

A Systems Biological Approach Coupling Reward Gene Polymorphisms and a Nutraceutical (KB220Z) Pro-Dopamine Regulator (PDR) as Putative “Standard of Care” to Treat Reward Deficiency Syndrome (RDS): Emerging Evidence - Based Scientific Induction of “Dopamine Homeostasis”

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Abstract

The purpose of this editorial is to inform the entire scientific community, but more importantly the clinicians and professional on the front-line of caring for the victims of individuals with Reward Deficiency Syndrome (RDS) and a remarkable array of addictive, impulsive and compulsive behaviors. Over the last two decades, changes in the nomenclature of addictions suggest a significant shift in the conceptualization of addictions, where non-substance related behaviors can also be classified as addictions. A large amount of data provides empirical evidence that there are overlaps of different types of addictive behaviors in etiology, phenomenology, and in the underlying psychological and biological mechanisms. Recent results suggest a large overlap between the existence of these addictions and behaviors and underlies the importance of analyzing the possible common psychological, genetic and neural pathways. Most importantly, exhaustive data to date, further support concepts such as the Reward Deficiency Syndrome and the component model of addictions that propose a common phenomenological and etiological background of different addictive and related behaviors. With this information and known mechanisms of various neurotransmitter interactions in the brain reward circuitry, we should be “thinking out of the box” in face of a serious devastating opioid and other drugs crisis. We question the wisdom of the continued utilization of only reducing harm and not epigenetically attempting to repair either the trait (genetic) or state (epigenetic) neurochemistry of the brain reward circuit, especially during the known unwanted fatalities of modern day. The Opioid Crisis as eloquently discussed in Oesterle., et al. echoes these remarks. Finally, we are proposing that, in order, to successfully combat the widespread abuse of drugs and even non-drug behaviors (e.g. gambling etc.), one option, is to consider induction of “dopamine homeostasis” WC 285.

Keywords: Reward Deficiency Syndrome (RDS); Dopamine Homeostasis, Genetic Addiction Risk Score (GARS), Pro-dopamine regulator (PDR), systems biological approach, Precision Behavioral Management (PMB)

Introduction

A ‘systems biology’ therapeutic approach, in contrast to a reductionist approach, is not intended to blunt, block, inhibit, or mask a symptom(s) [1,2]. The systems biology approach relies primarily on therapeutic nutritional strategies to contribute molecular building blocks for the synthesis of the > 37 trillion cells that make up tissues, organs, and systems of the body. It is worthwhile to add that systems biology provides the most important criteria for optimal biological functioning via the effective monitoring and interactive feedback of bio-physiochemical signaling/functions of genes, proteins, and their metabolites that assess and regulate metabolic and signaling pathways, which guide biological behaviors [2]. ‘Systems biology’ characterizes the protein-ligand communication on a massive scale. System functionality requires nourishment and synthesis of molecular components necessary to optimize interactive, interdependent biological functions that positively influence the functional relationships and mechanistic interactions of an entire ‘suite’ (or ‘system’) of biomolecules. This effect is achieved through nutritional/nutrigenomic improvements (i.e. nutrition that influences gene expression, which influences system ‘functional behavior’). Unlike the systems approach, most often, the reductionist therapies have a significant list of potentially serious side effects [3]. However, reductionist therapies have had an important role in reducing and managing symptoms of acute crises. The take home message here, a systems biological paradigm is to provide nutritional resources that enable the body to create the ideal biological environment to optimize gene expression; enable optimal molecular arrangements and cellular, tissue, organ, and system functions to avail overall health and optimal systemic functionality. Finally, a systems biology approach promotes epigenetic corrections and biological recalibration by relying primarily on nutritional strategies to contribute molecular building blocks for synthesis of trillion cells that make up tissues, organs, and systems of the body [4].

Following the genetic work of Blum Noble, *et al.* [5] showing the novel association of the dopamine D2 receptor gene Taq A1 [DRD2A1] and severe alcoholism, on 6/30/20 there are a total of 5,032 articles listed in PUBMED using the term “dopamine D2 receptor Gene.” To date there is universal scientific confirmation concerning this first known association with alcoholism and of cause many addictive behaviors drug and non-drug, we termed in 1995 “Reward Deficiency Syndrome” (RDS) [5-8]. Certainly, there is strong genetic evidence revealing overlap on many psychiatric conditions as known subtypes to RDS [9]. Stemming from the initial concept of RDS, it is well-known that brain disorders exhibit epidemiological comorbidity and often share symptoms, provoking debate about their etiologic overlap. Brainstorm Consortium, *et al.* [9] quantified the genetic sharing of 25 brain disorders from genome-wide association studies of 265,218 patients and 784,643 control participants and assessed their relationship to 17 phenotypes from 1,191,588 individuals. They importantly found common genetic variations as risk factors for psychiatric disorders supporting the RDS concept.

Related to our proposal herein calling for novel ways to induce “dopamine homeostasis” to treat all RDS behaviors especially drug induced, there are two facets that provide a powerful integrative systems approach and include: 1) accurate candidate genetic risk testing for RDS behaviors at any age as early as possible to assist in the process of intervention therapies 2) induction of a systems biological approach primarily via nutrigenomic principles.

Our profane proposal is long overdue based on the unforeseen implosion of fatalities due to over prescribing of powerful addictive analgesics resulting in over 185 people dying every day due to opioid overdose [10]. In this regard over the three decades Blum’s group developed a novel patented Genetic Addiction Risk Score (GARS) testing panel involving ten reward genes and eleven individual singular risk alleles (SNPS). To date utilizing this genetic health risk test not for actual diagnosis, but risk liability is showing promise in the RDS related field [5,6,11-42]. In terms of the second required factor that loads onto the idea of “standard of care” the following published literature provides evidence based data showing many improved outcomes using the well-researched Pro-dopamine regulator (PDR) KB220 variants [43-72].

This KB220 variant has been the subject of at least 43 clinical and pre-clinical studies showing anti- RDS addictive behaviors via dopaminergic mechanisms (See annotated bibliography and review by Blum, *et al.* [43]) and figure 1).



Figure 1: Schematic showing list of RDS benefits of KB220 variants.

Summary

The scientific evidence is clear, dopamine is a major neurotransmitter pathway having important neurochemical effects whereby its deficit or dysfunction can lead to aberrant drug seeking behaviors [73]. The evidence for genetic vulnerability as an important antecedent to this unwanted behavior may be a determinant factor which must be identified early in life possibly in the future at birth rather than post-addiction to both drugs and non-drug behaviors termed RDS [74]. Based on a rather moderate published literature the role of reward gene polymorphisms set-up individuals with an increased risk for all subtypes of RDS behaviors including anhedonia [75]. With this mind our laboratory has developed the novel patented GARS test to help identify one’s risk for these addictive-like behaviors [12]. Even prior to this genetic test Blum’s laboratory developed a Pro-Dopamine Regulator (PDR) having KB220 nutraceutical complex as the primary constituent ingredient base [76]. Most recently, the coupling of GARS with KB220 variants whereby a semi-customized precision PDR matched to one’s GARS provided an increased efficacy in terms of treating RDS [38]. While it is generally accepted that balancing the brain reward circuit or achievement of “Dopamine Homeostasis” is a laudable goal, instead of blocking natural dopamine or administering a powerful opioid to overcome opioid addiction [77]. We are encouraging both the neuroscience and clinical science community to potentially embrace this disruptive technology with a futuristic view of addressing the notion of what constitutes “standard of care” in the face of our current opioid/psychostimulant/alcohol crisis [78]. While more research is required, out-of-the-box thinking, at least to initiate acceptable guidelines that include the understanding of RDS as an umbrella terminology for all addictive behaviors, can be morphed by utilizing a systems biological approach as outlined herein.

Conclusion

Balancing the brain reward circuit or achievement of “Dopamine Homeostasis” is a plausible goal, instead of blocking natural dopamine or administering a powerful opioid to overcome opioid addiction [64]. Both the neuroscience and clinical science community should

potentially embrace this disruptive technology with a futuristic view of addressing the notion of what constitutes “standard of care” in the face of our current opioid/psychostimulant/alcohol and food addiction pandemic. Certainly, more research is required, but in the spirit of making progress, we encourage important key opinion leaders in the addiction medicine space such as the certified specialists aligned with the American Society of Addiction Medicine (ASAM) to at least initiate acceptable guidelines that include the understanding of RDS as an umbrella terminology for all addictive behaviors. Understanding the importance of neurogenetics as pointed out herein, the scientific community utilizing a systems biological approach (Precision Behavioral Management) seems most prudent and represents a step forward in redeeming joy to the multi-billions afflicted globally.

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