Published in final edited form as:
J Addict Res Ther. ; 3(5): 139–. doi:10.4172/2155-6105.1000139.

Neurogenetics and Nutrigenomics of Neuro-Nutrient Therapy for Reward Deficiency Syndrome (RDS): Clinical Ramifications as a Function of Molecular Neurobiological Mechanisms

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Abstract

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Conflict of Interest Kenneth Blum, B. William Downs, Margaret Madigan, Merlene Miller and David Miller, own stock in LifeGen, Inc, the exclusive recipient of patents related to NAAT. John Giordano and Mary Hauser are LifeGen partners. There are no other conflict of interest issues.

In accord with the new definition of addiction published by American Society of Addiction Medicine (ASAM) it is well-known that individuals who present to a treatment center involved in chemical dependency or other documented reward dependence behaviors have impaired brain reward circuitry. They have hypodopaminergic function due to genetic and/or environmental negative pressures upon the reward neuro-circuitry. This impairment leads to aberrant craving behavior and other behaviors such as Substance Use Disorder (SUD). Neurogenetic research in both animal and humans revealed that there is a well-defined cascade in the reward site of the brain that leads to normal dopamine release. This cascade has been termed the “Brain Reward Cascade” (BRC). Any impairment due to either genetics or environmental influences on this cascade will result in a reduced amount of dopamine release in the brain reward site. Manipulation of the BRC has been successfully achieved with neuro-nutrient therapy utilizing nutrigenomic principles. After over four decades of development, neuro-nutrient therapy has provided important clinical benefits when appropriately utilized. This is a review, with some illustrative case histories from a number of addiction professionals, of certain molecular neurobiological mechanisms which if ignored may lead to clinical complications.

Keywords

Neuro-nutrient therapy; Neuroadaptagen Amino-Acid Therapy™ (NAAT); Brain reward circuitry; Reward Deficiency Syndrome(RDS); Neurogenetics; Nutrigenomics; Dopamine; Reward Genes

Introduction

Feelings of well being are experienced in the mesolimbic site of the brain. In this part of the brain termed the “reward center”, chemical messengers, including serotonin, enkephalin, and GABA work in concert to provide a net release of dopamine (DA) at the nucleus accumbens (NAc), a region in the mesolimbic system. It is well known that genes control the synthesis, vesicular storage, metabolism, receptor formation and catabolism of neurotransmitters. Polymorphic-versions of these genes have certain variations that can lead to an impairment of the neurochemistry involved in the neuronal release of DA. This cascade of these neuronal events has been termed the “Brain Reward Cascade” (BRC) [1] (Figure 1). Disruption of the cascade will ultimately lead to a deregulation of DA function. The DA molecule because of its effects is considered the “pleasure molecule” and the “anti-stress molecule,” and any reduction in function can result in reward deficiency, leading to deviant substance seeking behavior and lack of wellness [2,3].

It is well established that DA and a number of other linked neurotransmitters are responsible for feelings of well being. However, attempts to attenuate irregularities in the brain reward circuits using pharmaceutical agents have been met with disastrous results [4,5] and in some cases suicidal ideation [6]. The result of using powerful neurotransmitter agonists is down regulation instead of the much needed up-regulation of the specific receptors being targeted [7]. Bromocriptine a powerful DA D2 agonist has been shown to down regulate DA D2 receptors following chronic administration [8].

L-dopa used to treat Parkinson disease has also been shown to down-regulate DA receptors with associated unwanted side effects [9]. The challenge is to find a safe, non-addicting natural substance that would activate the “brain reward site” causing up-regulation of DA receptors (D2 in particular) without side effects, but having therapeutic value. Since the early 70's our laboratory has been developing natural dopaminergic agonists and published on D-phenylalanine as an anti-alcohol craving substance in rodents [10]. Since that time until the present, we have published extensively on the beneficial clinical outcomes of using a number of tested variants, and suggesting the adoption of this neuroadaptogen we have

called KB220 and KB20Z as an adjunctive treatment for Substance Use Disorder (SUD). As a result of this intensive research, the addiction field has recognized the importance of its use, and starting back in the mid-80s it has been adopted in many clinics across America [11,12]. Although our terminology for KB220 and KB20Z has changed over the years from "Neuro-nutrient Therapy" to "Amino Acid Therapy", to the current nomenclature "KB220Z Neuroadaptogen Amino-Acid Therapy (NAAT)". For simplicity in this paper we will use the current nomenclature NAAT to represent variants of KB220 and KB20Z.

Brain Reward Cascade (BRC)

Since addiction is a product of brain reward deficiency, it is well-known that addicted patients who present to a treatment center involved in chemical dependency or other documented reward dependence behaviors (with or without co-morbid drug abuse), have impaired brain reward circuitry. This impairment can lead to aberrant craving behavior and other behaviors such as Substance Use Disorder (SUD) and morbid obesity. Basic research has revealed that there is a well-defined cascade in the reward site of the brain that leads to normal DA release. Any impairment of this BRC due to either genetics or environmental influences can reduce the amount of DA released in the brain reward site resulting in hypodopaminergic function. This well-characterized neurotransmitter cascade in the mesolimbic system of the brain was first reported by Blum and Kozlowski [1]. The schematic (Figure 1) helps explain the known interaction of the neurotransmitters within the mesolimbic system. The schematic also shows how DA is released and regulated. In essence, serotonin, by activating serotonin receptors (5HT2c) in the hypothalamus, stimulates the release of enkephalin (opioid peptides). Mu opioid receptors (MOR) are activated by enkephalin and thereby fine tune the release of the inhibitory neurotransmitter GABA in the Substantia nigra, reducing GABA release. Then, in turn, GABA inhibits the release of DA at the Ventral Tegmental Area (VTA) via GABA receptors (GABA A) and the correct amount of DA, to bring about wellbeing, under normal circumstances, is released at the NAc, the reward site of brain (Figure 2) [13].

The GABA Paradox

Understanding the above as it relates to DA regulation strongly suggests that GABA control is tantamount to a physiological normal brain ("happy brain") [14]. A recent study has eloquently shown that if you knock out (KO) the gene that codes for the β3 subunit of the GABA(A) receptor, electrically stimulated neurons elicited more DA release in the NAc of β3-KO mice with enhanced reward learning and even decision-making [14]. Specifically, DA neurons in midbrain slices from β3-KO mice exhibited attenuated GABA-evoked GABA-gated inhibitory postsynaptic currents (IPSCs). Additionally, measured by fast-scan cyclic voltammetry, electrical stimulation of excitatory afferents to DA neurons elicited increased DA release in the NAc of β3-KO mice. β3-KO mice were more active than controls when given morphine. This effect correlated with potential compensatory up regulation of GABAergic tone onto DA neurons. β3-KO mice learned faster in two food-reinforced learning paradigms, but extinguished their learned behavior normally. Enhanced learning was specific for appetitive tasks, as aversive learning was unaffected in β3-KO mice. Finally, Parker et al. [14] found that β3-KO mice had an enhanced risk preference in a probabilistic selection task that required mice to choose between a small certain reward and a larger uncertain reward. According to the authors, collectively, these findings identify a selective role for GABA (A) signaling in DA neurons in appetitive learning and decision-making.

With this said, there is a paradox that relates to the fact that patients in treatment have enormous stress. Based on known pharmacological principles, the benzodiazepine-GABA –

complex is the target to combat anxiety [15]. Thus the widespread use of benzodiazepines as tranquilizers to treat all kinds of stress is being abused by pharmaceutical companies [16]. While there is a benefit in the short term, especially for alcohol detoxification, benzodiazepine is not recommended for long-term use because it is well known that benzodiazepines can lead to not only tolerance and addiction, but impaired mood [17]. With this knowledge mostly based on the initial neurotransmitter research by Blum et al. [18–21] and the development by our group in the 1980s of the first NAAT, clinicians adopted amino-acid therapy as a tool to treat drug and alcohol dependent patients [11,12]. There is some evidence for the treatment of drug addiction with l-glutamine [22] or N-acetyl cysteine, a substance known to activate the cysteine-glutamate exchange, thereby normalizes dysregulated glutamate levels within the striatum and reducing cocaine intake in rodents [23]. However, a number of clinics have inappropriately utilized the amino acid-l-Glutamine in high amounts to mimic benzodiazepines to reduce stress and treat barbiturate/benzodiazepine dependence as well as other addictions. Unfortunately, a number of respected clinicians have also erroneously prescribed the substance GABA to treat addiction. Monitoring of the impact of GABA therapy in a treatment facility limits the time of evaluation to the short term duration of stay, usually 30 days or less, making it nearly impossible to evaluate longer term consequences of such therapy. This unfortunate short term clinical scenario provides the clinician with only the evidence that GABA therapy exerts an initial `calming effect' as a result of its known inhibitory mechanism of action. However, they are unable to observe that this inhibition has a seriously undesirable dopaminergic antagonistic effect, especially with continued intake. Their indiscriminate use of GABA is without consideration of the complex blood brain barrier that prevents the penetration of GABA into the brain. To make matters worse, since it is known that stress increases the permeability of the blood brain barrier BBB [24], and with stressed addicts there is the potential that a certain amount of GABA will penetrate the BBB, there is the potential to reduce NAc DA release and clinically induce an increase in aberrant craving behavior, among other serious consequences.

The message here is that the addition of high amounts of l-Glutamine to boost GABA synthesis is justifiably contraindicated and against the known proven principles of molecular neurobiology. Too much GABA in the brain leads to too little dopamine and a significantly reduced ability to experience reward from normal activities. Thus, even without any gene deficits in the BRC, the indiscriminate use of anything that will raise GABA, especially in the long-term, could compromise DA function, leading to anti-reward [25], a hypodopaminergic state, and serious behavioral and health consequences.

Interestingly, a single injection of cocaine or methamphetamine caused the brains of mice “to put the brakes on neurons that generate sensations of pleasure”, cellular changes that lasted for at least a week according to research by scientists at the Salk Institute for Biological Studies [26]. Cocaine or methamphetamine stimulates GABA transmission similarly to the effect of alcohol. These drugs influence GABA transmission reducing dopamine release potentially through DA D2 receptor interaction [27]. This is indeed the way the brain regulates the need to reduce DA release, which seems to last for one week. An understanding of the effects that these drugs of abuse have on GABA activity, even after the drugs are eliminated from the body, provides further impetus to overcome GABA inhibition on DA release by utilizing NAAT to direct dopaminergic activation.

After years of investigation, scientists have not been able to provide clear protocols to treat the benzodiazepine addict utilizing NAAT, but it is clear that alcoholics and barbiturate dependent individuals have been successfully treated with carefully developed neuroadaptagen therapy [28].

Analysis for the Detection of Neurotransmitter Deficiencies

The chemical messengers of the BRC include at least four known pathways: Serotonin, Opioid peptides, GABA and DAL:- cholinergic activation is also important. Impairments to specific neurotransmitters (serotonin, endorphins, GABA, DA) in the BRC can occur via genetics, stress and/or over-consumption of psychoactive substances like alcohol, drugs, nicotine and glucose [29]. However, due to the known interaction of these brain chemical messengers, it is the net DA release that translates to well-being.

While it would be important to know exactly what impairments are present in an individual such as deficits in the serotonergic, endorphinergic, GABAergic, and dopaminergic systems, there is no known scientific methodology to date such as neurotransmitter analysis from blood or urine that could definitively identify or categorize certain neurotransmitter behavioral domains or neurological neurotransmitter deficiencies. Overall, while a relationship between urinary neurotransmitter measurements and CNS levels has been suggested by some researchers, at the present time, the exact amount of CNS neurotransmitters that contribute to the overall urinary pool is unknown. Thus any urine test is at best still premature and involves guessing in terms of a real relationship between urine testing and CNS neurotransmitter levels [30].

The Blood Brain Barrier

The passage of molecules in and out of the central nervous system (CNS) is highly regulated by the BBB [31,32]. The brain microvasculature is comprised of three layers: endothelial cells, astrocytes end-feet, and pericytes [31]. The BBB is a single layer of specialized endothelial cells located within the capillaries that deliver blood to the brain; they are referred to as brain capillary endothelial cells (BCECs) [32]. BCECs are connected by highly resistant junctions which are polarized into luminal (blood–facing) and abluminal (brain–facing) plasma membrane domains [33]. The selective permeability of the BCECs protects the brain by limiting the passage of harmful molecules into the central nervous system (CNS) [34] (Figure 3).

The blood-brain barrier (BBB) is composed of endothelial cells, astrocytes and pericytes. The endothelial cells are connected by tight junctions. They are polarized into plasma membrane domains; luminal (blood-facing) and abluminal (brain-facing). Specific transporters (protein carriers) in the endothelial cell layer regulate the passage of neurotransmitters in and out of the CNS.

NAAT and other Proteins

The BBB is the reason for the instruction to take the first dose of oral NAAT before breakfast and the second dose before dinner after at least a two-hour protein fast. It is well established that an amino-acid carrier system in the brain means that amino-acids derived from protein compete for a place on the carrier to enter the brain from the periphery. Since NAAT contains select precursor amino acids to build neurotransmitters, taking the oral NAAT without food present allows for the highest possible amounts of these select amino-acids to enter the brain and start the synthesis of specific neurotransmitters like serotonin, GABA, and DA (Figure 3).

There is a large body of research demonstrating that BCECs possess specific transporters that regulate the passage of neurotransmitters into and out-of the CNS [32–36] (Figure 4).

Neurotransmitter transport across the blood brain barrier is mediated by known and specific transporters. The transporters are specific for various neurotransmitters allowing access from the brain to the blood and vice versa (Marc et al. [30]).

Following Von Euler earlier published data on the excretion of urinary neurotransmitters and their metabolites [37,38] urinary neurotransmitter levels in various psychological disorders have been tested extensively [30,37,39,40]. These studies suggest that urinary neurotransmitter assessments might be a viable means to describe a disease state and to monitor therapeutic interventions [41–46]. However, as stated the blood–CNS barrier limits the transport of neurotransmitters from the periphery to the CNS, and many believe that peripheral markers such as plasma or urinary neurotransmitters levels, are poor indicators of CNS function [35].

While information related to the primary drug of addiction as well as the utilization of our developed “Neurotransmitter Questionnaire” [47] provides some basis for the analysis of neurotransmitter deficits, in our opinion, the only way to accurately determine specific neurotransmitter deficits is to genotype an individual for risk behavior. This genetic testing known as Genetic Addiction Risk Score (GARS) is under validation and will not be commercialized until appropriate validation is completed [48]. There are, however, numerous informative studies (14,436 Pubmed 11-15-12) that have already been published on the GARS panel.

Neuroadaptogen Amino-Acid Therapy (NAAT): A Natural Dopaminergic Agonist

Understanding the need to provide adequate amino-acids to support the synthesis of a number of select reward circuitry neurotransmitters, the proposed formula of NAAT reviewed recently [49] contains adequate amounts of neurotransmitter precursors and facilitators to optimize neuro-nutrients in hypodopaminergic brains.

The idea of utilizing precursor amino-acids as building blocks for the synthesis of brain neurotransmitters has been known for many decades. The discovery of natural opioid peptides is relatively recent and occurred in the mid 70's [50]. Prior to this discovery Pert and Snyder [51] reported in *Science* on the first identification of the opiate receptor. Interestingly, at about the same time, but published a decade later, Blum and associates working on rodent models discovered that the substance D-phenylalanine (DPA) reduced the alcohol craving in genetically craving high alcohol preferring mice [52]. The mechanism for such a finding resides in the important innate property of D-amino acids to block the enzyme enkephalinase (responsible for the catabolism–breakdown-of opioid peptides, including enkephalins) and as such significantly raise brain enkephalin levels [52]. Other experiments had found that high drinking genetically bred mice had low levels of brain enkephalins [53]. Important subsequent experiments showed that the administration of direct brain injections of endorphines and/or oral and IV injections of D-Phenylalanine resulted in significant reductions of alcohol drinking in these deficient methionine enkephalin mice [54]. Following years of human trials, it was found that a combination of certain precursor amino acids and enkephalinase inhibitors (DPA) promoted the release of DA at the reward site of the brain. Rhodiola *rosea*, a natural substance that inhibits catabolizing enzymes catecholamine-o-methyltansferase (COMT) and mono-amineoxidase (MOA) was included. Table 1 represents the most recent list of ingredients that has been rigorously researched in now many human clinical trials, including double and triple blinded randomized placebo controlled evaluations [49] (Table 2, a listing of published studies to date).

FTIR Explanation

Fourier Transform-Infrared Spectroscopy (FTIR) is used to identify organic and inorganic materials using a process that measures the absorption of infrared radiation by the material(s) being analyzed. The molecular components and structures are identified as bands of infrared absorption in the resulting `interferogram', a sort of `fingerprint.' When a material is irradiated, absorbed infrared radiation excites molecules into a state of higher vibration. The wavelengths that are absorbed by the sample are specific to and characteristic of its molecular structure. The FTIR spectrometer uses an interferometer to process the wavelength from a broadband infrared source. The signal obtained from the detector, which measures the intensity of transmitted or reflected light, is called an `interferogram'. To obtain a single-beam infrared spectrum, a computer using Fourier transforms must be used to analyze the `interferogram'. The resulting `fingerprint' is compared to the reference standard fingerprint in the database to confirm compositional compliance of the tested material with the reference standard.

After the radiation meltdown in Fukshima, Japan, the original high quality amino acid supply was abandoned, in order to avoid any purity and safety issues in the preparation of the NAAT. Amino acids are relatively simple chemical structures. The FTIR of the original reference standards were matched with ingredient candidates before any amino-acids were incorporated into the formula.

Neuroimaging Evidence of NAAT Effects at the Neurological Sites of Craving and Relapse

The evidence is emerging, using neuroimaging tools such as quantitative electroencephalograph (qEEG) and functional magnetic resonance imaging (fMRI), suggesting that NAAT is the first effective natural dopamine agonist. Most importantly, it is well-known from the work of many, including Nora Volkow, director of NIDA, that aberrant craving behavior occurs at the NAc and relapse occurs at the pre-frontal cingulate gyrus (Figure 5). These two pathways are interconnected and involves DA [55]. This specific NAAT in both the intravenous [56] and oral [57] forms, utilizing qEEG, has shown that this compound regulates the dysregulated brain waves in the cingulated gyrus in abstinent alcoholics, heroin and cocaine dependent patients. In fact, NAAT has been shown one hour after administration to bring about calming by increasing alpha waves (~40%) along with increasing low beta waves (~68%) (Figure 6). This important effect, according to Joel Lubar, the past president of the American Society of Neurofeedback and a co-author [57], would otherwise take between 10 – 20 neurofeedback sessions.

Previously, resting state functional abnormalities in heroin-dependent individuals that affected brain functional organization were found using fMRI. That these functional impairments could negatively impact decision-making and inhibitory control provided a new understanding of the effect of heroin abstinence on brain reward circuitry [58]. Moreover, in support of earlier reports of blunted subjective response to affective stimuli in addicts, it was found that heroin addicts when compared to normal controls showed reduced activation in right amygdala in response to cue-exposure. Other studies have shown persistent abnormalities in the brain function following one month of heroin withdrawal in the orbitofrontal cortex. In opiate-dependent subjects compared to controls Zijlstra et al. [59] found that baseline D2R availability in the left caudate nucleus was lower and that years of opiate use correlated negatively with D2R availability in the putamen. Additionally, compared to controls, higher DA release after cue-exposure in the right putamen was demonstrated in Opiate-dependent subjects. This DA release was positively correlated with chronic craving and anhedonia. An interesting approach to prevent relapse in opiate

addiction then may reside in treatment strategies that increase D2 receptors. To this aim, we evaluated the role of KB220Z on reward circuitry in a triple blinded – randomized placebo controlled cross-over study in five heroin addicts undergoing protracted abstinence, for an average of 16.9 months. In preliminary unpublished work by Liu et al. [48], fMRI was used to measure the effect of KB200Z one hour after administration in controls and abstinent heroin addicts in China (Figure 7). Neuroimaging with fMRI showed profound activation of DA pathways of the caudate-accumbens region of the brain and a smoothing out of hyperexcitability (BOLD) of DA in the putamen. While this is preliminary and unpublished data, for this review we report that KB220Z induced a BOLD activation of caudate-accumbens dopaminergic pathways compared to placebo following one-hour acute administration KB200Z. Furthermore, the NAAT also reduced the higher DA activity in the putamen (these findings will be formerly published elsewhere).

There is genetic evidence for reduced DA D2 receptor availability in heroin dependent subjects. According to Li et al. [60], a series of exposures to heroin-related cues were able to induce craving in a cohort of Chinese heroin abusers (n=420) recruited from the natural abstinence center at Shanghai. Individuals carrying D2 DA receptor gene (DRD2) ***TaqI*** RFLP A1 allele demonstrated a significantly stronger cue-elicited heroin craving than was found in the non-carriers ($P<0.001$). No significant association of cue-elicited cravings was found with the nine-repeat allelic variants in DA transporter gene (DAT) SLC6A3 or with the dinucleotide repeat polymorphism (DRP) 148 bp allele in D5 dopamine receptor gene (DRD5). These results suggest that DA pathways in the human brain are involved in cue-induced heroin craving through this now known mechanism and, as noted in many studies, the use of the NAAT can reduce craving behavior as well as stress [49,61,62].

Moreover, the effect of NAAT on Against Medical Advice (AMA) rates as well is seen in figure 8. Certainly, you can never get patients into recovery if you cannot keep them in treatment. The importance here is that NAAT reduces the need for benzodiazepines, reduces withdrawal tremors, reduces building up to drink scores (BUD) and increases recovery scores [28,61,63,64–66].

NAAT and Relapse Prevention

Neuro-nutrient therapy potentially utilizing a combination of both intravenous and oral NAAT is the missing piece in the recovery community. It is an intervention that can be used to stabilize the neuro-circuitry of the brain, especially in those patients that have a genetic predisposition to Reward Deficiency Syndrome (RDS). Sustained intake, following discharge, is important to reduce stress and replenish nutritional needs to support normal neurochemistry. Although NAAT is especially important for carriers of the DRD2 ***TaqI*** A1 allele (because it can positively influences gene expression) victims of addiction, due to or compounded by environmental stress and the toxic effects of the substances themselves, must embrace a continuation of brain repair to prevent relapse. The role of NAAT in relapse prevention is based on peer reviewed publications (Table 2). Not providing any method to offset the impaired reward circuitry of discharged patients, by activation of brain dopaminergic pathways to prevent relapse, for them is like "*Jumping out of a plane without a parachute"* [67].

Methods of relapse prevention include:

- Normalization of brain wave dysregulation at the Pre-frontal Cortex- Cingulate Gyrus important in executive function. By increasing alpha and low beta bands, this site will be regulated and relapse reduced [56,57].

- Attenuation of aberrant craving behavior by activation of caudate-accumbens-dopaminergic pathways [48].
- A major problem with addiction is that there are poor executive function abilities, which are due to genetic deficits and environmental elements leading to hypodopaminergic function and poor memory and focus [68,69]. NAAT significantly increased focus (p 300) after 30 days as measured by qEEG in healthy volunteers (Figure 9) [70]. This is important clinically because rebalancing the impaired BRC with NAAT provides the patient with a better chance of sustainable recovery. This is because it makes it possible for the patient to concentrate on programs like The 12 Steps and The 12 Traditions with more clarity rather than having to deal with uncontrollable cravings.

Drug abuse counselors are very familiar with the importance of stress as a factor in relapse in the recovery community. It is well known that stress is a major reason for relapse and withdrawal against medical advice (AMA) from in-patient residential programs. In a randomized – double-blind placebo –controlled study of the NAAT, variant stress was significantly reduced in patients attending a residential treatment facility [62]. In the study of 62 alcoholic and polydrug abusers, skin conductance level (SCL) was used to evaluate stress responses, especially related to initial residential group interaction. Patients receiving NAAT had a significantly reduced stress response as measured by SCL compared to patients receiving placebo. Significant differences as a function of Time ($p<0.001$), and Treatment ($p<0.025$) as well as a Time–by–Treatment interaction ($p<0.01$) were revealed by a Two factor ANOVA analysis. These results indicate that in inpatient settings NAAT may have a role to play in improvement of treatment responses by reducing stress related behaviors (Figure 10) [62].

It is important to boost immunity in after care patients during recovery because stress reduces brain endorphines with concomitant reduced immunity. Published papers show the importance of endorphines as a regulator of one's immunity [71]. One of the key ingredients in NAAT is D-Phenylalanine known to raise brain endorphines which subsequently leads to an increase in brain blood flow, brain oxygenation and an improved immunity [52,72].

Especially in the world of legally prescribed pain killers, patients who have detoxified from prescription opiates may still have pain. Interestingly, dopaminergic tone positively impacts pain tolerance and or sensitivity and is tantamount to pain control. NAAT increases brain endorphins our natural pain killer system and DA release [73]. Zhang et al. [74] found changes in the caudate nucleus of rats with morphine dependence. They were decreases in the inhibitory duration of pain-inhibition neuronal (PIN) discharges and decreases in the latency of pain-excitation neuronal (PEN) discharges; that resulted in a net increase in the activity of PEN and PIN neurons. Additionally, they described a role for DA in pain moderation due to the inhibition the electrical activities of PEN discharges and the enhancement in the activity of PIN discharges.

In support of relapse prevention, the following graphs represent the culmination of NAAT - Oral (Figure 10) and NAAT-IV (Figure 11) studies showing a very significant relapse reduction in alcohol, heroin and cocaine dependent patients [47].

Intravenous Delivery of NAAT

Most of the scientific evidence documented in the literature is on oral NAAT however, over many years there have been thousands of patients successfully detoxified and treated in both outpatient and residential treatment facilities using intravenous (IV) NAAT for nutritional replenishment under medical supervision.

In two case studies we found that one intravenous treatment of NAAT normalized abnormal neurological activity in an abstinent alcohol patient and an abstinent opiate patient using qEEG [56].

IV is the fastest means of delivering brain healing nutraceutical neuroadaptoagens to the brain while bypassing the gut. Many alcoholics and drug addicted individuals suffer malabsorption due to chronic substance-induced damage of the intestinal tract that interferes with the absorption of nutrients. Malabsorption This problems are eliminated with intravenous delivery. An additional important benefit of reducing cravings and substance use is that NAAT IV administration eliminates the substance-induced insult to GI tract tissues, allowing the healing of those tissues and recovery of GI tract function. IV delivery can quickly achieve therapeutic levels, delivering much larger doses with a more immediate and lasting effect. IV delivery provides immediate relief from chronic abstinence symptoms and a reduction in the severity of symptoms that can usually take weeks or months to diminish. As stated earlier, this provides a jump start to recovery that allows patients to better participate in the other aspects of addiction treatment and to do so with more clarity, optimism, and hope.

With that said, there are two studies that have been published [56,75] and one that has been accepted for publication, [47] showing significant benefit in terms of the severity of symptoms for patients treated with a combination of oral and intravenous NAAT. While oral NAAT therapy has been consistently shown to be significantly more effective than conventional recovery protocols, it is noteworthy that the use of early IV intervention has demonstrated more rapid and less troublesome recovery than oral NAAT alone. This finding should provide impetus to any clinician and or treatment facility to incorporate the IV NAAT therapy early on in the patient's recovery. In addition, follow–up studies have shown prevention of relapse with patients claiming high rates of sobriety. Another important factor in the recovery process is the finding that with using NAAT intravenously there is a reduction in the severity of withdrawal of symptoms during the first days of residential treatment. This keeps the the patient undistracted and engaged in their recovery early on when they are most likely to walk out of treatment [76]. We evaluated intravenous delivery of NAAT along with oral variants directed toward overcoming hypodopaminergic function. A pilot experiment (in press [47]) found a significant reduction of chronic symptoms as measured by the Chronic Abstinence Symptom Severity (CASS) Scale after one week of IV NAAT combined with 30 days of oral, compared to oral-only administration. Specifically, the IV-plus-oral group did significantly better than the oral-only group over the first week, as well as over the following 30-day period (Figure 12).

In the second experiment (in press [47]), consisting of 129 subjects receiving both IV and oral NAAT for five days, three factors with eigenvalues greater than one were extracted for the baseline CASS-R (CASS-Revised) variables: craving, anxiety, sense of emptiness, internal shakiness, restlessness, impulsiveness, difficulty concentrating, memory problems, depression, irritability, sleep problems, fatigue, hypersensitivity to stress, hypersensitivity to noise/sight/touch, and sensitivity to pain. We showed significant declines ($p=0.00001$) from pre- to post-treatment: $t=19.1$ for Emotion, $t=16.1$ for Somatic, and $t=14.9$ for Impaired Cognitive Ability (Figure 13).

In a follow-up study of 23 subjects who underwent NAAT-IV therapy (at least five IV treatments over a seven day period) plus orals for at least 30 days: 21 (91%) were sober at six months with 19 (82%) having no relapse; 19 (82%) were sober at one year with 18 (78%) having no relapse; 21 (91%) were sober at the time of contact with 16 (70%) having no relapse (in press [47]). The significance of these results in stark contrast to conventional methodologies confirms the need for a major paradigm shift in addiction treatment protocols

as is indicated by the new definition of addiction published by ASAM on August 15, 2011. Awaiting additional required research, due to limitations and sampling analysis, we cautiously propose that NAAT-IV therapy (a putative dopaminergic agonist) may provide important therapeutic outcomes in residential treatment programs (Figure 14).

High Resolution Brain SPECT Imaging and Intravenous Amino-Acid Therapy (AAT) in Substance Abuse: The Good, Bad and Ugly

It is very important to understand that increases in GABA, possibly due to the administration of L-Glutamine, known to synthesize GABA in neurons [77], will induce a hypodopaminergic response and as such chronic administration could induce suicide ideation as seen in recent studies involving the cannabinoid B1 receptor inhibitor Acomplia [78,79]. This is so because the CB1 receptor inhibitor significantly reduces DA release by enhancing GABA neurotransmission (Figure 2). Based on our positive qEEG outcomes [56,57] coupled with unpublished preliminary fMRI studies in China [48] showing direct activation of the NAc with an acute does of NAAT, one of us (DN) decided to incorporate an IV amino-acid formulation as adjunctive therapy to two SUD patients. Pre and post high resolution brain SPECT imaging was utilized as a diagnostic tool to determine benefits or risk following treatment with IV amino-acid solutions.

SPECT imaging uses nuclear isotopes bound to specific neuropharmaceuticals to evaluate regional cerebral blood flow (*r*CBF) and thus the metabolic activity of the brain. Substance abusers have demonstrated a number of cerebral perfusion abnormalities in brain areas related to behavior, especially in the frontal and temporal lobes that have been observed in patients with SUD. Volkow et al. [80] found significant decreases in DA receptors following long-term use of cocaine and methamphetamine in high dose stimulants abusers. The authors suggested that acute and chronic disruptions of the orbital frontal system may be caused by these DA receptor decreases. Interestingly, chronic amphetamine and cocaine abusers display multiple cerebral perfusion defects on SPECT [81–83].

Case Reports

Two brief reports are presented here as examples that confirm the administration of an IV solution containing high amounts of L-Glutamine to one of the patients following SPECT scanning is inappropriate. We are cognizant that this inappropriate use of NAAT was based on misinformation about the overall benefits of targeting GABA by the prescribing clinician. Based on our research and understanding of brain reward neurochemistry, we suggest that it is necessary to caution other interested clinicians involved in the treatment of RDS [2,3] especially SUD, to carefully implement the correct use of amino-acid therapy in their practice. In our earlier published works we have expressed our concerns regarding the use of agents known to chronically block DA release by directly or indirectly affecting GABAergic signaling [14], and have explained this premise earlier in this paper.

These cases histories involve two highly addicted males both in their late 50's, and are presented here to illustrate these concerns regarding the chronic use of high amounts L-Glutamine. Each patient's brain functioning and *r*CBF was evaluated using high resolution SPECT at the Amen Clinic in Tacoma Washington. Each patient signed a consent form and all results were kept confidential and followed HIPPA law.

Each patient had received Resting and Concentration SPECT scans using Tc99m exametazime. Differences in cerebral blood flow for frontal regions of interest were assessed in three conditions (resting, concentration, and their difference, or “delta”). The method used

for the pre and post scans of each patient follows the standard procedure developed by Amen et al. [23].

For patient #1, the pre–scan was performed while the patient was taking only Propranolol. All other previously prescribed medications were eliminated for the test. For patient #2 the pre-scan was performed while the patient was taking Prilosec (dose taken at 9 AM the day of the test), Ziac blood pressure medication was also taken at 9.AM the day of the test, and finally Glucophage, the last dose of which was taken at 6 PM the day of the pre-scan.

While the details of these case reports are being reviewed elsewhere, it is an example that illustrates some of the issues of overprescribing neuro-nutrients designed to target GABA discussed earlier. These two cases were brought to our attention many months after the patients received treatment and SPECT evaluation.

The male patient # 1 age 57 was first scanned on 12-30-2009. When compared to the prior Concentration Scan, the scan on 2-04-2010, following approximately a month of treatment, which consisted of NAAT targeted for serotonergic enhancement, the post scan showed a marked increased activity of the anterior cingulate, bilateral basal ganglia, and thalamo-limbic system, (a diamond pattern). There was also some decreased of internal cerebellar activity. There was significant improvement of the left and right temporal lobes of the left and right inferior orbital prefrontal cortex, but activity of the anterior medial prefrontal cortex was still decreased, which is slightly worse. There continues to be decreased activity of the medial parietal lobe, and dorsal medial prefrontal cortex where scalloping is mild.

The male patient #2 aged 59 was first scanned on 12-22-2009. Compared to the prior Concentration Scan, the scan on 2-04-2010 followed approximately a month of treatment, which consisted of Amino Acid Therapy based on amino acid testing and a conceptual clinical orientation targeting GABA enhancement. The post scan showed improvement in right focal thalamo-limbic activity, but the left focal thalamo-limbic activity was still significantly increased. Moreover, there was moderately decreased activity of the left and right inferior orbital prefrontal cortex; there was still decreased activity of the left and right temporal lobes. While there was some improvement of the medial parietal lobe, there is still mild decreased activity of the left and right parietal lobe. There was decreased activity of the anterior medial prefrontal cortex pole, also decreased activity of the dorsal anterior prefrontal. There is also moderate scalloping that continues. There is decreased activity of the internal cerebella. There is an area below the left temporal lobe extending to the top of the cerebellum region that is non-filling. There still are findings suggestive of a past history of brain trauma. Moreover, there are very mild findings of possible ventricular enlargement suggested by decreased activity; in the region of the third ventricle, centrally, and in the surrounding white matter, and by deceased activity in the region of the occipital horns/atria and surrounding white matter.

Interestingly, patient #1 received an appropriate IV solution, and significantly improved in terms of Post scan evidence as well as clinical features, including reduced craving behavior. in contrast, patient # 2 worsened. We are proposing that the chronic infusion of an L-glutamine solution to enhance GABA function is not only wrong, but potentially very dangerous. This is not surprising based on past evidence and an understanding of the mechanism responsible for normally derived motivation and feelings of well-being [84,85].

Moreover in patient #2, ventricular enlargement is of great concern. Evidence of ventricular dilation may be seen alone or accompanying cortical atrophy as well as in congenital and developmental deformities and possibly even in drug abuse disorders. When present alone or out of proportion with cortical atrophy, evidence of ventricular dilation requires close clinical correlation and possible follow up imaging with MRI. Ventricular dilation is

suggested by decreased activity in the regions of the ventricles, ventricular horns and the surrounding white matter. Displacement of the Corpus Callosum is further evidence of ventricular dilation. It is noteworthy that the patient showing ventricular dilation may also present with a separation of thalamic hemispheres. It is no wonder that with these brain abnormalities, by potentially enhancing GABA transmission, the patient worsened and had significant drug craving issues, which led him to relapse and incarceration. We have explained this relapse phenomena and potential therapy as Deprivation-Amplification Relapse-Therapy (DART) [86]. In the paper [86] we carefully explained that the phenomena could be due in part to genetics (carrying the DRD2 A1 allele and a low number of D2 receptors leading to DA super-sensitivity) or due to enhanced GABA signaling as possibly evidenced in the case of patient #2.

On the other hand, the positive finding observed from the post Scan for patient #1 is encouraging and is in agreement with our other findings. To reiterate, we found an increase in alpha and in low beta bands in the prefrontal cortex of polydrug and psychostimulant dependent individuals carrying at least one neurotransmitter risk allele [13]. Moreover we found that one dose of oral NAAT similar to that used on patient #1 but in an oral formulation, reduced dysregulation in the qEEG of the *Cingulate gyrus* region of the brain in protracted polydrug abusers [57]. Based on these results, we want to caution professionals in the addiction field to become familiar with the extensive knowledge base concerning precursor amino-acid-enkephalinase-COMT inhibition therapy [49].

This very small number of the above case reports is a major limitation and they must be cautiously interpreted. In fact, we cannot categorically ascribe a direct link to any worsening of the *r*CBF as measured by SPECT to patient #2. It is only a cautionary note to the field in general. The worsening could have been caused by other physiological factors not at all due to the IV treatment. Certainly there is continuing evidence for the positive effects of IV-NAAT [47]. However, even though this issue merits additional research, the mechanistic effects and potential clinical consequences of GABA enhancement therapy already noted compel the authors to question the ethical and moral aspects of such research that impose the risks of depression and suicide ideation on a substance abuse population already predisposed to such conditions and behaviors. Because of the observed negative effects in the patient with the IV L-Glutamine solution, we do not expect to have any planned follow–up using this obtrusive formula. There are numerous animal studies which suggest that GABA – induces a blockade of dopamine release in the NAc [87,88].

Understanding this, provides the clinician with the impetus to avoid high amounts of any GABA promoting compounds, including L-Glutamine or GABA extracts, especially in treating RDS pro-bands. The use of benzodiazepines, that bind to specific Benzodiazepine-GABA-Chloride ion channel receptors, as detoxifying agents for alcohol withdrawal, has its place in the short term at best, but not in the long term [89].

KB220Z as an Adjunct to Suboxone Maintenance Patient

One of us (ES) has been incorporating KB220Z into the treatment of opioid addicts in combination with Suboxone with positive outcomes. One such case is presented. A 23 year-old, white female presented for treatment after a near fatal overdose of opioids. She reported a history of anxiety since childhood and the onset of panic attacks in her late teens, which included self-mutilation by cutting as a means of self-soothing. She had been on multiple medication trials for depression and anxiety including Cymbalta, Paxil, Lexapro, Prozac, Trazodone, Xanax, Klonopin, and Effexor. Her first experience with opioids was in the form of heroin injected by her boyfriend after which she reported that she was “immediately hooked”. Despite being from a prominent family, she began a downward spiral during

college, which involved multiple car accidents, arrests, and a significant drop in her college GPA and attendance. This period was interspersed with two inpatient rehabilitation treatments and finally a psychiatric hospitalization following her near fatal overdose on 24 bags of IV heroin. Her past medical history was significant for sexually transmitted disease (human papilloma virus) and irregular menses surrounding her increasing opioid use. She had a history of a significant head trauma concussion in a motor vehicle accident during her drug use. In this accident, she suffered a head trauma, impacting her windshield as an unrestrained passenger with questionable loss of consciousness. She did not seek medical attention due to her ongoing drug seeking behavior.

Her family psychiatric history was significant for a sister with Generalized Anxiety Disorder and Major Depressive Disorder without psychosis resulting in one inpatient psychiatric hospitalization. Sally reported PTSD signs and symptoms related to a date rape in college, and a later pregnancy and abortion, while dating her addicted boyfriend. Additional significant stressors during the peak of her drug use were her parent's separation and divorce. At initial intake, her Beck Depression Score was a 24, significant for Moderate depression and her Connor's Continuous Performance Task was not consistent with an Attention Deficit Disorder.

Prior Brain SPECT Imaging, following her overdose, revealed increased cingulate, left and right basal ganglia congruous with her over focused anxiety and panic symptomatlogy. Deep Limbic Thalamic over activity was congruous with her depressive symptoms. Left and right temporal lobe over activity was suggestive of mood liability and difficulty with information processing, while decreased tracer activity in her left and right inferior orbital prefrontal cortex was consistent with her prior impulsive behavior.

She was initially started on Suboxone Film 8/2 mg as she reported that since her overdose, she was secretly using oral opioids mainly in the form of Percocet intermittingly to manage her cravings. She was started on Pristiq 50 mg daily for depression and anxiety, a high quality multivitamin, a B-Complex, Omega 2 Fish Oil 4 grams daily, and Serotonin and GABA amino acid supplementation. Additional efforts were made for collaboration of treatment recommendations for transitional housing, outpatient 12-step meetings, and the court system regarding her ongoing legal hearings.

The patient felt more hopeful and did well on the initial supplementation schedules. In the interim, the patient, was able to get a part time job, and appeared in court 2 months later where her sentence was mitigated to supervised-outpatient probation. At this time the patient reported increased cravings, anxiety, and her Suboxone was increased by 2/0.5 mg.

At the next 2 visits, the patient reported increased anxiety regarding alleged drug use by a member of her residential housing group. She was approaching six months clean and sober and reported no cravings on the increased dose of Suboxone. During the Thanksgiving and Christmas holidays the patient struggled with her early recovery, facing ongoing issues surrounding her parent's divorce and holiday schedules, and her growing boredom at work, causing an increase in her Nicotine use. Wellbutrin XL 150 mg was added. During the next session the patient appeared more anxious and was also in the process of moving from her transitional housing to her first apartment, given ongoing problems in her transitional living house. The patient's urine drug screen came back positive for cannabis and she admitted to befriending a male coworker who was smoking on his work breaks. The following month, the patient's urine drug screen was positive for both cannabis and cocaine. She admitted to finding a small amount of cocaine and paraphernalia in her packing boxes that had been in storage. The patient reported persistent anxiety and ongoing coping and harm reduction strategies were discussed. During the follow-up visit, the patient had a family blow up with

her parents who suspected the patient was slipping, and disapproved of contact with an old boyfriend. Wellbutrin was discontinued and KB220Z, newly available, was started at 2 tablets twice daily on an empty stomach. Her prior serotonin and GABA supplements were discontinued.

On the follow-up visit, the patient had a profound response to the KB220Z adjunct while Suboxone and Pristiq were maintained at their prior doses. She reported she felt significantly better, specifically an increase in energy, a decrease in cravings, and an overall “better mood”. She reported significant cognitive improvement and was more insightful. She was able to make significant progress in cutting off from risky friends, managed to change her job, and enrolled in college for the fall semester. Her parents reported that their daughter seemed significantly improved in insight, judgment and motivation. There has been no relapse to date, and the patient continues to do very well. There is a significant improvement in mood, and affect, and a reported mild weight loss, with which the patient seemed pleased. She has continued to report zero cravings and a sense of normalcy that she had not felt on the Suboxone alone. We are in the process of discussing a step-down in her Suboxone, and to date the patient continues to do well at each monthly follow-up. She remains hopeful about her future and will return to school in the fall semester. This case regarding the use of NAAT as an adjunct to Suboxone, although encouraging, requires considerably more research and must await future long-term studies.

NAAT (KB200Z) and Antidepressant Withdrawal

Miss J.D., now 18, developed symptoms of depression (“feeling blue”, a weight-gain of 15 lbs, loss of interest in ordinarily pleasant activities, staying in bed, missing school) in the fall of 2010 at age 16. She initially attributed the symptoms to stress, but with persistent problems, sought evaluation in January of 2011. She was diagnosed with depression and a trial of Celexa prescribed. This was not effective, but the second medication trial, this time of duloxetine (Cymbalta) proved helpful. She had resolution of the more troublesome symptoms: while still `down', she was able to get out of bed, get dressed, and go to school. She took Cymbalta for several months, with no desire to discontinue the medication. She had a disconcerting experience in the summer of 2011 while on annual vacation with her family, when she inadvertently forgot to take her medication, the symptoms; vertigo, hand numbness and feeling of near syncope, were so pronounced that she sought an evaluation in the ER. The assessment was of withdrawal from duloxetine. In the fall of 2011, she felt she was sufficiently well to begin a medication taper, reducing the dose from 90 mg to 60 mg without difficulty. She was noticeably uncomfortable with the decrease to 30 then to 20 mg. daily in December, 2011, and again experienced unbearable discomfort when she attempted to discontinue the medication completely. She would experience nausea, vertigo, intense anxiety, near syncope so unpleasant that she could endure these symptoms for only a day before deciding to resume duloxetine therapy. She made several attempts over the early part of 2012, with similar results; withdrawal symptoms would be unpleasantly evident after missing a dose by only 2 hrs. She resigned herself to taking the medication indefinitely even though she felt that the depression had lifted. She felt her body dependent on the medication. In the summer of 2012, she began taking KB220Z at a dose of 1 tablet twice daily. She had been taking the supplement for 2 weeks when it was time again for vacation and she again forgot to take the duloxetine. The withdrawal symptoms however, were so mild that she did not notice them, only realizing that she had forgotten to take duloxetine when she found the medication bottle. She elected, therefore, not to resume duloxetine therapy. In her words, KB220Z “not only made it easier to stop taking the anti-depressant, but also made it unnecessary for me to need one at all.” Indeed, the depression appears to be either resolved or in complete remission.

This case illustrates both the value of KB220Z in alleviating the withdrawal syndrome from antidepressant medication, and the value of KB220Z as a safer first line therapy for mild depression.

Summary: Evidence Based Perspective on Nutrients in RDS

In accord with the new definition of addiction espoused by the American Society of Addiction Medicine (ASAM) it is well-known that individuals who present to a treatment center involved in chemical dependency or other documented reward dependence behaviors have impaired brain reward circuitry.

Evidence supporting the role of the NAAT, consisting of amino-acid neurotransmitter precursors and enkephalinase-catecholamineo- methyl-transferase (COMT) inhibition, in the treatment of deficits in brain reward function, is presented in this document. Ongoing research repeatedly confirms the numerous clinical effects of this novel formulation, known to activate the brain reward circuitry. This is of particular value in the treatment of individuals who have the genetic antecedents for addictive, compulsive, impulsive, and obsessive behaviors. These behaviors are classified under the rubric of RDS. To-date over 54 articles about RDS have been retrieved from PUBMED. For example Oberlin et al. [90] suggested that frontal and limbic reward circuits of those with significant anti-social density (ASD) are less responsive to reward cues in general, and particularly to alcohol cues in the medial Orbital Frontal Cortex (OFC) and amygdala. These findings are broadly consistent with the RDS hypothesis, although positive correlation in the striatum suggests regional variability.

In this article we presented some preliminary findings from China using fMRI and qEEG studies from the United States that demonstrate the activation of brain reward circuitry in victims of SUD with the use of NAAT. As already mentioned, we await further data using a 2×2 design and fMRI at resting state of NAAT in comparison to placebo that in preliminary investigation has shown activation of the caudate brain region and potentially a smoothing out of heroin-induced abnormal connectivity in the putamen (a site for emotionality). Larger investigations are required to confirm these pilot studies and these together with continuing Chinese studies and the qEEG results published in America, that show that NAAT increase in alpha and low beta one hour after administration, may demonstrate the positive impact that NAAT can have on treatment outcomes and offer a much improved paradigm shift in treatment protocols.

Evidence suggests that in terms of treatment outcomes, carriers of the DRD2 A1 allele seem to require dopaminergic agonistic intervention [91,92]. Recently, Diana [93], pointed out that a reduction of DA receptors in the ventral striatum of cocaine, heroin and alcohol dependent subjects has been visualized in imaging studies, offering visual proof of decreased endogenous release of DA in drug dependant subjects. This new objective study supports the concept of RDS [2,94] and its treatment with DA agonist therapy to reduce cravings, drug seeking behavior and prevent relapse.

It is suggested that the overall successful symptom resolution during recovery may be due to the strengthening of dopaminergic activity. Since its inception in the middle of the1980s, we have learned through clinical experience that by appropriately adhering to a number of important principles, the utilization of NAAT will potentially enhance treatment outcomes and prevent relapse. In order to optimize the synthesis of brain mesolimbic serotonin, the use of l-tryptophan and or 5-hydroxytryptophan must be combined with a chromium salt such picolinate or polynicotinate since the latter has been shown to increase the BBB penetration of peripheral tryptophan. Moreover, Chromium Picolinate (CRP) has been shown to increase insulin receptor sensitivity [95]. This takes on real importance when we

consider the role of insulin and dopaminergic signaling [96]. In fact, our laboratory reported [97] that CRP induced changes in body composition as a function of the DRD2 gene polymorphism in double-blind randomized placebo controlled study. Specifically, carriers of the DRD2 ***Taq1*** A1 allele, because of increased craving behavior, masked the effects of CRP compared to carriers of DRD2 A2 allele. Secondarily it is important to augment the synaptic presence of DA once released from the pre-synaptic neuron. Understanding the dynamics of neurotransmitter catabolism; the combination of dose-specific l-phenylalanine and tyrosine inhibit the activity of the DA cellular transporter controlled by the DAT1 gene [98]. There are many studies showing that psychoactive drugs augment the DA transporter activity leading to a significant decrease of needed synaptic DA, thereby stimulating aberrant craving behavior [99]. Moreover, it is known that polymorphisms of the DAT1 gene associate with drug- seeking behavior [100]. Along similar lines, it is important to maintain an effective synaptic quantum of DA to target dopamine D2 receptors. The enzyme responsible for the catabolism of synaptic DA is catecholamine-o-methyl-transferase (COMT). At specific evidence-based levels, the neuroadaptagen Rhodiola *rosea* is useful because it known to inhibit not only COMT but MOA-B as well [66,101]. This is even more important since it is well established that certain gene polymorphisms in both of these catabolizing enzymes have been shown to induce aberrant craving behavior in humans [102].

In this article we have provided some evidence as well as pointing out established molecular mechanisms to caution against the inappropriate use of the precursor amino-acid L-Glutamine and or even GABA by itself because of the inhibitory nature of GABA to reduce mesolimbic release of dopamine [14]. We hypothesize that those benefits from NAAT, as shown in many publications [49,103], will not be optimal unless rigorous adherence to these known and proven principles is adopted by clinicians treating RDS. It is also important to understand that the justification for using NAAT is not based on a `snapshot' of amino acid status from blood or urine, but is based on an extensive long-term assessment of how certain nutraceuticals influence gene expression, especially in populations that carry specific genetic polymorphisms. Finally, it is important to utilize only the best quality ingredients because, unless these ingredients meet high standard specs, one cannot ensure their safety, efficacy, and/or consistency of effects. This can be achieved by using descriptive infra-red finger printing as described above [104].

Conclusion

Empirical and clinical research has revealed that there is a well-defined cascade in the reward site of the brain that leads to normal DA release. This cascade has been termed the BRC. Any impairment due to either genetics or environment of this cascade will result in a reduced amount of DA release in the brain reward site. Finally, optimization of the function of all components of the BRC has been successfully achieved with neuro-nutrient therapy over four decades of research and development, providing important clinical benefits when utilized appropriately. If, however, the molecular neurobiological mechanisms elucidated here are not considered in the use of NAAT, clinical complications and treatment failures may ensue. Certainly we encourage additional randomized–placebo-controlled studies independent of our group, such as the studies of precursor amino-acids that have been shown to attenuate heroin withdrawal in China by Chen et al. [105] to broaden our knowledge base related to the utilization of nutraceuticals to assist in recovery of victims of RDS and associated addictive behaviors. We are cognizant that directly targeting dopaminergic pathways has to date failed (for example, blockade of dopamine action; utilization of the powerful dopamine D2 receptor agonists bromocriptine) However, required research into the appropriate use of natural dopamine D2 agonists seems warranted.

Future research must include animal models of reward circuitry impairments, which will enable a better understanding of this most complex neurotransmitter based system. Reward circuitry function of the mesolimbic brain region can be dysregulated in a range of neurodevelopmental and psychiatric disorders and genetic syndromes. Dichter et al. [106] reviewed pre-clinical animal models and clinical evidence of reward-pathway dysfunction in a range of disorders, including psychiatric disorders (i.e., substance-use disorders, affective disorders, eating disorders, and obsessive compulsive disorders), neurodevelopmental disorders (i.e., schizophrenia, attention-deficit/hyperactivity disorder, autism spectrum disorders, Tourette's syndrome, conduct disorder/oppositional defiant disorder), and genetic syndromes (i.e., Fragile X syndrome, Prader-Willi syndrome, Williams syndrome, Angelman syndrome, and Rett syndrome). Utilizing animal models across a spectrum of disorders inclusive of food addiction as developed by Avena et al. [107] and Kufahl & Olive [108] for drug reinforcement and Gardner's group in terms of cocaine dependence [109], Nestler's group for knock out dopaminergic mice models [110], biological contribution to social influences on alcohol drinking utilizing animal models [111] and finally Thanos and associates in terms of gene therapy approaches to alcoholism and other drugs of abuse [112–114] will continue to pave the way for improved genetically based diagnosis as well as genomic therapeutic targets.

Acknowledgments

The authors would like to acknowledge Margaret A. Madigan who edited the entire manuscript. We are thankful or the entire research group of PATH Foundation NY, especially Richard Smayda, and Elizabeth Mo. We are also thankful to Kim Downs of LifeGen, Inc. San Diego, California and Electronic Waveform Labs of Huntington Beach, California for financial support of this project. The writing of this paper was supported in part by funds from the National Institutes of Health, NIAAA (RO1-AA07112 and K05-AA00219) and the Medical Research Service of the US Department of Veterans Affairs (Marlene-Oscar-Berman).

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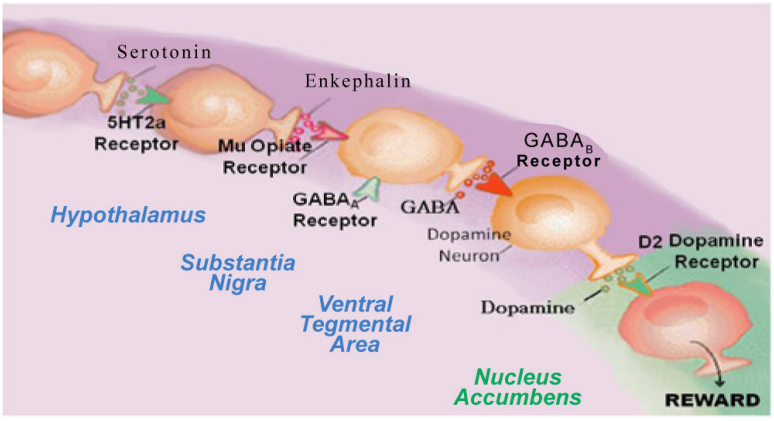


Figure 1.
Interaction of neurotransmitters within the mesolimbic reward system.
(Modified from Erickson C (2007). The Science of Addiction .W.W. Norton & Co.: New York, New York).

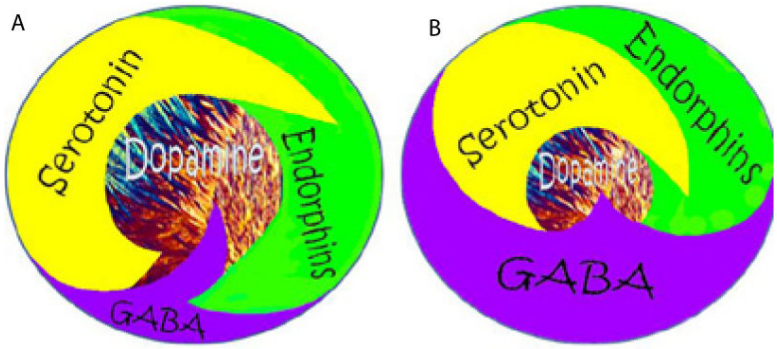


Figure 2.
Brain reward cascade (normal and hypodopaminergic state).
2A. Happy Brain: Represents the normal physiologic state of the neurotransmitter interaction at the mesolimbic region of the brain. Briefly, serotonin in the hypothalamus stimulates neuronal projections of methionine enkephalin in the hypothalamus that, in turn, inhibits the release of GABA in the substania nigra, thereby allowing for the normal amount of Dopamine to be released at the Nucleus Accumbens (NAc); reward site of the brain [13].
2B Unhappy Brain: Represents hypodopaminergic function of the mesolimbic region of the brain. The hypodopaminergic state is due to gene polymorphisms as well as environmental elements, including both stress and neurotoxicity from aberrant abuse of psychoactive drugs (i.e. alcohol, heroin, cocaine etc) and genetic variables [13].

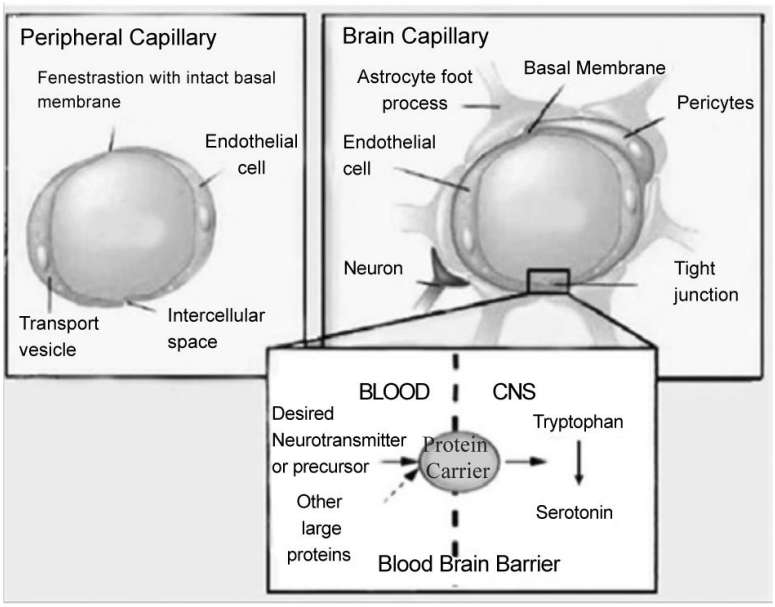


Figure 3.
Blood brain barrier and protein transport.
(Modified from Marc et al. [30].)

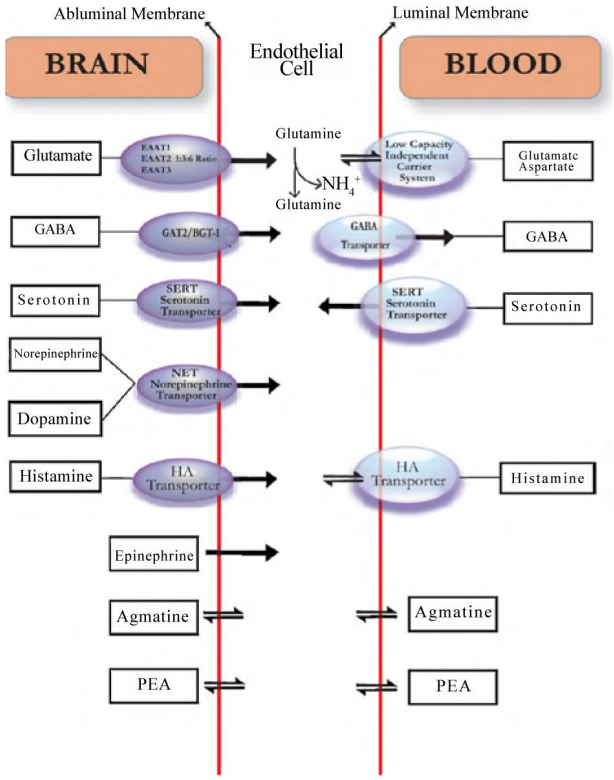


Figure 4.
Neurotransmitter transport across the blood brain barrier.

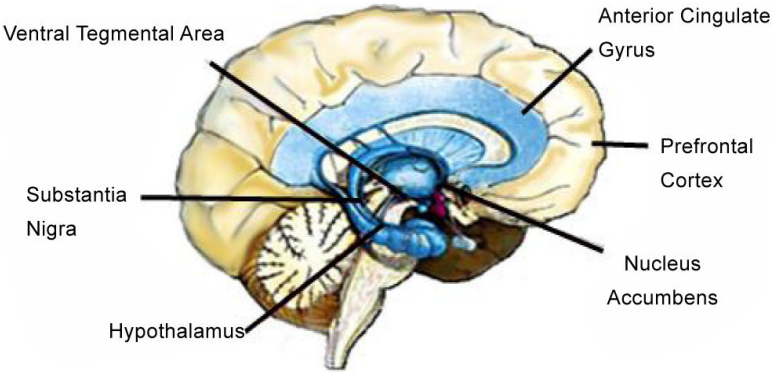


Figure 5.
Sites of BRC and relapse.
(Modified from brain illustration: http://prorecovery.blogspot.com).

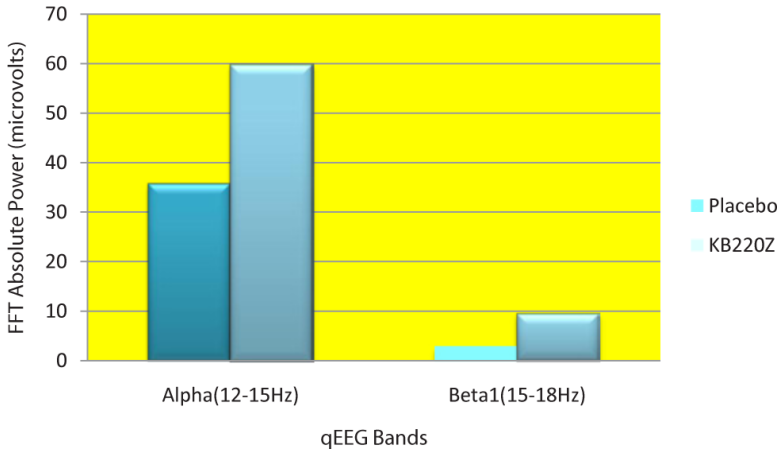


Figure 6.
qEEG analysis of NAAT vs. placebo in psychostimulant addicts. (Modified with permission Blum et al. 2010 [57]).

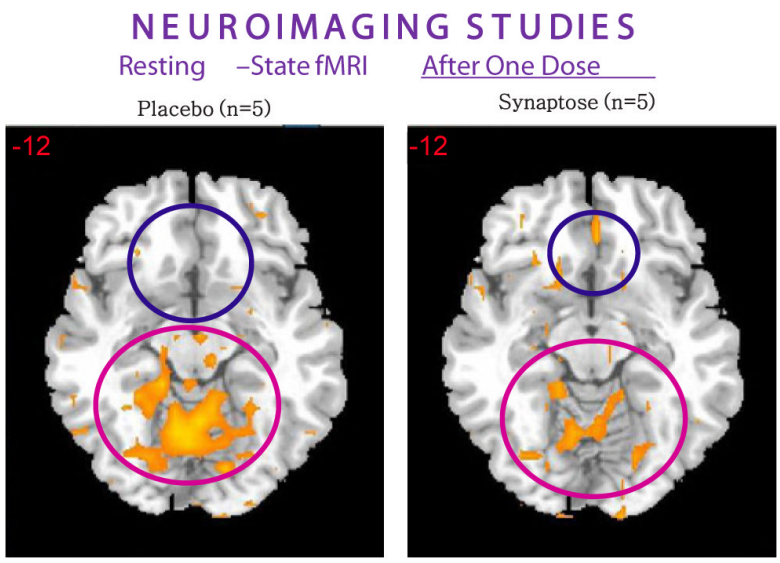
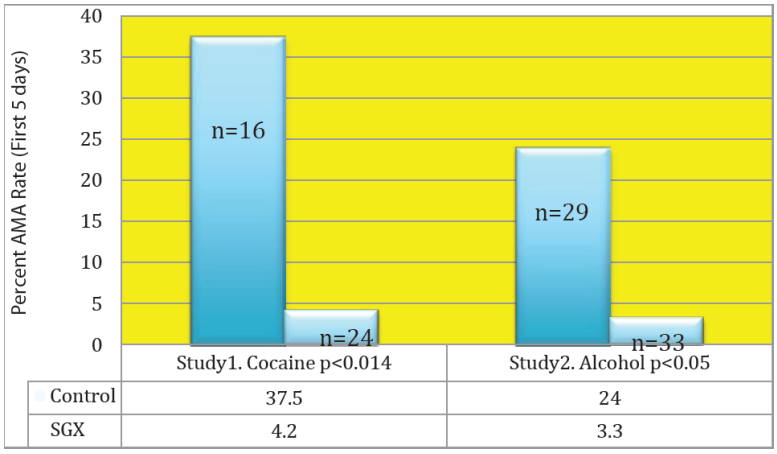


Figure 7.

fMRI study comparing the NAAT (termed Synaptose) with Placebo one hour-hour after dosing in abstinent heroin dependent patients in China.

This 2X2 design experiment shows the resting state of the fMRI scan of the same five protracted abstinent Heroin addicts one hour after receiving an acute dose of Placebo or NAAT. The scan represents the effect of an acute dose of NAAT on the caudate-accumbens-putamen brain region. Notice in the **blue circles** that there is a strong activation of the dopamine reward site. Moreover, NAAT induced a “normalization” of the putamen region-**purple circles**. It is hypothesized that NAAT caused dopaminergic agonistic activation of dopamine D2 receptors promoting enhanced reward and normalization (Modified: Liu et al. [unpublished]; Blum et al. 2011).

Liu et al. unpublished 2010.



	Study1. Cocaine p<0.014	Study2. Alcohol p<0.05
Control	37.5	24
SGX	4.2	3.3

Figure 8.
AMA Rate NAAT (depicted as SGX) vs Placebo in Cocaine and Alcohol. (Modified with permission Blum et al. 1988 [28] Blum et al. 1989 [61])

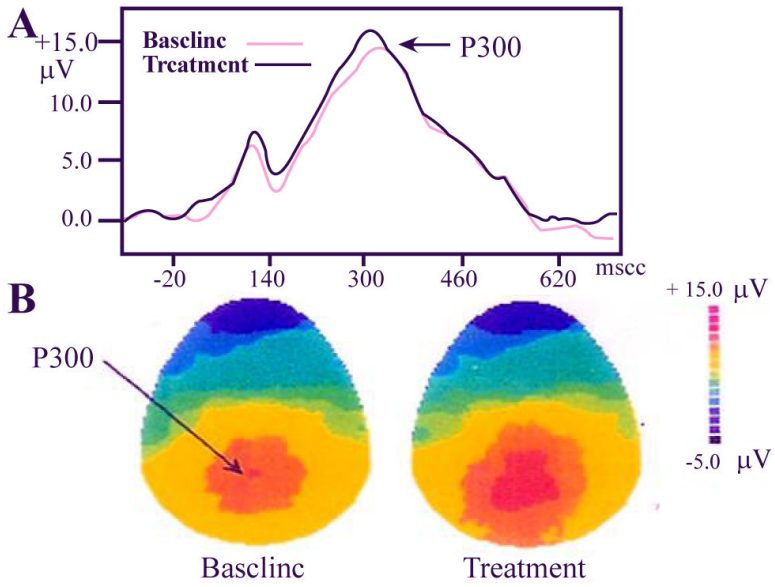


Figure 9.
NAAT variant increases focus in healthy volunteers.
(Modified from Defrance et al. 1997 [70].)

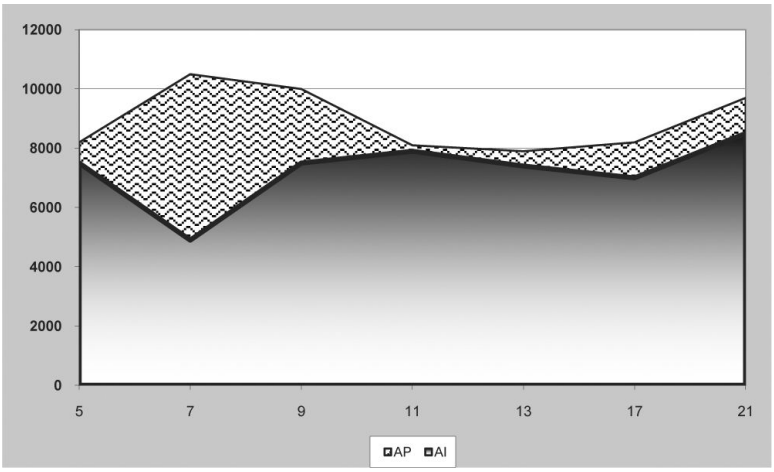
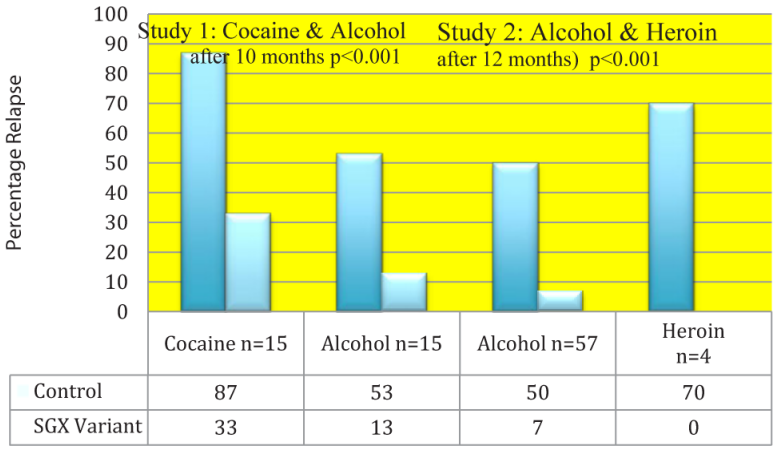


Figure 10.

Stress as measured by skin conductance: Placebo vs. NAAT [69].

The Skin Conductance Level (SCL) Y axis, is shown for both the substance AP (placebo) and investigational substance AI (NAAT). The curves for the two groups mirror one another up to day seven. The lower SC value of the NAAT group indicates less stress. (Modified from Blum et al. 2009 [62]).



	Cocaine n=15	Alcohol n=15	Alcohol n=57	Heroin n=4
Control	87	53	50	70
SGX Variant	33	13	7	0

Figure 11.
Relapse Prevention Studies: Controls Compared to NAAT Oral (depicted as SGX). (Modified from Blum et al. [66] and Blum et al. [75]).

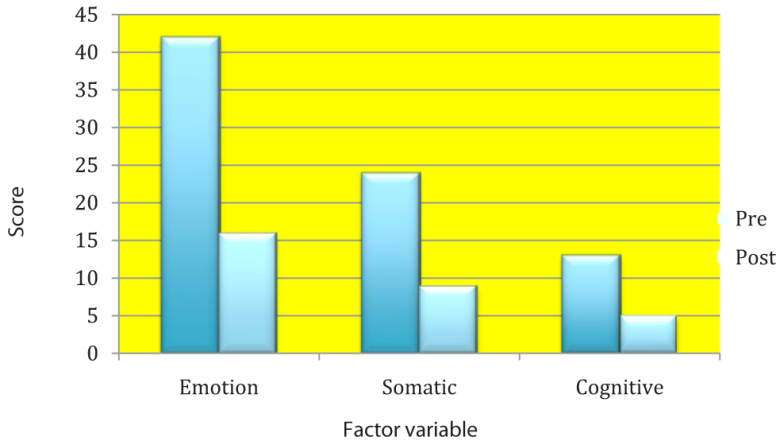


Figure 12.
The Chronic Abstinence Symptom Severity Scale with IV and oral NAAT compared to oral NAAT alone.
(Miller etal 2012 (in press) [47]).

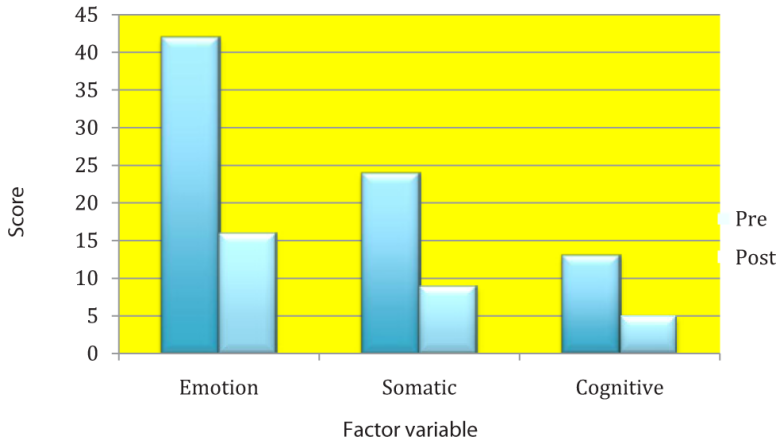


Figure 13.
CASS-R pre and post oral and IV (after 5 days) [47].
(Miller et al. 2012 in press [47].)

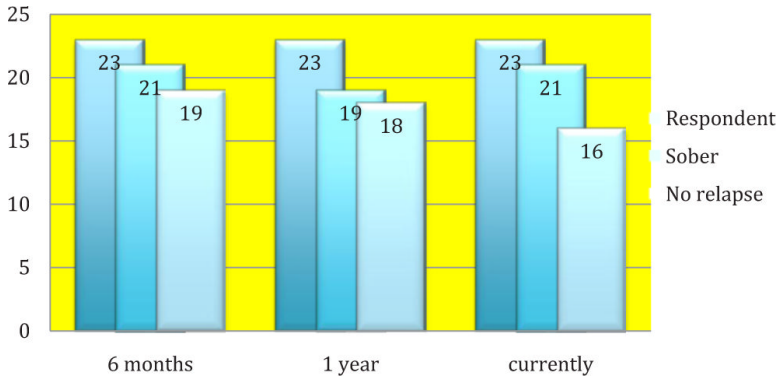


Figure 14.
Relapse in number of Recovering Subjects.
(Miller et al. 2012 in press [47].)

Table 1

Neuroadaptagen Amino-Acid Therapy (NAAT).

Gras Listed Nutrient	Neuroadaptagen Target
D-Phenylalanine	Opioid peptides
L-Phenylalanine	Dopamine
L-tryptophan	Serotonin
L-Tyrosine	Dopamine
L-Glutamine (low dose)	GABA
Chromium	Serotonin
Rhodiola rosea	COMT/MOA
Passion Flower (low dose)	Benzodiazepine=GABA complex
Pyridoxine	Enzyme Catalyst

Published Reference	Key Points
[18] Blum K, Calhoun W, Merritt J, Wallace JE (1973) L-DOPA: effect on ethanol narcosis and brain biogenic amines in mice. Nature 242: 407–409.	• Increased brain L-DOPA increases brain dopamine in mice and causes alcohol induced inebriated mice to sleep longer. • Dopamine, 1-tryptophan and alcohol work similarly in the brain.
[19] Blum K, Wallace JE, Calhoun W, Tabor RG, Eubanks JD (1974) Ethanol narcosis in mice: serotonergic involvement. Experientia 30:1053–1054.	• When mice were given alcohol and 1-tryptophan compared to saline the L-tryptophan plus alcohol group slept longer than saline plus alcohol group. • 1 -tryptophan and alcohol work similarly in the brain.
[28] Blum K, Allison D, Trachtenberg MC, Williams RW, Loeblich LA (1988) Reduction of both drug hunger and withdrawal against advice rate of cocaine abusers in a 30 day inpatient treatment program by the neuronutrient Tropamine. Current Therapeutic Research 43: 1204–1214.	• Comparison of the effects of Tropamine [T] – (amino acid and vitamin supplement), SAAVE [S]-(a neuronutrient supplement) and no supplement [C] on a group of cocaine abusers in a 30 day hospital treatment program. • AMA rate:-[C] 37.5% – [S]26.6% ■ -[T]4.2% • Tropamine decreased the AMA rate by significant reduction of drug hunger.
[48] Blum K, Stice E, Liu Y, Giordano J, Morse S, et al. (2011) “Dopamine Resistance” in brain reward circuitry as a function of DRD2 gene receptor polymorphisms in RDS: Synaptamine complex variant (KB220) induced “Dopamine Sensitivity” and enhancement of happiness. XIX World Congress of Psychiatric Genetics, September 10–14th, Washington DC.	• In a cross over triple –blind –placebo controlled study on ten Chinese abstinent (16 months) heroin dependent patients, fMRI was utilized to assess dopaminergic BOLD activation in the brain. • KB220Z was administered to each patient and after one hour it was found that the complex induced BOLD activation of caudate-accumbens dopaminergic activation. • The BOLD activation was significantly different compared to placebo. • In addition KB220Z also reduced the hyper-excitability of putamen. • The authors suggest that KB220Z induces “dopamine sensitivity” in genetically prone “dopamine resistant “patients genotyped for various reward gene polymorphisms.
[52] Blum K, Briggs AH, Trachtenberg MC, Delallo L, Wallace JE, (1987) Enkephalinase inhibition: regulation of ethanol intake in genetically predisposed mice. Alcohol 4:449–456.	• Mice genetically predisposed to like alcohol have a measured deficiency in enkephalin. • D-phenylalanine and hydrocinnamic acid are substances known to stop the breakdown of enkephalin in the brain -the amount of enkephalin available in the brain increases. • When the amount of enkephalin available in the brain increases both voluntary and forced intake of alcohol decreases. – D-phenylalanine is one of the ingredients in NAAT.
[56] Miller DK, Bowirrat A, Manka M, Miller M, Stokes S, et al. (2010) Acute intravenous synaptamine complex variant KB220™ “normalizes” neurological dysregulation in patients during protracted abstinence from alcohol and opiates as observed using quantitative lectroencephalographic and genetic analysis for reward polymorphisms: part 1, pilot study with 2 case reports. Postgrad Med 122: 188–213.	• Combination of both IV –NAAT and oral forms • Two case reports of an alcoholic and heroin addict • Both patients were genotyped for a number of 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 val 158 met SNP (rs4680), monoamine oxidase A upstream VNTR (MAOA-uVNTR), and serotonin transporter-linked polymorphic region (5HTTLPR, locus symbol SLC6A4). • Both patients showed prevalence of at least one risk allele. • qEEG analysis revealed dys-regulation in the PFC-Cingulate Gyrus in both addicts. • IV-NAAT and oral produced a regulation of widespread theta activity

Published Reference	Key Points
	• These results have relevance for relapse prevention because of its effect on the part of brain involved in relapse (PFC-Cingulate Gyrus).
[57] Blum K, Chen TJ, Morse S, Giordano J, Chen AL, et al. (2010) Overcoming qEEG abnormalities and reward gene deficits during protracted abstinence in male psychostimulant and polydrug abusers utilizing putative dopamine D2 agonist therapy: part 2. Postgrad Med 122:214–226.	• In a cross over study a total of 10 abstinent Psychostimulant dependent patients were randomized in a triple –blind –placebo controlled study. • Each patient was genotyped for a number of reward genes for addiction risk assessment. • 100% of the patient carried a least on risk allele. • qEEG analysis was performed on each patient one-hour after administration of KB220Z powder. • KB220Z™ showed an increase of alpha waves and low beta wave activity in the parietal brain region (relapse area). • Authors propose that utilization of KB220Z may up-regulate dopamine receptors in patients having moderate to high genetic addiction risk.
[61] Blum K, Trachtenberg MC, Elliott CE, Dingler ML, Sexton RL (1988) Enkephalinase inhibition and precursor amino acid loading improves inpatient treatment of alcohol and polydrug abusers: double-blind placebo-controlled study of the nutritional adjunct SAAVE. Alcohol 5: 481–493.	• Double blind placebo controlled clinical trial of SAAVE of 62 people with Substance Use Disorder (SUD). • Results: – reduced stress as measured by skin conductance, – improved Physical and BESS (behavioral, emotional, social and spiritual) Scores, – Six-fold decrease in leaving Against Medical Advice (AMA) rates.
[62] Blum K, Chen ALC, Chen TJH, Bowirrat A, Waite RL, et al. (2009) Putative targeting of Dopamine D2 receptor function in Reward Deficiency Syndrome (RDS) by Synaptamine Complex™ Variant (KB220): Clinical trial showing anti-anxiety effects. Gene TherMolBiol 13:214–230.	• Double-blind-placebo controlled study to determine anti-anxiety effects of KB220 (Synaptamine Variant) in 62 alcoholic and poly-drug abusers • This was an objective test not subjective because antianxiety effect evaluated by skin conductance level (SCL). • Significant reduction of stress in the KB220 group compared to placebo including a Time by-treatment interaction. Positive anti-anxiety effect as monitored throughout a 28 day treatment period is most significant at the 7th day (a time with the most severe anxiety). • These findings may be relevant to prevention of relapse.
[63] Blum K, Trachtenberg MC, Ramsay JC (1988) Improvement of inpatient treatment of the alcoholic as a function of neurotransmitter restoration: a pilot study. The International Journal of the Addictions 23: 991–998.	• First small clinical trial of SAAVE (precursor amino acid loading and enkephalinase inhibition -earliest version of NAAT). • • Designed to elevate levels of enkephalin(s), serotonin, catecholamines, and regulate GABA, thought to be deficient in alcoholics. • • Compared to controls those who took SAAVE had: – lower building up to drink score, – required no PRN benzodiazepines, – ceased having tremors 24 hrs earlier – had less depression.
[65] Brown RJ, Blum K, Trachtenberg MC (1990) Neurodynamics of relapse prevention: a neuronutrient approach to outpatient DUI offenders Journal of Psychoactive Drugs 22:173–187.	• Relapse prevention using neuronutrients SAAVE and Tropamine in DUI offenders; either alcohol or cocaine. • Reduced relapse rates and enhanced recovery in 10 week outpatient setting. • After 10 months recovery rate was SAAVE 73% and Tropamine 53%. • These recovery rates are significantly better than the literature average for both alcoholism and cocaine dependence.

Published Reference	Key Points
[70] DeFrance JF, Hymel C, Trachtenberg MC, Ginsberg LD, Schweitzer FC et al. (1997) Enhancement of attention processing by Kantroll in healthy humans: a pilot study. Clinical Electroencephalography 28: 68–75.	• Cognitive processing speeds in normal young adult volunteers were measured before and after 28–30 days of supplementation with a combination of amino acids-enkephalinase inhibition (NAAT), vitamins and minerals. • Cognitive processing speeds were enhanced by statistically significant amplitude of the P300 component of the Event Related Potentials (ERPs). FOCUS IMPROVED • These findings have relevance to relapse prevention because the resultant enhanced effect following NAAT as measured by the Contingent Continuous Performance Task (CCPT); Spatial Orientation Task (SOT) and focus reflects better judgment and thus decision making.
[75] Blum K, Chen TJH, Downs BW, Meshkin B, Blum SH, et al. (2007) Synaptamine (SG8839), TM An Amino-Acid Enkephalinase Inhibition Nutraceutical Improves Recovery of Alcoholics, A Subtype of Reward Deficiency Syndrome (RDS). Trends in Applied Sciences Research 2 (3): 132–138.	• n an open clinical study Intravenous plus oral Amino-Acid Enkephalinase Inhibition Nutraceutical improved symptomatology of 600 recovering Alcoholics. • Emotional and behavioral recovery scores significantly improved after administration of oral and intravenous Synaptamine. • Mean reductions for craving, depression, anxiety, anger, fatigue, lack of energy and crisis were all significantly greater than 50% ($p<0.001$).
[92] Blum K, Chen TJH, Chen ALC, Rhodes P, Prihoda TJ, et al. (2008) Dopamine D2 Receptor Taq A1 allele predicts treatment compliance of LG839 in a subset analysis of pilot study in the Netherlands. Gene Ther Mol Biol 12: 129–140.	• This study evaluated the importance of carrying the dopamine D2 receptor A1 allele and treatment compliance of n in an Obese Dutch population nutraceutical intervention to combat obesity. • Candidate genes to be associated with obesity include amongst others the dopamine D2 receptor (DRD2), methylenetetrahydrofolate reductase (MTHFR), serotonin receptor (5-HT2a), Peroxisome Proliferator Activated Receptor gamma (PPAR-γ), and Leptin (OB) genes. • Compliance 2 fold better in carriers of DRD2 A1 allele compared to DRD2 A2 allele. • Suggests if you need to enhance dopamine compliance is better.
[97] Chen TJH , Blum K, Kaats G, Braverman ER, Eisenberg A, et al. (2007) Chromium Picolinate (Crp) A putative Anti-Obesity Nutrient Induces Changes In Body Composition As Function Of The Taq1 Dopamine D2 Receptor polymorphisms in a randomized double-blind placebo controlled study. Gene Therapy and Molecular Biology 11: 161–170.	• Chromium Picolinate (CrP) was tested against placebo in groups of obese patients tested for the Taq1 Dopamine D2 Receptor Gene. • In carriers of the DRD2 A2 genotype weight loss and other changes in body composition were significant. • They were not significant for patients with the A1/A1 or A1/A2 allele. • These results suggest that the dopaminergic system, specifically the density of the D2 receptors, confers a significant differential therapeutic effect of CrP in terms of weight loss and change in body fat. • It is speculated that carriers of the DRD2 A1 allele had aberrant sugar cravings which masked the effects of CRP.
[103] Chen TJ, Blum K, Waite RL, Meshkin B, Schoolfield J, et al. (2007) Gene Narcotic Attenuation Program attenuates substance use disorder, a clinical subtype of reward deficiency syndrome. Advances in Therapy 24:402–414.	• 1-year prospective study that evaluated the effects of taking Haveos (SynaptamineTM) on 61 compliant patients in a comprehensive outpatient clinical program. • Results after 12 weeks: • Results after 1 year: • Building up to relapse scores and ability to refrain from drug-seeking behavior both significantly improved. • Dropout rate: Alcohol users 7% and Psychostimulant users 73%
[105] Chen D, Liu Y, He W, Wang H, Wang Z (2012) Neurotransmitter-precursor-supplement Intervention for Detoxified Heroin Addicts. Med Sci 32: 422–427.	• In the cluster-randomized placebo-controlled trial, 83 detoxified heroin addicts were evaluated during withdrawal. • This study examined the effects of combined administration of tyrosine, lecithin, L-glutamine and L-5-hydroxytryptophan (5-HTP) on heroin withdrawal syndromes and mental symptoms.

Published Reference	Key Points
	• The experimental group compared to placebo had reduced insomnia, and reduced withdrawal scores. • After 6 days of treatment compared to placebo the experimental group had a d significant reduction in tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia and total mood disturbance, and a greater increase in their vigor-activity symptoms (all P<0.05).
[115] Blum K, Trachtenberg MC, Cook DW (1990) Neuronutrient effects on weight loss in carbohydrate bingers; an open clinical trial. Curr Ther Res 48: 217–233.	• Examine the effects of PCAL-103 (NAAT) on compulsive eating and weight loss in 27 outpatients attending a supervised diet-controlled treatment program. • The PCAL-103 average weight loss was 26.96 lbs vs 10.2 lbs in the control group. Relapse 18.2% in the PCAL-103 group vs 81.8% in the control group.
[116] Cold, Julie A (1996) NeuRecover-SATM in the Treatment of Cocaine Withdrawal and Craving: A Pilot Study. Clinical Drug Investigation 12: 1–7.	• Small preliminary double-blind, placebo-controlled study of efficacy of NeuRecover-SATM (formerly Tropamine+TM) in the treatment of cocaine withdrawal and craving. • Cocaine craving decreased significantly in the NeuRecover-SATM group compared to placebo.
[117] Blum K, Cull JG, Chen TJH, Swan SG, Holder JM, et al. (1997) Clinical evidence for effectiveness of Phencal™ in maintaining weight loss in an open-label, controlled, 2-year study. Current Therapeutic Research 58: 745–763.	• Of 247 Outpatients in a very-low-calorie fasting program 130 who were having difficulty attaining their desired weight or maintaining their desired weight constituted the experimental group who took PhenCal™ plus Centrum Vitamins and the rest 117 took only vitamins (Centrum) 117 were the control group. • The PhenCal™ group compared to the control: • - lost twice as much weight, • - regained 14.7% of the weight while the control group regained 41.7%, • - decrease in food cravings (sugar) for females 70% and males 63%, • - decrease in binge eating for females 66% and males 41 %.
[118] 1st Conference on Reward Deficiency Syndrome: Genetic Antecedents and Clinical Pathways. San Francisco, California, USA. November 12–13, 2000. Abstracts. Amino-acid precursor and enkephalinase inhibition therapy: evidence for effectiveness in treatment of “Reward Deficiency Syndrome (RDS) with particular emphasis on eating disorders. Julia Ross. Mol Psychiatry. Feb; 6(1 Suppl 1):S1–8, 2001.	• Preliminary evaluation of six randomly selected former eating disordered female clients (three were also chemically dependent), contacted at 9 months and 3 years of treatment with amino-acid precursor and enkephalinase inhibition therapy. • All 6 reported initial benefit, one relapsed at 6 months the other 5 all sustained, and in some cases exceeded expectations. • 98% of 100 patients similarly treated and evaluated reported significant improvement in both mood and reduced substance craving.
[119] Chen TJ, Blum K, Payte JT, Schoolfield J, Hopper D, et al. (2004) Narcotic antagonists in drug dependence: pilot study showing enhancement of compliance with SYN-10, amino-acid precursors and enkephalinase inhibition therapy. Medical Hypotheses 63: 538–548.	• A combination of Trexan (a narcotic antagonist) and amino-acids was use to detoxify either methadone or heroin addicts. • Results were dramatic in terms of significantly enhancing compliance to continue taking Trexan: • -Trexan alone for rapid detoxification the average number of days of compliance calculated on 1000 patients is 37 days. • -12 subjects tested, receiving both the Trexan and amino-acid therapy continued to take the combination for an average of 262 days. • Suggests:- coupling amino-acid therapy and enkephalinase inhibition, while blocking the delta-receptors with a pure narcotic antagonist as a novel method to induce rapid detox in chronic methadone patients and prevent relapse; • - testing this hypothesis with the sublingual combination of the partial opiate mu receptor agonist buprenorphine.
[120] Blum K, Chen TJ, Meshkin B, Downs BW, Gordon CA, et al. (2006) Reward deficiency syndrome in obesity: a preliminary cross-sectional trial with a Genotrim variant. AdvTher23: 1040–1051.	• Consumption of large quantities of alcohol or carbohydrates (carbohydrate bingeing) stimulates production and usage of dopamine within the brain. • Obesity is due to the need to make up for inadequate dopaminergic activity in the reward center of the brain.

Published Reference	Key Points
	• This has been called reward deficiency syndrome (RDS) used to categorize such genetic biologic influences on behavior. • RDS must be addressed at the same time as behavioral modifications are implemented to adequately treat obese patients. • In this small observational trial; 24 individuals completed a survey on which they documented 15 categories of benefit during their experience with a GenoTrim a NAAT formulation customized to DNA. • Statistical analysis of the survey results demonstrated that stress reduction lead to: • -(1) improved sleep, enhanced energy, and improved focus and performance; • - (2) reduced appetite, loss of unwanted weight, decreased body inches, and enhanced well-being.
[121] Blum K, Chen TJH, Williams L, Chen ALC, Downs WB, et al. (2008) A short term pilot open label study to evaluate efficacy and safety of LG839, a customized DNA directed nutraceutical in obesity: Exploring Nutrigenomics. Gene Ther Mol Biol 12: 371–382.	• Preliminary investigational study to evaluate the impact of polymorphisms of five candidate genes on treatment for obesity with NAAT. • The formula for each patient was customized based on their genetic results. • Pre- NAAT compared to Post-NAAT had significantly lower BMI. • Pre- NAAT compared to Post-NAAT had significantly lower pounds. • Pre- NAAT compared to Post-NAAT had trends for reduced late night snacking, carbohydrate craving reduction, reduction of stress, reduction of waist circumference.
[122] Blum K, Chen AL, Chen TJ, Rhoades P, Prihoda TJ, et al. (2008) LG839: anti-obesity effects and polymorphic gene correlates of reward deficiency syndrome. Adv Ther 25: 894–913.	• First DNA Customized analysis of LG839 for weight management effects. • Out of 1058 Dutch participants a subset of 27 self –reported obese subjects were genotyped and based on their polymorphisms each subject utilized a customized LG839 variant assessed for pre –and post for after 80 days of usage. • Significant results were observed for weight loss, sugar craving reduction, appetite suppression, snack reduction, reduction of late night eating (all $P<0.01$), increased perception of overeating, enhanced quality of sleep, increased happiness (all $P<0.05$), and increased energy ($P<0.001$). • The study points to the importance of genotyping patients and providing DNA customized nutraceutical intervention to combat obesity.
[123] Braverman ER, Braverman D, Acrui V, Kerner M, Downs BW, Blum K (2010) Sustainable Weight Loss and Muscle Gain Utilizing the Rainbow Diet™: Targeting Noradrenergic and dopaminergic Mechanistic Sites, Hormonal Deficiency Repletion Therapy and Exercise: A case report. The American Journal of Bariatric Medicine 25: 18–28.	• Case study of 58 Y old male identified as being obese utilized a special Rainbow Diet. • Patient received Noradrenergic drug; NAAT (a natural D2 agonist); hormonal deficiency replacement therapy and light exercise. • After one year BMI decreased; Percent body fat decreased; improved cardiac function; fasting glucose level declined; Prostate Specific Antigen (PSA) tripled; memory improved; testosterone levels increased. • There was sustainable weight loss and muscle gain.
[124] Merlene Miller, Amanda LC Chen, Stan D. Stokes, Susan Silverman, Abdalla Bowirrat, et al. Early Intervention of Intravenous KB220IV- Neuroadaptagen Amino-Acid Therapy (NAAT)™ Improves Behavioral Outcomes in a Residential Addiction Treatment Program: A Pilot Study. Journal of Psychoactive.	• In 129 patients a combination of IV and oral NAAT therapy (generic KB220) were assessed for Chronic Abstinence Symptom Severity (CASS) Scale over a 30 day period. • Three scales were constructed based on this factor analysis: Emotion, Somatic, and Cognitive. • All three scales showed significant declines ($p=.00001$) from pre- to post-treatment: $t=19.1$ for Emotion, $t=16.1$ for Somatic, and $t=14.9$ for poor - Cognitive. • A two year follow-up in a subset of 23 patients showed: 21 (91 %) were sober at 6 months 19 (82%) having no relapse; 19 (82%) were sober at one year with 18 (78%) having no relapse; 21 (91 %) were sober at two years post-treatment with 16 (70%) having no relapse.