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Editorial

Reward Deficiency Solution System (RDS): A Tale of Three Scientists

by separate national institutes for addiction alcohol and narcotics. This concern was highlighted by the original work of Virginia Davis [8], Gerald Cohen [9], Michael Collins [10] and others [11] who found that common neurochemical mechanisms underlie addiction to alcohol and opiates [12]. Blum and his group coined the term *Reward Deficiency Syndrome (RDS)* to describe these mechanisms publishing the concept in the Royal Society of Medicine in 1996 [13].

Working independently Mark Gold proposed an important role for dopamine in the effects of cocaine known as the “Dopamine Depletion Hypothesis” [14] which stands today followed by a plethora of supporting studies [15]. Specifically, the euphoric properties of cocaine lead to the development of chronic abuse, and appear to involve the acute activation of central dopamine (DA) neuronal systems. They proposed that DA depletion results from overstimulation of these neurons and excessive synaptic metabolism of the neurotransmitter. Dopamine 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 the same researchers proposed that one way to treat cocaine addiction was to embrace dopamine agonist therapy such as utilizing the powerful dopamine D2 agonist Bromocriptine. In fact this compound was found to significantly reduce cocaine craving from only a single dose [16]. As such their data 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. In more recent times Lawford et al. [17] reported that in a double-blind study, bromocriptine, a dopamine D2 agonist, 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 dopamine D2 receptor gene (DRD2) gene. 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 [18].

Based on these earlier studies both Blum’s group and Gold’s group continued to propose dopamine agonist therapy rather than dopamine antagonistic therapy currently favored by the approved FDA drugs as medical assisted treatment [19]. Specifically, Blum et al. [20] proposed that D2 receptor stimulation can be accomplished via the use of KB220Z [21], a complex therapeutic nutraceutical formulation that potentially induces DA release, causing the same induction of D2-directed mRNA and thus proliferation of D2

Introduction

Prior to 1990 there was a paucity of studies directed at psychiatric genetics and in fact there was only one study by Egeland et al. [1], whereby an analysis of the segregation of restriction fragment length polymorphisms (RFLP) in an Old Order Amish population (pedigree) localized a dominant gene linked to a strong predisposition to manic depressive disease to chromosome 11 possibly tyrosine hydroxylase. This finding was retracted in 1989 by Kelsoe et al. [2]. 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 [3]. While this sparked some controversy [4] it was confirmed [5] and remains the most widely studied gene in psychiatric genetics and lead to the development of an entire field of medicine (PubMed 8/8/14- 14,661) –known as **Psychiatric Genetics**.

Specifically, drug and alcohol dependence is considered a relapsing chronic condition with compulsive seeking –behavior (including non-substance addictive behaviors) despite harmful negative consequences. 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 [6]. A meta-analysis of the studies carried out by Le Foll et al. [5] evaluating DRD2 and alcohol dependence, indicates a significant association. 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. Others have shown significant linkage between carriers of the DRD2 *Taq A1* allele and familiar alcoholism [7].

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

In 1995, one of us (KB) was concerned by ‘the disconnect’ reflected



receptors in the human. This proliferation of D2 receptors in turn will induce the attenuation of craving behavior. In fact, this model has been proven in research showing 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 [22] as well as cocaine –self administration [23].

Utilizing less powerful dopaminergic repletion therapy to promote long term dopaminergic activation will ultimately lead to a common, safe and effective modality to treat Reward Deficiency Syndrome (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 [24]. It is our hypothesis that D2 receptor stimulation signals negative feedback mechanisms 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. Along these lines Delis et al. [25] observed that in the presence of a stressful environment, low DRD2 levels are associated with increased ethanol intake and preference and that under this condition, increased ethanol consumption could be used as a strategy to alleviate negative mood this also supports dopamine agonist therapy not antagonistic. Moreover, recent work by Willuhn et al. [26] surprisingly found that phasic dopamine decreased in the ventral medium striatum (VSM) as the rate of cocaine intake increased, with the decrement in dopamine in the VMS significantly correlated with the rate of escalation. Moreover, 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 [27].

Understanding the current literature we are further proposing that the true phenotype for addiction is not any one single addictive behavior drug or otherwise but is indeed RDS [28]. The basis of this bold concept has received support from a number of PUBMED listed articles (72 as of 8-12-14). Indeed our laboratory [29] 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 ($P < 0.001$) [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. 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 research has been underscored by the earlier suggestion that food and drugs are both addictive substances and as such share common neurogenetic and neurobiological mechanisms and as such are subsets of RDS [30].

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. These interrelated behaviors involving dopaminergic genes have been classified as Reward Deficiency Syndrome (RDS) [31].

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 [32].

Statistical analysis of data from a urine drug monitoring program; the Comprehensive Analysis of Reported Drugs (CARD) was used to evaluate treatment outcome for RDS, in six eastern states. 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 psychoactive drugs, were evaluated. Significant evidence for both non-compliance ($P < 0.0001$) and non-abstinence ($P < 0.0001$) during treatment was found in all states involved. However there was significant improvement as evaluated through a longitudinal analysis for both compliance to treatment medications and abstinence [33].

This important outcome data strongly suggests the need for better therapy. Over the last four decades our laboratory has developed the first dopamine D2 agonist complex (KB220Z) to significantly enhance brain dopamine “sensitivity in the Prefrontal Cortex (PFC), the Cingulate Gyrus (site of relapse) and Nucleus Accumbens (site of reward and craving) utilizing qEEG and fMRI imaging respectively [34]. 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” [35].

Rajendra D. Badgaiyan has pioneered novel neuroimaging methods [36,37] to detect dopamine across the entire human brain to assist in the determination of functional connectivity. Studies using this methodology will result in further understanding of how our dopaminergic hard –wiring predicts future aberrant substance and non-substance seeking behavior [38].

Conclusion

Thus, we are proposing for the first time ever a 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 [35].

The unanswered question is can we overcome DNA polymorphisms by promoting positive epigenetic effects which can be transferred from generation to generation [39]. We have been “licking our pups” enough? Could we possibly attenuate substance and non-substance seeking- behaviors through love?

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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., Nupathways, 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. There are no other conflicts.

References

- Egeland JA, Gerhard DS, Pauls DL, Sussex JN, Kidd KK, et al. (1987) Bipolar affective disorders linked to DNA markers on chromosome 11. *Nature* 325: 783-787.
- Kelsoe JR, Ginns EI, Egeland JA, Gerhard DS, Goldstein AM, et al. (1989) Re-evaluation of the linkage relationship between chromosome 11p loci and the gene for bipolar affective disorder in the Old Order Amish. *Nature* 342: 238-2343.
- Blum K, Noble EP, Sheridan PJ, Montgomery A, Ritchie T, et al. (1990) Allelic association of human dopamine D2 receptor gene in alcoholism. *JAMA* 263: 2055-2060.
- Baron M (1993) The D2 dopamine receptor gene and alcoholism: a tempest in a wine cup? *Biol Psychiatry* 34: 821-823.
- Le Foll B, Gallo A, Le Strat Y, Lu L, Gorwood P (2009) Genetics of dopamine receptors and drug addiction: a comprehensive review. *Behav Pharmacol* 20: 1-17.
- Di Chiara G, Imperato A (1988) Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci USA* 85: 5274-5278.
- Hill SY, Hoffman EK, Zezza N, Thalamuthu A, Weeks DE, et al. (2008) Dopaminergic mutations: within-family association and linkage in multiple-alcohol dependence families. *Am J Med Genet B Neuropsychiatr Genet* 147B: 517-526.
- Davis VE, Walsh MJ (1970) Alcohol addiction and tetrahydropapaveroline. *Science* 169: 1105-1106.
- Cohen G, Collins M (1970) Alkaloids from catecholamines in adrenal tissue: possible role in alcoholism. *Science* 167: 1749-1751.
- Collins MA, Kahn AJ (1982) Attraction to ethanol solutions in mice: induction by a tetrahydroisoquinoline derivative of L-DOPA. *Subst Alcohol Actions Misuse* 3: 299-302.
- Hamilton MG, Blum K, Hirst M (1978) Identification of an isoquinoline alkaloid after chronic exposure to ethanol. *Alcohol Clin Exp Res* 2: 133-137.
- Blum K, Hamilton MG, Hirst M, Wallace JE (1978) Putative role of isoquinoline alkaloids in alcoholism: a link to opiates. *Alcohol Clin Exp Res* 2: 113-120.
- Blum K, Sheridan PJ, Wood RC (1996) The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. *J R Soc Med* 89: 396-400.
- Dackis CA, Gold MS (1985) New concepts in cocaine addiction: the dopamine depletion hypothesis. *Neurosci Biobehav Rev* 9: 469-477.
- Freund N, MacGillivray HT, Thompson BS, Lukkes JL, Stanis JJ, et al. (2014) Sex-dependent changes in ADHD-like behaviors in juvenile rats following cortical dopamine depletion. *Behav Brain Res*. 2014 Aug 15; 357-63.
- Dackis CA, Gold MS, Sweeney DR, Byron JP Jr, Climko R (1987) Single-dose bromocriptine reverses cocaine craving. *Psychiatry Res* 20: 261-264.
- Lawford BR, Young RM, Rowell JA, Qualicheckski J, Fletcher BH, et al. (1995) Bromocriptine in the treatment of alcoholics with the D2 dopamine receptor A1 allele. *Nat Med* 1: 337-341.
- Bogomolova EV, Rauschenbach IY, Adonyeva NV, Alekseev AA, Faddeeva NV, et al. (2010) Dopamine down-regulates activity of alkaline phosphatase in *Drosophila*: the role of D2-like receptors. *J Insect Physiol* 56: 1155-1159.
- Volkow ND, Frieden TR, Hyde PS, Cha SS (2014) Medication-assisted therapies--tackling the opioid-overdose epidemic. *N Engl J Med*. 370: 2063-2066.
- Blum K, Chen AL, Chen TJ, Braverman ER, Reinking J, et al. (2008) Activation instead of blocking mesolimbic dopaminergic reward circuitry is a preferred modality in the long term treatment of reward deficiency syndrome (RDS): a commentary. *Theor Biol Med Model* 5: 24.
- Blum K, Oscar-Berman M, Stuller E, Miller D, Giordano J, et al. (2012) 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* 3: 139.
- Thanos PK, Rivera SN, Weaver K, Grandy DK, Rubinstein M, et al. (2005) Dopamine D2R DNA transfer in dopamine D2 receptor-deficient mice: effects on ethanol drinking. *Life Sci* 77: 130-139.
- Thanos PK, Michaelides M, Umegaki H, Volkow ND (2008) D2R DNA transfer into the nucleus accumbens attenuates cocaine self-administration in rats. *Synapse* 62: 481-486.
- Blum K, Gardner E, Oscar-Berman M, Gold M (2012) "Liking" and "wanting" linked to Reward Deficiency Syndrome (RDS): hypothesizing differential responsivity in brain reward circuitry. *Curr Pharm Des* 18: 113-118.
- Delis F, Thanos PK, Rombola C, Rosko L, Grandy D, et al. (2013) Chronic mild stress increases alcohol intake in mice with low dopamine D2 receptor levels. *Behav Neurosci* 127: 95-105.
- Willuhn I, Burgeno LM, Groblewski PA, Phillips PE (2014) Excessive cocaine use results from decreased phasic dopamine signaling in the striatum. *Nat Neurosci* 17: 704-709.
- Caprioli D, Calu D, Shaham Y (2014) Loss of phasic dopamine: a new addiction marker? *Nat Neurosci* 17: 644-646.
- Blum K, Oscar-Berman M, Demetrovics Z, Barh D, Gold MS (2014) Genetic Addiction Risk Score (GARS): Molecular Neurogenetic Evidence for Predisposition to Reward Deficiency Syndrome (RDS). *Mol Neurobiol* [Epub ahead of print].
- Blum K, Chen AL, Oscar-Berman M, Chen TJ, Lubar J, et al. (2011) Generational association studies of dopaminergic genes in reward deficiency syndrome (RDS) subjects: selecting appropriate phenotypes for reward dependence behaviors. *Int J Environ Res Public Health* 8: 4425-4459.
- Blum K, Liu Y, Shriner R, Gold MS (2011) Reward circuitry dopaminergic activation regulates food and drug craving behavior. *Curr Pharm Des* 17: 1158-1167.
- Blum K, Oscar-Berman M, Barh D, Giordano J, Gold M (2013) Dopamine Genetics and Function in Food and Substance Abuse. *J Genet Syndr Gene Ther* 4. pii: 1000121.
- Blum K, Oscar-Berman M, Dinubile N, Giordano J, Braverman ER, et al. (2013) Coupling Genetic Addiction Risk Score (GARS) with Electrotherapy: Fighting Iatrogenic Opioid Dependence. *J Addict Res Ther* 4: 1000163.
- Blum K, Han D, Femino J, Smith DE, Saunders S, et al. (2014) 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 9: e104275.
34. Blum K, Chen TJ, Morse S, Giordano J, Chen AL, et al. (2010) Overcoming qEEG abnormalities and reward gene deficits during protracted abstinence in male psychostimulant and polydrug abusers utilizing putative dopamine D agonist therapy: part 2. Postgrad Med 122: 214-226.
35. Blum K, Femino J, Teitelbaum S, Giordano J, Oscar-Berman M, et al. (2013) “Molecular Neurobiology of Addiction Recovery”: The 12 Step Program & Fellowship. Springer Briefs in Neuroscience, Springer New York.
36. Badgaiyan RD, Fischman AJ, Alpert NM (2003) Striatal dopamine release during unrewarded motor task in human volunteers. Neuroreport 14: 1421-1424.
37. Badgaiyan RD (2014) Imaging dopamine neurotransmission in live human brain. Prog Brain Res 211: 165-182.
38. McLaughlin T, Oscar-Berman M, Simpatico T, Giordano J, Jones S, et al. (2013) Hypothesizing repetitive paraphilia behavior of a medication refractive Tourette's syndrome patient having rapid clinical attenuation with KB220Z-nutrigenomic amino-acid therapy (NAAT). Journal of Behavioral Addictions 2: 117-124.
39. Starkman BG, Sakharkar AJ, Pandey SC (2012) Epigenetics-beyond the genome in alcoholism. Alcohol Res 34: 293-305.

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