

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

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Abstract

Work from our laboratory in both in-patient and outpatient facilities utilizing the Comprehensive Analysis of Reported Drugs (CARD)TM found a significant lack of compliance to prescribed treatment medications and a lack of abstinence from drugs of abuse during active recovery. This unpublished, ongoing research provides an impetus to develop accurate genetic diagnosis and holistic approaches that will safely activate brain reward circuitry in the mesolimbic dopamine system. This editorial focuses on the neurogenetics of brain reward systems with particular reference to genes related to dopaminergic function. The terminology "Reward Deficiency Syndrome" (RDS), used to describe behaviors found to have an association with gene-based hypodopaminergic function, is a useful concept to help expand our understanding of Substance Use Disorder (SUD), process addictions, and other obsessive, compulsive and impulsive behaviors. This editorial covers the neurological basis of pleasure and the role of natural and unnatural reward in motivating and reinforcing behaviors. Additionally, it briefly describes the concept of natural dopamine D2 receptor agonist therapy coupled with genetic testing of a panel of reward genes, the Genetic Addiction Risk Score (GARS). It serves as a spring-board for this combination of novel approaches to the prevention and treatment of RDS that was developed from fundamental genomic research. We encourage further required studies.

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]. Polymorphic versions 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 polymorphic 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 β_3 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).

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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 -B ₃ Receptor Gene
PENK Gene
Mono-Amine -Oxidase A Gene
Catecholamine -Methyl-Transferase Gene
Cytochrome P450 Gene

Table 1: Proposed Genetic Addiction Risk Score (GARS).

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(beta gamma). The effect of these changes is to shift mu-opioid receptor-coupled signaling from predominantly G(i alpha) inhibitory to (G(i)-derived) G(beta gamma) 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

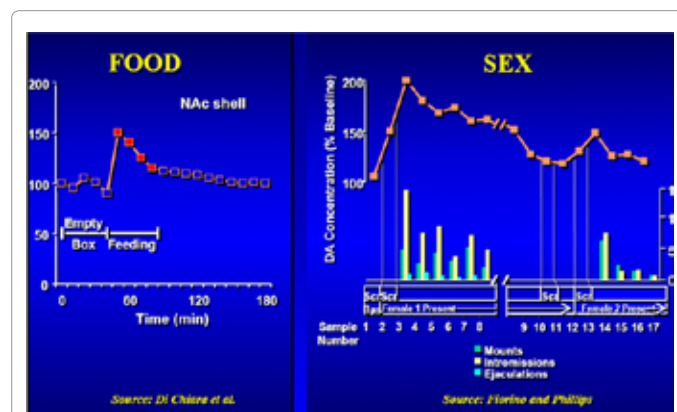
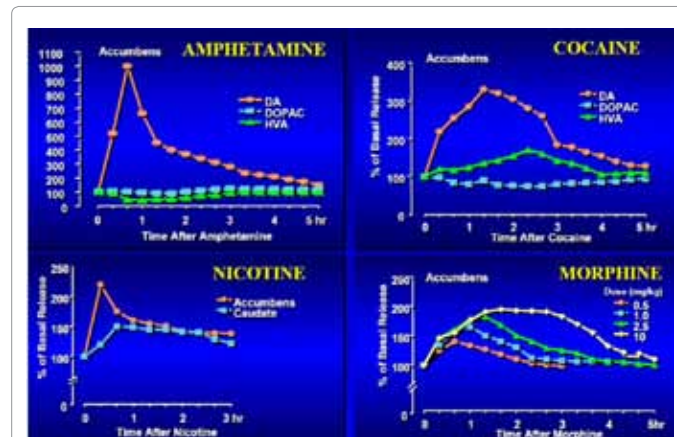


Figure 1A: Natural rewards and dopamine release.



[Modified from Di Chiara G and Imperato, 1988 and Fiorino & Phillips, 1999]

Figure 1B: Unnatural rewards and dopamine release.

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 further 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 posterolateral 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 lobule, 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 KB220 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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Source: Modified from Blum, et al. *Omics-Addiction Research & Therapy* (2012). Proceedings of Conference, August 2012 with permission

Table 2: Phase 1 and Phase 2 Clinical Trials of Neuro-nutrient Amino Acid Therapy (NAAT).

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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 Houser 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.

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