

# Molecular neuro-biological and systemic health benefits of achieving dopamine homeostasis in the face of a catastrophic pandemic (COVID-19): A mechanistic exploration

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## Abstract

In the face of the global pandemic of COVID 19, approaching 1.75 Million infected worldwide (4/12/2020) and associated mortality (over 108,000 as of 4/12/2020) as well-as other catastrophic events including the opioid crisis, a focus on brain health seems prudent [1] (<https://www.coronavirus.gov>). This manuscript reports on the systemic benefits of restoring and achieving dopamine homeostasis to reverse and normalize thoughts and behaviors of Reward Deficiency Syndrome (RDS) dysfunctional conditions and their effects on behavioral physiology; function of reward genes; and focuses on digestive, immune, eye health, and the constellation of symptomatic behaviors. The role of nutrigenomic interventions on restoring normal brain functions and its benefits on these systems will be discussed. We demonstrate that modulation of dopamine homeostasis using nutrigenomic dopamine agonists, instead of pharmaceutical interventions, is achievable. The allied interlinking with diverse chronic diseases and disorders, roles of free radicals and incidence of anaerobic events have been extensively highlighted. In conjunction, the role of dopamine in aspects of sleep, rapid eye movement and waking are extensively discussed. The integral aspects of food indulgence, the influence of taste sensations, and gut-brain signaling are also discussed along with a special emphasis on ocular health. The detailed mechanistic insight of dopamine, immune competence and the allied aspects of autoimmune disorders are also highlighted. Finally, the integration of dopamine homeostasis utilizing a patented gene test and a research-validated nutrigenomic intervention are presented. Overall, a cutting-edge nutrigenomic intervention could prove to be a technological paradigm shift in our understanding of the extent to which achieving dopamine homeostasis will benefit overall health.

## Introduction: The proposal

Since November/December of 2019, a series of patients with atypical pneumonia have been reported in Wuhan, China. On 12 January 2020, the World Health Organization (WHO) temporarily named this new virus as the 2019 novel coronavirus (2019-nCoV) and on 11 February 2020, the disease caused by the 2019-nCoV was named coronavirus disease (COVID-19). The COVID-19 pandemic has spread all over the world. To make matters worse the USA is still facing over 185 deaths per day due to the opioid epidemic. Together these catastrophes not only caused hundreds of thousands of premature fatalities, but the entire globe is under enormous stress

because currently there is no treatment for this disease. There is therefore a need for out of the box thinking [2,3].

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It is well-known that many polymorphic genes, particularly the genetic determinants of hypodopaminergia, are associated with Substance Use Disorder (SUD). These genes are also associated with a predisposition to stress [4,5]. The National Institutes of Health (NIH) support neuroimaging research and molecular genetic applied technologies to improve understanding of the complex functions of brain reward circuitry that play crucial roles in addiction and stress symptomatology [6].

It is noteworthy that mice lacking adaptive immunity are significantly more susceptible to develop psychiatric symptoms like PTSD when compared with mice that have normal immune systems [7].

In this context it is worth mentioning that raising Endorphinergic function significantly increases the immune response. On the contrary, chronic administration of exogenous opioids significantly suppresses the immune response and increase vulnerability to infections. Moreover, exogenous opioids such as morphine and fentanyl have been found to impair the function of macrophages, natural killer cells and T-cells and to weaken the gut barrier in vitro and in animal studies. However, in contrast, immune cells, including neutrophils, macrophages and T-cells, have been shown to secrete endogenous opioid peptides such as endorphins, enkephalins and dynorphins, which then bind to peripheral opioid receptors to relieve inflammatory and neuropathic pain. In addition to cytokines, hormones and bacterial products, the release of opioid peptides is stimulated by the application of exogenous opioids [8]. Along these lines, Blum's work validated by neurochemical measurements, showed that the enkephalinase inhibitor D-Phenylalanine (DPA) not only increases brain endorphins in animal models but also reduces stress in humans [9,10]. Importantly, there are a large number of interactions at molecular and cellular levels between the nervous system and the **immune** system. Certainly, Janković & Radulović, demonstrated that the opioid neuropeptide methionine-**enkephalin** (Met-Enk) is involved in humoral and cell-mediated **immune** reactions [11]. Therefore, based on this previous research, one way to treat catastrophic stress is to enhance endorphin function by utilization of enkephalinase inhibitors like DPA.

Relevant genotype-phenotype relationships can be characterized using the Genetic Addiction Risk Score (GARS) [12]. Based on GARS values, dopamine homeostasis may be achieved via customization of neuro-nutrient supplementation with particular emphasis on enhancement of immunological function [13-16]. Precision Behavioral Management (PBM), and putative pro-dopamine regulation should be accompanied by interventions like mindfulness and trauma therapy. Recognizing the immune system as a "sixth sense" may shift the paradigm in treating such disorders [17-21]. This out of the box

thinking is hereby supported by the following commentary provided in this treatise.

### Understanding reward deficiency syndrome (RDS)

It is well established that integrity of the neurotransmitter system is essential for normal homeostatic functioning of the brain. Discovering and understanding Reward Deficiency Syndrome (RDS) and defining how genetic factors underlying aberrant neurotransmission in RDS behaviors are influenced by lifestyle activities (i.e. epigenetics) has been the life's work of one of our authors (KB). The primary research objective has been identifying genetic predispositions that induce the expansive range of RDS dysfunctional conditions and behaviors, restoring dopamine homeostasis with nutrigenomic interventions, thereby restoring normal brain function, reward processing and the integrity of resting-state functional connectivity essential for healthy homeostatic functioning [22]. Discovery of the association of severe alcoholism with the Dopamine D2 Receptor TaqI A1 allele by Blum and Noble was published in JAMA in 1990 [23]. Continued efforts to challenge or refute this seminal discovery resulted in a veritable multitude of clinical studies over a 20-year span, almost all of which unintentionally but overwhelmingly confirmed the validity of this paradigm-shifting discovery. Subsequently, on August 15, 2011, a culmination of this validation resulted in the American Society of Addiction Medicine (ASAM) publishing a change in the definition of addiction. This position statement was most recently confirmed again on September 15, 2019 [24]. The ASAM position statement established that addiction was no longer considered purely a psychological disorder. Instead, addiction was defined as "a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences." The consequence is an imbalance in the neurobiochemical 'hardwiring' of the brain; having at least a 50% etiological contribution by genetic predispositions in the brain's reward circuitry.

Reward Deficiency Syndrome (RDS) has emerged as a widely accepted condition with a constellation of symptomatic behaviors and manifestations that have also been published in the SAGE Encyclopedia of Abnormal & Clinical Psychology 2017 [25]. A sampling of the expansive range of RDS conditions and behaviors is indicated in Table 1.

The notion of the authors has been that reducing cravings; restoring self-control, reward satisfaction, and mental sharpness; and redeeming happiness in life is best accomplished by achieving dopamine homeostasis with nutrigenomic dopamine agonists rather than by pharmaceutical interventions [22]. Many pharmaceutical therapies for RDS conditions are dopamine antagonists that can, in short term, simply induce pharmacological interference in neurotransmitter

**Table 1.** Different reward deficiency syndrome (RDS) behaviors: A function of reward genes

Addictive Behaviors		Impulsive Behaviors		Obsessive Compulsive Behaviors	Personality Disorders
Substance related	Non substance related	Spectrum Disorders	Disruptive Impulsive		
Alcohol	Thrill Seeking (novelty)	ADD/ADHD	Anti-Social	Body Dysmorphic	Paranoid
Cannabis	Sexual Sadism	Tic Syndrosme	Conduct	Hoarding	Schizoid
Opioids	Sexual Masochism	Tourette Syndrome	Intermittent Explosive	Hair-Pulling (Trichotillo-mania)	Borderline
Sedatives/Hypnotics	Hyper-sexuality	Autism	Oppositional Defiant	Excoriation (Skin Picking)	Bipolar & Depression
stimulants	Gambling	Stuttering	Exhibitionism	Non-suicidal Self-Injury (mutilation)	Anger & Pathological Violence
Tobacco	Internet Gaming		Kleptomania	Pathological Gambling	Narcissistic
Glucose & Fat			Pyromania		Avoidant
Food					Dependant

transactions and act as dopamine antagonists to manage symptoms to blunt unhealthy deviant RDS behaviors. Research has demonstrated that achieving dopamine homeostasis with nutrigenomic dopamine agonists provides more successful and sustainable benefits [22].

Most RDS behaviors can be categorized into one of the following categories of addictions, obsessions, compulsions, impulsions and personality disorders. Up to this time, attention has been primarily focused on the importance of the functional competence of neurotransmitters in the *Brain Reward Cascade (BRC)* and their influence on those behaviors, resulting in a plethora of clinical studies and published papers. By default, this intense focus of attention is the result of an epidemic of mental health, mood, pain and behavioral disorders leading to an epidemic of opioid prescriptions and addictions [26].

According to the National Alliance of Mental Health Disorders, 1 in 5 Americans will experience a mental health disorder [27]. This statistical reality translates to an enormous need for effective therapeutic interventions, which, under the current treatment protocols, results in a massive usage of prescribed opioids [28]. However, conventional pharmaceutical treatments, therapies, programs and fellowship programs (i.e. AA, Celebrate Recovery, etc.) do not seem to have consistently and/or significantly reduced recidivism rates nor blunted the incidence of opioid usage or rate of prescriptions [29].

### **Chronic diseases, reactive oxygen species (ROS) and anaerobic events**

Considering the prevalence of diverse chronic disorders and diseases, it is not logical to assume that an individual experiencing a mental health/behavioral disorder is otherwise completely healthy. Impairments in the functional competence of the BRC, by default, are generally accompanied by impaired functions in various other tissues of the body and disorders including, diabetes, obesity, CVD, digestive disorders, arthritis and numerous other inflammatory dysfunctions. Neurotransmitters in the brain reward cascade (BRC) have a significant influence on human health and different organs, tissues, and cellular and subcellular tissues in the body. Therefore, other important salient features that contribute to functional impairments are significant therapeutic targets that merit serious investigation.

### **Oxidative stress and free radicals – aka ‘reactive oxygen species’ (ROS)**

Reactive Oxygen Species (ROS) are produced primarily from 3 different sources: 1. As by-products of cellular energy production; 2. from exposure to exogenous sources such as environmental pollutants; and 3. as a result of a loss in the ability of cells to effectively use available oxygen (contributed to by chronic nutrient deficiencies and exposure to environmental pollutants, etc.) that impair intracellular organelles’ structures and functions. These events result in an increase in anaerobic/hypoxic events and pathologies. All chronic diseases are characterized by a significant increase in anaerobic (increased acidic/hypoxic bio-environment) pathological events and a consequential reduction in the ability to effectively utilize available oxygen [30]. Excessive oxygen free radical-induced oxidative stress and subsequent damages to lipids, proteins and cellular macromolecules are prevalent factors that can significantly impair neuronal functioning and exert damaging effects on all biological tissues, enzymes and fluids. Such oxidative distress induces a greater demand on endogenous antioxidant enzymes, Ex.: SOD, GSH, Dehydrogenases, CYP 450 enzymes, etc. Research evaluating the damaging effect of oxidative agents on the

functionality of neuronal brain cells and the ability to repair neuronal function with neurotrophic factors is of great interest.

Bagchi *et al.* have shown that dementia is an anaerobic pathology characterized by an increase in hydrogen peroxide, peroxy radical, hypochlorite radical, hypochlorous acid,  $\text{OCl}\cdot + \text{HOCl}$  and hydroxyl radical. Individually and collectively, these oxidative species can cause significant injury to the neuronal cells leading to neurological damage, neuromuscular injury and even fibrillation [31]. The key feature of these anaerobic, hypoxic, and increased acidic pathological events is a reduced ability to effectively use oxygen and water, which promotes a sequela of anaerobic and inflammatory events. Moreover, an increase in the anaerobic/hypoxic properties of tissues creates a suitable biological environment for the incubation and proliferation of anaerobic organisms and processes such as yeasts, worms, mold, bacteria (i.e. infections), inflammation, parasites, viruses, etc. that progresses to definable chronic degenerative pathological conditions. In fact, the evidence indicates that the herpes virus contributes to the etiology of chronic neurodegenerative disorders like Parkinson’s Disease, Alzheimer’s Disease, MS, ALS, Encephalitis, Meningitis, Mononucleosis, Epstein Barr Virus, cytomegalovirus, etc. [32].

Correcting the hypoxic state of brain tissues by improving *Blood Oxygen Level Dependent* signaling and functioning not only improves BRC neurotransmitter functioning and cross talk but reduces oxidative stress and damage to and symptoms of those anaerobic disorders. RDS conditions are also characterized by a reduced ability to achieve healthy *Blood Oxygen Level Dependent* functions and signaling in the brain, which are also anaerobic pathological events. Animal and human research confirm the benefits of improving *Blood Oxygen Level Dependent* signaling with a pro-dopaminergic agent [33]. In addition to improving and effectively managing reward circuitry and reward processing, reversing anaerobic sequela and promoting Blood Oxygen Level Dependent signaling and functionality also restores healthy aerobic metabolism, important for optimizing gene expression and systemic health. A clinical study demonstrated that the KB220Z, a nutrigenomic dopamine agonist, restores *Blood Oxygen Level Dependent* signaling and functionality and improved functional connectivity, or ‘cross talk’ in 10 abstinent heroin addicts [34]. Increased functional connectivity (‘cross talk’) was observed in a putative network that included the dorsal anterior cingulate, medial frontal gyrus, nucleus accumbens, posterior cingulate, occipital cortical areas and cerebellum in one hour after oral administration.

### **Behavioral physiology: Sleep, rapid eye movement and waking**

It is well established that sleep is necessary and responsible for optimal functions required for systemic bio-homeostasis. Animal research in dopamine D2 Receptor (DRD2) knock out mice demonstrates that dopamine is important in sleep-wake regulation. However, the mice experienced an increased number of periodic awakenings and non-Rapid Eye Movement (nREM) sleep. This indicates that dopamine plays some role in achieving sustainable sleep but a vital role in wakefulness [35]. Another study demonstrates that serotonin (5-HT) and dopamine (DA) are involved in promoting waking and inhibition of slow wave sleep (SWS) and/or rapid-eye-movement sleep (REMS). This research demonstrates that there is an upsurge of firing activity of DA neurons simultaneously with an increased release of DA in the ventral tegmental area (VTA) and allied forebrain structures during waking and REM Sleep. During waking, dopamine neurons, located in the ventral periaqueductal grey matter, induce an expression of FOS

proteins, which have a critical function in regulating the development of cells destined to form and maintain the skeleton and are reported to have an important role in signal transduction, cell proliferation and differentiation. Confirming other research, these researchers conclude that dopamine neurons may participate in the promotion of waking [36].

Normal dopamine homeostasis is crucial for an optimal quality of life, especially for recovering addicts [36,37]. Sleep has also been linked with metabolic clearance of neurotoxins. It was also demonstrated in mice that natural sleep is associated with a 60% increase in interstitial space indicating an increase in convective exchange of cerebrospinal fluid with interstitial fluid. This process was shown to result in an increase in  $\beta$ -amyloid clearance during sleep [34,38]. Moreover, achieving dopamine homeostasis with a nutrigenomic dopamine agonist (KB220Z) has also been shown to facilitate complete amelioration of long-term terrifying lucid nightmares, also improving dopamine stability and functional connectivity between networks of the brain reward circuitry in both rodents and humans; resulting in happy dreams in humans [39].

It has been suggested that a dopaminergic deficit may be responsible for circadian rhythm dysregulation, which occurs during onset of neurodegeneration. Researchers have demonstrated that the contribution of slow brain oscillations including delta, theta, alpha, and sigma frequencies (0.5-16 Hz) to the sleep electroencephalography (EEG) is regulated by circadian and homeostatic influences and reflects functional aspects of wakefulness and sleep [40,41]. Thus, it was hypothesized that restitution of rapid eye movement (REM) sleep and an improvement in Parkinson disease's symptoms could be achieved with the regulated use of dopamine agonists during the night. A study was conducted in twenty Parkinson's patients over a period of one month following treatment with subcutaneous nocturnal administration of apomorphine, a dopamine receptor agonist, at the beginning of each REM stage. Based on the results of symptomatic benefits, the researcher concluded that sleep alteration in Parkinson's disease can be improved by stimulation of D2 receptors [42].

### **Dopamine homeostasis and gastrointestinal health**

An example of the mechanistic effects of dopamine on colon function is observed in Parkinson's Disease (PD). In animal models, Garrido-Gil *et al.* found that a reduction in central dopamine levels caused a reduction in colonic dopamine types 1 and 2 receptor expression along with an increase in the colonic levels of dopamine and a reduction in the levels of acetylcholine. This is believed to contribute to a significant lowering in gut motility. An increase in the colonic levels of inflammatory and oxidative stress markers following depletion of central dopaminergic system, along with activation of the pro-inflammatory Renin Angiotensin System (RAS) was observed. The researchers also found that gut inflammation induced changes in nigrostriatal dopaminergic homeostasis, dopaminergic neuron death, and increased levels of nigral pro-inflammatory markers accompanied by RAS pro-inflammatory activity. The researchers concluded that dysregulation of the neural bidirectional gut-brain interaction may be responsible for the early gut disturbances observed in parkinsonian patients now considered as having a subtype of RDS. They also indicate that the increase in vulnerability of nigral dopaminergic neurons occurs after gut inflammation [43]. This research strongly suggests that effectively promoting dopamine synthesis, transport, reception, and

degradation/reuptake could be an effective way to improve not only PD neurological symptoms but gut motility and function as well.

### **Food intake**

#### **Taste sensors and gut-brain signaling**

Nutrient receptor 'chemosensors' in the gut have been the subject of extensive research to evaluate taste sensory properties. Nutrient appetite is influenced by oral sugar, fat, salt and savory taste receptors [44]. These receptors and other gut receptors are linked to digestive, metabolic, and satiating effects that influence nutrient utilization and inhibit appetite. Furthermore, gut chemosensors provide positive feedback signals that condition food preferences and stimulate appetite. It has been well demonstrated that postoral sensors (taste sensors situated in the posterior of the mouth) influence carbohydrate and fat responses in the brain dopamine reward system [45]. This research reveals that chemosensors are one of the mechanisms that initiate food preference learning, stimulate appetite and reward signaling and feedback, and contributes to our understanding of the relationship of both neural and hormonal gut-brain signaling pathways.

### **Vision and eye health**

An increase in dopamine release has been demonstrated during light adaptation and is accompanied by a suppression of rod signaling in light-adapted retinas. Current studies have demonstrated that dopamine, mediating through DAD1 receptors, could potentially induce a sensitization of the rod pathway in dim light conditions through GABA type C receptors [46]. Vision has been shown to adapt to the extensive changes in light intensity occurring over a period of 24 hours. This unique adaptation process is highly dependent on the rhythms in cellular and molecular processes to synchronize the pathways linking the cell-specific molecular machineries to their cognate outputs. The process is orchestrated by a network of circadian clocks located within the retina of the eye that recognize changes in light and respond accordingly, which are regulated by genes in the retina. The circadian clocks are synchronized to respond to day/night cycles along with simultaneous fine-tune detection and processing of light information that occur over a 24-hour period. This recognition and response signaling process is what regulates retinal homeostasis. It is known that both melatonin and dopamine participate in a regulatory role in this physiological process, being both outputs and inputs for clocks. This research provides insight into a novel mechanistic intervention that reveals a potential role for dopamine and melatonin in resolving retinal degeneration [47]. However, while regulating melatonin is important, health care professionals must be cognizant that increased levels of brain melatonin can lead to increased alcohol intake [48].

### **Role of dopamine in immune competence**

Psychosocial stress is a significant risk factor for depression. Stress leads to peripheral and central immune activation; immune activation is associated with reduced dopamine (DA) neural function; and DA function underlies reward interest. A reduced interest in or inability to experience reward interest is a core symptom of depression. Research in mice demonstrated that Chronic Social Stress (CSS) mice exhibited higher spleen levels of granulocytes, inflammatory monocytes and T helper 17 cells; increased plasma levels of inducible nitric oxide synthase (iNOS); and liver expression of genes encoding kynurenine pathway enzymes, which are involved in vasodilation during inflammation and regulation of immune response [49,50]. In this research, the effect of CSS in the ventral tegmental area resulted in higher levels of kynurenine



and the microglia markers Iba1 and Cd11b and higher binding activity of DAD1 receptor; and in the Nucleus accumbens (NAcc) to higher kynurenine, lower DA turnover and lower c-Fos expression. CSS mice exhibited less reward-directed behavior. Therefore, this mouse study demonstrates that a chronic social stress leads to changes in each of the immune, neural and behavioral states proposed to mediate between stress and disruption of DA-dependent reward processing. The indication is therefore that boosting dopamine functional competence promotes greater stress tolerance and immune competence. Numerous studies demonstrate that a nutrigenomic dopamine agonist, KB220Z and variants, results in improved stress tolerance [39,51-53].

### Autoimmune disorders

Autoimmune disorders are complex multifaceted pathophysiological disorders. While therapeutic interventions that target immune suppression and anti-inflammatory mechanisms can provide a degree of symptomatic management and relief, they are limited from addressing the broader systemic range of etiological factors, such as 1. errors in the synthesis of tissues requiring the appropriate perfect 3-dimensional structures for immunological acceptability; 2. Inadequate neurotransmitter influences; 3. Impaired hormonal influences, to name a few. Up until the writing of this paper, approximately 80 autoimmune disorders have been identified and explored, and the critical role of an aberrant immune response has been intricately associated with different organs and tissues. Hormonal homeostasis has great influence in achieving healthy and competent immune system function. Prolactin, which plays an essential role in metabolism, regulation of the immune system and pancreatic development, is secreted from the pituitary gland and biochemically acts as a hormone as well as a cytokine, which also prompts modulation of the immune system. Aberrant immune function is the dominant feature in patients suffering from diverse autoimmune diseases. However, upregulated 'autoimmune' attacks on the body's own tissues may have been misconceptualized. What appears to be an aberrant autoimmune attack could be a relentless and defensive upregulated immune response to imperfectly formed molecular structures being immunologically identified as antigens [54].

For example, hyperprolactinemia pushes immune responsivity and is evident in many autoimmune disorders including rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, multiple sclerosis, autoimmune thyroid disease and systemic sclerosis. Dopamine agonist therapy has been shown to exhibit benefits in autoimmune patients and offers a potential for therapeutic intervention with promising results [55].

### Optimizing dopamine homeostasis utilizing a patented gene test and a research validated nutrigenomic intervention

Blum's group invested over 60 years of diligent devoted scientific research investigating the dose dependent inter-relationships of various nutraceutical ingredients and how they synergistically promote optimal gene expression and neurotransmitter 'cross-talk' between Serotonin, Enkephalin, Endorphin, GABA, Cannabinoids, and Dopamine, which he systemically termed the '*Brain Reward Cascade*' (BRC). The research led to the development of the KB220 and subsequently the KB220Z nutrigenomic technology based on the dose-dependent relationships of ingredients that positively influenced gene expression in the BRC. The synergistic dose-dependent functional inter-relationships between the ingredients demonstrates that there is not one ingredient in the patented technology responsible for the expansive range of therapeutic

effects on the BRC; it is the synergistic net effect of "The orchestra of nutrition playing the symphony of neurobiology".

The need to restore dopamine functionality by optimizing gene expression for all neurotransmitters in the BRC to reanimate neurotransmitter interconnectivity (i.e. 'cross talk') led Blum to develop the patented Genetic Addiction Risk Score (GARS) gene test for a DNA-Designed Precision Nutrigenomic technology in the form of the next generation of the KB220Z PBM ('Precision Behavioral Management') [56-59]. In addition to the other benefits cited above regarding dopamine function, the KB220Z nutrigenomic technology has been shown in no less than 43 published clinical studies to reduce cravings and relapse [60], relieve stress, anxiety and nightmares [39,59,61]; enhance focus, concentration, cognition, and executive function; improve Blood Oxygen Level Dependent functioning [57,59,61,62], and elevate mood [63], among others. Consequently, other systemic beneficial effects cited above in this paper have not received the same notoriety owing to the societal magnitude of the opioid epidemic and the need for effective non-drug interventions. However, the purpose of this treatise is to provide greater mechanistic insight into the more expansive range of systemic benefits by coupling GARS and the Pro-dopamine regulator KB220Z PBM [64].

### Achieving happiness induces immunity:

It is very interesting that older cultures such as Bhutan, believe that enlightenment through multiple paths, including Meditation, Yoga, and spiritual teachings, lead the way to satisfaction and fulfillment. In 1972 the then King of the country proclaimed that instead of measuring success by wealth or the "Gross National Product" it should be measured by "Gross National Happiness." Through many incarnations, one may become enlightened and reach the ultimate state of nirvana. Buddha described nirvana as the perfect peace of the state of mind that is free from craving, anger, and other afflictive states (Klesha) (The subject is at peace with the world, has compassion for all, and gives up obsessions and fixations). This peace is achieved when the existing volitional formations are pacified, and the conditions for the production of new ones are eradicated. In Nibbana, the root causes of craving and aversion have been extinguished such that one is no longer subject to human suffering (*dukha*) or further states of rebirths in (*samsara*).

With this in mind and being grateful for having this uplifting cultural mandate one could make a suggestion that NIRVANA is indeed an important acronym whereby it could be defined as "*Neurotransmitter Interaction at Reward Ventral tegmental Accumbens leading to Neuronal Adaptation* (NIRVANA)" Or Happiness. It is well-known that stress increases inflammatory agents while happiness reduces them. We are hereby proposing a novel model to help achieve better health during the Covid 19 pandemic (Figure 1).

Our view is that since many of aberrant behaviors are a consequence of and fall under RDS, one initial goal in the scientific pursuit of happiness in the human would be to first identify those gene polymorphisms associated with RDS and then utilize genomic principles to develop novel tailor-made pro-happiness agonists utilizing immunological compatible ('body friendly') natural substances. It is important to realize that everything that our brain does is ultimately the result of an interaction between our genes and our environment. For some traits, our genes play a major role, while for others, environment is a primary factor; for most, it is a combination of the two. On average, depending upon the trait, the genetic contribution accounts for 40 to 90 percent of a trait. In the latter case, it is a combination of many genes,

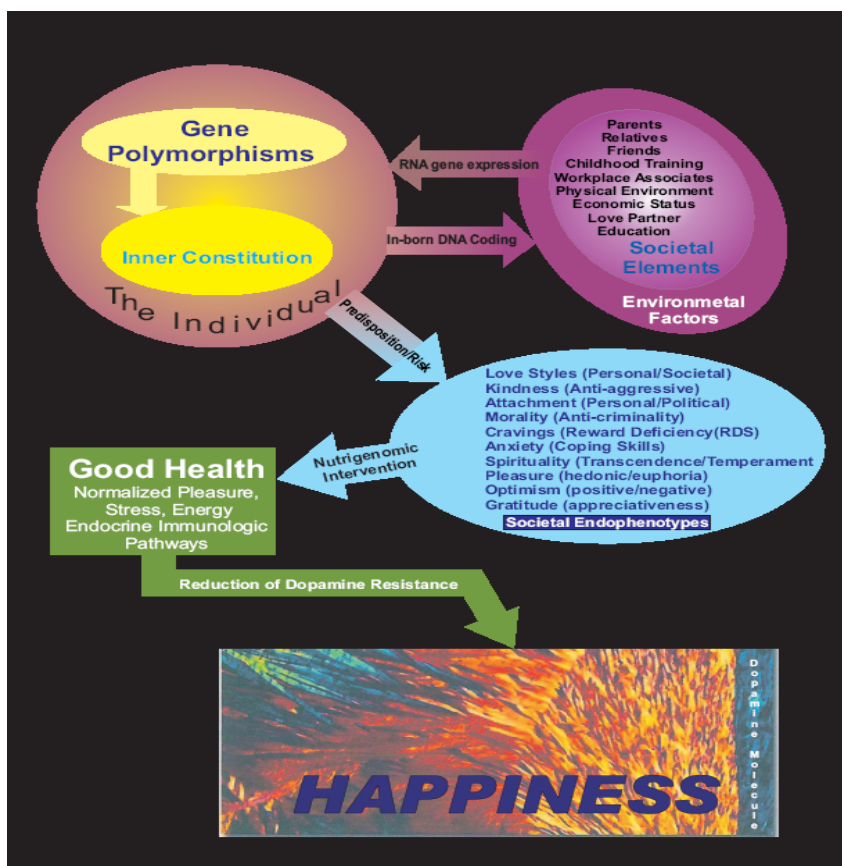


Figure 1. Happiness model: Schematic of genetic and environmental interactions leading to a reduction of “dopamine resistance” and a state of happiness [65]

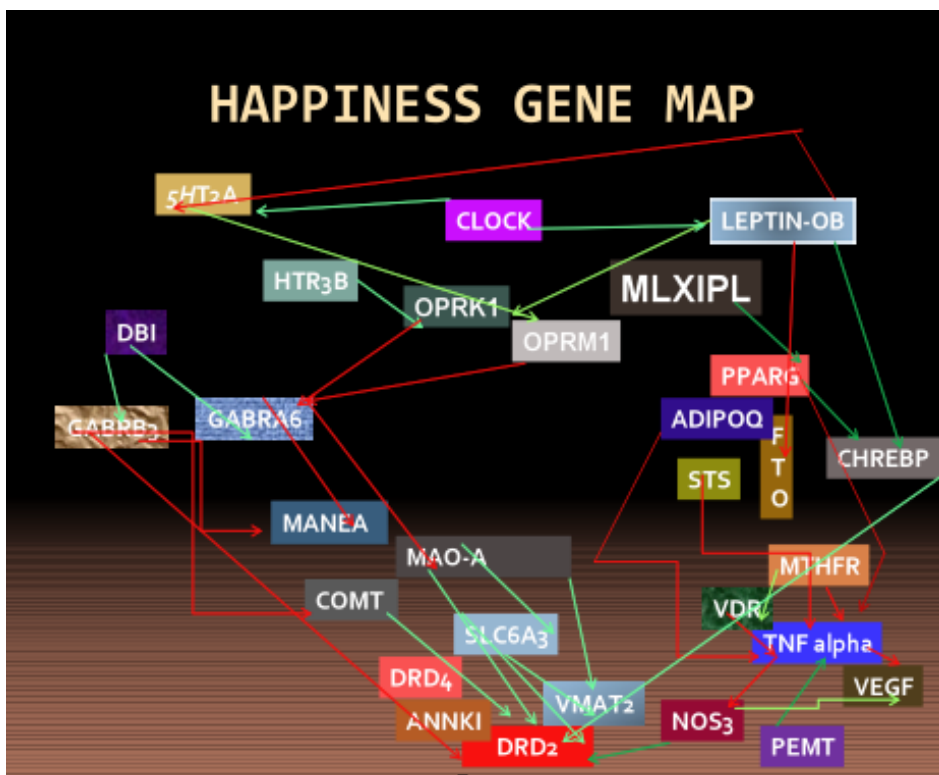


Figure 2. Proposed happiness gene map [65]

referred to as “polygenic inheritance”. To reiterate, it is well established that “polygenic inheritance” is due to the additive and epistatic interaction of many genes, each accounting for only a small percent of the total trait and interacting with the environment [65,66] (Figure 2).

## Conclusion

An extensive dossier of clinical and animal research indicates that in addition to promoting manageable reduction in addiction, obsession, compulsion, impulsion and an expansive range of aberrant personality disorders, achieving dopamine homeostasis with a number of epigenetic anti-dopaminylation insults possibly including a DNA-designed precision nutrigenomic intervention (KB220Z PBM) provides evidenced based systemic benefits including: restoring optimal aerobic metabolism in the brain by improving Blood Oxygen Level Dependent signaling and functioning; reducing anaerobic pathologies and the generation of Reactive Oxygen Species; inducing neurotransmitter interconnectivity (aka ‘crosstalk’); promoting restful sleep and waking accompanied by an increase in happy dreams; improving gut-brain signaling; reducing gastrointestinal inflammation and promoting GI tract functional competence; improving appetite regulation and food intake; improving vision and circadian rhythm regulation; and, importantly, reducing the effects of stress and improving immune competence [9-23,30,33, 34,52,53,58,60,63,64] This treatise expands our understanding of the health benefits of achieving dopamine homeostasis.

## Conflicts of interest

Kenneth Blum, PhD assigned his IP to GARS IP, LLC., Hollywood Florida. Drs. Blum and Brewer are paid employees of GARS IP, LLC., and Geneus Health, LLC.

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## Author contribution

All authors contributed equally.

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