. Finding ways to increase DA D2 density, instead of blocking dopaminergic function, may be the best strategy to unlock the elusive addiction riddle and attenuate abuse [34,46].

Certainly, new treatment and diagnostic (genetic) approaches are required in view of our most recent unpublished work derived from studies with CARD™. We evaluated both compliance and abstinence during treatment using 5,838 specimens from 2,919 patients located in various treatment settings across six eastern states in years 2010 and 2011. Preliminary, we found compliance to prescribed medications in our sample during treatment to be 67.2% while 60.8% of these patients were found to be still abusing drugs. In Opiate Treatment Programs whereas 87.4% of 1298 patients were compliant to Buprenorphine only 53.1% were abstinent, as measured by the first and last urine samples. For Methadone, 91.6% of 693 patients were compliant but only 50.9% were abstinent, again as measured by the first and last urine samples [47].

Finally, for the first time, we are proposing a new paradigm shift called “Reward Deficiency Solutions System™” that includes the coupling of:

1. Genotyping of individuals for candidate reward genes to determine stratification of genetic risk for all RDS behaviors (GARS™) [48,49]
2. The use of natural D2 agonist therapy (e.g. KB220Z™) to activate dopaminergic pathways in the NAC (affecting abnormal craving) and other brain regions (affecting decision –making)
3. And the use of CARD™ during active recovery to assess compliance to prescribed treatment medications and abstinence from drugs of abuse.

These tools provide the clinician the means to engender better diagnosis and recovery rates. Further research in terms of reinforcement experiments in nonhuman animal models [50] and human trials will assist in promotion of these novel strategies for the early diagnosis, prevention, treatment and attenuation of relapse in RDS [51,52] including process addictions [53].

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Conflict of Interest

Kenneth Blum, PhD., holds a number of US and Foreign patents related to diagnosis and treatment of RDS, which has been exclusively licensed to LifeGen, Inc. Lederach, PA. Mary House is Vice President of Dominion Diagnostics Inc., and along with Lifegen, Inc., they are actively involved in the commercial development of GARS. Kenneth Blum, Thomas Simpatico, John Femino, are paid consultants of Dominion Diagnostics, Inc. John Giordano is also a partner in LifeGen, Inc. There are no other conflicts of interest and all authors read & approved the manuscript.

References

1. Hodge CW, Cox AA (1998) The discriminative stimulus effects of ethanol are mediated by NMDA and GABA(A) receptors in specific limbic brain regions. Psychopharmacology (Berl) 139: 95-107.
2. Archer T, Oscar-Berman M, Blum K (2011) Epigenetics in Developmental Disorder: AHD and Endophenotypes. J Genet Syndr Gene Ther 2: p1. 1000104.
3. Blum K, Noble EP, Sheridan PJ, Montgomery A, Ritchie T, et al. (1990) Allelic association of human dopamine D2 receptor gene in alcoholism. JAMA 263: 2055–2060.
4. Blum K, Braverman ER, Holder JM, Lubar JF, Monastra VJ, et al. (2000) Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. J Psychoactive Drugs 32: 1-112.
5. Blum K, Chen TJ, Morse S, Giordano J, Chen AL, et al. (2010) Overcoming qEEG abnormalities and reward gene deficits during protracted abstinence in male psychostimulant and polydrug abusers utilizing putative dopamine D agonist therapy: part 2. Postgrad Med 122: 214-226.
6. Blum K, Sheridan PJ, Wood RC, Braverman ER, Chen TJ, et al. (1996) The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. J R Soc Med 89: 396-400.
7. Blum K, Wood RC, Braverman ER, Chen TJ, Sheridan PJ (1995) The D2 dopamine receptor gene as a predictor of compulsive disease: Bayes’ theorem. Funct Neurol 10: 37-44.
8. Grandy DK, Litt M, Allen L, Bunzow JR, Marchionni M, et al. (1989) The human dopamine D2 receptor gene is located on chromosome 11 at q22-q23 and identifies a TaqI RFLP. Am J Hum Genet 45: 778-785.
9. Hauge XY, Grandy DK, Eubanks JH, Evans GA, Civelli O, et al. (1991) Detection and characterization of additional DNA polymorphisms in the dopamine D2 receptor gene. Genomics. 10: 527-530.
10. Blum K, Braverman ER, Wood RC, Gil J, Li C, et al. (1996) 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 6: 297-305.
11. Blum K, Noble EP, Sheridan PJ, Finley O, Montgomery A, et al. (1991) Association of the A1 allele of the D2 dopamine receptor gene with severe alcoholism. Alcohol 8: 409-416.
12. Comings DE, Muhlem M, Gysin R (1996) Dopamine D2 receptor (DRD2) gene and susceptibility to posttraumatic stress disorder: a study and replication. Biol Psychiatry 40: 368-372.
13. Boundy VA, Lu L, Molinoff PB (1996) Diffferential coupling of rat D2 dopamine receptor isoforms were expressed in Spodoptera frugiperda moth caterpillar cells. J Pharmacol Exp Ther 276: 784-794.
14. Boundy VA, Pacheco MA, Guan W, Molinoff PB (1995) Agonists and antagonists differentially regulate the high affinity state of the D2L receptor in human embryonic kidney 293 cells. Mol Pharmacol 48: 956-964.
15. Blum K, Chen AL, Chen TJ, Braverman ER, Reinking J, et al. (2008) 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 5: 24.
16. Brownell K & Gold MS (2012) Food and Addiction: A comprehensive handbook. Oxford University Press, Oxford, England & New York, USA.
17. Volkon ND, Wang GJ, Fowler JS, Tomasi D (2012) Addiction circuitry in the human brain. Annu Rev Pharmacol Toxicol 52: 321-336.
18. Volkon ND, Chang L, Wang GJ, Fowler JS, Ding YS, et al. (2001) Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. Am J Psychiatry 158: 2015-2021.
19. Volkon ND, Wang GJ, Begleiter H, Porjesz, B, Fowler JS, (2006) High levels of dopamine D2 receptors in unaffected members of alcoholic families: possible protective factors. Arch Gen Psychiatry 63: 999-1008.
20. Volkon ND (2001) Drug abuse and mental illness: progress in understanding comorbidity. Am J Psychiatry 158: 1181-1183.
21. Volkon ND, Fowler JS, Wang GL (2003) The addicted human brain: insights from imaging studies. J Clin Invest 111: 1444-1451.
22. Dackis C, Gold MS (1985) Neurotransmitter and neuroenocrine abnormalities associated with cocaine use. Psychiatr Med 3(4): 461-483.
23. Hietala J, West C, Syvälahti E, Näkkär K, Leikikoinen P, et al. (1994) Striatal D2 dopamine receptor binding characteristics in vivo in patients with alcohol dependence. Psychopharmacology (Berl) 116: 285-290.
24. Hietala J, Syvälahti E, Vuorio K, Näkkär K, Leikikoinen P, et al. (1994) Striatal D2 dopamine receptor characteristics in neuroleptic-naive schizophrenic patients studied with positron emission tomography. Arch Gen Psychiatry. 51: 116-123.
25. Braverman ER, Blum K (1996) Substance use disorder exacerbates brain electrophysiological abnormalities in a psychiatrically-ill population. Clin Electroencephalogr 27: 5-27.
26. Gintzler AR, Charkabarti S (2006) Post-opioid receptor adaptations to chronic morphine; altered functionality and associations of signaling molecules. Life Sci 79: 717-722.
27. McGeary JE, Monti PM, Rhsenow DJ, Tidey J, Swift R, et al. (2006) Genetic moderators of naltrexone’s effects on alcohol cue reactivity. Alcohol Clin Exp Res 30: 1288-1296.
28. Rothman RB, Blough BE, Baumann MH (2007) Dual dopamine/serotonin releasers as potential medications for stimulant and alcohol addictions. AAPS J 9: E10-10.
29. Volkon ND, Wang GJ, Fowler JS, Tomasi D (2012) Reward Deficiency Syndrome. J Genet Syndr Gene Ther 3:e115.
39. Thanos PK, Volkow ND, Freimuth P, Umegaki H, Ikari H, et al. (2001) Overexpression of dopamine D2 receptors reduces alcohol self-administration. J Neurochem 78: 1094-1103.
40. Bell RP, Foxe JJ, Nierenberg J, Hoptman MJ, Garavan H (2011) Assessing white matter integrity as a function of abstinence duration in former cocaine-dependent individuals. Drug Alcohol Depend 114: 159-168.
41. Yuan Y, Zhu Z, Shi J, Zou Z, Yuan F, et al. (2009) Gray matter density negatively correlates with duration of heroin use in young lifetime heroin-dependent individuals. Brain Cogn 71: 223–228.
42. Zhang Y, Tian J, Yuan K, Liu P, Zhuo L, et al. (2011) Distinct resting–state brain activities in heroin-dependent individuals. Brain Res 1402: 46-53.
43. Chen TJ, Blum K, Mathews D, Fisher L, Schnautz N, et al. (2005) 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 65: 703-707.
44. Oberlin BG, Dzemidzic M, Bragulat V, Lehigh CA, Talavage T, et al. (2012) Limbic responses to reward cues correlate with antisocial trait density in heavy drinkers. Neuroimage 60: 644-652.
45. Tanji J, Hoshi E (2008) Role of the lateral prefrontal cortex in executive behavioral control. Physiol Rev 88: 37-57.
46. Blum K, Chen AL, Giordano J, Borsten J, Chen TJ, et al. (2012) The addictive brain: all roads lead to dopamine. J Psychoactive Drugs 44:134-143.
47. Blum K., Giordano J, Han D (2012) Coupling the Genetic Addiction Risk Score (GARS), Comprehensive Analysis of Reported Drugs (CARD) and KB220Z showing reward circuitry activation of Dopaminergic pathways with KB220Z for in treatment of Reward Deficiency Syndrome (RDS): A Paradigm Shift. Keynote Presented at International Conference on Genetic Syndromes & Gene Therapy, November 19th, San Antonio, Texas.
48. Blum K, Werner T, Games S, Games P, Bowirrat A, et al. (2012) Sex, drugs, and rock ‘n roll: hypothesizing common mesolimbic activation as a function of reward gene polymorphisms. J Psychoactive Drugs 44: 38-55.
49. Wang GJ, Geleider B, Volkow ND, Telang FW, Logan J, et al. (2011) Enhanced striatal dopamine release during food stimulation in binge eating disorder. Obesity (Silver Spring) 19:1601-1608.
50. Sanchis-Segura C, Grisel JE, Olive MF, Ghozland S, Koob GF, et al. (2005) Role of the endogenous opioid system on the neurophysiological effects of ethanol: new insights about an old question. Alcohol Clin Exp Res 29:1522-1527.
51. Blum K, Chen AL, Oscar-Berman M, Chen TJ, Lubar J, et al. (2011) Generational association studies of dopaminergic genes in reward deficiency syndrome (RDS) subjects: selecting appropriate phenotypes for reward dependence behaviors. Int J Environ Res Public Health 8: 4425-459.
52. Blum K, Payne JE (1991) “Alcohol & the Addictive Brain: New Hope for Alcoholics from Biogenetic Research”. The Free Press Simon & Schuster, Inc. New York, ISBN 0-02-903701-8.
53. Fiorino DF, Phillips AG (1999) Facilitation of sexual behavior and enhanced dopamine efflux in the nucleus accumbens of male rats after D-amphetamine-induced behavioral sensitization. J Neurosci 19: 456-463.