Hypothesizing Benefits of the Incorporation of Genetic Addiction Risk Score (GARS™Rx™) and Dopamine Agonist Modalities (DAM) in Clinical Addiction Medicine.

K. Blum1,2,3,7-11, PhD, DE. Smith2, MD, J. Femino3, MD, AK.Roy4, MD, T. Simpatico5, MD, D. Inaba6, Pharm D., G. Agan7, BSc., JL.Fratantonio8, Pharm D., M. Febo1, PhD, F Fornari7, PhD, M Hauser7, MSc, D. Barh8, PhD

1Department of Psychiatry and McKnight Brain Institute, University of Florida, College of Medicine, Gainesville, Florida, USA
2Institute of Health & Aging, University of California, San Francisco
3Department of Clinical Medicine, Meadows Edge Recovery Center, North Kingston, Rhode Island, USA.
4Behavioral Medical Corporation, Metairie, LA, USA
5Human Integrative Services & Translational Science, University of Vermont and Department of Psychiatry, University of Vermont College of Medicine, Burlington, Vermont, USA
6Division of Alcohol & Drug Studies, University of Utah, Salt Lake City, UT
7Dominion Diagnostics, LLC, North Kingstown, USA
8Centre for Genomics and Applied Gene Technology, Institute of Integrative Omics and Applied Biotechnology (IIOAB), Nonakuri, PurbaMedinipur, West Bengal 721172, India
9Department of Addiction Research & Therapy, Malibu Beach Recovery Center, Malibu Beach, California, USA
10RDSolutions LLC, Del Mar, CA, USA
11Victory Nutrition International, LLC, Lederack, PA, USA

*Corresponding author: Kenneth Blum, PhD, Department of Psychiatry & McKnight Brain Institute, University of Florida College of Medicine, Gainesville, FL., USA, Tel 352-294-4911; Fax 352-392-9887; Email: drd2gene@gmail.com

Introduction

Blum et al. [1] coined the term The Reward Deficiency Syndrome (RDS) to describe a dysfunction in the Brain Reward Cascade [2] which directly links abnormal craving behavior with a deficit in a number of reward genes including dopaminergic, serotonergic, endorphinergic, GABAergic, adrenergic, opioidergic, cholinergic as well as many second messengers. Dopamine regulates...
feelings of well-being and is one of the most powerful neurotransmitters [3,4]. The interaction with other brain chemicals and neurotransmitters such as serotonin, and the opioids (neuropeptides), reduce stress and produce a sense of wellbeing. Good examples are the association of low levels of serotonin with depression and of high levels of opioids (the brain’s opium) with a sense of well-being [5].

In order for one to feel individual pleasure these powerful neurotransmitters produced complex interactions in the brain and through a transcription process involving mRNA that regulate neurotransmitter receptor production. These processes ultimately regulate dopaminergic activity of the brain in the reward center, the mesolimbic system and particularly in the nucleus accumbens (NAc). We provide a brief explanation of not only RDS, but potential genetic predisposition diagnosis and possibly the beneficial effects of natural D2 agonist therapy in Substance Use Disorder (SUD) patients - see review Chen et al. [6].

As stated earlier, RDS, which is emerging, as an acceptable explanation of the interrelatedness of the impulsive, compulsive and addictive behaviors including “process addictions”, has been the subject of concern by many notable investigators. The dopamine D2 receptor, part of the dopaminergic system is involved in mesolimbic circuitry and brain reward mechanisms. Any dysfunction of the D2 dopamine receptors can result in aberrant seeking of substances such as drugs, alcohol, tobacco and including food as well as eating disorders such as binge eating and anorexia nervosa. Decades of research since the initial findings of Blum’s group [2] indicate that genetics play a pivotal role in vulnerability to severe substance seeking behavior. Blum et al. [7] utilized Bayes theorem to predict future substance and process addictions. We proposed that (DRD2 A1 allele) variant of the D2 dopamine receptor gene is an important, common genetic determinant in predicting addictive disorders [1,7-9]. In those studies, future RDS behaviors were predicted in subjects carrying the DRD2 Taq A1 allele at 74%. Many neuroimaging studies have recently supported the RDS concept that links food craving and drug craving behavior [10,11]. While many genes are involved in RDS behaviors, it is apparent that a major role is played by the dopamine D2 receptor [12]. Johnson and Kenney [13] found compulsive-like feeding behavior, measured as palatable food consumption that, like all addictions, resisted disruption by an aversive conditioned stimulus, in obese, but not lean rats. Down regulation of striatal dopamine D2 receptors, has been reported, in both obese rats and drug addicted humans. Moreover, knockdown of striatal D2 receptors mediat ed by lentivirus, the development of reward deficits that were addiction-like and the onset of compulsive-like food seeking was rapidly accelerated in rats when given extended access to palatable high-fat food. This data demonstrates that neuroadaptive responses in brain reward circuits that drive the development of compulsive eating are indeed triggered by overconsumption of palatable food. The authors suggest that obesity and drug addiction have common underlying hedonic mechanisms [13].

It is noteworthy that others found that, in the ventromedial hypothalamus (VMH) of mice, selective BDNF depletion resulted in obesity due to hyperphagic behavior. Specifically, Cordeira et al [14] found that in the ventral tegmental area of wild-type mice BDNF and TrkB mRNA expression was influenced by consumption of palatable, high-fat food. It is particularly interesting that deficits have been noted in evoked release of dopamine in the dorsal striatum and NAc shell, but normal secretion in the NAc core was recorded in amperometric brain slices of mice depleted of central BDNF [14]. In addition, Lobo et al [15] recently showed that activation of D2+ neurons, mimic the loss of TrkB and suppresses cocaine reward while, the activation of D1+ neurons induces the opposite effect. These insights into the molecular regulation of D1+ and D2+ neuronal activity at the circuit-level identify the contribution these cell types make to cocaine reward [16].

The reward gene DRD2 has been has been associated with pleasure [2] and the Taq1 A1 allele with reduced receptor density in the NAc [17]. The evidence suggests that there is a three part interaction that begins with dopamine receptor deficiency and results in a tendency to abuse alcohol, and a reduced sensitivity to rewards. Based on these genetic characteristics, individuals from certain ethnic groups have a greater tendency toward alcoholism than others such as American-Indians, Asians and Irish descent [18]. The DRD2 has been one of the most widely studied genes in neuropsychiatric disorders in general, and in alcoholism and other addictions in particular (PUBMED 3748 articles obtained 7/26/14). The Taq1 A1 allele of the dopamine D2 receptor gene has been associated with comorbid psychiatric conditions including antisocial personality disorder symptoms [19], high novelty seeking, obesity, spectrum disorders, gambling and other process addictions [20]. The mesocorticolimbic dopaminergic pathway may be a common denominator for addictions and plays an especially prominent role in mediating reinforcement by abused drugs [21-23].

When the mesocorticolimbic-dopamine reward system breaks down, perhaps caused by certain genetic variants, the result is RDS and subsequent drug-seeking behaviors. To reiterate, RDS refers to reward cascade dysfunction, and resultant aberrant behaviors, due to genetic and environmental influences [8]. Accordingly, neuronal release of brain dopamine that can satisfy unhealthy

cravings and reduce negative feelings is activated by most positive reinforcers including alcohol and other drugs of abuse. Individuals are predisposed to a high risk for multiple addictive, impulsive, and compulsive behaviors if they have a deficiency of D2 receptors. Although other neurotransmitters, like glutamate, gamma-aminobutyric acid (GABA), and serotonin, may be necessary in stimulating the rewarding effects of ethanol and other drugs, initiating and reinstating drug use during protracted abstinence may be the providence of dopamine [23,24]. All roads do lead to dopamine.

Exploration of various treatment approaches utilizing Dominion’s Comprehensive Analysis of reported Drugs (CARD)™ found significant non-compliance to prescribed treatment medications and non-abstinence during out-patient/in-patient generally and in opioid treatment programs using Suboxone® and Methadone [25]. Moreover, continued drug hunger and poor outcomes in terms of relapse prevention continue to plague the “Recovery” field in general. Rather than correcting or compensating for pre-morbid dopamine system deficits, pharmacological therapies focused on either interference with drug euphoria or harm reduction with opioid maintenance, have had limited success [3]. In 2010 Blum and Gold [26] proposed the incorporation of genetic testing and neuroadaptogen amino acid precursor enkephalinase -catecholamine –methyltransferase (COMT) inhibition therapy into residential, non-residential and aftercare addiction services. In order to treat the genetic basis of addiction they proposed the identification risk alleles for hypodopaminergic brain reward function (RDS) coupled with a natural, but therapeutic nutraceutical formulation that could potentially produce dopamine release and cause the induction of D2-directed mRNA proliferation of D2 receptors in the human. They hypothesized that this proliferation of D2 receptors will induce the attenuation of drug-like craving behavior. These concepts await further confirmation via required neuro-imaging studies. Very recent studies, may shine some new light, and result in potential therapeutic approaches that include, for example, targeting the heteromeric A(2A)-D(2) receptor complex [27].

Dopaminergic Activation through Nutrigenomics

Although the use of nutritional approaches to treat the health related consequences of addiction are well researched, there are not enough studies that involve treatment of addiction by the manipulation of neurotransmission in the brain reward system based on identified polymorphic genetics. In [28] using single-gene candidates, microarray, proteomics, Li et al integrated 2,343 items of evidence that linked genes and chromosome regions to addiction. The evidence was collected from peer-reviewed articles published between 1976 and 2006. In these studies, they identified 1,500 human addiction-related genes and developed the first molecular database for addiction-related genes KARG [29]. They performed a meta-analysis of 396 genes. Of these genes, each supported by two or more items of evidence in the literature, they were able to identify 18 molecular pathways that were statistically significant and covered both upstream signaling events and downstream effects. They identified five molecular pathways as common pathways, found to have associations with a remarkable list of addictive drugs (alcohol, cocaine, cannabis, nicotine, glucose etc.), which may be involved with addictive and rewarding actions. They connected the common pathways into a hypothetical common molecular network for addiction. Two new pathways, GnRH signaling pathway and gap junction were identified. Clues to explain some of the irreversible features of addiction may be provided by their observation that, fast and slow positive feedback loops were interlinked through CAMKII. The common thread involves dopaminergic and glutamatergic genes.

Interestingly the dopamine molecule promotes both “pleasure” and “stress coping abilities”. Wellness constitutes an enhanced state of pleasure with tranquility while, a major link to overeating is uncontrollable stress and carbohydrate craving. We designed a study to evaluate the process of DNA-customization of a nutritional solution for both wellness and weight management. For this study, we genotyped 1,058 subjects, these subjects were administered a patented Nutraceutical based on polymorphic outcomes. In a subset-simple t-tests comparing a number of parameters, before treatment and after 80 days on the Nutraceutical were performed. Significant results (P<0.01) were observed for appetite suppression, for sugar craving reduction, weight loss, snack reduction, reduction of late night eating; (P<0.05) for enhanced quality of sleep, increased perception of overeating, increased happiness and (P<0.001) for increased energy. Positive clinical parameters were tested by Blum et al in 2008 [30] against a number of genes (LEP, PPAR-gamma2, MTHFR, 5-HT2A, and DRD2 genes) and polymorphic correlates were obtained. In their study of all the polymorphisms and outcomes, only the DRD2 gene polymorphism (A1 allele) had the only significant Pearson correlation with days on treatment (r=0.42, P=0.045). This 2 fold increase indicates that the A1 allele polymorphism is a very important genotype for compliance in treatment [31].

Neuroimaging Evidence of NAAT in RDS

In a cross-over, triple blinded randomized, placebo-controlled, qEEG study involving oral NAAT-KB220Z, increased low beta activity and increased alpha wave activity were demonstrated, using quantitative electroencephalographic (qEEG) imaging, in the parietal brain loci. Using t statistics, significant differences between
placebo and KB220Z were consistently observed during the first and then the subsequent, second week of analysis [32] [See Figure-1].

Figure 1. KB220Z compared to placebo in psychostimulant abusers. Illustrates positive response of KB220Z compared to placebo in triple blind randomized placebo -controlled study in psychostimulant abusers undergoing protracted abstinence. Modified Blum et al. [32] with permission (Modified from Source: Blum et al. [32]).

Treatment of addictive behaviors with D2 agonist therapy is in agreement with NIDA scientists as well as other authors who concluded that dopamine/5-HT releasers and D2 agonists could be useful as therapeutic adjuncts in the treatment of psychiatric disorders; attention deficit disorder and depression as well as cocaine and alcohol addiction and obesity [33]. In terms of relapse, the above qEEG experiment showed the involvement of the prefrontal cortex, which was especially evident in dopamine D2 A1 allele subjects. This was the first time that any laboratory reported qEEG responses to a natural putative D2 agonist [32].

Similar success has been also obtained by showing that KB220Z also activated Dopaminergic pathways using fMRI in Chinese Heroin addicts, undergoing protracted abstinence. Preliminary, unpublished results show significant differences in BOLD activation, of a number of Pre-frontal, Cingulate Gyrus and Caudate-Accumbens - Putamen brain regions. This experiment suggests that one-hour after KB220Z there is activation of dopaminergic pathways (personal communication Blum et al submitted elsewhere).

Attenuation of ‘Dopamine Resistance” leads to reduced drug seeking

Acute utilization of most psychoactive substances induces a feeling of well-being. Unfortunately if abuse is sustained and prolonged a toxic feeling of pseudo well-being results in tolerance, discomfort and dependence. The consequence of low dopamine receptor densities due to carrying the DRD2 A1 allelic genotype (30-40% lower numbers) is excessive craving behavior while, normal or high dopamine receptor densities result in low craving-induced behavior [17]. Prevention of excessive cravings might then be attained by the induction of dopamine D2 receptor proliferation in genetically prone individuals. Indeed experiments in vitro have shown that constant stimulation of the dopamine receptor system via a known D2 agonist in low doses, results in significant proliferation of D2 receptors, in spite of genetic antecedents [34,35]. Negative feedback mechanisms are signaled by D2 receptor stimulation that induces mRNA expression and causes proliferation of D2 receptors in the mesolimbic system [36]. Based on this molecular finding constant natural induction of dopamine release may also support the production of D2-directed mRNA and result in the proliferation of D2 receptors in humans. The proliferation of D2 receptors will, in turn, attenuate human craving behavior. This has been proven, using a form of gene therapy in work showing that, DNA-directed overexpression of the DRD2 receptors, results in a significant reduction in cocaine and alcohol craving-induced behavior in animals [36-40].

Role of mRNA expression in response to drugs of abuse and reward pathways

It is known that certain drugs of abuse and neuro-pathways interact in the genome to influence the biological function of mRNA as it relates to neurotransmission, enzymes involved in neurotransmitter metabolism as well as specific neuronal receptors, that are common in the production of feeling of well-being in the animal or human [41]. Hikida et al. found that the convergent input of dopaminergic modulation in the indirect striatopallidal pathways, and the direct striatonigral pathways, of the basal ganglia, are crucial in the rewarding and aversive learning involved in drug addiction. Hikida et al. [42] explored basal ganglia information processing and integration through these two pathways. Using a reversible blocking technique they blocked neurotransmission of each pathway selectively, using a doxycycline-dependent, specific expression of transmission-blocking tetanus toxin [42]. Two pathways with distinct but coordinated roles were found to be necessary for the modulation of dopamine-mediated acute psychostimulant actions. The direct pathway was prominent in reward learning and cocaine sensitization which is critical for making distinctions between associative from non-associative rewarding stimuli while the indirect pathway was predominant in aversive behavior, used to avoid aversive stimuli for rapid memory formation [42]. While this is true, we ask: What is the effect of drugs of abuse on mRNA in these pathways? This concept is being explored by
our laboratory and will be the subject of future papers.

"Neuroscience Module" in treatment: The new definition of addiction

The American Society of Addiction Medicine [43], the United States’ addiction specialty society of physicians, has recently redefined “addiction” as “addiction is a primary, chronic disease involving brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in persons compulsively pursuing reward and/or relief by substance use and other behaviors. Addiction cannot be cured but can be brought into remission through a program of treatment, abstinence from all psychoactive substances, and supported recovery” [43].

This new definition of addiction as a disease that involves brain reward, motivation, memory establishes the work of our laboratory as a pioneer in the field. Dedicated scientific rigor during our 40 year sojourn into the mechanisms of the mesolimbic system have provided insight into the addictive brain and the neurogenetics involved in man’s quest for happiness. To reiterate, feelings of well-being are experienced in the mesolimbic system of the brain [44]. In the mesolimbic system chemical messages including serotonin, enkephalins, GABA and dopamine work together to release of dopamine in NAc where one experiences feelings of well-being. A series of neuronal events termed “Brain Reward Cascade” was coined to describe the synthesis, vesicular storage, metabolism, and catabolism of neurotransmitters [28,30]. These events are controlled by genes and polymorphic-versions of these genes have certain variations which could lead to a breakdown of this cascade and ultimately dysregulation and dysfunction of the dopaminergic pathway. Any reduction in dopamine function, since dopamine is established as the pleasure and anti-stress molecule, albeit some debate, could lead to unhappiness, reward deficiency and result in aberrant substance and pleasure seeking behavior [20-22].

Homo sapiens are programmed to be motivated to drink, eat, have sex and desire pleasurable experiences. Impairments in these natural reward mechanisms are governed by genetic polymorphic antecedents and can promote multiple impulsive, compulsive and addictive behaviors in individuals. While many genetic variations are involved within the activity of the mesolimbic system, polymorphisms of genes that predispose individuals to excessive cravings and result in aberrant reward seeking behaviors [45] include, among others, the dopamine D2 receptor (DRD2); dopamine D4 receptor (DRD4), dopamine transporter (DAT1); the serotonergic- 2A receptor (5-HTT2a); serotonergic transporter (5HTTLPR); Catechol-o-methyltransferase (COMT), monoamine –oxidase (MOA);GABA receptors (GABAB) and Cytochrome P450.

As stated, RDS is the umbrella term used to describe multiple impulsive, compulsive and addictive behaviors with common genetic antecedents [46]. Individuals, especially in adolescence who have reduced numbers of dopaminergic and/or serotonergic receptors and an increased rate of synaptic dopamine catabolism will, due to high MOA activity or high catabolic activity due to the COMT gene, have a predisposition to use any means; substance or behavior, to activate dopamine release. Dopamine release is activated by the use of glucose, drugs like alcohol, opiates, psychostimulants and nicotine, and by process addictions, like gambling, sex, and even excessive internet gaming [46,47].

Use of most drugs of abuse, including alcohol, are associated with dopamine release in the “reward pathway of the brain” the mesocorticolimbic system and a new mechanism involving local electrophysiology for dopamine release has been proposed [48]. Activation of this dopaminergic system induces feelings of reward and pleasure, however dopamine release in the ventral tegmental area (VTA) is also caused by aversive or painful stimuli like finding pleasure from bondage [49].

Genetic Addiction Risk: Is it a function of Hypodopaminergic function

The hypothesis is that regardless of the source, the presence of a hypodopaminergic state/strain is a primary cause of drug-seeking behavior. Certainly, polymorphisms that induce hypodopaminergic functioning are the mechanism of a genetic predisposition to chronic drug use and relapse [50].

Numerous important studies that have explored the genetic risk for drug-seeking behaviors have reinforced the claim that individuals possessing dopaminergic gene variants are impulsive. These are association and linkage studies that implicate these alleles, as risk antecedents that impact the mesocorticolimbic system. Dopaminergic gene variants include DRD2, DRD3, DRD4, DAT1, COMT, MOA-A, SLC6A4, Mu and GABA. Our laboratory in conjunction with Dominion Diagnostics, Inc. are involved in development and research in nine select centers across the United States to validate the first ever patented genetic test to determine a patient’s genetic risk for RDS called Genetic Addiction risk Score™ (GARSXR™Rx™).

Benefits of GARSXR™Rx™ in Clinical Addiction Medicine

If early diagnosis is beneficial for positive treatment outcomes, then when should the scientific community
adopt the proposed paradigm shift using genotyping? There are laws and federal and state mandates that require gene testing at birth. The reasoning behind use of genotyping for diagnosing RDS is that, unlike certain rare diseases where there are limited treatment options (i.e., Huntington’s disease, phenylketonuria, congenital hypothyroidism, galactosemia, sickle cell anemia), RDS does have effective treatment options. Although having RDS is not life-threatening, related gene testing could allow for early diagnosis and non-pharmacologic interventions.

We might find that exercise, diet, parent-training, computer-assisted learning, or a safe non-stimulant nutraceutical dopaminergic agonist therapy reduces the impact of the gene abnormality. We would have to weigh the stigma and other factors, but it may be realistic to ask whether it is prudent to use such techniques to clarify the diagnosis and follow outcomes. It is known that for example a RDS subset ADHD diagnosed in children extends into adult ADHD, and if not treated appropriately, will result in psychoactive substance use disorder (PSUD), among other behaviors. To suggest that children, even at birth should be screened for potential ADHD risk alleles may seem both and premature. It may, however, be intelligent to at least explore the possibility in the future. In this regard, Bill Moyers of PBS has done some excellent work investigating the plight of future America, suggesting that we should diagnose ADHD very early in life (if not at birth), and couple diagnosis with a safe side-effect-free treatment. Certainly, we are cognizant of preteen and adolescent drug seeking behavior with under development of Pre-Frontal Cortices.

We must consider the established concept of RDS [1] to help define this complex array of behaviors, associated molecular dysfunctions. Victims of RDS carry polymorphic genes in dopaminergic pathways that results in hypo-dopaminergic function caused by a reduced number of dopamine D2 receptors reduced synthesis of dopamine (dopamine beta –hydroxylase) , reduced net release of pre-synaptic dopamine (dopamine D1 receptor) increased synaptic clearance due to a high number of dopamine transporter sites (dopamine transporter) and low D2 receptor densities (dopamine D2 receptor) making them more vulnerable to addictive activities.

These results provide preliminary support for the theory that dopaminergic genes, in particular the DRD2 and DAT1 polymorphisms, are significantly associated with the reward–dependent traits (i.e. cocaine dependence) and therefore warrants further research, albeit lack of association in select populations for example African Americans may result in spurious results. However there are many genes and SNPs involved in developing an accurate genetic test such as GARS RX™. In keeping with the theory of common neurogenetic mechanisms we now propose that RDS is a basic phenotype covering many reward behaviors and pertinent psychiatric disorders including spectrum disorders that should be included in the future in DSM as a genetic umbrella for many psychiatric diagnosis.

We are providing the GARS RX™ as a preliminary test paving the way for future gene additions. Utilization of the GARS RX™ test in clinical practice will: 1) reduce denial; 2) reduce guilt; 3) reduce questioning of relapse chance 4) ultimately lead to appropriate therapeutic targets based on known gene polymorphisms; 5) medical monitoring for polymorphic based treatment response; and 6) explain polymorphic based treatment response.

Relapse

Drug-seeking behavior can be triggered by reduced activity of the dopamine system (hypodopaminergic functioning) [15]. Hypodopaminergic functioning can be induced by variant alleles through reduced dopamine receptor density, blunted response to dopamine, and/or enhanced dopamine catabolism in the reward pathway [51]. Possibly, cessation of chronic drug use also can induce a hypodopaminergic state that reinstates drug-seeking in an attempt to address the withdrawal state [52].

Paloyelis et al. [53] lent support to the impulsive nature of individuals possessing RDS genetics in a recent article that suggests that variants in the COMT gene can predict impulsive choice behavior and could be an indicator for treatment targets. That people with addictive disorders are at risk of relapse, returning to drug use even after prolonged periods of abstinence is well known and the subject of considerable research. In animal models of relapse drug-seeking behavior can be triggered by priming with injections of the drugs, by drug-associated environmental stimuli, and by stress (foot-shock stress). According to Self & Nestler [54], the neural mechanisms that are the basis of relapse can be viewed in general terms as drug-like, mini -withdrawal processes [55,56]. Bossert et al. [57] demonstrated that we cannot ignore the importance of neurochemical mechanisms involved in drug-induced relapse behavior. These investigators used a drug relapse model, previously shown to induce relapse by re-exposing rats to heroin-associated contexts. After the extinction of, drug-reinforced responding, they found that exposure to different heroin-associated contexts reinstated heroin seeking. Reinstatement was reduced when glutamate transmission was inhibited, in components of the mesolimbic dopamine system; the ventral tegmental area and medial accumbens shell [57]. This process enhances dopamine net release in the NAc. In brief, glutamate reduction increases dopamine release, this fits well with Li’s [28] KARG addiction network map.
Many studies have focused on activation of D2-like dopamine receptors in the NAc of mesolimbic dopamine system, as a crucial neural substrate where various stimuli produce release. Neural circuits from the prefrontal cortex, the hypothalamic-pituitary-adrenal axis and the amygdala may also be activated by drug-associated stimuli and stress [54]. There are other dopamine-independent mechanisms in relapse like up-regulation of the cAMP pathway in the NAc. This neuroadaptation represents a drug-opposite or opponent process that occurs after chronic drug exposure [58,59]. This system directly effects relapse to drug-seeking behavior. It is likely that the long lasting risks for relapse are mediated by neuroadaptations via drug-induced changes in gene expression (mRNA) at both the NAc and Prefrontal Cortex-Cingulate Gyrus regions [54,55] see Figures -2.

Figure 5. Reward circuitry (Source: Blum et al. [60] Journal Addiction Res. and Therapy)

Neurogenetics of clinical issues in pain relief: Preventing Iatrogenic Addiction

Understanding the role of neurogenetics in pain relief including pharmacogenomics and nutrigenomic aspects will pave the way to better treatment to the millions suffering from both acute and chronic pain. We now know that dopaminergic tone is involved in pain sensitivity mechanisms [61,62].

Neurological loci for sensitivity to pain, may reside in the mesolimbic system where a number of genes and polymorphisms associated with a predisposition to tolerance or intolerance to pain reside. The identification of certain gene polymorphisms as unique, therapeutic targets may assist in the treatment of pain. Pharmacogenetic testing for certain candidate genes, like mu receptors, PENK, is proposed as a means to improve clinical outcomes by provision of treatment personalized to each patient guided by their unique genetic makeup [61]. The use of GARSRX™ as described above to identify clients with high addiction risk, by providing valuable information about genetic predisposition to opioid addiction, could become an important frontline approach, on admission to pain clinics.

One notable paper evaluated the role of both mu-opioid receptors (MORs) and delta-opioid receptors (DORs) two genes expressed in the VTA that are thought to be involved in the addictive properties of opiates. Researchers David et al [63] found that knockout of the MOR gene abolished intra-VTA morphine self-administration at all doses tested while male and female WT and DOR-/mice exhibited self-administration similarly. Naloxone (4 mg/kg) disrupted this behavior in WT and DOR mutants, without triggering physical signs of withdrawal. Morphine ICSA was associated with an increase in FOS within the NAc, striatum, limbic cortices, amygdala, hippocampus, the lateral mammillary nucleus (LM), and the ventral posteromedial thalamus (VPM). This latter structure was found to express high levels of FOS exclusively in self-administering WT and DOR-/ mice. Abolition of morphine reward in MOR-/mice was associated with a decrease in Fos-positive neurons in the mesocorticolimbic DA system, amygdala, hippocampus (CA1), LM, and a complete absence within the VPM. David et al [63] conclude that (i) VTA MORs, but not DORs, are critical for morphine reward and (ii) the role of VTA-thalamic projections in opiate reward deserves to be further explored.

Moreover, clinical and laboratory studies indicate that the MOR gene contributes to inheritable vulnerability to the development of opiate addiction. Naturally occurring polymorphisms have been identified in the MOR gene. Substitutions occur at high allelic frequencies (10.5% and 6.6%) in two coding regions single nucleotide polymorphisms (SNPs), the A118G and C17T respectively, of the MOR gene. These SNPs cause amino acid changes in the receptor that impact on an individual’s response to opioids and can influence increases or decreases vulnerability to opiate addiction [64]. Thus, the A118G substitution encodes a variant receptor with binding and signal transduction differences in response to beta-endorphin in cellular assays [64].

Finally, to firmly establish the role of MOR in reward and response to Buprenorphine, Ide et al. [65] found that Buprenorphine anti-nociception, assessed by hot-plate and tail-flick tests, was significantly reduced in heterozygous mu-opioid receptor knockout (MOR-KO) mice and abolished in homozygous MOR-KO mice. Buprenorphine on the other hand, was able to establish a conditioned place preference (CPP) in homozygous MOR-KO, although as the number of copies of wild-type mu-opioid receptor genes was reduced the magnitude of place preference was reduced. This study revealed that mu-opioid receptors mediate most of analgesic properties of buprenorphine [65].
NAAT evidence in RDS

There is a series of published articles concerning the basic platform of utilizing Neuroadaptagen Amino-Acid Therapy (NAAT) to treat various RDS behaviors [6]. These results coupled with other qEEG studies of this compound suggest a putative anti-craving/anti-relapse role in drug addicts by direct or indirect dopaminergic interaction [13,66,67], and ongoing fmRI studies in both animal and humans. We are suggesting that the coupling of GARSRX™ with NAAT will potentially overcome unwanted iatrogenic induction of addiction by reducing powerful opioids.

Conclusions

Our laboratory recently reviewed the role of dopaminergic activation and genetic stratification in process addictions, in a paper concerning “Sex, Drugs and Rock 'N' Roll” [20]. We concluded that the reinforcing effects of drugs of abuse and sex, food, and other addictions are mediated within the ventral striatum NAc. This structure also mandates motivated behaviors such as eating, drinking, and sexual activity, which are stimulated by natural rewards. We have discussed the mechanisms that are the basis of human motivation. Based on abundant scientific research, they share molecular-genetic antecedents with powerful biological drives for survival, which if impaired, lead to aberrant compulsive, obsessive and impulsive behaviors. We have hypothesized that neurotransmitter-related candidate genes and their polymorphisms can be used to predict predisposition to addiction and other RDS behaviors. The use and further development of dopaminergic agonistic agents to target specific gene polymorphisms has been proposed, and evidence that the proliferation of D2 receptors can attenuate human craving behavior was explored.

Innovative experiments have been developed during many years of scientific research into the nature of addiction. The challenge is to incorporate them in treatment programs for patients attending inpatient/out-patient addiction clinics. A go forward model to assist in diagnosis, understanding treatment outcome and potential relapse prevention is proposed herein to include the following: 1) the Genetic Addiction Risk Score (GARS RX™) for appropriate RDS diagnosis; 2) Comprehensive Analysis Of Reported Drugs CARD™ to determine both compliance and abstinence during treatment; 3) D2 agonistic therapy (NAAT-KB220™); 4) and eventually, mRNA testing (patent pending) to determine pre and post candidate gene expressions in Reward Deficiency Syndrome (RDS). We are, therefore, proposing a paradigm shift we have called "Reward Deficiency Solutions System (RDSS)™

Acknowledgements:

The authors appreciate the expert editorial assistance of Margaret A. Madigan. Marcelo Febo is the recipient of R01DA019946. Kenneth Blum is the recipient of a grant from LifeExtension Foundation, Ft. Lauderdale, Florida awarded to Path Foundation NY.

Conflict of Interest

It is acknowledged that Dr. Blum is the owner of US and foreign patents related to KB220™. Through an exclusive license agreement between IGENE LLC (owned by Dr. Blum) and Dominion Diagnostics the GARSRX™RX™ will be commercialized and protected by US issued and pending patents as well as a PCT.

References


29. KARG (Knowledgebase for Addiction Related Genes).


Cite this article: Blum K. Hypothesizing Benefits of the Incorporation of Genetic Addiction Risk Score (GARS™) and Dopamine Agonist Modalities (DAM) in Clinical Addiction Medicine. J Addic Ther. 2014, 1(2): 999.


