

Reward Deficiency Syndrome (RDS): Is there a Solution?

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Introduction

In the early sixties we knew relatively very little about the workings of the brain especially the interrelatedness of the brain reward circuitry and the Pre-frontal cortices. Understanding the importance of the main neurotransmitters such as serotonin, GABA, dopamine and acetylcholine were unknown for the most part and endorphins was not even a part of our scientific acumen. The 1956 doctrine of Jellinek and the disease concept of alcoholism was new and not generally accepted [1]. At that time most scientists working in the field of addiction agreed that alcoholism is the result -at least in part -of deficiencies or imbalances in brain chemistry-perhaps genetic in origin. However so little was known that nothing specific was espoused by the then newly called neuroscientists.

For thousands of years, human beings have had a love/hate relationship with alcohol. No one knows when the first beer was brewed, but it was earlier than 5,000 B.C. In fact, wine dates back to 3,000 B.C.; brandy appeared late in the twelfth or early thirteenth century, but grain-based 'hard' liquors such as whiskey and gin had very little impact until the seventeenth century.

It was Claudia Black [2] who promoted the concepts of the term Children of Alcoholics (COAS) as well as Adult Children of Alcoholics (ACOAS) that now constitutes over 30 million in the United States alone. The major hazard for this group is that they may carry risk alleles that could drive them to drink or carry behaviors of a dry drunk. This is important since the understanding that children of alcoholics could carry certain genes in variant forms (unknown at that time) similar to their parents and or siblings, and that these genetic polymorphisms could induce aberrant behaviors including drug seeking was at best just a plausible thought. In the early days of treatment it was difficult to overcome patient denial and the acceptance of alcoholism as a real disorder of the brain was dismissed by most of the populace up until 1990. Although the conviction that alcoholism was a disease rather than a symptom of moral weakness was growing in the late nineteenth and early twentieth centuries, there was no knowledge of how the disease might be acquired or treated and such was largely guesswork. In fact, one theory suggested that alcoholism was the result of an infection, and as such a few patients were treated with germicidal agents without any positive effect. The first somewhat effective treatment of alcoholism on record is from the 1930's whereby "aversion therapy" was first employed by Charles Shadel which later became the Schick-Shadel hospital [3]. It is noteworthy, that many of the treatment goals employed today began with the advent of utilization of counselors. In the early 1950's it was Daniel J. Anderson, a psychologist at Willmar State Hospital in Minneapolis, that first used a recovering person from AA, to serve as recovery coach which resulted in the development of the field designated as a "Counselor of Alcoholism".

The Search for the Solution

At the beginning of the 1940's most research into alcoholism

could be classified under three headings: observation and analysis of psychological behaviors; observation and analysis of cultural and social variables; laboratory investigation into the physiological effects of alcohol on the body.

Early clues came from laboratory experiments such as the work of Jorge Mardones who pioneered the concept of nutrigenetics. He showed that one important factor (coined the N1 factor); having reduced vitamin B complex caused increased alcohol consumption in rats. This effect was significantly attenuated by the administration of yeast rich in vitamin B complex. Then in later experiments in which he tested voluntary consumption of alcohol under dietary deficiency, he employed rats that had been inbred for seven generations. Mardones found that young rats preferred alcohol if their parents had also preferred alcohol before them [4].

Roger Williams from the University of Texas at Austin furthered developed the concept of "metabolic individuality" and drawing from the work of Mardones advanced the concept of "genotropic theory of alcoholism". The theory held that some people carried a deficiency of glutamine due to a genetic deficiency of an enzyme. In conjunction with Bill Shive they found that by isolating an amino acid from human liver called *L-Glutamine*, followed by experiments in rats showing that there was a 35% reduction of alcohol consumption in the group that was administered L-glutamine compared to placebo. However, the response diminished over time, but indicated an important nutritional component tied to genetics [5].

In 1952, it was Leonora Mirone who first found that the inbred mouse strain C57 when given a choice of water or 5% ethanol in water more often chose ethanol over water supporting Williams concept on "genotropic theory of alcoholism" [6]. With this previous research it was Gerald McClearn of the Institute of Behavioral Genetics at the University of Colorado, Boulder that refined the mouse model by selective breeding and today stands as the father of "animal models of alcoholism" [7].

In the 1960's many laboratories turned to the concept that stress was a factor in increasing alcohol consumption. This work was led by

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notables such as Masserman and Yum who showed that neurotic cats following a stressful event when given a choice of milk or an alcoholic beverage chose the ethanol beverage of milk [8]. This was further supported by others Casey [9] and Nobles group [10] suggesting the importance of stress in alcoholism.

Finally, it was Robert D. Myers of Purdue University that showed that the more you drink alcohol the more you want. He accomplished this by injecting different concentrations of alcohol into the brains of rats up to 1,000 infusions and following a time period the rats infused more consumed higher amounts of alcohol when deprived of food and water [11]. Then in subsequent experiments Myers and Veale in 1968 devised an experiment whereby they found that administration of a substance para-chlorophenylalnine (pCpA) that reduced the amount of the neurotransmitter serotonin in the brain induced a long-term aversion to alcohol suggesting the significant role of serotonin in alcohol intake. This work also was extended to another substance known to reduce both dopamine and norepinephrine call alpha-methyl- para - tyrosine alpha-mPT) also shown to induce aversion to ethanol. These experiments were the beginning of understanding neurotransmitter imbalances and subsequent alcohol intake in humans [12]; including the dopamine antagonistic therapy for alcohol and opiate addiction favored by FDA approved drugs.

Understanding these earlier concepts including other work involving common mechanisms of action between opiates and alcohol and aldehyde-dopamine adducts [13,14] the rest of the paper further presents newer solutions along with the prospects of better genetic diagnosis and nutrigenomic intervention favoring dopamine agonistic not antagonistic therapies.

Embracing New Solutions and Genetic Risk Assessment

Prior to 1990 there was only one study directed at psychiatric genetics [15]. Egeland et al. [15] analyzed the segregation of Restriction Fragment Length Polymorphisms (RFLP) in an Old Order Amish population (pedigree) and localized a dominant gene, possibly tyrosine hydroxylase in chromosome 11, linked to a strong predisposition to manic depressive disease. This finding was retracted in 1989 by Kelsoe et al. [16]. Following these very early studies Blum and Noble and their respective groups reported on the first ever confirmed association of the dopamine D2 receptor gene (DRD2) and severe alcoholism [17]. While the findings were controversial at the time, [18] it is confirmed [19] and remains the most widely studied gene in psychiatric genetics. The discovery lead to the development of an entire field of medicine-known as Psychiatric Genetics and it has 14,937 publications as of 10/26/14 on PubMed.

Despite harmful negative consequences, drug and alcohol dependence is considered a relapsing chronic condition with compulsive seeking behaviors (including non-substance addictive behaviors). All psychoactive drugs including cannabis, ethanol, opioids, stimulants, nicotine as well as disruptive behaviors such as internet gaming, dysfunction sex, overeating amongst others lead to neuronal release of dopamine [20].

Le Foll et al. [19] carried out a meta-analysis and found a significant association between DRD2 and alcohol dependence. Further studies have shown significant linkage between carriers of the DRD2 *Taq A1* allele and familiar alcoholism [21]. Overall, this indicates that different aspects of the addiction phenotype are critically influenced by dopaminergic receptors and that variants of those genes seem to influence some addiction phenotypes in humans.

Support for Reward Deficiency Syndrome (RDS) as the “True Phenotype”

In 1995, Blum questioned the validity of the theorized neurochemical mechanisms of a number of psychoactive drugs such as alcohol and opiates. This concern was highlighted by the original work of Virginia Davis [22], Gerald Cohen [23], Michael Collins [24] and others [25] related to common mechanisms between alcohol and opiates [26]. As such in 1996 Blum and his group coined the term *Reward Deficiency Syndrome (RDS)* publishing the concept in the Royal Society of Medicine [27].

Mark Gold’s theory, the “Dopamine Depletion Hypothesis”, proposed an important role for dopamine in the effects of cocaine [28,29]. Euphoric properties of cocaine lead to the development of chronic abuse, and appear to involve the acute activation of central DA neuronal systems. Dopamine depletion is hypothesized to result from overstimulation of these neurons and excessive synaptic metabolism of the neurotransmitter. DA depletion may underlie dysphoric aspects of cocaine abstinence, and cocaine urges. Neurochemical disruptions caused by cocaine are consistent with the concept of “physical” rather than “psychological” addiction. In follow-up research, it was proposed that one way to treat cocaine addiction was to embrace dopamine agonist therapy such as utilizing the powerful dopamine D2 agonist bromocriptine. This compound was found to significantly reduce cocaine craving after a single dose [30]. It was suggested that bromocriptine may be effective as a new, non-addictive pharmacological treatment for cocaine addicts and support the notion that functional dopamine depletion occurs with chronic cocaine use.

Open trials indicate that low-dose bromocriptine may be useful in cocaine detoxification. Recently, Lawford et al. [31] conducted a double-blind study, where bromocriptine or placebo was administered to alcoholics with either the A1 (A1/A1 and A1/A2 genotypes) or only the A2 (A2/A2 genotype) allele of the DRD2. The greatest improvement in craving and anxiety occurred in the bromocriptine-treated A1 alcoholics and attrition was highest in the placebo-treated A1 alcoholics. However, we know now that chronic administration of this D2 agonist induces significant down-regulation of D2 receptors thereby preventing its use clinically [32].

Blum and Gold’s groups continued to propose dopamine agonist therapy rather than dopamine antagonistic therapy, which is currently favored by the approved FDA drugs as medical assisted treatment [33]. Specifically, Blum et al. [34] proposed that D2 receptor stimulation can be accomplished via the use of KB220Z [35], a complex therapeutic nutraceutical formulation that potentially induces DA release, causing the same induction of D2-directed mRNA and thus proliferation of D2 receptors in the human. This proliferation of D2 receptors in turn will induce the attenuation of craving behavior. The research of this model has shown DNA-directed compensatory overexpression (a form of gene therapy) of the DRD2 receptors, resulting in a significant reduction in alcohol craving behavior in alcohol preferring rodents [36] as well as self-administration of cocaine [37].

The promotion of long term dopaminergic activation by lower potency dopaminergic repletion therapy will lead to a common, safe and effective modality to treat RDS behaviors including Substance Use Disorders (SUD), Attention Deficit Hyperactivity Disorder (ADHD), obesity and other reward deficient aberrant behaviors. This concept is further supported by the more comprehensive understanding of the role of dopamine in the NAC as a “wanting” messenger in the meso-limbic DA system [38]. It is our hypothesis that D2 receptor stimulation

signals a negative feedback mechanism in the mesolimbic system to induce mRNA expression causing proliferation of D2 receptors.

In fact, stress and dopamine D2 receptor levels play a significant role in alcohol seeking behaviors. Delis et al. [39] observed that in the presence of a stressful environment, low DRD2 levels are associated with increased ethanol intake. Under this condition, increased ethanol consumption could be used as a strategy to alleviate negative mood, which further supports dopamine agonist therapy. Recently, Willuhn et al. [40] found that phasic dopamine decreased in the Ventral Medium Striatum (VMS) as the rate of cocaine intake increased, with the decrement in dopamine in the VMS significantly correlated with the rate of escalation. Administration of the dopamine precursor L-DOPA at a dose that replenished dopamine signaling in the VMS reversed escalation, demonstrating a causal relationship between diminished dopamine transmission and excessive drug use. This work seems to support the “deficit” rather than the “surfeit” theories related to drug seeking behavior [41].

The current literature proposes that the true phenotype for addiction is not any one single addictive behavior, drug, or otherwise but is indeed RDS [42]. The basis of this bold concept has received support from a number of PUBMED listed articles (74 as of 10/28/14). Indeed our laboratory [43] evaluated a number of dopaminergic polymorphisms in two families up to five generations and discovered that polymorphisms of the DRD2 and DAT alleles significantly associated with multiple RDS behaviors. We proposed a nonspecific RDS phenotype. Utilization of a nonspecific “reward” phenotype may be a paradigm shift in future association and linkage studies involving dopaminergic polymorphisms and other neurotransmitter gene candidates. This work has been underscored by the suggestion that food and drugs are both addictive substances and share common neurogenetic and neurobiological mechanisms and as such subsets of RDS [44].

Interestingly, this common mechanism concept that food and drugs have shared neurochemistry is underscored by the work initiated in Europe showing the importance of blocking cannabinoid CB1 receptors for the development of a strong anti-obesity agent having anti-drug qualities as well. The drug known as Acomplia[®] was adequately shown to block dopamine release and as such attenuate both food and psychoactive drug abuse but resulted in severe mood changes including suicide ideation [45].

In this regard, we are cognizant that there may be much to learn from understanding the mechanisms of action of for example marijuana, a substance causing much debate in recent years. In recent debates over legalizing marijuana, from total acceptance by Colorado and Washington states and many other states legalizing medical marijuana, the scientific question of the role of this substance as a potential gateway drug (i.e., a drug that lowers the threshold for addiction to other agents) has historically loomed greatly in the scientific community. With the advent of the field of neuroepigenetics new scientific information is shedding light on this old age subject which will surprise both opponents and proponents of legalization.

While environment plays a significant role it has been estimated via scientific analysis that variant genes contribute as much as 70% of overall substance abuse or substance use disorder. Since dopamine could also be released by behaviors such as gambling, sex, music, food, internet gaming all RDS behaviors it is a very important link to cannabis pharmacology [46].

Scientific studies in Sweden have clearly shown that relapse to

drugs of abuse like alcohol is due in part to the genetic antecedent of carrying the Dopamine D2 receptor A1 allele (variant).

Understanding the importance of the dopamine D2 receptor gene variant and its relation to drug craving as well as relapse is further underscored by the work of Dinieri and others published in Biological Psychiatry [47]. In their neuroepigenetic study striatal or brain dopamine and opioid-related genes were studied in human fetal subjects exposed to cannabis. Surprisingly they found prenatal cannabis exposure decreased dopamine receptor D2 (DRD2) messenger RNA expression in the human ventral striatum (nucleus accumbens [NAc]), a key brain reward region. No significant alterations were observed for the other genes in cannabis-exposed subjects. In fact it was further found that decreased DRD2 expression was accompanied by reduced dopamine D2 receptor (D(2)R) binding sites and increased sensitivity to opiate reward in adulthood.

So with these undisputable data we as parents and care givers must relate this scientific information to our offspring and warn females of the potential gateway dangers of exposing human fetuses to marijuana. Certainly people at birth that carry the A1 form of the DRD2 gene would be most vulnerable to drug abuse even without being exposed to maternal cannabis. However, we must be cognizant that the unfortunate combination of maternal exposure of cannabis in carriers of the A1 form of the DRD2 gene could ultimately lead to uncontrollable substance seeking behavior in later life. A few people who smoke marijuana as a symbolic gesture of defiance might stop using. In contrast, there is increased numbers of users who will become daily indulges. There is also evidence that many chronic marijuana users never move onto heavier drugs of abuse [48].

Proposing RDS Solution

Numerous studies have revealed an association between dopaminergic gene polymorphisms and several reward dependent thoughts and behaviors including addictive, obsessive, compulsive and impulsive tendencies classified as RDS [49]. Previously we associated polymorphisms of both the D2 receptor gene (DRD2), and the Dopamine Transporter gene (DAT1) in RDS subjects derived from two families over five generations of genotyping ($P < 0.001$) [29]. By demonstrating this association, not only do we confirm the role of dopaminergic polymorphisms in RDS behaviors but demonstrate the importance of a nonspecific RDS phenotype. Subsequent studies published and underway reveal the important utility of a novel panel of candidate genes termed “GARS” enabling the stratification of genetically based severity of addiction liability. One study performed in both the United States and China utilizing GARS, revealed that 74% of abstinent psycho stimulant and heroin dependent patients had a moderate to severe genetic liability [50].

Our associates have utilized the CARD in six eastern states and over 24,000 specimens to evaluate two important clinical issues: 1) compliance with prescribed treatment medications during in-patient or out-patient recovery programs; 2) Abstinence from all non-prescribed licit or illicit psycho active drugs. By utilizing CARD we found significant evidence for both non-compliance ($P < 0.0001$) and non-abstinence ($P < 0.0001$) during treatment in all states involved. However there was significant improvement as evaluated through a longitudinal analysis for both compliance to treatment medications and abstinence [51].

This outcome data strongly suggests the need for better therapy. Over the last four decades our laboratory has developed the first

complex dopamine D2 agonist (KB220Z) to significantly enhance brain dopamine “sensitivity” in both the PFC (prefrontal Cortex) and the Cingulate Gyrus (site of relapse) and Nucleus Accumbens (site of reward and craving) utilizing qEEG and fMRI imaging respectively [52]. These latter studies if confirmed will provide the rationale to include KB220Z as a frontline agent to attenuate the negative effect of unwanted hypodopaminergic function or “dopamine resistance” [53]. Certainly utilizing novel methods [54,55] to detect dopamine across the entire brain to assist in determining functional connectivity seems prudent and will result in further understanding of how our dopaminergic pathway predicts future substance and non-substance aberrant seeking behavior [56].

Conclusion

Thus, we are proposing for the first time ever an holistic-therapeutic model for RDS which includes GARS (diagnostic); CARD (outcome measure) and KB220 (prolonged D2 agonist therapy) along with 12 step fellowship and other holistic modalities (e.g. low glycemic index diet; yoga, meditation etc.) known to naturally release neuronal dopamine [53].

Can we overcome DNA polymorphisms by promoting positive epigenetic effects which can be transferred from generation to generation [57]? With this in mind we wonder if we have been “licking our pups” enough, so that we could potentially attenuate substance and non-substance seeking- behaviors through love-understanding that “love needs care” [58,59].

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Conflict of Interest

Kenneth Blum, PhD through his company Synaptamine, Inc., licensed a number of retail companies including RD Solutions, LLC, Victory Nutrition, LLC, Nature's Plus, Inc., Nu pathways, Inc. to market KB220 variants based on issued and pending patents. Dr. Blum also exclusively licensed the Genetic Addiction Risk Score (GARS) to Dominion Diagnostics, LLC in the US, Canada and Europe. Both Dr. Gold and Blum are paid consultants by Rivermend LLC, owners of Malibu Beach Recovery Centers. Gozde Agan is a Dominion Diagnostic intern and James Fratantonio is a Dominion Diagnostic paid employee. There are no other conflicts.

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