Current Neuropharmacology, **2017**, *15*, 184-194

REVIEW ARTICLE

Common Neurogenetic Diagnosis and Meso-Limbic Manipulation of Hypodopaminergic Function in Reward Deficiency Syndrome (RDS): Changing the Recovery Landscape

Kenneth Blum[1-6,8,11,12,14,*], Marcelo Febo[1], Rajendra D. Badgaiyan[7], Zsolt Demetrovics[8], Thomas Simpatico[2], Claudia Fahlke[9], Oscar-Berman M[10], Mona Li[11], Kristina Dushaj[11] and Mark S. Gold[12,13]

[1]Department of Psychiatry, University of Florida College of Medicine and McKnight Brain Institute, Gainesville, FL, USA; [2]Department of Psychiatry, University of Vermont, Burlington, VT, USA; [3] Division of Neuroscience Based Therapy, Summit Estates Recovery Center, Las Gatos, CA, USA; [4]Dominion Diagnostics, LLC, North Kingstown, RI, USA; [5]IGENE, LLC, Austin, TX, USA; [6]Department of Nutrigenomics, RDSolutions, Inc., Salt Lake City, UT, USA; [7]Division of Neuroimaging, Department of Psychiatry, University of Minnesota College of Medicine, Minneapolis, MN, USA; [8]Department of Psychology, Eotvos Lorand University, Budapest, Hungary; [9]Department of Psychology, University of Gothenburg, Göteborg, Sweden; [10]Departments of Psychiatry and Anatomy & Neurobiology, Boston University School of Medicine and Boston VA Healthcare System, Boston, MA, USA; [11]PATH Foundation NY, New York, NY, USA; [12]Departments of Psychiatry & Behavioral Sciences' Keck School of Medicine of USC, Los Angeles, CA, USA; [13]Department of Psychiatry, Washington University School of Medicine. St. Louis, MO, USA; [14]Division of Neuroscience Research and Addiction Therapy, The Shores Treatment and Recovery, Port Saint Lucie, FL, USA

Abstract: ***Background***: In 1990, Blum and associates provided the first confirmed genetic link between the DRD2 polymorphisms and alcoholism. This finding was based on an earlier conceptual framework, which served as a blueprint for their seminal genetic association discovery they termed "Brain Reward Cascade." These findings were followed by a new way of understanding all addictive behaviors (substance and non-substance) termed "Reward Deficiency Syndrome" (RDS). RDS incorporates a complex multifaceted array of inheritable behaviors that are polygenic.

Objective: In this review article, we attempt to clarify these terms and provide a working model to accurately diagnose and treat these unwanted behaviors.

Method: We are hereby proposing the development of a translational model we term "Reward Deficiency Solution System™" that incorporates neurogenetic testing and meso-limbic manipulation of a "hypodopaminergic" trait/state, which provides dopamine agonistic therapy (DAT) as well as reduced "dopamine resistance," while embracing "dopamine homeostasis."

Result: The result is better recovery and relapse prevention, despite DNA antecedents, which could impact the recovery process and relapse. Understanding the commonality of mental illness will transform erroneous labeling based on symptomatology, into a genetic and anatomical etiology. WC: 184.

Kenneth Blum

ARTICLE HISTORY

Received: September 08, 2015
Revised: April 11, 2016
Accepted: April 21, 2016

DOI: 10.2174/1570159X13666160512150918

Keywords: Dopamine homeostasis, genetics, reward deficiency solution system, Reward Deficiency Syndrome (RDS).

INTRODUCTION

Nobel prize winners, Arvid Carlsson, Paul Greengard, and Eric Kandel, supported initial studies on dopamine as a neurotransmitter playing a significant part in the Central Nervous system (CNS). Carlsson was rewarded for his seminal work in the 1950's showing that dopamine, thought only to be a precursor to Norepinephrine, was indeed a neurotransmitter by itself having an important role in brain function. Greengard received the Nobel Prize because he showed the role of Dopamine in the synapse and Kandel received the Nobel Prize for his contribution to the role of Dopamine in learning and memory [1].

The work of Carlsson lead to not only the successful treatment of Parkinson Disease, but depression and even Schizophrenia. However, it is accepted that by using the strong dopamine D2 receptor agonist L-Dopa there are issues related to motor control and dyskinesia [2]. Moreover, the

*Address correspondence to this author at the Department of Psychiatry & McKnight Brain Institute, University of Florida, College of Medicine, Box 100183 Gainesville, FL, USA 32610-0183; Tel: 352-392-6680; Fax: 352-392-8217; E-mail: drd2gene@ufl.edu

1875-6190/17 $58.00+.00

role of antidepressants involving transporter systems and inhibition of the catabolic enzymes Monoamine–Oxidase (MOA-A,B) and Catecholamine-Methyl-Transferase (COMT) for depression is fraught with many issues related to side effects and even mood alterations [3]. Finally, the utilization of an anti-psychotic agent like Haloperidol that block dopamines response at D2 receptors could result in severe mood changes as well and they have significant side effects [4]. With due respect of these important findings still important in today's medical arsenal against these intrusive brain disorders, we can improve on these important medicaments. Interestingly, prior to 1968, little was known about the role of Dopamine and for example, ethanol abuse, intoxication and clinically induced alcoholism. However, following the development of the Institutes of both drug abuse (National Institute of Drug Abuse) and alcoholism (National Institute of Alcohol Abuse & Alcoholism) by the National Institutes of Health, the understanding of how these diverse addictive substances (*e.g.* glucose, alcohol, cocaine, heroin, nicotine, *etc.*) pharmacologically act, especially in the CNS and their commonality of neuro-functionality across mental illness has been a wonderful work in progress [5].

Since the 1960's and 70's, the role of Dopamine was beginning to entice scientists and it was not until 1969 that the very first Neuroscience Society meeting occurred, consisting of less than 100 members. In fact, Blum [6] was the first to show the role of dopamine at the neuromuscular junction revealing that tremors could occur as a motor response to dopamine. This had relevance to the role of dopamine in Parkinsonism. Other work by Blum *et al*. [7-9] revealed that dopamine played an important role in alcohol withdrawal symptomatology similar to morphine withdrawal. This served, along with the seminal work of Davis and Walsh [10], as the basis of common mechanisms. In 1977, Blum edited a book "Alcohol & Opiates" devoted to common mechanisms between these two seemingly diverse chemical structures [11]. Melchoir and Myers in the mid 70's also showed genetic differences in ethanol drinking of various rat strains utilizing methods to destroy serotonergic and dopaminergic pathways [12]. Following these earlier studies, Dackis & Gold developed the concept of the "dopamine depletion hypothesis" specific for cocaine addiction [13]. Over a five-year period, there has been a plethora of research devoted to the role of neurotransmitters and brain function [14]. During this time, Blum & Kozlowski [15] developed and published on the concept they coined "Brain Reward Cascade," which served as a blue print for the first identification of the link between the dopamine D2 receptor (DRD2) gene Taq A1 allele and severe alcoholism [16].

Blum *et al*. [15] conceived "Reward Deficiency Syndrome" (RDS), which results from issues occurring during the "Brain Reward Cascade" [15] explicitly associating atypical cravings and poor executive function (decision-making). The RDS concept included several reward gene deficits such as dopaminergic, serotonergic, endorphinergic, catecholaminergic, gabaergic, adrenergic, opioidergic, cholinergic, as well as many second messengers across prefrontal cortex and meso-limbic systems. Following many studies, it is generally agreed that dopamine is a dominant brain neurotransmitter that regulates perception of welfare *via* the balancing of D1/D2 receptors [17, 18]. The combination of dopamine as well as additional neurotransmitters like serotonin, neuropeptides, and other dominant brain enzymes is responsible for producing this sense of well being. For example, decreased levels of serotonin are connected to episodes of depression.

Opioids in the reward circuitry of the brain are particularly connected to feelings of well being [19]. The multiplex of such neurotransmitters are produced in the brain and so are their receptors through transcription process involving mRNA [20]. We are cognizant that there are many associations of non-coding microRNAs (miRNAs) in all addictions.

It is known that miRNAs are small non-coding RNAs that function as translational repressors and represent an important element in cellular development as well as mental illness. MicroRNA sequences and their target sites in miRNAs reveal a degree of commonality across species. It has now been adequately researched and found that a single miRNA can recognize the 3'untranslated region of miRNAs in a sequence- specific manner to repress the protein expression of hundreds of targeted miRNAs. Most importantly, the human genome encodes more than 1000 miRNAs which effects over 60% of mammalian and human transcripts. Current data proposes that miRNAs control expression of mu opiate receptors and in fact it is known that an opiate agonist like morphine and fentanyl can alter specific miRNAs signaling as well. The interaction between specific miRNAs and opiates and their respective receptors will impact not only cell development, but analgesia, pain tolerance, and addiction [21]. He and Wang [22] suggested that the let- 7 family of miRNAs is a critical regulator of mu opiate receptor function in opioid tolerance.

Most *et al*. [23] has suggested that miRNA manipulation may cause cocaine-seeking behavior, reward processing of cocaine, and self-administration rates of alcohol – all addiction-related behaviors. It has been adequately shown that miR-212 causes a level of susceptibility in cocaine addiction. This is supported by a number of findings:

1) Compulsive cocaine-related behaviors are caused by increased miR-212 manifestation within the rat dorsal striatum; 2) increased miR-212 manifestation protects from cocaine addiction, because virus interference within striatal miR-212 reduces cocaine rat ingestion; 3) miR-212 has shown amplified striatal cAMP response element-binding protein (CREB) signaling *via* relevant pathways to activate Raf1 kinase; and 4) miR-212 regulates cocaine ingestion by inhibiting striatal delivery of methyl CpG binding protein 2 (MeCP2), lowered protein concentrations of brain-derived neurotrophic factor (BDNF) and potential alteration of dopamine release and therefore attenuates motivation for cocaine abuse [24].

Undoubtedly, cocaine, heroin, amphetamines, and alcohol promote continual neuroadaptive adjustments by increasing certain gene regulative pathways advancing towards addiction. The commonly known 'reward pathway,' or the synaptic elasticity of the mesolimbic dopaminergic

organization, is critical for drug dependence. Clearly, miR-16 creates flexibility in serotonin transporter construction; miR-133b is uniquely manifested within midbrain dopaminergic neurons, and controls the creation of tyrosine hydroxylase (rate-limiting enzyme) and the dopamine transporter; miR-212 influences creation of striatal brain-derived neurotrophic factor (BNDF) and synaptic elasticity following chronic cocaine abuse [25].

Understanding these basic facts and concepts provides a framework illustrating the realization that non-substance and substance related addictive behaviors along with a number of psychiatric illnesses such as major depression, schizophrenia and potentially bipolar disorder might have common anatomical and genetic antecedents. The importance here is to lay down some findings that reveal common shared neurogenetic and other structural brain elements that may be important for therapeutic targeting and relapse-prevention, in terms of drug and non-drug repetitive behaviors. In order for one to feel good the complex interaction of many genes and transcription processes of these particular genes, ultimately control the brain's dopaminergic actions within its reward center or mesolimbic center, or particularly the nucleus accumbens (NAc) and through resting state functional connectivity allows *Homo sapiens* to make good decisions deriving from frontal cortices activation.

NEUROCHEMICAL COMMONALITY OF SEEKING BEHAVIOR

As mentioned previously, RDS is currently evolving as the conventional understanding for the connections between impulsive, compulsive, and addictive behaviors, known as "process addictions" [26], in which Blum *et al*. [27] employed Bayes' theorem to forecast future substance-seeking and deviant behavior. Brain reward mechanisms in the mesolimbic system have played a role in the dopaminergic structure, and more so, the DRD2 gene. Deviant substance (drug, tobacco, alcohol, and food) pursuing actions can be attributes of D2 dopamine receptor dysfunction. Years of research since the initial findings of Blum's group [16] point to genetics playing a part in making an individual susceptible to substance pursuance. It is our suggestion that multiple alternatives of DRD2 A1 allele may serve as genetic factors in suspecting addiction (Blum *et al*. 1996). In this particular study, the anticipated assessment for those carrying the DRD2 Taq A1 allele and their future RDS actions was 74%. Many studies have taken a stand along with this report, maintaining the link between food craving and drug craving behavior *via* neuroimaging [28, 29].

The dopamine D2 receptor remains to be a major player in RDS behaviors, despite the involvement of other genes [30]. Johnson and Kenney observed compulsive feeding behavior only in obese rats, which was tracked *via* resistant food consumption to harshly habituated stimuli. In obese rates, striatal dopamine D2 receptors were down-regulated, as had been similarly described in humans experiencing addiction. Furthermore, the acceleration of the creation of reward deficiency and the start of eating compulsion in rats with availability to increased fatty food was caused by Lentivirus- mediated downfall of striatal D2 receptors. These data indicates that the overconsumption of food may cause similar addictive neuroadaptive responses in the brain's reward systems and pushes towards compulsive eating habits. The authors propose that obesity and drug addiction are related to common hedonic mechanisms [31].

It has been recognized that some researchers have found selective BDNF deficiency in a mouse ventromedial hypothalamus (VMH), which caused hyperphagic behavior and obesity. Cordeira *et al*. [32] observed ventral tegmental manifestation of BDNF and TrkB mRNA in wild-type mice, caused by the ingestion of appetizing, increased fatty foods.

Additionally, deficits in the nucleus accumbens (NAc) and dorsal striatum dopamine release and regular release in the NAc crux occurred after depletion of central BDNF in the brain slices of mice found in amperometric recordings. Lobo *et al*. [33] found that suppression of cocaine reward was activated by D2+ neurons, imitating TrkB loss, but occurred with contrasting effects prompted by D1+ neuron activation. These data allows further understanding of D1+ and D2+ neuronal activity molecular control and also the influence these cells have on cocaine reward.

The DRD2 is commonly correlated with hedonism, while the DRD2 A1 allele has been denoted as the reward gene [16]. Research indicates that a three-way collaboration occurs between deficiency of dopamine receptors, susceptibility to alcoholism, and decreased reward sensitivity. This relationship is dependent on individual genetic features, with specific ethnic groups having an increased propensity toward alcoholism compared to other groups [34]. DRD2 is a prominent component of neuropsychiatric disorders and conditions, as well as alcoholism and other addictions (PUBMED 3,886 articles obtained 4/18/15). The dopamine D2 gene, its receptor, including the TaqI A1 allele may also play a role in antisocial personality disorder, obesity, gambling, and analogous [4] characteristics such as high novelty seeking, and other psychiatric conditions [35]. The mesocorticolimbic dopaminergic pathway system often mediates the strengthening of drugs abused, and may very well take part in other addictions, including alcoholism [36].

RDS and its resulting drug pursuing behaviors are caused by the dysfunction of the mesocorticolimbic dopamine reward system (perhaps initiated by particular genetic variants). To reiterate, RDS indicates interruptions in the reward cascade and subsequent abnormal behaviors, all caused by genetic and environmental effects with the realization that all roads lead to dopamine [37]. Alcohol and other commonly abused drugs, including positive reinforcers, trigger the dopamine activation and neuronal release, which may reduce negative emotions and please unusual cravings. In the event of a D2 receptor deficiency or absence, predisposed persons are at an increased risk of several addictive, compulsive, and impulsive actions. While additional neurotransmitters (*e.g.*, gamma-aminobutyric acid (GABA), glutamate, and serotonin) can define rewarding and motivating ethanol effects, dopamine may be important for drug initiation and returning to drug use after prolonged abstinence [38].

REWARD GENES COMMONALITY FOR PRE-DISPOSITION TO ADDICTIVE BEHAVIORS AND DEPRESSION

Understanding the role of many neurotransmitter related genes and their interaction with respective receptors regulated by appropriate vesicle storage, synthesis and release mechanisms is tantamount to developing successful therapies. The realization that the chemical structure of various drugs of abuse is dissimilar and quite diverse, while the basic neurobiology of these substances has many similarities especially when RDS behaviors are considered. [11]. Since the early 90s, global research into the neurological and neurogenetic mechanisms and the interplay between many genes and the addictive process has paved the way for the development of accurate genetic tests to identify and provide risk stratification.

It is well accepted that neuropsychiatric disorders are considerabley hereditary, with support implying that these disorders have in common, a coinciding series of neuro-molecular and neuronal foundations. These disorders include attention deficit hyperactivity disorder (ADHD), autistic spectrum disorders (ASD), anxiety disorders (Anx), bipolar disorder (BD), depressive disorder (DD), and schizophrenia (SCZ) among others. Using GWAS studies, Lotan *et al*. [39] found the most common grouping of genes in five of six disorders included: ANK3, AS3MT, CACNA1C, CACNB2, CNNM2, CSMD1, DPCR1, ITIH3, NT5C2, PPP1R11, SYNE1, TCF4, TENM4, TRIM26, and ZNRD1. Together, these genetic factors are responsible for 20-30% of the genetic load. However, in a recent meta –analysis conducted by Gatt *et al*. [40] considering the same set of psychiatric disorders as Lotan *et al*. [39] they found 13 genetic variants were mutually shared among multiple disorders (APOE e4, ACE Ins/Del, BDNF Val66Met, COMT Val158Met, DAOA G72/G30 rs3918342, DAT1 40-bp, DRD4 48-bp, HTR1A C1019G, MTHR C677T, MTHR A1298C, SLC6A4 5-HTTLPR, SLC6A4 VNTR and TPH1 218A/C).

While the above seems relevant for psychiatric disorders excluding addiction, others have suggested other shared candidate genes. Levran *et al*. [41] evaluated 801 African Americans and the relationship between 98 individual nucleotide polymorphisms and 13 dopamine-linked genes occurring with heroin addiction (OD) and/or cocaine addiction (CD). They found separate-marker analyses rendered important indications for connections of 24 SNPs in DRD1, ANKK1/DRD2, DRD3, DRD5, DBH, DDC, COMT and CSNK1E. A DRD2 7-SNPs haplotype that contained SNPs rs1075650 and rs2283265, observed as modifying D2S/D2L merging, was specified in both dependencies. The COMT Val158Met allele was correlated to defense from OD. This finding was not significant following multiple testing and while it suggests the importance of these candidate genes, appropriate utilization of a very specific set of alleles maybe causing the loss of significance. According to Li *et al* [42] their products demonstrated that amphetamine feedback, diabetes mechanisms, dopamine receptors, energy metabolism, glucose control of insulin release, locomotor behaviors, mitochondrial electron transport, negative control of cell movement, NGF signaling, respiratory electron transport chain, signal transduction, synaptic transmission, are responsible for addictive behaviors and provide information regarding shared genetics. Along similar lines Levey *et al* [43] employed the translational Convergent Functional Genomics (CFG) in order to identify the alcoholism genes *via* gene combination of a Genome-Wide Association Study (GWAS) data taken from German alcoholic population as well as alcoholism from USA samples. While they found only nominal significance in the German cohort, when they chose the top CFG genes – eleven has a nominal significance in terms of predicting alcoholism ($P < 0.041$). The main CFG alcoholism gene from the first discovery stage, synuclein alpha (SNCA) [helps regulate dopamine] stayed as the initial gene even after stress-sensitive animal model cross-verification. Following extensive research Levey *et al* [43] correctly suggested that the compelling genetic overlay with other neuropsychiatric disorders provided a foundation for comorbidity and dual examination, and as such, introduces alcoholism in a greater background of modifying the psychological panorama, which includes RDS.

In addition Pearson-Fuhrhop *et al*. [44] were able to link a number of dopamine genes and associated polymorphisms to depression risk. In their study, five genes with functional polymorphisms were identified in synaptic dopamine possibility (COMT and DAT) were combined together with dopamine receptor binding (DRD1, DRD2, DRD3) to create a genetic risk score. They found that depression evidence ($\beta = -0.80$, $p = 0.003$), with decreased dopamine genetic addiction risk scores (signifying reduced dopaminergic neurotransmission), was related to the genetic addiction risk score overall, forecasting increased levels of depression. Importantly, they suggest that sequential difference appearing in several genes that control dopamine neurotransmission can effect depressive symptoms, especially in terms of addiction. This work is in agreement with Blum's group in unpublished studies showing that a very specific panel of reward genes and associated risk alleles causing a hypo-dopaminergic trait significantly predicted Addiction Severity Index (ASI –Media Version) for both alcoholism ($p < .004$) and drugs ($P < 0.05$).

ABNORMALITIES OF NEUROANATOMICAL STRUCTURES ACROSS RDS CONDITIONS

We are entering a new era of genomic medicine and neuroimaging and as such our understanding of brain functions especially as it relates to mental illness remarkably is providing new fundamental answers to age old questions of "Nature (neurogenetics) vs. Nurture (neuro epigenetics)." Most recently, Goodkind *et al*. [45] provided some important answers related to the fact that while psychiatric examinations are determined by groups of distinct symptoms, genetic and clinical investigations locate comparisons across a large range of diagnoses. This new work suggests that familiar neurobiological substrates can occur in different mental conditions. Specifically, they found a voxel-based morpho-metry meta-analysis of 193 studies composed of 15,892 subjects across 6 different diagnostic bodies (addiction, anxiety, bipolar disorder, depression, obsessive-compulsive disorder, and schizophrenia), in which loss of gray matter

met across diagnoses in 3 brain areas: the dorsal anterior cingulate, left insula, and right insula. Further work from their laboratory also found that decreased gray matter was correlated to poor executive functioning. Goodkind *et al*. [5] have found an important hallmark network revealing that across psychiatric diagnoses there is a commonality of abnormalities associated with an anterior insula/dorsal anterior cingulate-based system, which may reveal deficiency of executive functions seen across diagnoses including complex RDS behaviors [45].

Other works from Oscar-Berman's group support these concepts and show the commonality of brain volume abnormalities in both smoking and alcoholism. Specifically, Luhar *et al*. [46] provided clear evidence linking brain irregularities and poor performance on neuropsychological exams to alcoholism and smoking (separately and together). They show that compared to non-smoking/non-alcoholics, smoking alcoholics had a number of volumetric brain abnormalities: the amygdala, lateral ventricle, pallidum, parahippocampal and temporal pole areas, pre- and para-central frontal cortical areas, rostral middle frontal white matter, ventral diencephalic region. One primary issue related to these significant findings is that carriers of brain volume abnormalities show reduced executive function and decision-making abilities, which could impact both drug and non-drug seeking addictive behaviors and subsequent relapse. Other work from Ruiz *et al* [47] revealed that effects of alcohol particularly on white matter and ventricular volumes are gender distinctive, with alcoholic females exhibiting the most change in frontal, temporal, ventricular, and corpus callosum regions, while males exhibited responses primarily in the corpus callosum.

This work has been highlighted because in that in any given year, nearly 20% of Americans exhibit symptoms that meet criteria for a psychiatric illness diagnosis. The goal is to shift the emphasis from symptomatology to neuropsychiatric trajectories involving etiological genetic mechanisms, epigenetics and genomic-based solutions especially in children [48].

NEUROGENETICS OF RELAPSE

Homo *sapiens* are physiologically and biologically motivated to engage in behavior resulting in pleasure, such as gluttony, consumption of alcohol, and sexual intercourse. Abnormal impairment of these behavioral inclinations results in impulsive, compulsive, and addictive behaviors further dictated by genetic predispositions. While there are a variety of genetic variations that control mesolimbic activity, polymorphisms of the serotonergic-2A receptor (5-HTT2a), dopamine D2 receptor (DRD2), and the Catechol-o-methyl–transferase (COMT), GABA receptors (A, B Units) and many other genetic combinations predispose individuals to increased compulsive cravings and similar impulses that precede relapse.

Understanding the neurogenetics of relapse from all addictive behaviors will be most beneficial clinically and could provide new therapeutic targets to prevent reinstatement of drug and non-drug seeking behavior. One avenue of investigation in this arena involves dopaminergic genetics. Alcoholism associated with the TaqIA polymorphism of the dopamine D2 receptor (DRD2) gene has been closely observed [16], and the TaqI A1 allele appears to be over-represented in alcohol-dependent individuals [49, 50]. This allele is also linked to a significantly higher mortality rate of individuals who abuse alcohol [51]. Dahlgren *et al*. [52] found that 89% (16/18) of carriers of the A1 allele reported relapse, in contrast to 53% (17/32) of non-carriers ($P = 0.01$; odds ratio = 7.1). They suggested that despite this small number and the first report, an increased relapse rate associated with the Taq1 allele seems likely. Other work revealed that in terms of nicotine dependence that other dopaminergic genes such as the dopamine –beta – hydro-xylase gene (rs1541333) has also been tied to relapse [53].

There are numerous studies involving many reward genes across many drugs of abuse and subsequent clinical outcomes relative to relapse behavior [54-62]. Similarly, others have discussed the possible role of specific genes (such as the DRD2 and associated polymorphisms) as a potential cause for relapse, expanding their view to define a psychological basis for such relapse impacted by genetic antecedents [63]. Others have discussed similar genetic antecedents concerning gambling behavior as well [64].

With this new information are we in a position to provide a genomic-based solution to impact relapse behavior in a clinically meaningful way. The answers may reside in embracing a nutrigenomic approach.

DOPAMINERGIC ACTIVATION THROUGH NUTRI-GENOMICS

There is much research on utilizing nutritional therapy to RDS-related health consequences. However, there is significantly less exploration in research on biochemical control of neurotransmitters within the neural reward system and genetic polymorphic identification [65]. Li *et al*. [66] integrated 2,343 items of evidence from peer-reviewed publications from 1976 to 2006 that linked specific genes and respective chromosomal regions to addiction by single-gene strategies microarray, proteomics, or genetic studies. In these studies, Li *et al*. (2008) found 1,500 human addiction-related genes and created the first molecular database of its kind for addiction-related genes, KARG (http://karg.cbi.pku.edu.cn). Li *et al*. (2008) then showed a meta-analysis of 396 genes supported by at least 2 evidence items to identify 18 molecular pathways, covering both upstream and downstream signaling events. Five molecular pathways for four different categories of addictive substances were identified as common mechanisms that may be components of shared reward and addictive behavior. Among the five pathways were two new mechanisms: the GnRH signaling pathway and gap junction. These two pathways were formulated into a potential molecular network of addictive behavior and they observed that both fast and slow positive feedback loops are linked through CAMKII, which could explain the irreversible aspects of addiction. Notably this motif centers around dopaminergic and glutaminergic genes. Indeed, the dopamine molecule propagates behavioral responses of pleasure and stress-induced coping mechanisms.

In light of this evidence, we wanted to evaluate the process of DNA-manipulation in diet and nutrition-based solution wellness and weight management. This study genotyped 1,058 individuals who were administered with a patented nutraceutical based on polymorphic outcomes. In a subset- simple t -tests comparing a number of parameters before and 80 days after nutraceutical were performed. There were notable results for weight loss, appetite suppression, snack reduction, decreased sugar cravings, decreased late night eating (all $P<0.01$), increased perception of overeating, improved sleep quality, increased happiness (all $P<0.05$), and improved energy ($P<0.001$). Polymorphic correlates for specific genes were obtained (LEP, PPAR-gamma2, and MTHFR, 5-HT2A, and DRD2 genes) with positive clinical parameters. Of these results and polymorphisms, only the DRD2 gene polymorphism (A1 allele) demonstrated a significant Pearson correlation with treatment days ($r=0.42$, $P=0.045$) This two -fold increase is a critical genotype for compliance in treatment [67].

FUTURE PERSPECTIVES

Decades of peer-reviewed and established research on the mesolimbic system have shed light on the mechanics of the addictive brain and other underlying neurogenetic dispositions. The mesolimbic system is the site of the brain in which sensations of pleasure, perceived happiness and well-being occur [68] and has been appropriately named, the "reward center." Chemical messengers such as enkephalins, GABA and dopamine (DA), combine to release DA at the n. accumbens (NAc). It has been established that genes dictate the synthesis, storage, metabolism, receptor formation and neurotransmitter catabolism. Certain polymorphic variations may lead to an impairment of neurophysiologic events leading to the release of DA. This event series of is referred to as the "Brain Reward Cascade" [15, 69]. The disruption of this cascade can ultimately precede a dysregulation and/or dysfunction of DA. Any impairment in the function of DA, the "pleasure molecule" and "anti-stress molecule," may result in reward deficiency and subsequent aberrant substance-seeking behavior.

In a number of articles we have suggested a novel approach that could have clinical importance called "Reward Deficiency Solution System™" [70] and provided rationale for the coupling of genetic testing [71], exploration of various treatment approaches utilizing Comprehensive Analysis of reported Drugs (CARD) ™ [72] and incorporation of a genomic-based putative dopaminergic agonist KB220z that has been shown to restore resting state functional connectivity in abstinent heroin addicts [73]. Two major therapeutic platforms involving anti-drug vaccines [74] and gene therapy [75] have also been recently addressed with cautious consideration.

We are cognizant that research in the Recovery field, in general, has revealed poor outcomes, notably in relapse prevention and continued drug-seeking behavior [17]. Furthermore, Blum and Gold [17] proposed a new precedent in clinical care and aftercare that incorporates genetic testing to identify risk alleles together with D2 receptor stimulation using a neuroadatogen amino acid precursor enkephalinase-catecholamine-methyltransferase (COMT) inhibition therapy. This method, which is both natural and therapeutic, may induce dopamine release, potentially resulting in the induction of D2-directed mRNA and enhanced proliferation of D2 receptors. Blum and Gold further hypothesized that the proliferation of D2 receptors in turn will induce the diminishing of drug-seeking behavior. Pharmacological methods have demonstrated limited success because such agents are focused solely on the maintenance or interference of feelings of pleasure or euphoria post drug use rather than the individuals' existing dopamine system deficits. Future neuro-imaging studies may confirm these patterns, though recent studies propose a variety of potential therapeutic approaches including the targeting of the heteromeric A (2A)-D (2) receptor complex [76].

UNDERSTANDING COMMON THERAPEUTIC TARGETS AND ISSUES

In terms of future targets to prevent cocaine relapse for example, it is well known that the reinforcing and rewarding properties of cocaine are attributed to its ability to increase dopaminergic transmission in NAc. Moreover, this action reinforces drug taking and seeking and leads to long-lasting associations between the rewarding effects of the drug and the cues associated with its availability. One important key to preventing relapse is to target dopamine receptors in the NAc. Dopamine produces these effects by controlling the activity of two subpopulations of NAc medium spiny neurons (MSNs) that are defined by their predominant expression of either dopamine D1 or D2 receptors. Research has demonstrated that optogenetically stimulating D1 MSNs promotes reward, whereas stimulating D2 MSNs produces aversion or attenuation of drug seeking. It is believed that acute administration of cocaine stimulates D1 receptors and promotes reward. However, chronic cocaine exposure deregulates these D1 signals to both prevent extinction and facilitate reinstatement of drug seeking to drive relapse. These data elucidate the responses of D1- and D2-type MSNs in NAc to acute cocaine and during the formation of context-reward associations and define how prior cocaine exposure selectively deregulates D1 signaling to drive relapse [77].

In addition, it has been discovered by Epstein's group that carriers of the Met/Met genotype of the COMT gene had a greater intensity of the novelty-seeking trait than carriers of the Val/Val and Val/Met genotypes, though this association was seen only in women. Furthermore, the presence of the C allele of the DRD4 gene in carriers of the Met/Met genotype showed high levels of extraversion and hypomania [78]. Other work by Noble's group observed that total Novelty Seeking score of the Tridimensional Personality Questionnaire (TPQ) was significantly higher in boys having, in common, all three minor (A1, B1, and Intron 6 1) alleles of the DRD2 compared to boys without any of these alleles. Additionally, boys with the DRD4 7 repeat (7R) allele also had a significantly higher Novelty Seeking score than those without this allele. Finally, the combined DRD2 and DRD4 polymorphisms contribute more markedly to this behavior than when these two gene polymorphisms are individually considered [79].

Importantly, a number of studies have suggested that DRD2/ANKK1 TaqIA genotype predicted smoking initiation and subsequent use [80]. In fact, Doran *et al*. [80] showed that logistic regression indicated that the A1 allele was associated with initiation (p = .003). This effect was partially mediated by sensation seeking and negative urgency. This takes on even more significant meaning when you consider the work of others [52] showing that DRD2/ ANKK1 TaqIA genotype A1 allele was high in subjects who relapsed with alcohol compared to A2 carriers. In addition, Iordanidou *et al*. [81] showed significant association between 5-HT (2C) receptor gene polymorphisms and smoking initiation in male Caucasian subjects, but not in all races tested. Work by Grzywacz *et al*. [82] further confirm statistically significant associations between SNP in exon 8 A/G in the DRD2 gene and alcohol withdrawal syndrome with seizures, and between SNP in promoter -141 C I/D in the DRD2 gene and early onset of alcohol dependence (AD). Specifically, the A/A genotype in the exon 8 A/G polymorphism is a positive predictive factor for the presence or the lack of seizures in alcohol withdrawal syndrome. The A/G genotype is possibly a protective factor for this AD phenotype. The authors suggest that dopamine receptor 2 gene polymorphisms are associated with alcohol addiction and alcohol withdrawal syndrome. These results provide rationale for therapeutic intervention.

Another important issue is how to treat RDS behaviors that are drug and non-drug related. There are those who support the view that the best approach to treat RDS is to attenuate the release and function of dopamine. This would include substances that act as antagonists of dopamine function like naloxone/naltrexone and others approved by the FDA as Medication Assisted Treatments (MATs) [83]. For the most part, MATs and/or antagonists of the dopamine system have systematically failed [84]. In terms of RDS patients having low dopamine tone, there are a number of studies involving measurement of tonic dopamine in cocaine addicts [85] and resting state dopamine tone in ADHD [86]. In the former case, it has been shown that as dopamine is reduced, there is escalation of cocaine abuse [85]. In the latter case, it has been shown that the dopamine tone in ADHD is reduced compared to non-ADHD controls [86]. There is also evidence that the drug Modafinil, a substance that acts as a selective, relatively weak, atypical dopamine reuptake inhibitor, has been shown to modulate dopaminergic transmission and produce enhanced reward- related brain activity in the NAc in healthy subjects. While there have been some positive effects especially with nicotine dependence, it has abuse liability [87]. Additionally, we believe that the popular GABA promoting drugs like Topiramate should not be used in the long-term because of possible attenuated dopamine release and suicide ideation [88]. The proposal herein is to promote long-term "dopamine homeostasis" [89].

There are a plethora of studies showing the relationship of many behavioral addictions and reward deficiency. One example involves the work of Han *et al*. [90, 91] showing that both alcohol dependence (AD) and Internet Gaming Disorder (IGD) subjects have positive functional connectivity between the dorsolateral prefrontal cortex (DLPFC), cingulate, and cerebellum. In addition, both groups have negative functional connectivity between the DLPFC and the orbitofrontal cortex. However, the AD subjects have positive functional connectivity between the DLPFC, temporal lobe, and striatal areas, while IGD subjects have negative functional connectivity between the DLPFC, temporal lobe, and striatal areas. Understanding these differences may provide important differential therapeutic targets.

CONCLUSION

It is known that specific drugs of abuse and neuropathways link up in the genome to effect miRNA biological functioning in its relation to neurotransmission, enzymes that take part in neurotransmitter metabolism, and particular neuronal receptors known for inducing feelings of well-being in human and nonhuman animals alike [92]. Dopaminergic alteration and manipulation of direct striatonigral and indirect striatopallidal pathways in the basal ganglia are vital factors in rewarding and adverse patterns and drug addiction [93]. In order to determine how the basal ganglia processes and integrates data through these specific pathways, other researchers have created a reversible neurotransmission obstructive technique, in which pathway transmission is impeded by particular expressions of transmission-blocking tetanus toxin in a doxycycline- dependent approach [94]. These outcomes have shown that the synchronized variation of these pathways is imperative for dopamine-mediated acute psycho stimulant activity. Nonetheless, this variation has transferred its role between the direct pathway of reward feedback and cocaine stimulation and the indirect of aversive behavior. These two pathways therefore have two separate roles: the direct pathway is responsible for categorizing the appropriate rewarding stimuli from non-appropriate ones and the indirect pathway for increased memory formation in order to evade aversive stimuli. While we agree with this information, we also probe the role abused drugs have on mRNA within these pathways. This notion continues to be investigated by our laboratory and will hopefully become the subject of many future papers. However, we are indeed proposing a novel approach challenging the entire recovery field to incorporate the following: Genetic Addiction Risk Score (GARS) ™ for appropriate RDS diagnosis; CARD™ analysis to establish both agreement and self-restraint throughout treatment; Natural D2 Agonistic Therapy (NAAT-KB220™); mRNA to determine pre and post candidate gene expressions in RDS patients attending inpatient/out-patient treatment programs. We therefore propose a shift in clinical care to "Reward Deficiency Solutions System (RDSS) ™" [95].

CONFLICT OF INTEREST

Dr. Blum through his company Synaptamine owns U.S. and foreign patents on both nutraceuticals and genetic testing. The authors confirm that this article content has no other conflict of interest.

ACKNOWLEDGEMENTS

The authors appreciate the expert edits by Margaret A. Madigan and assistance of Jia A. Blum. We acknowledge the grants of Marcelo Febo, recipient of R01DA019946 and R21

DA038009, and Rajendra D. Badgaiyan supported by the National Institutes of Health grants www.ncbi.nlm.nih.gov/ 1R01NS073884.

REFERENCES

[1] Physiology or Medicine for 2000 - Press Release *Nobelprize.org. Nobel Media AB 2014. Web.* http://www.nobelprize.org/ nobelprizes/ medicine/laureates/2000/press.html, 2015 Apr6

[2] Fahn, S. The medical treatment of Parkinson disease from James Parkinson to George Cotzias. *Mov. Disord,* **2015**, *30*(1), 4-18. [http://dx.doi.org/10.1002/mds.26102] [PMID: 25491387]

[3] Kemp, D.E. Managing the side effects associated with commonly used treatments for bipolar depression. *J. Affect. Disord.,* **2014**, *169*(Suppl. 1), S34-S44. [http://dx.doi.org/10.1016/S0165-0327(14) 70007-2] [PMID: 25533913]

[4] Furukawa, T.A.; Levine, S.Z.; Tanaka, S.; Goldberg, Y.; Samara, M.; Davis, J.M.; Cipriani, A.; Leucht, S. Initial severity of schizophrenia and efficacy of antipsychotics: participant-level meta-analysis of 6 placebo-controlled studies. *JAMA Psychiatry,* **2015**, *72*(1), 14-21. [http://dx.doi.org/10.1001/jamapsychiatry. 2014. 2127] [PMID: 25372935]

[5] Goodkind, M.; Eickhoff, S.B.; Oathes, D.J.; Jiang, Y.; Chang, A.; Jones-Hagata, L.B.; Ortega, B.N.; Zaiko, Y.V.; Roach, E.L.; Korgaonkar, M.S.; Grieve, S.M.; Galatzer-Levy, I.; Fox, P.T.; Etkin, A. Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry,* **2015**, *72*(4), 305-315. [http://dx. doi.org/10.1001/jamapsychiatry.2014.2206] [PMID: 25651064]

[6] Blum, K. The effect of dopamine and other catecholamines on neuromuscular transmission. *Arch. Int. Pharmacodyn. Ther.,* **1969**, *181*(2), 297-306. [PMID: 4326551]

[7] Blum, K.; Calhoun, W.; Merritt, J.; Wallace, J.E. L-DOPA: effect on ethanol narcosis and brain biogenic amines in mice. *Nature,* **1973**, *242*(5397), 407-409. [http://dx.doi.org/10.1038/242407a0] [PMID: 4735636]

[8] Blum, K.; Eubanks, J.D.; Wallace, J.E.; Schwertner, H.A. Suppression of ethanol withdrawal by dopamine. *Experientia,* **1976**, *32*(4), 493-495. [http://dx.doi.org/10.1007/BF01920816] [PMID: 944645]

[9] Blum, K.; Wallace, J.E.; Schwerter, H.A.; Eubanks, J.D. Morphine suppression of ethanol withdrawal in mice. *Experientia,* **1976**, *32*(1),79-82. [http://dx.doi.org/10.1007/BF01932634] [PMID: 942927]

[10] Davis, V.E.; Walsh, M.J. Alcohol addiction and tetrahydro-papaveroline. *Science,* **1970**, *169*(3950), 1105-1106. [PMID: 5465179]

[11] Blum, K., Ed.; *Alcohol & Opiates: Neurochemical and Behavioral Actions*;

[12] Melchior, C.L.; Myers, R.D. Genetic differences in ethanol drinking of the rat following injection of 6-OHDA, 5,6-DHT or 5,7-DHT into the cerebral ventricles. *Pharmacol. Biochem. Behav.,* **1976**, *5*(1), 63-72. [http://dx.doi.org/10.1016/0091-3057(76)90289-6] [PMID: 996042]

[13] Dackis, C.A.; Gold, M.S. New concepts in cocaine addiction: the dopamine depletion hypothesis. *Neurosci. Biobehav. Rev.,* **1985**, *9*(3), 469-477. [http://dx.doi.org/10.1016/0149-7634(85)90022-3] [PMID: 2999657]

[14] Ng Cheong Ton, J.M.; Gerhardt, G.A.; Friedemann, M.; Etgen, A.M.; Rose, G.M.; Sharpless, N.S.; Gardner, E.L. The effects of delta 9-tetrahydrocannabinol on potassium-evoked release of dopamine in the rat caudate nucleus: an *in vivo* electrochemical and *in vivo* microdialysis study. *Brain Res.,* **1988**, *451*(1-2), 59-68. [http://dx.doi.org/10.1016/0006-8993(88)90749-4] [PMID: 2855215]

[15] Blum, K.; Kozlowski, G.P. Ethanol and neuromodulator interactions: a cascade model of reward. *Prog. Alcohol Res.,* **1990**, *2*, 131-149.

[16] Blum, K.; Noble, E.P.; Sheridan, P.J.; Montgomery, A.; Ritchie, T.; Jagadeeswaran, P.; Nogami, H.; Briggs, A.H.; Cohn, J.B. Allelic association of human dopamine D2 receptor gene in alcoholism. *JAMA,* **1990**, *263*(15), 2055-2060. [http://dx.doi.org/10.1001/jama. 1990.03440150063027] [PMID: 1969501]

[17] Blum, K.; Gold, M.S. Neuro-chemical activation of brain reward meso-limbic circuitry is associated with relapse prevention and drug hunger: a hypothesis. *Med. Hypotheses,* **2011**, *76*(4), 576-584. [http://dx.doi.org/10.1016/j.mehy.2011.01.005] [PMID: 21306831]

[18] Park, K; Volkow, ND; Pan, Y; Du, C Chronic cocaine dampens dopamine signaling during cocaine intoxication and unbalances D1 over D2 receptor signaling. *J. Neurosci.,* **2013**, *33*(40), 15827-36. [http://dx.doi.org/10.1523/JNEUROSCI.1935-13.2013]

[19] Pierce, R.C.; Kumaresan, V. The mesolimbic dopamine system: the final common pathway for the reinforcing effect of drugs of abuse? *Neurosci. Biobehav. Rev.,* **2006**, *30*(2), 215-238. [http://dx.doi.org/ 10.1016/j.neubiorev.2005.04.016] [PMID: 16099045]

[20] Eipper-Mains, J.E.; Eipper, B.A.; Mains, R.E. Global Approaches to the Role of miRNAs in Drug-Induced Changes in Gene Expression. *Front. Genet.,* **2012**, *3*, 109. [http://dx.doi.org/ 10.3389/fgene.2012.00109] [PMID: 22707957]

[21] Barbierato, M.; Zusso, M.; Skaper, S.D.; Giusti, P. MicroRNAs: emerging role in the endogenous μ opioid system. *CNS Neurol. Disord. Drug Targets,* **2015**, *14*(2), 239-250. [http://dx.doi.org/ 10.2174/1871527314666150116123932] [PMID: 25613510]

[22] He, Y; Wang, ZJ Let-7 microRNAs and Opioid Tolerance. *Front Genet,* **2012**, *3*, 110. eCollection 2012 [http://dx.doi.org/10.3389/ fgene.2012.00110]

[23] Most, D; Workman, E; Harris, RA Synaptic adaptations by alcohol and drugs of abuse: changes in microRNA expression and mRNA regulation. *Front. Mol. Neurosci.,* **2014**, *7*, 85. [http://dx.doi.org/ 10.3389/fnmol.2014.00085]

[24] Bali, P; Kenny, P.J. MicroRNAs and Drug Addiction. *Front Genet.,* **2013**, *4*, 43. [http://dx.doi.org/10.3389/fgene.2013.00043]

[25] Dreyer, J.L. New insights into the roles of microRNAs in drug addiction and neuroplasticity. *Genome Med.,* **2010**, *2*(12), 92. [http://dx.doi.org/10.1186/gm213] [PMID: 21205279]

[26] Smith, D.E. The process addictions and the new ASAM definition of addiction. *J. Psychoactive Drugs,* **2012**, *44*(1), 1-4. [http://dx. doi.org/10.1080/02791072.2012.662105] [PMID: 22641960]

[27] Blum, K.; Wood, R.C.; Braverman, E.R.; Chen, T.J.; Sheridan, P.J. The D2 dopamine receptor gene as a predictor of compulsive disease: Bayes' theorem. *Funct. Neurol.,* **1995**, *10*(1), 37-44. [PMID: 7649500]

[28] Burger, K.S.; Stice, E. Frequent ice cream consumption is associated with reduced striatal response to receipt of an ice cream-based milkshake. *Am. J. Clin. Nutr.,* **2012**, *95*(4), 810-817. [http://dx.doi.org/10.3945/ajcn.111.027003] [PMID: 22338036]

[29] Stice, E.; Yokum, S.; Blum, K.; Bohon, C. Weight gain is associated with reduced striatal response to palatable food. *J. Neurosci.,* **2010**, *30*(39), 13105-13109. [http://dx.doi.org/10.1523/ JNEUROSCI.2105-10.2010] [PMID: 20881128]

[30] Dunn, J.P.; Kessler, R.M.; Feurer, I.D.; Volkow, N.D.; Patterson, B.W.; Ansari, M.S.; Li, R.; Marks-Shulman, P.; Abumrad, N.N. Relationship of dopamine type 2 receptor binding potential with fasting neuroendocrine hormones and insulin sensitivity in human obesity. *Diabetes Care,* **2012**, *35*(5), 1105-1111. [http://dx.doi.org/ 10.2337/dc11-2250] [PMID: 22432117]

[31] Johnson, P.M.; Kenny, P.J. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nat. Neurosci.,* **2010**, *13*(5), 635-641. [http://dx.doi.org/10.1038/ nn.2519] [PMID: 20348917]

[32] Cordeira, J.; Rios, M. Weighing in the role of BDNF in the central control of eating behavior. *Mol. Neurobiol.,* **2011**, *44*(3), 441-448. [http://dx.doi.org/10.1007/s12035-011-8212-2] [PMID: 22012072]

[33] Lobo, M.K.; Covington, H.E., III; Chaudhury, D.; Friedman, A.K.; Sun, H.; Damez-Werno, D.; Dietz, D.M.; Zaman, S.; Koo, J.W.; Kennedy, P.J.; Mouzon, E.; Mogri, M.; Neve, R.L.; Deisseroth, K.; Han, M.H.; Nestler, E.J. Cell type-specific loss of BDNF signaling mimics optogenetic control of cocaine reward. *Science,* **2010**, *330*(6002), 385-390. [http://dx.doi.org/10.1126/science.1188472] [PMID: 20947769]

[34] Barr, C.L.; Kidd, K.K. Population frequencies of the A1 allele at the dopamine D2 receptor locus. *Biol. Psychiatry,* **1993**, *34*(4), 204-209. [http://dx.doi.org/10.1016/0006-3223(93)90073-M] [PMID: 8399816]

[35] Palomo, T.; Archer, T.; Kostrzewa, R.M.; Beninger, R.J. Comorbidity of substance abuse with other psychiatric disorders. *Neurotox. Res.,* **2007**, *12*(1), 17-27. [http://dx.doi.org/10.1007/ BF03033898] [PMID: 17513197]

[36] Blum, K.; Sheridan, P.J.; Wood, R.C.; Braverman, E.R.; Chen, T.J.; Comings, D.E. Dopamine D2 receptor gene variants: association and linkage studies in impulsive-addictive-compulsive behaviour. *Pharmacogenetics,* **1995**, *5*(3), 121-141. [http://dx.doi.org/10.1097/00008571-199506000-00001] [PMID: 7550364]

[37] Blum, K.; Chen, A.L.; Giordano, J.; Borsten, J.; Chen, T.J.; Hauser, M.; Simpatico, T.; Femino, J.; Braverman, E.R.; Barh, D. The addictive brain: all roads lead to dopamine. *J. Psychoactive Drugs,* **2012**, *44*(2), 134-143. [http://dx.doi.org/10.1080/02791072.2012.685407] [PMID: 22880541]

[38] Wang, G.J.; Smith, L.; Volkow, N.D.; Telang, F.; Logan, J.; Tomasi, D.; Wong, C.T.; Hoffman, W.; Jayne, M.; Alia-Klein, N.; Thanos, P.; Fowler, J.S. Decreased dopamine activity predicts relapse in methamphetamine abusers. *Mol. Psychiatry,* **2012**, *17*(9), 918-925. [http://dx.doi.org/10.1038/mp.2011.86] [PMID: 21747399]

[39] Lotan, A; Fenckova, M; Bralten, J; Alttoa, A; Dixson, L; Williams, RW; van der Voet, M. Neuroinformatic analyses of common and distinct genetic components associated with major neuropsychiatric disorders. *Front Neurosci.,* **2014**, *6*, 8-331. eCollection 2014 [http://dx.doi.org/10.3389/fnins.2014.00331]

[40] Gatt, J.M.; Burton, K.L.; Williams, L.M.; Schofield, P.R. Specific and common genes implicated across major mental disorders: a review of meta-analysis studies. *J. Psychiatr. Res.,* **2015**, *60*, 1-13. [http://dx.doi.org/10.1016/j.jpsychires.2014.09.014] [PMID: 25287955]

[41] Levran, O.; Randesi, M.; da Rosa, J.C.; Ott, J.; Rotrosen, J.; Adelson, M.; Kreek, M.J. Overlapping dopaminergic pathway genetic susceptibility to heroin and cocaine addictions in African Americans. *Ann. Hum. Genet.,* **2015**, *79*(3), 188-198. [http://dx.doi.org/10.1111/ahg.12104] [PMID: 25875614]

[42] Li, Z.H.; Liu, Y.F.; Li, K.N.; Duanmu, H.Z.; Chang, Z.Q.; Li, Z.Q.; Zhang, S.Z.; Xu, Y. Analysis of functional and pathway association of differential co-expressed genes: a case study in drug addiction. *J. Biomed. Inform.,* **2012**, *45*(1), 30-36. [http://dx.doi.org/10.1016/j.jbi.2011.08.014] [PMID: 21907308]

[43] Levey, D.F.; Le-Niculescu, H.; Frank, J.; Ayalew, M.; Jain, N.; Kirlin, B.; Learman, R.; Winiger, E.; Rodd, Z.; Shekhar, A.; Schork, N.; Kiefer, F.; Wodarz, N.; Müller-Myhsok, B.; Dahmen, N.; Nöthen, M.; Sherva, R.; Farrer, L.; Smith, A.H.; Kranzler, H.R.; Rietschel, M.; Gelernter, J.; Niculescu, A.B. Genetic risk prediction and neurobiological understanding of alcoholism. *Transl. Psychiatry,* **2014**, *4*, e391. [http://dx.doi.org/10.1038/tp.2014.29] [PMID: 24844177]

[44] Pearson-Fuhrhop, K.M.; Dunn, E.C.; Mortero, S.; Devan, W.J.; Falcone, G.J.; Lee, P.; Holmes, A.J.; Hollinshead, M.O.; Roffman, J.L.; Smoller, J.W.; Rosand, J.; Cramer, S.C. Dopamine genetic risk score predicts depressive symptoms in healthy adults and adults with depression. *PLoS One,* **2014**, *9*(5), e93772. [http://dx.doi.org/10.1371/journal.pone.0093772] [PMID: 24834916]

[45] Kember, R.L.; Georgi, B.; Bailey-Wilson, J.E.; Stambolian, D.; Paul, S.M.; Bućan, M. Copy number variants encompassing Mendelian disease genes in a large multigenerational family segregating bipolar disorder. *BMC Genet.,* **2015**, *16*(1), 27. [http://dx.doi.org/10.1186/s12863-015-0184-1] [PMID: 25887117]

[46] Luhar, R.B.; Sawyer, K.S.; Gravitz, Z.; Ruiz, S.M.; Oscar-Berman, M. Brain volumes and neuropsychological performance are related to current smoking and alcoholism history. *Neuropsychiatr. Dis. Treat.,* **2013**, *9*, 1767-1784. [http://dx.doi.org/10.2147/NDT.S52298] [PMID: 24273408]

[47] Ruiz, S.M.; Oscar-Berman, M.; Sawyer, K.S.; Valmas, M.M.; Urban, T.; Harris, G.J. Drinking history associations with regional white matter volumes in alcoholic men and women. *Alcohol. Clin. Exp. Res.,* **2013**, *37*(1), 110-122. [http://dx.doi.org/10.1111/j.1530-0277.2012.01862.x] [PMID: 22725728]

[48] Insel, T.R. Mental disorders in childhood: shifting the focus from behavioral symptoms to neurodevelopmental trajectories. *JAMA,* **2014**, *311*(17), 1727-1728. [http://dx.doi.org/10.1001/jama.2014.1193] [PMID: 24794359]

[49] Berggren, U.; Fahlke, C.; Aronsson, E.; Karanti, A.; Eriksson, M.; Blennow, K.; Thelle, D.; Zetterberg, H.; Balldin, J. The taqI DRD2 A1 allele is associated with alcohol-dependence although its effect size is small. *Alcohol Alcohol.,* **2006**, *41*(5), 479-485. [http://dx.doi.org/10.1093/alcalc/agl043] [PMID: 16751215]

[50] Gullo, M.J.; St John, N.; McD Young, R.; Saunders, J.B.; Noble, E.P.; Connor, J.P.; Connor, J.P. Impulsivity-related cognition in alcohol dependence: Is it moderated by DRD2/ANKK1 gene status and executive dysfunction? *Addict. Behav.,* **2014**, *39*(11), 1663-1669. [http://dx.doi.org/10.1016/j.addbeh.2014.02.004] [PMID: 24629326]

[51] Berggren, U.; Fahlke, C.; Berglund, K.J.; Wadell, K.; Zetterberg, H.; Blennow, K.; Thelle, D.; Balldin, J. Dopamine D2 receptor genotype is associated with increased mortality at a 10-year follow-up of alcohol-dependent individuals. *Alcohol Alcohol.,* **2010**, *45*(1), 1-5. [http://dx.doi.org/10.1093/alcalc/agp041] [PMID: 19654188]

[52] Dahlgren, A.; Wargelius, H.L.; Berglund, K.J.; Fahlke, C.; Blennow, K.; Zetterberg, H.; Oreland, L.; Berggren, U.; Balldin, J. Do alcohol-dependent individuals with DRD2 A1 allele have an increased risk of relapse? A pilot study. *Alcohol Alcohol.,* **2011**, *46*(5), 509-513. [http://dx.doi.org/10.1093/alcalc/agr045] [PMID: 21613303]

[53] Leventhal, A.M.; Lee, W.; Bergen, A.W.; Swan, G.E.; Tyndale, R.F.; Lerman, C.; Conti, D.V. Nicotine dependence as a moderator of genetic influences on smoking cessation treatment outcome. *Drug Alcohol Depend.,* **2014**, *138*, 109-117. [http://dx.doi.org/10.1016/j.drugalcdep.2014.02.016] [PMID: 24667010]

[54] Bannon, M.J.; Johnson, M.M.; Michelhaugh, S.K.; Hartley, Z.J.; Halter, S.D.; David, J.A; Kapatos, G.; Schmidt, C.J. A molecular profile of cocaine abuse includes the differential expression of genes that regulate transcription, chromatin, and dopamine cell phenotype. *Neuropsychopharmacology.,* **2014**, *39*(9),2191-2199.

[55] Di Ciano, P.; Grandy, D.K.; Le Foll, B. Dopamine D4 receptors in psychostimulant addiction. *Adv. Pharmacol.,* **2014**, *69*, 301-321. [http://dx.doi.org/10.1016/B978-0-12-420118-7.00008-1] [PMID: 24484981]

[56] Loweth, J.A.; Scheyer, A.F.; Milovanovic, M.; LaCrosse, A.L.; Flores-Barrera, E.; Werner, C.T.; Li, X.; Ford, K.A.; Le, T.; Olive, M.F.; Szumlinski, K.K.; Tseng, K.Y.; Wolf, M.E. Synaptic depression *via* mGluR1 positive allosteric modulation suppresses cue-induced cocaine craving. *Nat. Neurosci.,* **2014**, *17*(1), 73-80. [http://dx.doi.org/10.1038/nn.3590] [PMID: 24270186]

[57] Schank, J.R.; King, C.E.; Sun, H.; Cheng, K.; Rice, K.C.; Heilig, M.; Weinshenker, D.; Schroeder, J.P. The role of the neurokinin-1 receptor in stress-induced reinstatement of alcohol and cocaine seeking. *Neuropsychopharmacology,* **2014**, *39*(5), 1093-1101. [http://dx.doi.org/10.1038/npp.2013.309] [PMID: 24173499]

[58] Xu, K.; Seo, D.; Hodgkinson, C.; Hu, Y.; Goldman, D.; Sinha, R. A variant on the kappa opioid receptor gene (OPRK1) is associated with stress response and related drug craving, limbic brain activation and cocaine relapse risk. *Transl. Psychiatry,* **2013**, *3*, e292. [http://dx.doi.org/10.1038/tp.2013.62] [PMID: 23962922]

[59] Xu, K.; Seo, D.; Hodgkinson, C.; Hu, Y.; Goldman, D.; Sinha, R. Antecedents and consequences of drug abuse in rats selectively bred for high and low response to novelty. *Neuropharmacology,* **2013**, *76*(Pt B), 425-36.

[60] Miguéns, M.; Botreau, F.; Olías, O.; Del Olmo, N.; Coria, S.M.; Higuera-Matas, A.; Ambrosio, E. Genetic differences in the modulation of accumbal glutamate and γ-amino butyric acid levels after cocaine-induced reinstatement. *Addict. Biol.,* **2013**, *18*(4), 623-632. [http://dx.doi.org/10.1111/j.1369-1600.2011.00404.x] [PMID: 22004520]

[61] Blum, K.; Oscar-Berman, M.; Jacobs, W.; McLaughlin, T.; Gold, M.S. Buprenorphine Response as a Function of Neurogenetic Polymorphic Antecedents: Can Dopamine Genes Affect Clinical Outcomes in Reward Deficiency Syndrome (RDS)? *J. Addict. Res. Ther.,* **2014**, *5*, 1000185. [http://dx.doi.org/10.4172/2155-6105.1000185] [PMID: 25664200]

[62] Ujike, H.; Katsu, T.; Okahisa, Y.; Takaki, M.; Kodama, M.; Inada, T.; Uchimura, N.; Yamada, M.; Iwata, N.; Sora, I.; Iyo, M.; Ozaki, N.; Kuroda, S. Genetic variants of D2 but not D3 or D4 dopamine receptor gene are associated with rapid onset and poor prognosis of methamphetamine psychosis. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2009**, *33*(4), 625-629. [http://dx.doi.org/10.1016/j.pnpbp.2009.02.019] [PMID: 19275926]

[63] Balldin, J.; Berggren, U.; Berglund, K.; Fahlke, C. [Why some people relapse in alcohol dependence. There is a relation to a specific gene variant in the dopamine system and to psychology]. *Lakartidningen,* **2013**, *110*(1-2), 21-23. [PMID: 23373179]

[64] Gyollai, A.; Griffiths, M.D.; Barta, C.; Vereczkei, A.; Urbán, R.; Kun, B.; Kökönyei, G.; Székely, A.; Sasvári-Székely, M.; Blum, K.; Demetrovics, Z. The genetics of problem and pathological gambling: a systematic review. *Curr. Pharm. Des.,* **2014**, *20*(25), 3993-3999. [http://dx.doi.org/10.2174/13816128113199990626] [PMID: 24001288]

[65] Blum, K.; Oscar-Berman, M.; Stuller, E.; Miller, D.; Giordano, J.; Morse, S.; McCormick, L.; Downs, W.B.; Waite, R.L.; Barh, D.; Neal, D.; Braverman, E.R.; Lohmann, R.; Borsten, J.; Hauser, M.; Han, D.; Liu, Y.; Helman, M.; Simpatico, T. Neurogenetics and Nutrigenomics of Neuro-Nutrient Therapy for Reward Deficiency Syndrome (RDS): Clinical Ramifications as a Function of Molecular Neurobiological Mechanisms. *J. Addict. Res. Ther.,* **2012**, *3*(5), 139. [PMID: 23926462]

[66] Li, C.Y.; Mao, X.; Wei, L. Genes and (common) pathways underlying drug addiction. *PLOS Comput. Biol.,* **2008**, *4*(1), e2. [http://dx.doi.org/10.1371/journal.pcbi.0040002] [PMID: 18179280]

[67] Blum, K.; Chen, A.L.; Chen, T.J.; Rhoades, P.; Prihoda, T.J.; Downs, B.W.; Waite, R.L.; Williams, L.; Braverman, E.R.; Braverman, D.; Arcuri, V.; Kerner, M.; Blum, S.H.; Palomo, T. LG839: anti-obesity effects and polymorphic gene correlates of reward deficiency syndrome. *Adv. Ther.,* **2008**, *25*(9), 894-913. [http://dx.doi.org/10.1007/s12325-008-0093-z] [PMID: 18781289]

[68] Satoshi Ikemoto Brain reward circuitry beyond the mesolimbic dopamine system: A neurobiological theory. *Neurosci. Biobehav. Rev., 35*(2), 129-150. [http://dx.doi.org/10.1016/j.neubiorev.2010.02.001]

[69] Koob, G.F. Neurocircuitry of alcohol addiction: synthesis from animal models. *Handb. Clin. Neurol.,* **2014**, *125*, 33-54. [http://dx.doi.org/10.1016/B978-0-444-62619-6.00003-3] [PMID: 25307567]

[70] Blum, K.; Febo, M.; McLaughlin, T.; Cronjé, F.J.; Han, D.; Gold, S.M. Hatching the behavioral addiction egg: Reward Deficiency Solution System (RDSS)™ as a function of dopaminergic neurogenetics and brain functional connectivity linking all addictions under a common rubric. *J. Behav. Addict.,* **2014**, *3*(3), 149-156. [http://dx.doi.org/10.1556/JBA.3.2014.019] [PMID: 25317338]

[71] Blum, K.; Oscar-Berman, M.; Demetrovics, Z.; Barh, D.; Gold, M.S. Genetic Addiction Risk Score (GARS): molecular neurogenetic evidence for predisposition to Reward Deficiency Syndrome (RDS). *Mol. Neurobiol.,* **2014**, *50*(3), 765-796. [http://dx.doi.org/10.1007/s12035-014-8726-5] [PMID: 24878765]

[72] Blum, K.; Han, D.; Femino, J.; Smith, D.E.; Saunders, S.; Simpatico, T.; Schoenthaler, S.J.; Oscar-Berman, M.; Gold, M.S. Systematic evaluation of "compliance" to prescribed treatment medications and "abstinence" from psychoactive drug abuse in chemical dependence programs: data from the comprehensive analysis of reported drugs. *PLoS One,* **2014**, *9*(9), e104275. [See comment in PubMed Commons below]. [http://dx.doi.org/10.1371/journal.pone.0104275] [PMID: 25247439]

[73] Blum, K.; Liu, Y.; Wang, W.; Wang, Y.; Zhang, Y.; Oscar-Berman, M.; Smolen, A.; Febo, M.; Han, D.; Simpatico, T.; Cronjé, F.J.; Demetrovics, Z.; Gold, M.S. rsfMRI effects of KB220Z™ on neural pathways in reward circuitry of abstinent genotyped heroin addicts. *Postgrad. Med.,* **2015**, *127*(2), 232-241. [http://dx.doi.org/10.1080/00325481.2015.994879] [PMID: 25526228]

[74] Blum, K.; Badgaiyan, R.D.; Anges, D.H.; Gold, M.S. Should We Embrace Vaccines for Treating Substance-Related Disorder, A Subset of Reward Deficiency Syndrome (RDS)? *J. Reward. Defic. Syndr.,* **2015**, *1*(1), 3-5. [http://dx.doi.org/10.17756/jrds.2015-001]

[75] Blum, K.; Thanos, P.K.; Badgaiyan, R.D.; Febo, M.; Oscar- Berman, M.; Fratantonio, J.; Demetrovics, Z.; Gold, M.S. Neurogenetics and Gene Therapy for Reward Deficiency Syndrome (RDS): Are we going to the Promised Land? *Cur. Exp. Opin. Biol. Ther.,* **2015**, *15*(7), 973-85.

[76] Filip, M.; Zaniewska, M.; Frankowska, M.; Wydra, K.; Fuxe, K. The importance of the adenosine A(2A) receptor-dopamine D(2) receptor interaction in drug addiction. *Curr. Med. Chem.,* **2012**, *19*(3), 317-355. [http://dx.doi.org/10.2174/092986712803414231] [PMID: 22335511]

[77] Calipari, E.S.; Bagot, R.C.; Purushothaman, I.; Davidson, T.J.; Yorgason, J.T.; Peña, C.J.; Walker, D.M.; Pirpinias, S.T.; Guise, K.G.; Ramakrishnan, C.; Deisseroth, K.; Nestler, E.J. *In vivo* imaging identifies temporal signature of D1 and D2 medium spiny neurons in cocaine reward. *Proc. Natl. Acad. Sci. USA,* **2016**, *113*(10), 2726-2731. [http://dx.doi.org/10.1073/pnas.1521238113] [PMID: 26831103]

[78] Golimbet, V.E.; Alfimova, M.V.; Gritsenko, I.K.; Ebstein, R.P. Relationship between dopamine system genes and extraversion and novelty seeking. *Neurosci. Behav. Physiol.,* **2007**, *37*(6), 601-606. [http://dx.doi.org/10.1007/s11055-007-0058-8] [PMID: 17657431]

[79] Noble, E.P.; Ozkaragoz, T.Z.; Ritchie, T.L.; Zhang, X.; Belin, T.R.; Sparkes, R.S. D2 and D4 dopamine receptor polymorphisms and personality. *Am. J. Med. Genet.,* **1998**, *81*(3), 257-267. [http://dx.doi.org/10.1002/(SICI)1096-8628(19980508)81:3<257::AID-AJMG10>3.0.CO;2-E] [PMID: 9603615]

[80] Doran, N.; Schweizer, C.A.; Myers, M.G.; Greenwood, T.A. A prospective study of the effects of the DRD2/ANKK1 TaqIA polymorphism and impulsivity on smoking initiation. *Subst. Use Misuse,* **2013**, *48*(1-2), 106-116. [http://dx.doi.org/10.3109/10826084.2012.733791] [PMID: 23153044]

[81] Iordanidou, M.; Tavridou, A.; Petridis, I.; Kyroglou, S.; Kaklamanis, L.; Christakidis, D.; Manolopoulos, V.G. Association of polymorphisms of the serotonergic system with smoking initiation in Caucasians. *Drug Alcohol Depend.,* **2010**, *108*(1-2), 70-76. [http://dx.doi.org/10.1016/j.drugalcdep.2009.11.015] [PMID: 20060656]

[82] Grzywacz, A.; Jasiewicz, A.; Małecka, I.; Suchanecka, A.; Grochans, E.; Karakiewicz, B.; Samochowiec, A.; Bieńkowski, P.; Samochowiec, J. Influence of DRD2 and ANKK1 polymorphisms on the manifestation of withdrawal syndrome symptoms in alcohol addiction. *Pharmacol. Rep.,* **2012**, *64*(5), 1126-1134. [http://dx.doi.org/10.1016/S1734-1140(12)70909-X] [PMID: 23238469]

[83] Volkow, N.D.; Frieden, T.R.; Hyde, P.S.; Cha, S.S. Medication-assisted therapies--tackling the opioid-overdose epidemic. *N. Engl. J. Med.,* **2014**, *370*(22), 2063-2066. [http://dx.doi.org/10.1056/NEJMp1402780] [PMID: 24758595]

[84] Lai, M.; Chen, W.; Zhu, H.; Zhou, X.; Liu, H.; Zhang, F.; Zhou, W. Low dose risperidone attenuates cue-induced but not heroin-induced reinstatement of heroin seeking in an animal model of relapse. *Int. J. Neuropsychopharmacol.,* **2013**, *16*(7), 1569-1575. [http://dx.doi.org/10.1017/S1461145712001563] [PMID: 23331426]

[85] Willuhn, I.; Burgeno, L.M.; Groblewski, P.A.; Phillips, P.E. Excessive cocaine use results from decreased phasic dopamine signaling in the striatum. *Nat. Neurosci.,* **2014**, *17*(5), 704-709. [http://dx.doi.org/10.1038/nn.3694] [PMID: 24705184]

[86] Badgaiyan, R.D.; Sinha, S.; Sajjad, M.; Wack, D.S. Attenuated Tonic and Enhanced Phasic Release of Dopamine in Attention Deficit Hyperactivity Disorder. *PLoS One,* **2015**, *10*(9), e0137326. [http://dx.doi.org/10.1371/journal.pone.0137326] [PMID: 26422146]

[87] Robertson, P., Jr; Hellriegel, E.T. Clinical pharmacokinetic profile of modafinil. *Clin. Pharmacokinet.,* **2003**, *42*(2), 123-137. [http://dx.doi.org/10.2165/00003088-200342020-00002] [PMID: 12537513]

[88] Olmsted, C.L.; Kockler, D.R. Topiramate for alcohol dependence. *Ann. Pharmacother.,* **2008**, *42*(10), 1475-1480. [http://dx.doi.org/10.1345/aph.1L157] [PMID: 18698008]

[89] Blum, K; Febo, M; Fahlke, C; Archer, T; Berggren, U; Demetrovics, Z; Dushaj, K; Badgaiyan, RD Hypothesizing Balancing Endorphinergic and Glutaminergic Systems to Treat and Prevent Relapse to Reward Deficiency Behaviors: Coupling D-Phenylalanine and N-Acetyl-L-Cysteine (NAC) as a Novel Therapeutic Modality. *Clin. Med. Rev. Case Rep.,* **2015**, *2*(8),076.

[90] Han, J.W.; Han, D.H.; Bolo, N.; Kim, B.; Kim, B.N.; Renshaw, P.F. Differences in functional connectivity between alcohol dependence and internet gaming disorder. *Addict. Behav.,* **2015**, *41*, 12-19. [http://dx.doi.org/10.1016/j.addbeh.2014.09.006] [PMID: 25282597]

[91] Han, D.H.; Kim, S.M.; Bae, S.; Renshaw, P.F.; Anderson, J.S. Brain connectivity and psychiatric comorbidity in adolescents with

Internet gaming disorder. *Addict. Biol.,* **2015**, *2015*(Dec), 22. [PMID: 26689148]

[92] Piechota, M.; Korostynski, M.; Solecki, W.; Gieryk, A.; Slezak, M.; Bilecki, W.; Ziolkowska, B.; Kostrzewa, E.; Cymerman, I.; Swiech, L.; Jaworski, J.; Przewlocki, R. The dissection of transcriptional modules regulated by various drugs of abuse in the mouse striatum. *Genome Biol.,* **2010**, *11*(5), R48. [http://dx.doi.org/10.1186/gb-2010-11-5-r48] [PMID: 20459597]

[93] Kononoff Vanhanen, J.; Nuutinen, S.; Tuominen, M.; Panula, P. Histamine H3 Receptor Regulates Sensorimotor Gating and Dopaminergic Signaling in the Striatum. *J. Pharmacol. Exp. Ther.,* **2016**, *357*(2), 264-272. [http://dx.doi.org/10.1124/jpet.115.230771] [PMID: 26945087]

[94] Hikida, T.; Kimura, K.; Wada, N.; Funabiki, K.; Nakanishi, S. Distinct roles of synaptic transmission in direct and indirect striatal pathways to reward and aversive behavior. *Neuron,* **2010**, *66*(6), 896-907. [http://dx.doi.org/10.1016/j.neuron.2010.05.011] [PMID: 20620875]

[95] Blum, K.; Febo, M.; Thanos, P.K.; Baron, D.; Fratantonio, J.; Gold, M. Clinically Combating Reward Deficiency Syndrome (RDS) with Dopamine Agonist Therapy as a Paradigm Shift: Dopamine for Dinner? *Mol. Neurobiol.,* **2015**, *52*(3), 1862-1869. [http://dx.doi.org/10.1007/s12035-015-9110-9] [PMID: 25750061]