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EC PSYCHOLOGY AND PSYCHIATRY
Editorial

Translational and Molecular Cytoarchitectural Genetic Guided Therapy to Induce Dopamine Homeostatic Neuro-signaling in Reward Deficiency and Associated Drug and Behavioral Addiction Seeking: A 60 Year Sojourn the Future is Now

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Received: July 26, 2021; **Published:** July 29, 2021

All addictions both drug and behavioral are considered debilitating disorders for the individual and very costly for society in the trillion dollar range globally [1]. Generally, it is accepted that while positive reinforcement may be a deterrent even in the face of polymorphic DNA reward genes, epigenetic negative reinforcement can be a trigger in the early stages of seeking behavior by self-medicating people [2]. It is well-known that while acute use of both substance and non-substance aberrant behavioral seeking increases the release of neuronal dopamine (DA) in the shell of the Nucleus Accumbens (NAc) [3], chronic abuse significantly reduces DA release thereby inducing changes in neural circuits that control motivational processes, including arousal, reward, cognition and stress [4].

The search for translational, solutions began in Blum's' laboratory in the late 60's related to dopamine and peripheral tremors in cats having importance to Parkinsonism [5]. Number of follow-up studies initially provided the first evidence for the anti- ethanol effects of narcotic antagonist paving the way for Naltrexone as a treatment for reward deficiency [6,7]. Additional work related to animal genetics that revealed the important role of endorphins, especially methionine -enkephalin in alcohol intake in genetically bred rodents [8]. As a result of this work, Blum., *et al*. [9] showed that chronic alcohol intake in Golden Syrian Hamsters had profound synthesis inhibition of endogenous Leu-enkephalin, in the basal ganglion.

During the mid- 80s, it was discovered that utilizing substances that inhibit the enzyme carboxypeptidase, like D-Phenylalanine, raised brain endorphins and significantly reduced ethanol intake in high alcohol [10].

Gold and Blum's early work led to the classic concept of DA depletion in psychostimulant abuse (i.e. cocaine) and DA and norepinephrine's (NE) role in alcohol/opiate withdrawal [11,12]. The wide-spread use of Clonidine or other alpha-agonists was first proposed by Gold's group [13] leading to concept of the dopamine depletion hypothesis [14].

In the 1990's Blum and Noble discovered the first genetic association of the DRD2 A1 allele and others severe alcoholism/reward deficit [15]. Recent support from Gelernter's Yale group revealed that GWAS on 2.5 million Veterans with major depression carried polymorphic alleles of the DRD2 gene as a top candidate [16]. In 1995, Blum coined the term "Reward Deficiency Syndrome (RDS)" [17] now featured in Sage Encyclopedia as a clinical psychological disorder. Twenty-five years later, came the development of the patented USA and European Genetic Addiction Risk Severity (GARS®) test [18]. The test consists of ten reward genes and eleven risk alleles that reflect a hypodopaminergia across the brain reward circuitry. Coupling the GARS test with matched allelic Pro-dopamine Regulation (KB220) in a number of both animal and human abstinent heroin and psychostimulant misusers, has been shown to induce "Dopamine Homeostasis" [19-21].

Moreover, in a large Alcohol-Use Disorder (AUD) meta-analysis representing approximately 110,000 cases and 120,000 controls utilizing the various risk alleles measured in GARS, we found significant Odds Ratios (ODs) for 8 of the 10 Genes and associated alleles in

favor of cases (DRD1-4, DAT1, COMT, OPMR, 5-HTTLR) [22]. The GARS test, not a diagnostic but a genetic risk assessment [23], has shown promise as a tool for early identification in SUD [24], medical monitoring capabilities [25], obesity[26] and eating disorder risk [27], high risk for addiction liability in pain clinics [28], negative emotionality in chronic Cannabis misusers [29], prediction of clinical outcomes in Bariatric patients [30,31], profound reduction of prison time for DWI offenders adjudicated to rehabilitation [32] and even in terms of providing genetic risk in children of alcoholics (COAs) [33].

Over many decades of research, a number of investigators provided a translational and molecular cytoarchitectural framework related to both genetic and epigenetic insults on reward deficiency and drugs of abuse [34,35], gene therapy [36,37] neurotransmitters and exercise [38] molecular mechanism of pain and anti-reward symptomatology [39] and unique dopamine measurement across the brain reward circuitry [40]. Based on this work we are suggesting a paradigm shift "Precision Behavioral Management®" whereby the future is now [41].

Author Contribution

KB developed the first draft and RDB commented and help edit and added to the manuscript.

Conflict of Interest

KB is the inventor of a number of USA and Foreign patents related to, genetic testing and Pro-dopamine regulation (KB220) licensed Ivitalize Inc.

Funding Support

KB is the recipient of a NIHD grant with Marjorie Gondre Lewis -R41 MD012318/MD/NIMHD NIH HHS/United States; RDB is the recipient of I01 CX000479/CX/CSRD VA/United States/VA United States.

Acknowledgements:

We appreciate the edits of Margaret A Madigan. The authors would like to thank Richard Green of Precision Translational Medicine located in San Antonio, TX., for the term " the future is now.

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Volume 10 Issue 8 August 2021