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Epigenetic repair of Reward Deficiency Syndrome (RDS) incorporating pro-dopamine regulation (KB220ZBR) in a neurological clinic

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Abstract

Aims: This case series demonstrates the epigenetic repair of the Brain Reward Cascade (BRC) by incorporating pro-dopamine regulation with KB220ZBR into treatment.

Case Series: Three case studies of patients with various conditions including mitochondrial metabolic disorder, dysautonomia, hyperacusis, unspecified mood and anxiety disorders, chronic fatigue syndrome, and restless leg syndrome are presented. Patients' responses to treatment of these conditions with the adjunctive chronic administration of a nutraceutical, pro-dopamine dietary supplement KB220ZBR, were assessed before supplementation and following chronic treatment.

Results: Significant improvements in psychiatric/neurological symptoms were documented.

Conclusions: Following confirmatory results, we encourage other neurologists to consider this safe alternative treatment.

Keywords

dopamine; reward; mitochondrial metabolic disorder; primary dysautonomia

Abbreviations

ADHD: Attention-deficit/hyperactivity disorder; BOLD: Blood oxygenation level dependent MRI sequence; BRC: Brain reward cascade; CEO: Chief executive officer; CFS: Chronic fatigue syndrome; D2: Specific dopamine receptor; D3: Specific dopamine receptor; DNA: Deoxyribonucleic acid; GABA: Gamma-Aminobutyric acid; HIPPA: Health insurance portability and accountability act of 1996; IRB: Institutional review board; LLC: Limited liability company; MMD: Mitochondrial metabolism disorder; mRNA: Messenger RNA; NY: New York; qEEG: Quantitative electroencephalography; RDS: Reward deficiency syndrome; RLS: Restless leg syndrome; VNI: Victory Nutrition International

Introduction

Dopamine is a ubiquitous neurotransmitter that plays a significant role in survival and feelings of pleasure, motivation, learning, memory and most important, well-being. In addition to ensuring survival, most activities (eating, work, sex, and play) produce positive feelings, or relieve negative ones; they

provide a release of dopamine from pre-synaptic neurons in the reward center of the brain; the nucleus accumbens. In the natural world, rewarding actions are used to keep us alive, motivated, functioning, and reproducing our DNA [1]. Reward motivation is an essential driver of our genetic survival programming.

Many other brain chemicals interact to facilitate activation of dopamine post-receptor sites in the brain reward center. Exactly what happens after the dopamine molecule combines with its respective receptor will soon be determined. Simply put, the quantity of dopamine released relies on the upstream chemical messenger serotonin, which acts to stimulate endorphins and enkephalin. Subsequently, endorphins regulate the activity of GABA whereby GABA regulates the actual release of dopamine in the reward site of the brain. Blum and Kozlowski [2] termed this process the Brain Reward Cascade (BRC). Humans seek adequate dopamine release in the reward center of the brain, which relies on the proper sequential interaction (via synthesis, transport, reception/function, and disposal with regulatory feedback controls) between all these chemicals and others not described here. Reward circuitry genes govern these functions. Reward Deficiency Syndrome (RDS) represents a group of behaviors found in studies to associate with reduced dopamine from the BRC [3,4]. It is noteworthy that RDS behaviors, both substance and non-substance addictive behaviors like music, food (glucose & fat), sex and internet-gaming, cause the preferential release of dopamine in the nucleus accumbens, which suggests that people self-medicate to obtain their required dopamine fix [5-7].

Although the acute release of dopamine leads to feelings of well-being in the short term, chronically compromised dopamine function, especially in genetically predisposed individuals, can impair functional competence (i.e. ADHD, stress intolerance, mood disorders, irritability, anger issues, anxiety disorders, etc.) and lead to RDS (dopamine seeking) behaviors. This deficiency can be initiated or exacerbated by environmental interactions; epigenetically, through methylation (reduced mRNA expression) and inhibition of deacetylation (increased mRNA expression) on histones in the chromatin material on DNA. This concept [8] is clarified by the simple formula, whereby Phenotype = Genetics + Environment (P = G + E). We now know that genetics contribute 50% and environment contributes to 50% of the variance of RDS conditions. If the hypodopaminergia is due to genes, then it is something humans are born with; can manifest in many ways, and stay with us for life. Regarding environmental impact, potential causes include malnutrition, extreme stress, abuse as a child, and excessive use of mood-altering substances. The very complex interaction of genes plus environment can involve many gene variations and their subsequent interaction with the environment.

The consequence of low dopamine can be anxiety, depression, restlessness, feelings of emptiness, lack of motivation, cognitive decline, and vague or specific cravings. Cravings could be for food, drugs, or certain thoughts and behaviors that can become addictive and lead to unhealthy self-medication and reward-seeking conditions [4]. They include fixated repetitive thoughts and other obsessive, impulsive, compulsive and addictive behaviors, like Attention Deficit Hyperactivity Disorder, Tics, Tourette Syndrome, and Spectrum Disorders. Feelings of dissatisfaction due to inadequate dopamine in the reward center of the brain were described by Blum et al. [3] as “Reward Deficiency Syndrome” (RDS).

Managing RDS requires replenishing dopamine supply to normalize its function

Regarding an attempt to achieve neurological balance with optimal interconnectivity across the BRC, research suggests that improved clinical outcomes may be obtained based on research that shows

BOLD activation of the reward circuitry with the KB220Z variant [9]. This research demonstrated the achievement of optimal interconnectivity across the BRC and a significant improvement in neurological balance with the KB220Z variant. In other research, Willuhn, Burgeno, Groblewski, and Phillips [10] reported that cocaine use and even non-substance-related addictive behaviors, increase as the dopaminergic function is decreased. Decreases in D2/D3 receptors are associated with chronic cocaine use. Additionally, this is paired with reduced activation to cues in occipital cortex and cerebellum, reviewed in PET studies by Tomasi et al [11] and Tomasi & Volkow [12].

Therefore, treatment strategies that conserve and induce homeostatic dopamine function may be an attractive approach to relapse prevention in psychoactive drug and behavioral addictions like pathological gambling and conditions like Tourette Syndrome, Attention Deficit Hyperactivity Disorder, and other Impulsive, Obsessive, Compulsive Disorders, and Oppositional Defiance Disorder.

A neuronutrient pro-dopamine regulator that imitates and potentiates the BRC was designed to induce dopamine homeostasis and has been tested in many clinical trials and animal studies. Blum, Liu, et al., [9] evaluated the effect of KB220Z on reward circuitry of 10-heroin addicts undergoing protracted abstinence (average 16.9 months). An increase in BOLD activation, compared to placebo one-hour after acute administration was elicited by KB220Z, specifically in caudate-accumbens-dopaminergic pathways. Additionally, KB220Z reduced the resting-state activity in the cerebellum in these abstinent heroin addicts. Within the second part of this pilot study, of 10-abstinent heroin-dependent subjects, some regions of interest in the brain were significantly activated from resting state by KB220Z compared to placebo ($p < 0.05$). Increased functional connectivity was found in a neural network that included the cerebellum, occipital cortex, posterior cingulate, nucleus accumbens, medial frontal gyrus and the dorsal anterior cingulate [9]. These results and other studies using quantitative electroencephalography (qEEG) suggest an anti-craving/anti-relapse role for the compound KB220Z in addiction by direct or indirect dopaminergic interaction [13].

KB220 and its previous and most recent variants have been formulated to optimize gene expression for and rebalance the neurotransmitters in the *entire reward cascade*. The latest version, KB220ZBR, used by these patients employs an exclusive proprietary multi-lamellar custodial phospholipid encapsulation technology to achieve greater absorption and beneficial effects. The amount of each amino acid and other co-factors was formulated to ensure optimal gene expression for each neurotransmitter in the BRC and achieve the ratios of serotonin, endorphins, and GABA, for beneficial dopamine function. The appropriate ratios enhance resting-state functional connectivity and connectivity volume (recruitment of neuronal firing), [9] to harmonize the sequela of neurochemical transactions in the BRC. The theorized effect is that the amount of dopamine released will help with stress reduction, feelings of satisfaction, and prevent the need for addictive substances or harmful and ultimately dysfunctional behaviors.

With this brief background, new case studies of three individuals are presented to explore a possible role of ID–KB220ZBR in treating various conditions, some being hypodopaminergic.

Case Series

The three patients described in this study signed an approved IRB consent form as developed by PATH Foundation, New York City, NY. The current study complied with HIPPA rules, carefully executed to ensure

the safety of each patient. Each patient in the study was informed about the research aspect and subsequently volunteered and signed a release authorizing publication.

We utilized clinical physician notes; a Likert scale commonly employed in research questionnaires; and patient self-report, the most widely used approach to scaling responses in survey research. The terms Likert or Likert-type scale are often used interchangeably with a rating scale even though the two are not synonymous. While not all symptoms have been analyzed, the following text and graphs represent those that showed significant improvements.

The Likert-type rating scale is used to assess the degree of change due to treatment with KB220ZBR: A rating of '5' represents that a condition is *severe*; a rating of '1' represents *no discernible abnormalities*.

Patient condition definitions

The following section provides a very brief description of the neurological conditions treated in this case series.

Mitochondrial myopathies (i.e., Mitochondrial Metabolism Disorder [MMD]) can include exercise intolerance/muscle weakness, heart failure and rhythm disturbances, vomiting, and seizures, movement disorders, dementias, stroke-like episodes, deafness, blindness, droopy eyelids, limited mobility of the eyes.

Dysautonomia/autonomic dysfunction is a disorder in which the autonomic nervous system malfunctions. Symptoms often include dysfunction of the bladder, heart, intestines, pupils, blood vessels, and sweat glands. Importantly, there are multiple causes, not all of which classify as neuropathic. Some diseases can feature dysautonomias, such as Parkinson's disease, multiple system atrophy, autonomic failure, postural orthostatic tachycardia syndrome, and autonomic neuropathy.

Hyperacusis is a health condition associated with hypersensitivity to various sound of specific frequency and often volume ranges (a collapsed tolerance to usual environmental sound).

Restless Leg Syndrome (RLS) is a condition in which you have an uncontrollable urge to move your legs, usually due to leg discomfort. The condition has been linked to dopamine dysfunction.

Ehlers-Danlos Syndrome is a cluster of disorders that affect connective tissues, which are tissues that support the structure of skin, bones, blood vessels, and other organs. Defects in connective tissues cause the signs and symptoms of Ehlers-Danlos Syndrome, which vary from mildly loose joints to life-threatening complications.

KB220ZBR ingredients and technology

The ingredients are a patented blend consisting of B6, O-coordinated Chromium di-nicotinate, precursor amino-acids (DL-Phenylalanine, L-Tyrosine, 5-hydroxytryptophan, L-Glutamine) Passion lower, Metallosaccharide complex, Rosavins, Gymnemic acids, and Huperzine A. This blend is Prodosomed [14].

Case #1

Age: 13 years 05/10/2004

Gender: Male

Condition/Diagnoses: Mitochondrial Metabolism disorder, Headaches**,** Dysautonomia, Hyperacusis, Ehlers- Danlos Syndrome

Symptoms: Lots of headaches; neurotransmitter abnormalities; always depressed; not able to attend school regularly, difficulty sleeping with night terrors; always exhausted with no quality of life; hates life.

Start date of KB220ZBR: 03/01/2017

Dosage: 6 capsules a day in addition to all other medications and supplements (**Table 1**).

Medications	**Supplements**
Ondansetron	Biomax 1 month.
Clonazepam 0.25 mg PRN (a couple s/week)	Prodovite 1 capful
Clonidine 0.2 mg at night	Brain Sustain
	Thion Extra, 4/day
	Brain Reward (KB220ZBR)
	Cannabidiol (CBD) Oil

Table 1: Medications and supplements used in Case #1.

Case #1 Results

***Patient/Parent-reports*:** A month after taking the KB220ZBR, behavior got better and night terrors decreased. In addition to changes in sleep and behavior, his mood and energy improved significantly to the point where his mother stated, "our son has had a normal summer for the first time in years." "His life is exactly like his peers" and "this experience has been priceless to us."

***Doctor Report*:** Noticed the significant change in patient's behavior and medical examination.

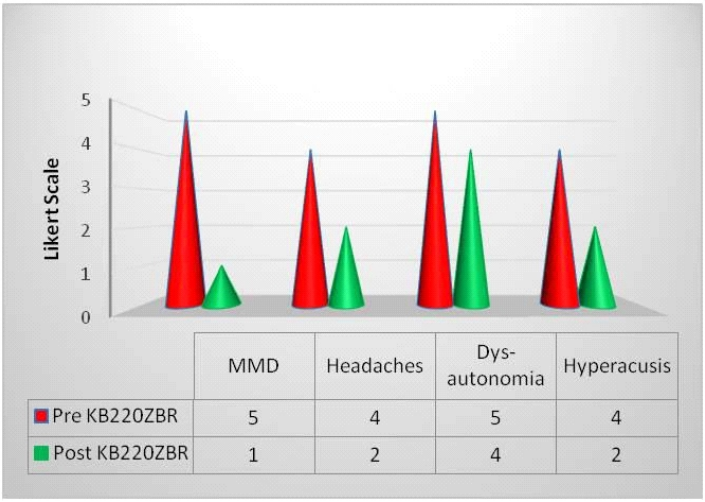


Figure 1: The effect of (pre- and post) KB220ZBR on medical conditions for a 13-year-old male after 90 days of treatment.

There was a clear reduction in symptoms related to Mitochondrial Metabolism Disorder (MMD); headaches; Hyperacusis and, to a lesser degree, symptoms associated with Dysautonomia (Figure 1).

Case #2

Age: 37 years 1/30/1980

Gender: Male, Master Personal Trainer and Coach.

Condition/Diagnoses: Unspecified Anxiety Disorder and Mood Disorder unspecified.

Symptoms: Gets frustrated, stressed, mood change without warning; feels uneasy; neurotransmitter test showed changes with catecholamines (Dopamine, Norepinephrine, and Epinephrine).

Start date of KB220ZBR: 9/21/2016

Dosage: began with ten capsules/day, then 15, now maintaining 11-12 capsules daily, in addition to other medications and supplements (Table 2).

Supplements
Fish Oil
Vayarin – prescription medical food
Vayacog – prescription medical food
Brain Reward (KB220ZBR)
Enlyte
Nutra Metrix
Isotonix supplements
Dietary supplements related to bodybuilding (like amino acids).

Table 2: Supplements used in Case #2.

Case #2 Results

***Patient Reports*:** Within the first-month patient noticed that when he was finished with his long work day, he was calmer during the drive home in addition to having more energy. He also wasn't dreading a six-day work week; He looked forward more to each day and the days went by quickly, tasks were accomplished, and he had a clearer mind of what he had to do that day and what could wait until the next day.

Now, nine months later, he has found that 11-12 pills work for him and for what he was hoping to overcome for his body to perform at its best. He reports that he is excited about this product, it's clinical backing, and research and enjoys seeing it change his clients' lives as well.

***Doctor Report*:** Notice significant improvement in mood and social skills.

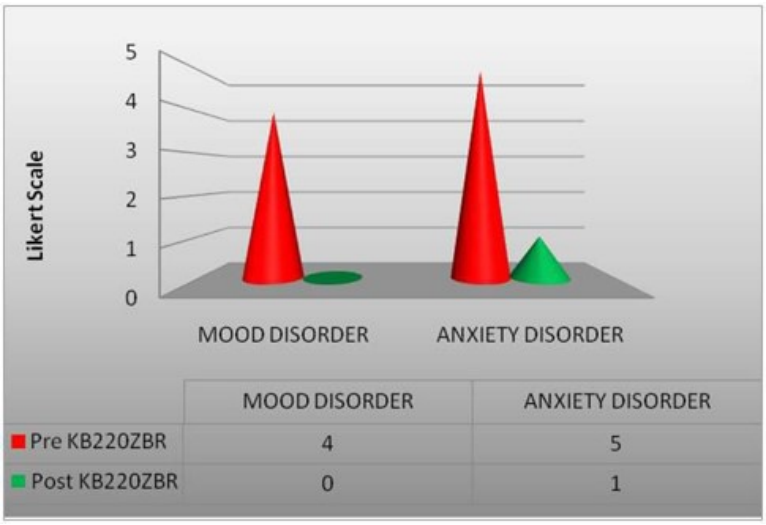


Figure 2: The effect of (pre- and post) nine months of treatment with KB220ZBR on mood and anxiety disorders for a 37-year-old male.

Case #3

Age: 51years DOB: 1/07/1966.

Gender: Male.

Condition/Diagnoses: Chronic Fatigue, Autonomic nervous system, Raynaud's syndrome, Restless leg syndrome

Symptoms: Struggled to deal with the difficulties of "life" for years. When things went wrong, it would cause the patient to get angry at the world, be in a bad mood and lash out.

Start date of KB220ZBR: 11/28/2016.

Dosage: 6 capsules daily in addition to other supplements (**Table 3**).

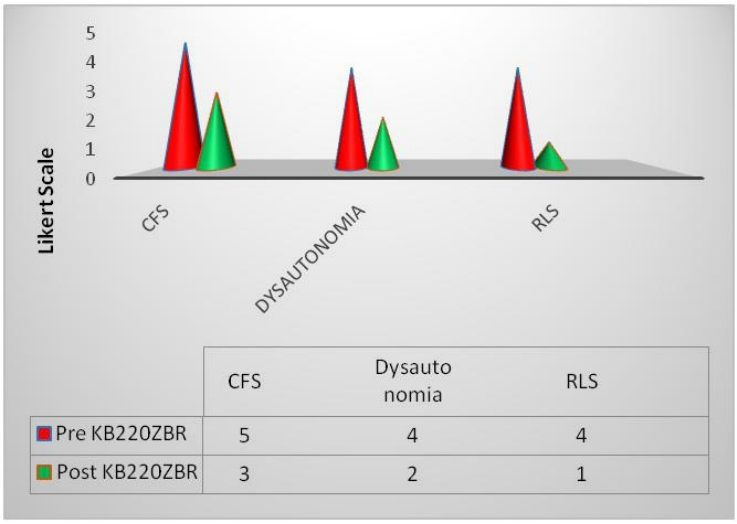
Medications	Supplements
Folic Acid (prescription)	Restore
	Methylated B
	Brain Reward (KB220ZBR)
	Vitamin C, D
	Lutein

Table 3: Medications and supplements used by subject #3.

Case #3 Results

***Patient Report*:** Since taking Brain Reward ('KB220ZBR'), the patient can handle the ups and downs of life. He doesn't have the almost uncontrolled reactions and can absorb and process them. He can respond more calmly and in a thoughtful manner. The change seemed subtle to him, almost unnoticeable. But, his wife says she sees a radical change. When he takes a moment to look back and compare how he reacts to challenging issues in comparison to a year ago, he tends to agree.

Doctor Report: Seen significant improvement in mood and the overall state of mind.



	CFS	Dysautonomia	RLS
Pre KB220ZBR	5	4	4
Post KB220ZBR	3	2	1

Figure 3: The effect of (pre- and post) eight months treatment with KB220ZBR on medical conditions for a 51-year-old male.

Following eight months of taking KB220ZBR the rating shows a reduced post-rating for Chronic Fatigue Syndrome (CFS), Dysautonomia and Restless Leg Syndrome (RLS) (**Figure 3**).

Discussion

The role of dopamine is underscored by these reported seemingly diverse neurological disorders.

A PubMed search for articles about dopamine and the conditions indicated resulted in:

Mitochondrial Metabolic Disorder (PubMed 119 articles listed 8-8-2017);

Dysautonomia (PubMed 119 articles listed 8-8-2017);

Hyperacusis (PubMed 1 article listed 8-8-2017);

Ehlers–Danlos Syndrome (PubMed 1 article listed 8-8-2017);

Mood Disorder (PubMed 2481 articles listed 8-8-2017);

Anxiety Disorder (PubMed 1866 articles listed 8-8-2017);

Headaches (PubMed 612 articles listed 8-8-2017)

Chronic Fatigue (PubMed 90 articles listed 8-8-2017);

Restless Leg Syndrome (PubMed 994 articles listed 8-8-2017).

It is noteworthy that, for example, Ehlers–Danlos Syndrome is not related to dopaminergic function and as expected KB220ZBR did not exhibit a discernible effect on this symptom. Moreover, Hyperacusis having only one paper pertaining to dopamine has only a slight improvement (from 5 to 4). However, Mood disorder (unspecified) showed the greatest response to KB220ZBR and had the highest PubMed listing of dopaminergic related studies (2,481).

In each of the subjects presented, various therapeutic approaches were used to try to help the symptoms which were considered refractory. The treatments used included various medications, including neuropsychiatric drugs, dietary interventions, and behavioral therapies (see tables 1, 2 and 3). There was still a missing element as evidenced by continued symptoms. These symptoms had a broad

range including fatigue, sleep-related disturbance, mood changes, anxiety, and behavior. In each case, treatment with KB220ZBR led to significant improvement of symptoms and a better quality of life. The breadth of these symptoms shows the extent of problems caused by or related to RDS and the BRC pathway. For example, subject #2 had significant mood and anxiety symptoms with a paroxysmal pattern that completely disrupted the quality of life at multiple levels (work and family). The changes seen in Subject #3, were described by the patient's wife as "radical change." Subjects 1 and 2 had underlying disorders (like mitochondrial disorder and dysautonomia) which contributed to their problems highlighting the coexistence of RDS with other medical and neurological conditions. When an underlying neurological or neuropsychiatric condition is present and is not responding to appropriate treatment, the coexistence of RDS should be considered and treated.

In 1996, Kenneth Blum coined the term "Reward Deficiency Syndrome (RDS) to explain feelings of dissatisfaction due to inadequate dopamine in the reward center of the brain (Blum et al., 1996). The key to managing anxiety, anhedonia (lack of pleasure), memory loss, and cravings requires replenishing and or balancing not only the supply of dopamine but normalizing its function (homeostasis) in the reward site of the brain along with other brain regions involved in memory and decision-making. Following a 40-year sojourn involving many clinical trials and animal mechanistic studies, the most effective means of inducing homeostasis is to mirror the BRC by providing epigenetic repair with neuronutrients like KB220ZBR.

Conclusion

Epigenetic repair of the BRC by incorporating the Pro-Dopamine Regulator KB220ZBR was demonstrated in these cases. For these three subjects, significant improvement of neurological symptoms followed chronic administration of KB220ZBR. The conditions include Mitochondrial Metabolic Disorder, Dysautonomia, Hyperacusis, Unspecified Anxiety and Mood disorders, chronic fatigue, and restless leg syndrome. Based on these case reports, notwithstanding the placebo effect, we encourage other neurologists to consider this safe alternative following confirmatory results.

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