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Opinion

Should We Embrace the Incorporation of Genetically Guided "Dopamine Homeostasis" in the Treatment of Reward Deficiency Syndrome (RSD) as a Frontline Therapeutic Modality?

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Abstract

In 2019, the US Center for Disease Control and Prevention provided vital statistics related to drug overdoses in the United State1. They concluded that in the USA the number of deaths at almost 72,000 was due to 66.6% of opioid overdoses. In fact, the rate is alarming and increasing yearly. To make 2021 even more scary is the daunting effect on increased drug usage due to COVID 19 as a pandemic, albeit the new vaccines. Specifically, in 2020, the death rate from opioid overdoses rose to 13% nationally and in some sates 30%. The common neuromodulating aspects of neurotransmission, and its disruption via chronic exposure of drugs and behavioral addictions, requires further intense research focus on developing novel strategies to combat these unwanted genetic and epigenic infractions as accomplished with heroin addiction by our group. The take home message is the plausible acceptance of the well-established evidence for hypodopaminergia, a blunted reward processing system, reduced resting state functional connectivity, genetic antecedents, anti- reward symptomatology, poor compliance with MAT, and generalized RDS. With this evidence it is conceivable that pursuit through intensive future research should involve an approach that incorporates "dopamine homeostasis". This required paradigm shift may consist of many beneficial modalities including but not limited to: exercise, pro-dopamine regula-

tion, nutrigenomics, cognitive behavioral therapy, hedonic hot spot targets brain, rTMRS, deep brain stimulation, diet, genetic edits, genetic guided therapeutics, epigenetic repair, amongst others. It is our opinion that nutrigenomics may assist the millions of people of getting out of a" hypodopaminergic ditch" WC 250.

Keywords: Reward Deficiency Syndrome; Anti reward Symptomatology; Hypodopaminergia; Genetic Addiction Risk Severity (GARS) Testing; Dopamine Homeostasis

Opinion

This perspective is proposing a unique combination coupling the compound Glutathione with known Enkephalinase Inhibitors as well as enkephalin and dopamine releasing compounds from a group of said inhibitors including but limited to DL-Phenylalanine to help detoxify and treat individuals diagnosed with Reward Deficiency Syndrome (RDS) utilizing a newly validated RDS index as well as genetic testing [1-5].

The preferred method of delivery is intravenous therapy or aqua-power imprints of the molecular structure including but not limited to NAD/NADH, glutathione and Dl-Phenylalanine [6]. It is also a preferred that a genetic addiction risk severity testing system will be utilized to determine a precision based oral formulae utilizing DNA for guided precision therapy [7]. It is theorized that coupling of outcome results following a DNA test with a minimum of four genes and four alleles [8].

This novel testing system we call Genetic Addiction Risk Severity (GARS®) will be followed up with additional steps to customize or semi-customize preferred formulae to be utilized to not only detoxify but to treat RDS victims [9]. It is anticipated that the novel utilization of a genetic risk testing system to prevent relapse in people in recovery or prior to entering a pain clinic to categorize ones' risk for subsequent opioid use disorder (OUD) is a required to reduce the overall death rates [10].

We hereby believe that this important disruptive industrial technology along precision epigenetic repair of infractions within the brain reward circuit due either to nature (genetic) or nurture(epigenetic) may eventually become a standard of care to treat RDS [11]. It is well established that in both food- and drug-addicted individuals, there is dopamine resistance due to an association with the DRD2 gene A1 allele among other dopamine related genetic polymorphisms [12]. Evidence is emerging whereby the potential of utilizing a natural, non-addicting, safe, putative D2 agonist may find its place in recovery from reward deficiency syndrome (RDS) in patients addicted to psychoactive chemicals [13]. Utilizing quantitative electroencephalography (qEEG) as an imaging tool, we have shown the impact of a KB220 variant as a putative activator of the mesolimbic system [14,15]. We demonstrated for the first time that its intravenous administration reduces or "normalizes" aberrant electrophysiological parameters of the reward circuitry site [16]. For that published pilot study, we report that the qEEG's of an alcoholic and a heroin abuser with existing abnormalities (i.e., widespread theta and widespread alpha activity, respectively) during protracted abstinence are significantly normalized by the administration of one intravenous dose of KB220 [2]. Specifically, both patients were genotyped for neurotransmitter reward genes to determine to what extent they carry putative dopaminergic risk alleles that may predispose them for alcohol or heroin dependence, respectively. The genes tested included the dopamine transporter (DAT1, locus symbol SLC6A3), dopamine D4 receptor exon 3 VNTR (DRD4), DRD2 TaqIA (rs1800497), COMT val158 met SNP (rs4680), monoamine oxidase A upstream VNTR (MAOA-uVNTR), and serotonin transporter-linked polymorphic region (5HTTLPR, locus symbol SLC6A4) [2,17,18].

We emphasize that these are many people that possess a high GARS at least in America [20], and it would be unlikely for all individuals to carry all putative risk alleles. Based on previous research and our qEEG studies), we cautiously suggest that long-term gentle activation of dopaminergic receptors (ie, DRD2 receptors) will result in their proliferation and lead to enhanced "dopamine sensitivity" and an increased sense of happiness, particularly in carriers of the DRD2 A1 allele [21,22].

This is supported by a clinical trial on KB220 variant using intravenous administration in > 600 alcoholic patients, resulting in significant reductions in RDS behaviors. It is also confirmed by the

expanded oral study on KB220 variant [23]. Future studies must await both functional magnetic resonance imaging and positron emission tomography scanning to determine the acute and chronic effects of oral KB220 on numbers of D2 receptors and direct interaction at the nucleus accumbens. Confirmation of these results in large, population-based, case-controlled experiments is necessary. These studies would provide important information that could ultimately lead to significant improvement in recovery for those with RDS and dopamine deficiency as a result of a multiple neurotransmitter signal transduction infractions in the brain reward cascade [24-26].

Moreover, the powerful effects of KB220 as evidenced by more recent neuroimaging studies have clearly showed the importance of Pro-dopamine regulation along the Brain Reward Cascade (BRC) (see figure 1).

Figure 1: Illustrates the interaction of at least seven major neurotransmitter-pathways involved in the Brain Reward Cascade (BRC). In the hypothalamus, environmental stimulation causes the release of serotonin, which in turn via, for example, 5HT-2a receptors activate (green equal sign) the subsequent release of opioid peptides from opioid peptide neurons, also in the hypothalamus. Then, in turn, the opioid peptides having two distinct effects, possibly via two different opioid receptors. One that inhibits (red hash sign) through the mu-opioid receptor (possibly via enkephalin) and projecting to the Substania Nigra to GABAA neurons. Another stimulates (green equal sign) Cannabinoid neurons (e.g., Anandamide and 2-archydonoglcerol) through Beta –Endorphin linked delta receptors, which in turn inhibits GABAA neurons at the substania nigra. Cannabinoids primarily 2-archydonoglcerol, when activated, can also indirectly disinhibit (red hash sign) GABAA neurons in the Substania Nigra through activation of G1/0 coupled to CB1 receptors. Glutamate neurons located in the Dorsal Raphe Nuclei (DRN) can indirectly disinhibit GABAA neurons in the Substania Nigra through activation of GLU M3 receptors (red hash sign). GABAA neurons, when stimulated, will, in turn, powerfully (red hash signs) inhibit VTA glutaminergic drive via GABAB 3 neurons. It is also possible that stimulation of ACH neurons that at the Nucleus Accumbens ACH can stimulate both muscarinic (red hash) or Nicotinic (green hash). Finally, Glutamate neurons in the VTA will project to dopamine neurons through NMDA receptors (green equal sign) to preferentially release dopamine at the Nucleus Accumbens (NAc) shown as a bullseye indicates a euphoria, or "wanting" response. The result is that when Dopamine release is low (unhappiness: Endorphin Deficiency). At the same time, general (usual) happiness depends on the dopamine homeostatic tonic set point (see figure 2). With Permission Blum., *et al.* [25].

In the midst, of the COVID 19 pandemic, there is also a global addiction crisis worldwide [27]. The devastation and deaths due to drug overdose, being highest in the United States is indeed a global issue requiring novel approaches [28]. The incorporation of opioids to treat the same problem with powerful opioids seems too simplified, albeit quite successful in reducing harm [29], but locks people in unwanted addiction [30]. Our group has been cognizant that while one primary benefit is to reduce harm, there is a paucity f studies providing evidence to address the root cause of RDS hypodopaminergia [31].

An additional approach is to utilize the narcotic antagonist Naltrexone especially implants [32], to induce "psychological extinction" via blocking D2 receptors [33]. The latter approach seems to be more acceptable, relative to treating opioids with opioids such as methadone and buprenorphine based on genotype [34], but compliance is a major issue due to long-term antireward properties [35]. The approved drug acamprosate, a NMDA receptor antagonist and a positive allosteric modulator of $GABA_A$ receptors disturbs dopaminergic signaling resulting in chronic hypodopaminergia [36]. Understanding the above premise and the further emerging acceptance of the umbrella term Reward Deficiency Syndrome (RDS) first coined by Blum in 1995, facilitates the co-occurrence mechanism hypothesis for drug and non -addictive behaviors [37].

Understanding the common neuromodulating aspects of neurotransmission and its disruption via chronic exposure of drugs and behavioral addictions, requires further intense research focus on developing novel strategies to combat these unwanted genetic and epigenic infractions [38] as accomplished with heroin addiction (see figure 2).

Conclusion

The take home message is the plausible acceptance of the well-established evidence for hypodopaminergia [39], a blunted reward processing system [40], reduced resting state functional connectivity [41], genetic antecedents [42], anti- reward symptomatology [43], poor compliance with MAT [44], and generalized RDS [45]. With this evidence it is conceivable that pursuit through intensive future research should involve an approach that incorporates "dopamine homeostasis". This required paradigm shift may consist of

Figure 2: The Reward Deficiency Syndrome Identification and Treatment model.

many beneficial modalities including but not limited to: exercise [46], pro-dopamine regulation [47], nutrition [48], cognitive behavioral therapy [49], hedonic hot spot targets brain [50], rTMRS [51], deep brain stimulation [52], diet[53], genetic edits [54], genetic guided therapeutics [55], epigenetic repair [56], amongst others related to augmented resting state functional connectivity [57].

We believe that "out of the box thinking" in the face the of the continued drug/behavioral addiction crisis during the current viral pandemic, and innovative systems biological approaches of any one singular, therapeutic target site may indeed become a frontline defense to prevent and or treat RDS like behavior. Nutrigenomics may assist the millions of people of getting out of a "hypodopaminergic ditch" [58].

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Contribution of Authors

KB wrote the initial manuscript. AB developed the pictorial model. All the coauthors reviewed and made edits and comments equally.

Conflict of Interest

KB is the inventor of GARS and Pro-dopamine regulator (KB220) either owned and or licensed to his various companies (Geneus Health LLC, Synaptamine, Ivitalize). BWD and DB are employed by Victory Nutrition International (VNI) and the recipient GARS and KB220Z license AR, TS, RH, RG, RB are supported in part by Ivitalize. Vis employment, or consultation services.AR is a member of Ivitalize Board of Directors. There are no other conflicts to report.

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