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Nutrigenomics of Neuradaptogen Amino-Acid-Therapy and Neurometabolic Optimizers: Overcoming carbohydrate bingeing and overeating through neurometabolic mechanisms

Kenneth Blum[1,3,4,7,8,9*], Debasis Bagchi[2], Abdalla Bowirrat[3], B. William Downs[4], Roger L. Waite[4], John Giordano[5], Siohban Morse[5], Margaret Madigan[4], Jaclyn M. Downs,[4] Eric R. Braverman,[6, 7]Margaret Polanin[7], Debmayla Barh[8], Frank Fornari[9], Thomas Simpatico[10]

[1]Department of Psychiatry, University of Florida, College of Medicine, Mcknight Brain Institute, Gainesville, Florida, USA; Director of Inovative Research and Clinical Trials, Iovate Inc., Toronto, Canada.[3]Clinical Neuroscience and Population Genetics, Ziv Government Medical Center, Israel; [4]Department of Personalized Medicine, Reward Deficiency Solutions, LLC, San Diego, California, USA; [5]Deaprtment of Holistic Medicine, G and G Hoistic Addiction Treatment Center, North Miami Beach, USA; [6]Department of Clinical Neurology, Path Foundation NY, New York, New York, USA; [7]Department of Neurological Surgery, Weill Cornell College of Medicine, New York, New York; [8]Centre for Genomics and Applied Gene Technology, Institute of Integrative Omics and Applied Biotechnology (IIOAB), Nonakuri, Purba Medinipur, West Bengal 721172, India,; Dominion Diagnostics Inc. North Kingstown, Rhode Island, [9]Community Mental Health Institute, Center for Clinical & Translational Science, University of Vermont and Department of Psychiatry, University of Vermont College of Medicine, Burlington, Vermont, USA

Corresponding author: Kenneth Blum, PO Box: 100256, Gainesville, FL, USA

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Abstract

Despite progress that has been made in the treatment of obesity, the epidemic continues to rise worldwide. While pharmacological treatment of obesity may be effective, medications may have significant side effects and can be potentially fatal. This review will provide significant evidence to substantiate the existence of *Reward Deficiency Syndrome* in Obesity and the role of catecholaminergic pathways in aberrant substance seeking behavior, in particular cravings for carbohydrates. The genetic basis for generalized craving behavior will be established. Evidence to support the augmentation of precursor amino acid therapy and enkephalinase, MOA and COMT inhibition leading to enhanced levels of neurotransmitters: serotonin, enkephalins, GABA and dopamine/norepinephrine as well increasing insulin sensitivity (affecting dopamine neuronal synthesis regulation) through the use of certain neurometabolic optimizers will also be provided. This review article cites many published studies to support a conceptual paradigm shift

towards the use of this proposed nutrigenomic formula. The analysis and research preceding this formulation is outlined. This formulation has a generalized anti-craving effect and can inhibit carbohydrate bingeing, inducing significant healthy fat loss and prevention of relapse. This is the first time that components of this formula have been combined, at the dosage levels indicated with the goal of promoting successful and sustainable body recomposition. We are encouraging other laboratories to further evaluate Neuroadtagen Amino-Acid Therapy (NAAT)/Nurometabolic optimizers as a putative anti-obesity complex in larger controlled blinded studies and await interpretation of must these needed studies.

Keywords: NAAT, Dopamine, Genes, Polymorphisms, Obesity, Craving Behavior, Overeating, Reward Deficiency Syndome, Nutrigenomics**.**

Background

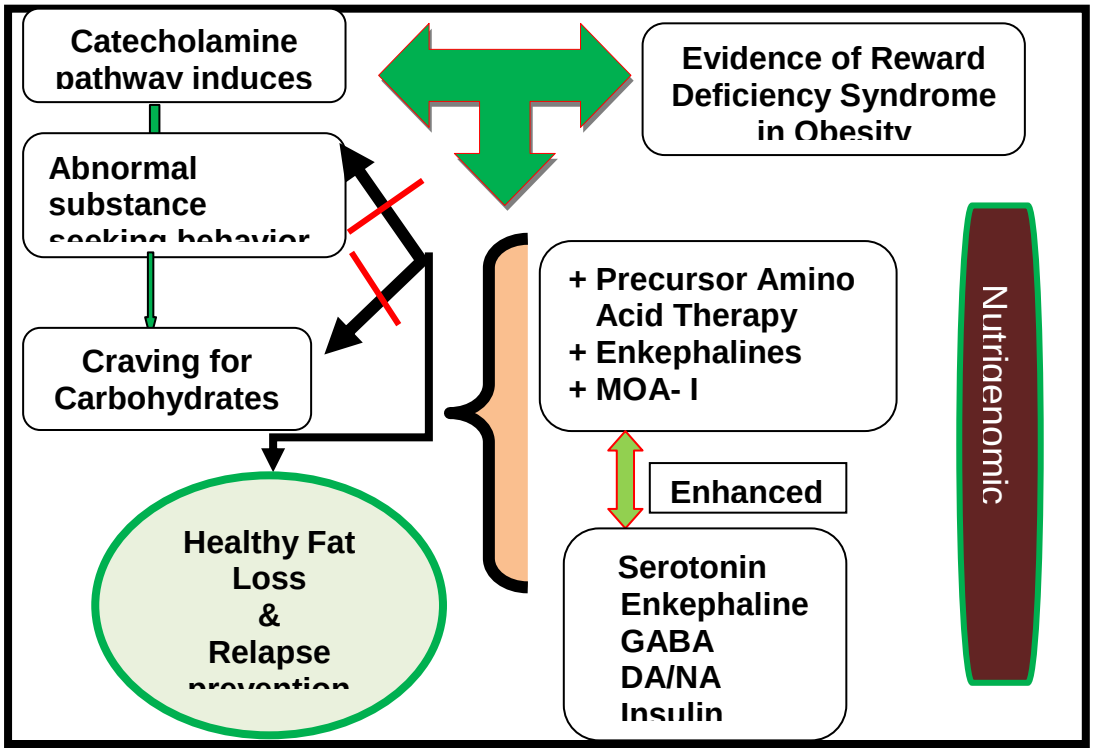
It is well-known that there is indeed an obesity epidemic worldwide. To alter this trend, new strategies and programs for weight maintenance as well as weight reduction must become a high public health priority. Our take on this, is that programs which promote the "just say no policy" will be doomed to fail. We must first begin to understand how the brain controls eating behavior and what are the genetic antecedents to abnormal "sugar cravings". In this rather large review we have attempted to provide a coherent detailed account accompanied with many data driven references to carefully frame these new but important concepts.

"Weight loss," "weight gain" and "weight management" are the most common terms used to express changes in body composition, particularly regarding fat mass. However, this review will present evidence showing that the focus on "weight" as the main criteria for measurment is in contradiction to the natural sequence of processes in recompositional metabolism. Given that fat is the lightest of pertinent macro molecules and more importantly, fat is usually the last to go in the body recomposition process talking about "weight loss" creates inappropriate expectations and does not provide an accurate perspective for evaluating healthy changes in body composition. Fat metabolism is influenced by many factors from genetics to lifestyle and the efficiency of energy metabolism. Existing "weight loss" tactics for the most part have failed to provide successful means to achieve sustainable healthy body composition and improve healthy fat loss. Commercialized "weight loss" programs, even medically supervised versions, do not consider the "bi-phasic" [1] nature of genetically regulated set point "defense response" mechanisms that mandate preservation of body fat stores against famine and survival threats simulated by aggressive weight loss tactics during phase 1. Further, existing tactics place an erroneous emphasis on caloric intake to the exclusion of considering nutrient quality and density of those calories, a factor far more important to metabolic competence than calories alone. This review provides support for a novel body recomposition and healthy body mass management technology. A unique formula and method to safely and naturally induce effective body recomposition and achieve healthy body mass management objectives is presented. This novel technology contrasts with existing tactics to manipulate body composition in that it is based on the fact that sufficient nutrition (as opposed to just calories) is required to fund a wide range of

factors involved in achieving healthy and efficient metabolic function. This technology combines synergistic nutraceutical ingredients necessary to simultaneously address symbiotic mechanisms that promote healthy metabolism in the energy management system, stress and inflammation management system, the pleasure/food craving management system (controlled by the brain), the immune management system and the neuroendocrine system. Importantly, these five systems are homeostatic and intimately interactive and interdependent in ensuring optimal metabolic function. This novel nutraceutical technology optimizes genetically programmed energy expenditure and storage functions, without inducing "Yo Yo" rebound weight gain consequences. In contrast to conventional short term expectations, "weight loss" might not be expected since the need to improve the health of the cellular energy producing apparatus might first result in increased muscle density and weight "gain" that is needed to promote healthy and permissible fat oxidation and loss. In fact, a more normal and expectable sequence of events might include initial water weight loss, increased muscle density and weight (muscle is heavier than fat and water) followed by permissible fat loss, which could take many months to achieve. Such a sequence could and has contributed to disappointment with short term "weight loss" results and abandonment of more intelligent programs that would lead to sustainable fat loss useing the healthy body recomposition dynamic.

Various minerals have been shown to be important in funding events leading up to and promoting healthy carbohydrate metabolism, insulin function, energy production, fat oxidation, serotonin release and availability in the brain, blood lipid metabolism and improving the success of fat loss and body composition management efforts.

Figure 1 Nutrigenomics of Neuradaptogen and Amino-Acid-Therapy (NAAT) ™ as a putative anti-obesity complex.



Based on the premise of this review, the novel nutraceutical technology presented herein provides ample evidence that the term "weight loss" is a misnomer. This term "weight loss" (or any terms using the "weight" language reference) is deliberately misused herein to emphasize the point of how conventional tactics (and language) contribute to erroneous, but unquestionably accepted, dogma. Current "weight loss" tactics, for the most part, are based on inducing calorie intake deprivation and artificially stimulate, deprive or inhibit the body's genetically programmed energy expenditure, storage, regulatory and management processes (see table 1).

Table 1 Current "weight loss" tactics

Central Nervous System Stimulants (CNSS) that artificially stimulate the rate of calorie burning (Basal Metabolic Rate [BMR]).
Appetite Suppressants
Fat Blockers
Starch Blockers
Diuretics (Water Pills)
Low Calorie Diets
Low Food Diets
Meal Replacement Programs (Diet Shakes, bars, etc.)
High Protein Diets
High Carbohydrate Diets
Low/No Carbohydrate Diets
Low Fat Diets
Pre-Meal Fiber/Water "Fill-You-Up" Programs
Fruit and Fruit juice "Rapid "weight loss"" Programs
Over Night "weight loss" Programs
Vegetable Soup Diet Programs
Liposuction
Radical Digestive Tract Surgeries
Acupuncture
Laxatives

Many of these tactics are used individually or in combination to achieve rapid "weight loss" results. As stated, the primary goal of these tactics is "weight loss" and/or image enhancement. These objectives are usually pursued without regard for or knowledge of the impact on health, the bodys' natural genetically mandated homeostatic response to such tactics, or the fact that depriving the body of resources essential to maintain health is counterproductive. Essentially, these types of tactics simulate the circumstances of a famine and induce genetically programmed energy conservation responses. In addition, at some point in the energy conservation sequela, increased appetite can result. Alarmingly, many of these tactics are approved, administered and/or supervised by medical or health professionals. While initially appearing to promote "weight loss" (phase 1), such tactics are destined to fail as gene-induced recalibration of energy management and storage instructions homeostatically adjusts to the artificially imposed influence of such tactics, generally by lowering the basal metabolic rate, increasing energy storage requirements and promoting increased fat retention (phase 2) [1, 2]. Chronic and repeated attempts to lose weight with such tactics are referred to as the yo-yo weight gain rebound effect.

This phenomenon is responsible for ever-increasing frustration, anxiety and a sense of helplessness caused by the out-of-control "weight loss"/gain juggernaut.

Ultimately, obesity is an energy-balance and nutrient deficiency-induced famine disorder characterized by a survival gene induced increase in fat storage, lowering of the Basal Metabolic Rate (to conserve energy) and increase in appetite. Following circumstances when a simulated famine is induced, certain genes, programmed to resist loss of body fat, prevail [3]. This programmed genetic predisposition is responsible for down-regulating the resting metabolic rate (RMR) in response to dietary and caloric restriction, which is significantly disrupted following rapid "weight loss" regimens, like those tactics indicated above. Over-consumption of food, especially nutritionally deficient high calorie food (excess energy intake), is a normal consequence contributing to weight gain and obesity. A resistance to the hormone leptin also characterizes common obesity. Insulin has been shown to increase leptin secretion by 25%. Ample evidence demonstrates that insulin resistance is also a primary contributor to obesity, suggesting that insulin resistance induced hyperinsulinemia can provoke leptin resistant hyperleptinemia with a consequential increase in fat synthesis and storage in adipocytes, characteristic sequela of Syndrome X or Metabolic Syndrome. Further, adipocytes from fatter animals secrete more leptin and a correlation between intracellular ATP concentration and the rate of leptin secretion appears to exist. As such, leptin concentration correlates positively with percent body fat. A low resting metabolic rate for a given body size and composition, a low rate of fat oxidation, and low levels of physical activity are risk factors for weight gain and common traits of obese individuals. It has been shown that a decrease in body weight as fat mass and fat free mass is accompanied by a greater decrease in resting energy expenditure and fat oxidation [4, 5, 6].

Effective fat loss and body recomposition strategies addressing the energy management pathways should simultaneously improve insulin, serotonin and fat oxidation metabolism; potentiate a healthy increase in resting metabolic rate and energy expenditure; and blunt excessive appetite cravings, given proper adequate nutrient and energy intake. The technology of the present invention replenishes the nutritional needs of at least five important systems, which are essential to healthy weight management as follows: 1. The biochemical mechanisms involved in nutrition and energy management regulating intake, expenditure and storage controls and feedback; 2. Attenuation of the effects of chronic stress and inflammation (which overburden the endocrine system and can cause things like excessive cortisol production) reducing fat storage; 3.The pleasure seeking needs and reward circuitry of the brain, influencing psychological and emotional need-induced food cravings; 4. Promotion and support of healthy immune system function (involved in catalyzing survival response to metabolic threats; and 5. Supporting and maintaining optimal health of the neuroendrocrine system through which the majority of metabolic signaling is processed. Nutritional and gene expression deficiencies in the Reward neurochemical pathway limit the brain's reward resources (specific neurotransmitters) and are responsible for a condition called "Reward Deficiency Syndrome, (RDS)" which causes excessive cravings [7].

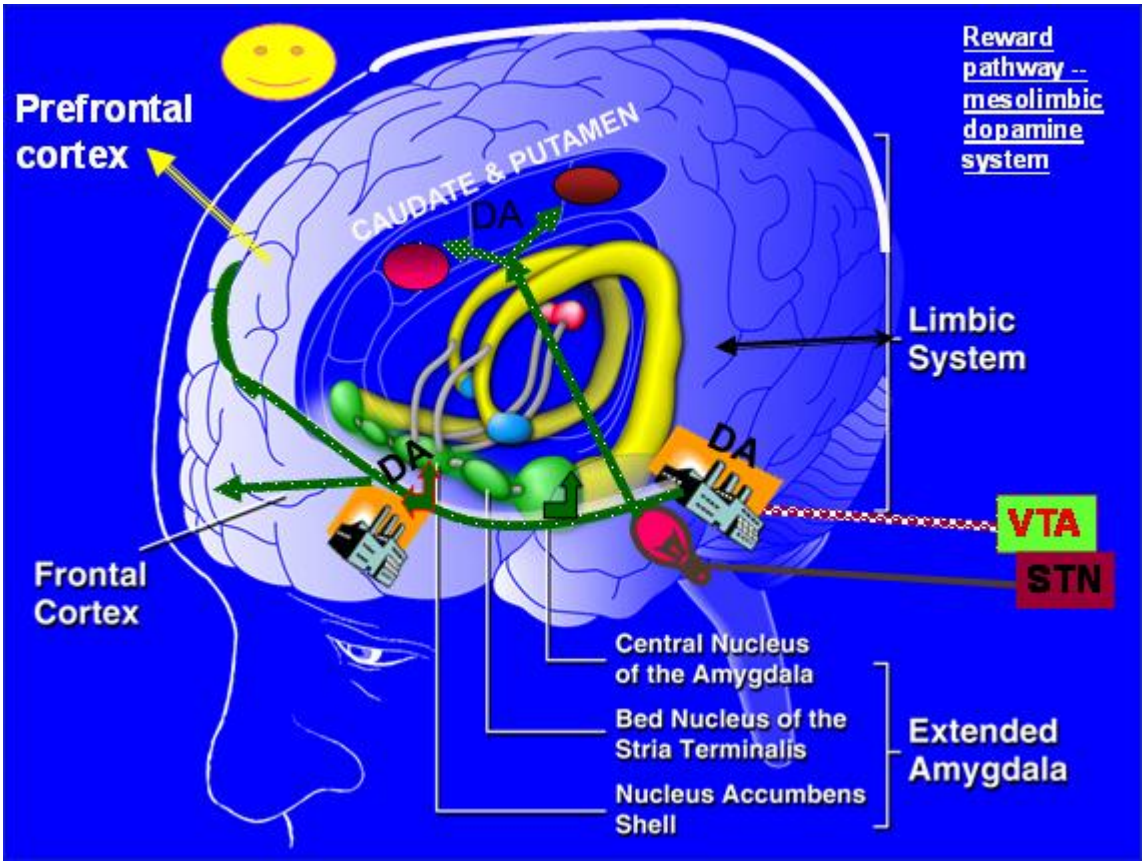
The *Reward Deficiency Syndrome* (RDS) results from a dysfunction in the Brain Reward Cascade, which directly links abnormal craving behavior with a defect in the DRD_2 Dopamine

Receptor Gene as well as other dopaminergic genes (D1, D3, D4, D5). Dopamine is a very powerful neurotransmitter in the brain, which controls feelings of well-being. This sense of well-being is produced through the interaction of dopamine and neurotransmitters such as serotonin, the opioids, and other powerful brain chemicals. Low serotonin levels are associated with depression. High levels of the opioids (the brain's opium) are associated with a sense of well-being. The complex interactions of these powerful neurotransmitters, ultimately regulating the Dopaminergic Activity in the Reward Center of the Brain, have been termed by Blum et al., "The Brain Reward Cascade" (See Figure 2 for anatomy) [8].

In individuals possessing an abnormality in the DRD2 Dopamine Receptor Gene, the brain lacks enough Dopamine receptor sites to use the normal amount of Dopamine in the Reward Center of the brain and thus reduces the function of Dopamine in this area of the brain. Individuals possessing the variant in the Dopamine Receptor Gene tend to be serious cocaine abusers, may have unhealthy appetites that can lead to obesity or overeating.

The overall effect is inadequate Dopaminergic Activity in the Reward Center of the Brain. This defect drives individuals to engage in activities, which will increase brain Dopamine function. Consuming large quantities of alcohol or carbohydrates (carbohydrate bingeing) stimulate the brain's production of and utilization of Dopamine. So too does the intake of crack/cocaine and the abuse of nicotine. Also, it has been found that the genetic abnormality is associated with aggressive behavior, which also stimulates the brain's use of Dopamine.

Figure 2 Anatomy of the Meso-limbic system of the brain reward site.



The Reward Deficiency Syndrome involves a form of sensory deprivation of the brain's reward or pleasure mechanisms. The Reward Deficiency Syndrome can be manifested in relatively mild or severe forms that follow as a consequence of an individual's biochemical inability to derive reward from ordinary, everyday activities. We believe that we have discovered at least one genetic aberration that leads to an alteration in the reward pathways of the brain. It is a variant form of the gene for the dopamine D_2 receptor, called the A1 allele. This genetic variant also is associated with a spectrum of impulsive, compulsive, and addictive behaviors. The concept of the Reward Deficiency Syndrome unites those disorders and may explain how simple genetic anomalies give rise to complex aberrant behavior (See Figure 3, The Reward Deficiency Syndrome).

Evidence for the existence of RDS in Substance Use Disorder:

In 1990, Blum and colleagues, using the *Taq1* polymorphism of the dopamine D2 receptor gene locus (DRD2), for the first time reported a strong association between a virulent form of alcoholism and the minor allele (A1) of the Drd2 gene in this population [8,9]. Other more recent studies further support an association of the A1 allelic form of the DRD2 gene with substance abuse vulnerability and other compulsive behaviors [10, 11, 12, 13, 14,15]. This association serves as the cornerstone of the biogenetic disease model and could ultimately lead us to better diagnosis and targeted treatment [16]. A complete review of this work can be found in the Journal of Psychoactive Drugs [17].

Figure 3: The Reward Defiency Syndrome.

Addictive Behaviors	Impulsive Behaviors	Compulsive Behaviors	Personality Disorders
severe alcoholism	attention-deficit disorder hyperactivity	aberrant sexual behavior	conduct disorder
polysubstance abuse	Tourette syndrome	Internet gaming	antisocial personality
smoking	autism	pathological gambling	aggressive behavior
obesity			

This treaties will highlight the importance of a new concept, which provides a clearer understanding of impulsive, addictive, and compulsive behaviors. It is our notion that the real genesis of all behavior, whether so-called normal (socially acceptable) or abnormal (socially

nonacceptable) behavior, derives from an individual's genetic makeup at birth. This predisposition due to multiple gene combinations and polymorphisms is expressed differently based on numerous environmental elements including family, friends, educational status, economical position, environmental pollutants, and availability of psychoactive drugs including food. We believe the core of predisposition to these behaviors is a set of genes, which promote a feeling of well–being via neurotransmitter interaction at the "reward site" of the brain (located in the meso-limbic system), leading to normal dopamine release. We also subscribe to the notion that at least one major gene, the dopamine D2 receptor gene, is responsible for the synthesis of dopamine D2 receptors. And further depending on the genotype (allelic form A1 versus A2), the dopamine D2 receptor gene dictates the number of these receptors at post-junctional sites.

A low number of dopamine D2 receptors suggest a hypodopaminergic function, as described by Eliot Gardner in a series of published works [18, 19]. When there is a paucity of dopamine receptors the person will be more prone to seek any substance (including glucose) or behavior that stimulates the dopaminergic system as a form of self-healing. In this regard we know that substances such as alcohol, cocaine, heroin, nicotine and glucose, as well as a number of behaviors like gambling and sex, preferentially release dopamine at the n. accumbens (the reward site). Understanding this preamble allows us to introduce the concept of reward deficiency syndrome into the field of addictive behavior, which will serve as a model to explain the commonality of a number of seemingly diverse addictions based on shared genetics and neurochemistry. In this regard, most recently, Qing–Shan Yan reported that ethanol, at a peak concentration within five to 10 minutes after interparenteral administration, significantly increased both extracellular dopamine and serotonin in the n. accumbens, supporting the role of these two neurotransmitters in the reinforcing properties of ethanol [20]. Moreover, Honkanen and associates also found low basal dopamine release in alcohol accepting (AA) compared to alcohol non-accepting (ANA) rats, showing that dopamine plays a role in high alcohol preference of AA rats [21].

One important study from Nora Volkow's group further provides support for the role of the dopamine D2 receptor gene in alcohol intake in rats. Utilizing a cDNA construct of the dopamine D2 receptor gene implanted into the n. accumbens of rats, they found that following a four-day treatment, the dopamine D2 receptors increased to 150% above pretreatment level and alcohol drinking was reduced by 50%. After a period of eight (8) days, the D2 receptor density returned to pretreatment level and so did alcohol drinking. Twenty–four days later, second injections of the same construct caused a similar increase in density with a two–fold decrease in drinking [22]. The same group has now confirmed this work in mice.

We will now turn our attention to the pharmacologic and genetic aspects of the inter relationship between Obesity, carbohydrate bingeing, glucose receptor sensitivity and dopamine.The intent of this work is to share with the scientifically informed, interested reader the basic scientific evidence which explains why people overeat and become overweight in a society where "thin is in". In order to accomplish this goal we first must consider the relationship between eating behavior and *"brain chemistry"* and the interaction of both genetic and environmental elements.

Weight gain: A prehistoric look

In consideration of the ability of our bodies to gain weight, we must review a few simple facts. Without our ability to gain weight, we as humans would have never survived. Ironically, whereas today the quantity of food is plentiful (although quality of nutrition is questionable), our goal is to turn away from food. In contrast, in the time of our prehistoric ancestors, the hunter-gatherers did not have a plentiful food supply. For example, when pristine sources of nutrient-rich berries and roots were in season and when wild animals were not hibernating, our ancestors ate well and "they fattened up". However, when these foods were not available, they relied on the stored fat to see them through the lean times.

To help us understand the importance of weight gain, two biological functions assisted our prehistoric ancestors as they struggled to survive this perpetual cycle known as "feast" and "famine". When there is an abundant supply of pristine quality food, our bodies efficiently store fat, and during times of a lack of food, our metabolism slows down. Scientists believe that abundant food induced efficient fat storage in our ancestors and when there was less fat their metabolism slowed to adjust to the smaller quantities programmed to adapt their metabolic rates to food intake. Those who survived were "blessed" with "fat-storage" genes, while those who lacked these genes perished. This suggests that the survivors passed their "thrifty" genes on to future generations-to you and me. Within the realm of modern times these ancient genes evolved over thousands of years and ultimately forced our bodies to store energy from nutrient-deficient concentrated sugars, processed carbohydrates, and adulterated fats to survive the famine that chronic intake of these types of low quality "foods" simulate [3].

Today we are faced with an obesity epidemic, which contributes to an estimated 300,000 deaths in people who die prematurely from this disease. In fact, obesity is a contributing risk factor for four of the seven leading causes of death. The Center for Disease Control has stated that Obesity is the number one health risk, greater than a lifetime of smoking, drinking and poverty [23]. Obesity in the United States is doubling every five years and the Institute of Medicine has declared war on the nation's "obesity epidemic".

To make sense out of all of this, we must understand that in today's modern world, no longer do we struggle through periods with very little food. Instead, we live in a perpetual calorie rich nutrient deficient food feast with a fast-food chain virtually around the corner for all Americans. This means that our bodies always are on "store mode"; except when we go on "low-fat diets", our brain loses control and there is an overwhelming call to "*eat"*. Thus, in all of us, there is a rebound effect, which reacts by quickly regaining the lost weight in preparation for the next food shortage, just as it did for our prehistoric ancestors.

An article in *Obesity Research* 1996 sums up the problem;

"[The] modern western lifestyle appears to provide the social and environmental conditions that favor maximum expression of underlying individual genetic differences in susceptibility to becoming overweight."[3]

This is an important view because we now know that in today's society, with its highly processed foods, chemicals and pollution, with regard to metabolic effects, the body's instinct is to prepare for and defend against famine, but there is even a **more** important facet to the genetic propensity to gain excess weight and it does not reside in genes which control fat storage, and/or

resting metabolic rates. Instead it is in the genes, which control our desire "*To Binge or Not to Binge"* [24]. These genes are termed "*reward genes".*

The biology of reward:

The pleasure and reward system in the brain was discovered by accident in 1954. The American psychologist James Olds was studying the rat brain's alerting process, when he mistakenly placed the electrodes in a part of the limbic system, a group of structures deep within the brain that generally are believed to play a role in emotions [25]. When the brain was wired so the animal could stimulate this area by pressing a lever, Olds found that the rats would press the lever almost nonstop, as much as 5,000 times an hour. The animals would stimulate themselves to the exclusion of everything else except sleep. They would even endure tremendous pain and hardship for an opportunity to press the lever. Olds clearly had found an area in the limbic system that provided a powerful reward for these animals.

Research on human subjects revealed the electrical stimulation of some areas of the brain *(medial hypothalamus,* which is in the limbic system) produced a feeling of quasi-orgasmic sexual arousal [25]. If certain other areas of the brain were stimulated, an individual experienced a type of light-headedness that banished negative thoughts. These discoveries demonstrated pleasure is a distinct neurological function that is linked to a complex reward and reinforcement system [26].

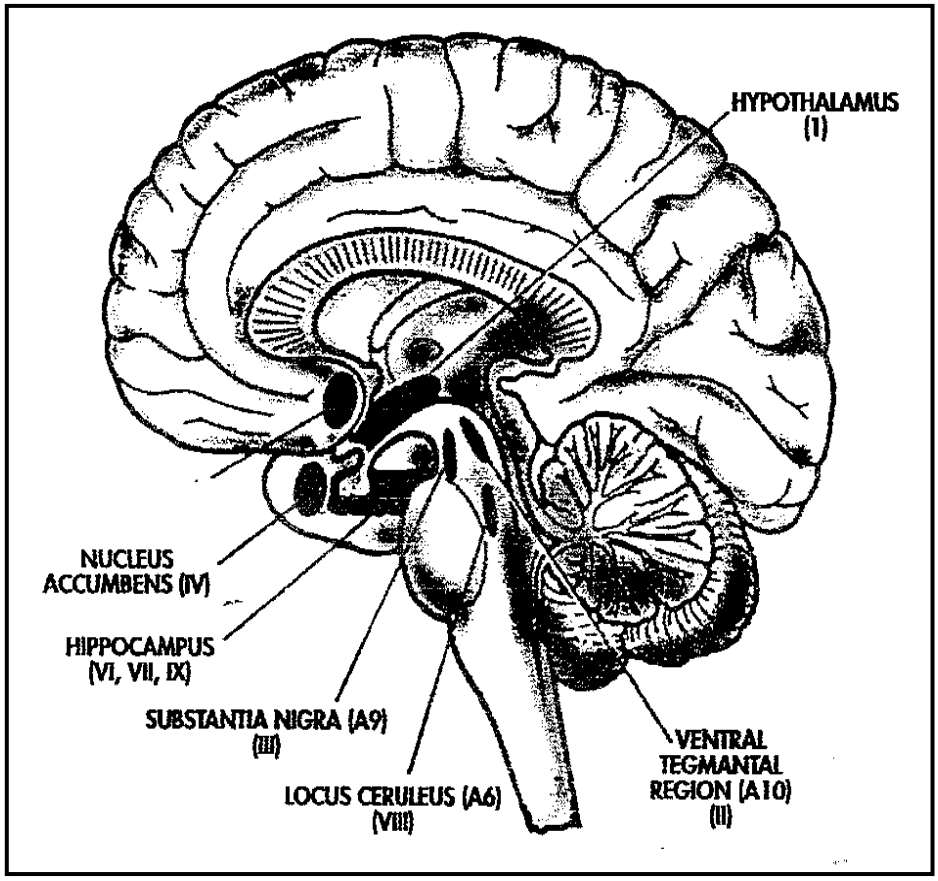
It is useful to think of the brain's reward system as a cascade in which one reaction triggers another. At the level of individual neurons, the reward cascade is catalyzed by a number of neurotransmitters [27]. Each neurotransmitter binds to certain types of receptors and serves a specific function. The binding of the neurotransmitter to a receptor on a neuron, like a key in a lock, triggers a reaction that is part of the cascade. Disruption of these intercellular cascades results in one form or another of the Reward Deficiency Syndrome.

The Cascade Theory of Reward: A blueprint for mapping obesity genes:

During the past four decades, considerable attention has been devoted to the investigation of neurochemical and neuroanatomical systems underlying chemical dependency. The research on the neuropharmacological basis of dependence (on alcohol, opiates, cocaine and glucose) points to the involvement of common biochemical mechanisms [28, 29]. It appears as if a *limbic-accumbens-pallidal* circuit is the critical substrate for the expression of drug reward [30]. However, while each substance of abuse appears to act on this circuit at a different step, the end result is the same, the release of dopamine the primary chemical messenger of reward at such reinforcement sites as the *nucleus accumbens* and the *hippocampus* [31].

In a normal person, neurotransmitters (the messengers of the brain) work together in a pattern of stimulation or inhibition, the effects spreading downward from complex stimuli to complex patterns of response like a cascade, leading to feelings of well-being: the ultimate reward (Cascade Theory of Reward) [27,28,33]. Although the neurotransmitter system is too complex and still not completely understood, the main central reward areas in the human brain's *meso-limbic* system are summarized in figure 4a and 4b.

F**igure 4a.** Neurotransmitter Relations in the Reward Cascade

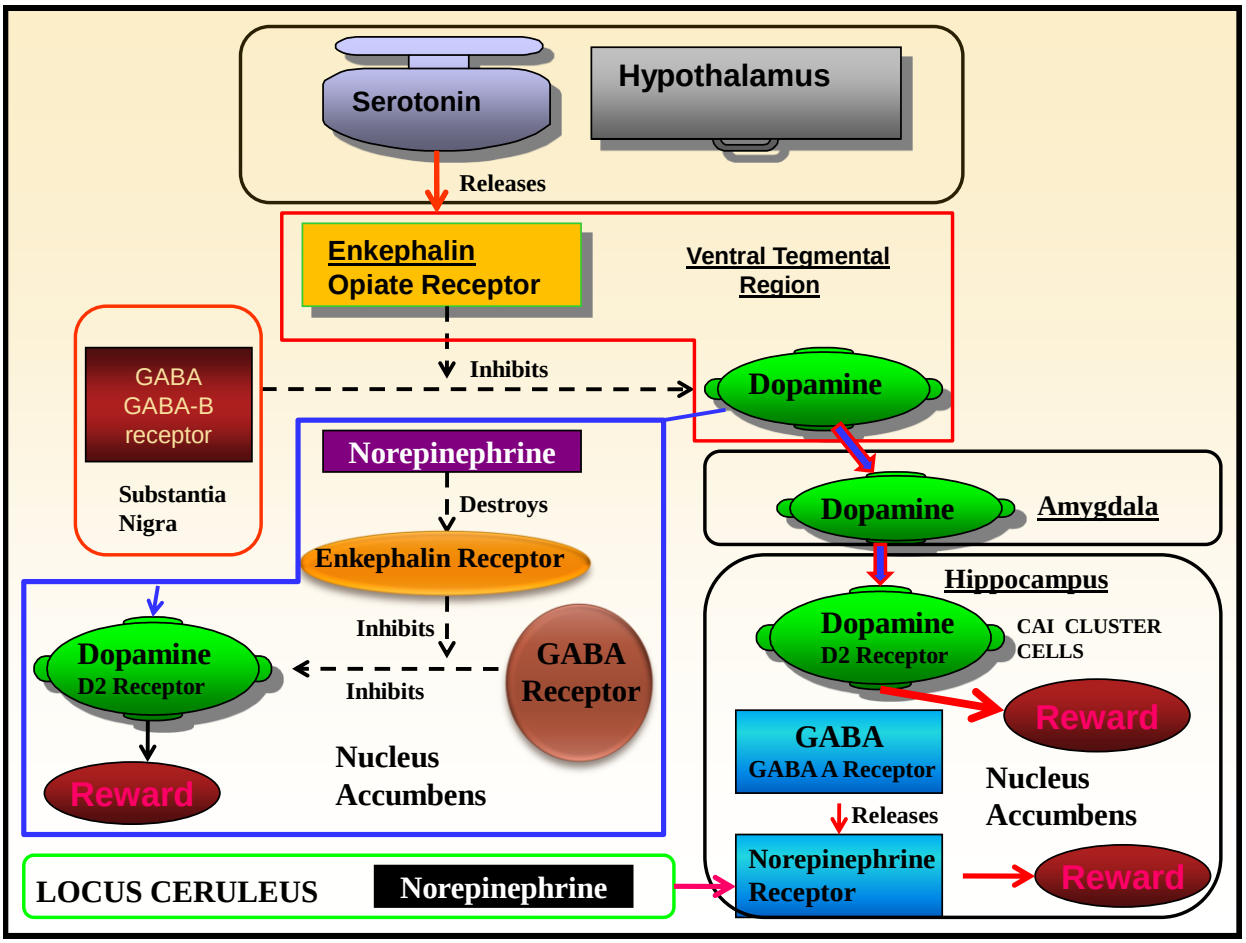


K.Blum (with J. Payne) *Alcohol and the Addictive Brain.* The Free Press, with permission p199 [276]

In the reward areas the following interactions take place [29,32]:
Serotonin (1) in the *hypothalamus* (I) indirectly activates opiate receptors (2) and causes the release of enkephalins, in the *ventral tegmental* region A10 (II). The enkephalins inhibit the firing of GABA (3) which originates in the *substantia nigra* A9 region (III);
GABA's normal role, acting through GABA B receptors (4), is to inhibit and control the amount of dopamine (5) released at the *ventral tegmental* regions (II) for action at the *nucleus accumbens* (IV). When the dopamine is released in the *nucleus accumbens* it activates dopamine D_2 receptors (6), a key reward site [there are at least five dopamine receptors, including D_2]. This release also is regulated by enkephalins (7) acting through GABA (8). The supply of enkephalins is controlled by the amount of the neuropeptidases (9) which destroy them.
Dopamine also may be released into the *amygdala* (V). From the *amygdala*, dopamine (10) reaches the *hippocampus* (IV) and the CA, cluster cells (VII) stimulates dopamine D_2 receptors (11), another reward site.
Norepinephrine involves an alternate pathway (12) in the *locus of ceruleus* A6 (VIII) whose fibers project into the *hippocampus* at a reward area centering around cluster cells which have not been precisely identified, but which have been designed a CAx (IX). When GABA A

receptors (13) in the *hippocampus* are stimulated, they cause the release of norepinephrine (14) at the CAx site (Figure 4b).

Figure 4b Neurotransmitter Relations in the Reward Cascade



It is to be noted that the glucose receptor (GR) in the *hypothalamus* is intrically involved and "links" the serotonergic system with opioid peptides leading to the ultimate release of dopamine at the *n. accumbens.*

In the "cascade theory of reward", these interactions may be viewed as activities of subsystems of a larger system, taking place simultaneously or in sequence, merging in cascade fashion toward anxiety, anger, low self-esteem, or other "bad feelings" or toward craving for a substance that will make these bad feelings go away, for example sugar (Cascade Theory for Carbohydrate Bingeing). Certainly, many overweight individuals also cross abuse other psychoactive substances (*e.g.* alcohol, cocaine, and nicotine) [27].

Alcohol activates the norepinephrine fibers of the *mesolimbic* circuitry through a cascade of events, including the interaction of serotonin, opioid peptides, and dopamine. In a more direct fashion, through the subsequent formation of the neuroamine condensation products TIQs, alcohol may either interact with opioid receptors or directly with dopaminergic systems [33, 27]. In fact we sowed the important relationship between dopaminergic activation through our novel natural agonist SYN (a KB220 variant) and the narcotic antagonist Naltrexone[34].

In the cascade theory of carbohydrate bingeing, genetic anomalies, long-continued stress, or long-term abuse of sugar can lead to a self-sustaining pattern of abnormal craving behavior in both animals and humans. Animal model support for the cascade theory can be derived from a series of experiments carried out by T.K. Li *et al.* [35-40] upon their substance-preferring (P) [seek carbohydrates, alcohol, opiates, *etc.*] and nonpreferring (NP) rat lines. They found that P rats have the following neurochemical profile:

- lower serotonin neurons in the *hypothalamus*;
- higher levels of enkephalin in the *hypothalamus* (due to a lower release);
- more GABA neurons in the *nucleus accumbens*;
- reduced dopamine supply at the *nucleus accumbens*;
- reduced densities of dopamine D_2 receptors in the *meso-limbic* areas.

This suggests a four-part cascade sequence leading to a reduction of net dopamine release in a key reward area. This was further confirmed when it was found that administering substances which increase the serotonin supply at the synapse, or by stimulating dopamine D_2 receptors directly, craving behavior could be reduced [39]. Specifically, D_2 receptor agonists reduce alcohol intake in high alcohol preferring rats whereas D_2 dopamine receptor antagonists increase alcohol drinking in these inbred animals [41].

In thinking about the causes of obesity and possible ways in which traditional and non-traditional treatments might be improved, we must turn our attention to “neurotransmitters” and the enzymes that control them. We now know as discussed above, there are at least four important neurochemical systems involved in the natural process of "reward” or the achievement of pleasurable states; serotonin, opioids, GABA, and catecholamines. Consideration of the various neurotransmitters and their individual effects on macro-selection of food is important if we want to understand the root causes of overeating (see figure 4).

Figure 5. Schematic of Brain reward Cascade: Normal and abnormal representation.

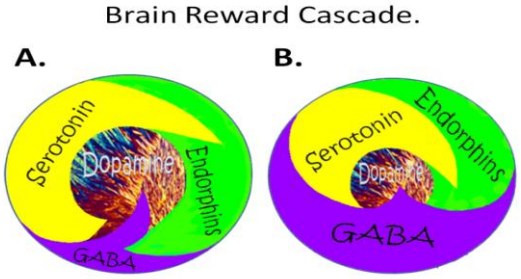


Figure 5(A) Represents the normal physiologic state of the neurotransmitter interaction at the mesolimbic region of the brain. Briefly, serotonin in the hypothalamus stimulates neuronal projections of methionine enkephalin in the hypothalamus that, in turn, inhibits the release of GABA in the substania nigra, thereby allowing for the normal amount of Dopamine to be released at the Nucleus Accumbens (NAc); reward site of the brain.

Figure 5 (B) 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.

The genetic variables include serotonergic genes (serotonergic receptors [5HT2a]; serotonin transporter 5HTlPR); endorphinergic genes (the mu OPRM1 gene; proenkephalin (PENK); PENK polymorphic 3' UTR dinucleotide (CA) repeats}; GABergic genes (GABRB3); and dopaminergic genes (including ANKKI Taq A; DRD2 C957T, DRD4 7R, COMT Val/met substitution, MAO-A uVNTR, and SLC6A3 9 or 10R). Any of these genetic and or environmental impairments could result in reduced release of dopamine and or reduced number of dopaminergic receptors [42].

Neurotransmitters and obesity: Animal studies

The literature on eating is very complex. The same chemical element or neurotransmitter commonly will have different effects when administered in low doses versus high doses, centrally versus peripherally, in short-term versus non-predisposed, in overweight versus normal weight versus anorectic animals, as function of paradigm, and so on. Detailed reviews have been published previously [4, 5, 6, 43, 44].

Eating-stimulatory neurotransmitters

The eating-stimulatory neurotransmitters include the catecholamine norepinephrine, acting through noradrenergic receptors, GABA, and three classes of neuro-peptides the opioids (endorphins, enkephalins, and dynorphins); the pancreatic polypeptides (neuro-peptide Y and YY), and galanin. These substances, when administered directly into the rat *hypothalamus*, potentiate eating in satiated animals [45].

Furthermore, chronic administration of certain monoamines (norepinephrine [NE]) and neuropeptides significantly alter daily food intake and weight gain [46, 47].

The eating-inhibitory neurotransmitters in the brain include the monoamines, dopamine, serotonin, and gut-brain peptides cholecytokinin-8 (CCK-8), neurotensin, calcitonin, glucogen, and corticotropin-releasing factor [48-54].

The effects of these neurotransmitters on eating are characterized primarily by a specific change in macro-nutrient selection, rather than an increase or decrease in total food intake. Many peptides, including CCK-8, bomesin, calcitonin, corticotropin-releasing factor, neurotensin, somatostatin, glucagon, and methionine-enkephalin have selective inhibitory actions on macro-nutrients [55, 56]. Leibowitz and associates [57-59] reported that *medial para-ventricular nucleus* (PVN) injections of NE in the rat induce a selective increase in carbohydrate ingestion with little or no change in fat and suppression of protein intake. Carbohydrate-craving behavior is observed consistently with chronic stimulation of NE and neuropeptide Y [49,60]. With regard to the all important monoamine Dopamine (released at the reward center), mixed effects have been observed with regard to the selective actions on macro-nutrient intake [51,61].

In contrast, serotonin, in the medial *hypothalamus*, may selectively suppress carbohydrate intake, while sparing protein intake [51,62,63]. Direct serotonergic agonists (*e.g.*, quipazine), indirect serotonergic agonists (*e.g.*, d-fenfluramine), or selective inhibitors of serotonin uptake into serotonergic neurons (e.g., fluoxine) decrease food ingestion in animal studies [64- 67]

reported that d-fenfluramine (Redux^R) reduced the consumption of a sucrose solution in non-deprived rats. Leander demonstrated that fluoxitine suppresses the ingestion of saccharin solutions in normal rats [68]. A similar finding was true for alcohol intake in preferring rat lines (animals genetically bred to prefer alcohol over water [69]. All the above indicates that direct and indirect serotonergic agonists depress a feeding response activated by sweet taste.

Opioid peptides and macro-nutrient selection

Current evidence suggests that the pharmacology of the opioidergic system on eating behaviors is very complex and it would therefore be difficult to a ascribe a generalized role, particularly in view of different effects observed with specific opioid peptides on macro-nutrient selection.

In support of the above observation, both increases in food intake [70-72] as well as decreases in food intake [73,74] have been observed under a variety of experimental conditions. In short-term experiments, administration of agonists, centrally or peripherally, results in feeding increases.

The results have been far more complicated than expected. In general, chronic administration of antagonists has been disappointing. Naltrexone caused some reduction in binge-eating in bulimics; however, it produced weight gain in anorexic patients [75]. Shimomura *et al.* observed increased food intake with chronic naloxone treatment and decreased food intake with chronic morphine [76]. Dhatt *et al.* had similar observations with chronic administration [55]. These observations suggest that while in acute situations opioid agonists increase and antagonists decrease food intake, *in chronic situations opposite effects prevail.* In this regard, it is noteworthy that the opioid peptides, as well as opiates acting through *mu, delta, and kappa* receptors, augment ingestion of fat and protein, while actually suppressing the relative proportion of carbohydrates ingested [56,62,76].Tepperman and Hirst showed that upon inducing neonatal reduction of endorphins, rats become overweight. Compared with control animals, these overweight rats chose a greater percentage of their daily calories as carbohydrates and lower percentages as fat and protein [77].

Inhibitors of Enkephalinase(s) and craving behavior

As stated earlier, although it is known that opiates and/or opioids reportedly increase food intake in animals and humans, some papers suggest the opposite-suppression of food intake, especially when one considers macro selection of food sources (*i.e.,* sugar/carbohydrates) [62,70,75,76,78-80]. Moreover, Broekkamp *et al.* reported that infusion of enkephalin into the *ventral tegmental* A10 area of the brain induces a short-term latency behavioral stimulant effect reminiscent of effects produced by stimulation of the *meso-limbic* dopamine pathway; this effect is blocked by pretreatment of the opiate receptor antagonist naloxone [81]. This takes on importance in terms of feeding behavior, as feeding has been shown to increase dopamine levels in various brain structures such as the *posterior hypothalamus*, the *nucleus accumbens*, and the *amygdala.*

It is well known that dopamine in sufficient concentration can inhibit food intake [82]. Gilman and Lichtigfeld proposed as an appropriate therapeutic for carbohydrate bingeing *(i.e.*, bulimia) a selective D_2 agonist such as bromocriptrine [or natural released dopamine], providing D_2 occupancy [83]. In this regard, using a push-pull cannula technique, Chesselet *et al.* were able to induce dopamine release in the "brain reward center" after local application of enkephalin,

which suggests regulation by delta receptor stimulation [84]. Indeed Kelotorphan (an inhibitor of the opioid peptide degrading enzyme) may protect against possible CCK-8 degradation by brain peptidiases. This important satiety neuropeptide is co-localized with dopamine in the *nucleus accumbens*, and there is a close interaction between CCK-8, dopamine, and endogenous opioid peptides (like enkephalins) [85].

The opioid peptides are involved not only in macro-nutrient intake, but have been implicated in substance seeking [86- 88], as well as brain self-stimulation behavior [89,90]. In essence, there are a substantial number of animal experiments which support not only the "*Brain Reward Cascade*" but the subsequent sequale induced by a defected reward cascade leading to a number of addictive, compulsive and impulsive behaviors-defined as the "*Reward Deficiency Syndrome"*[91].

In this regard, Blum *et al.* reversed alcohol-seeking behavior in genetically preferring C57Bl/6J mice with the chronic administration of an enkephalinase inhibitor [87]. In other work by George *et al*, they concluded that a relative lack of enkephalin peptides trans-synaptically, possibly resulting from enhanced enkephalin degradation, may contribute to increased alcohol consumption in C57Bl/6J mice [92]. Moreover, others showed that intracranial self-stimulation by rats was reduced by *nucleus accumbens* microinjections of kelatrophan, a potent enkephalinase inhibitor. In terms of food intake, Riviere and Bueno reported that central injections of the enkephalinase inhibitor, thiorphan, also reduced daily food intake in sheep [93]. These results suggest that human carbohydrate bingeing might be critically mediated by differences in patterns of endogenous peptides.

D2 Receptors and animal models:

Hamdi *et al.* studied the specific binding of [3H] YM –09151-2 to investigate the possible differences in age-associated changes in striatal D2 dopamine receptor properties in genetically obese (fa/fa) Zucker rats and their lean littermates. The maximal binding sites of D2DA receptors were found to decline with age in both obese and lean rats: the rate of decline in receptor Bmax was slightly higher in lean than obese rats. However, the Bmax of D2DA receptor in 6-, 12- and 18-month old obese rats was significantly lower compared to the age matched lean rats. The very important interpretation by the authors further supports the role of dopamine in obesity. According to the authors, their data indicate that obesity decreases the number of striatal D2DA receptors without affecting the rate at which receptor number decreases with age [94].

Hypothalamic neuropeptide Y (NPY) and corticotropin – releasing hormone (CRH) influence feeding and levels of plasma glucose, insulin, free fatty acids, and triglycerides. Treatment of genetically obese, ob/ob mice, with D1/D2 agonists normalizes hyperphagia, body weight gain, hyperglycemia, and hyperlipidemia. Bina and associates examined whether levels of NPY and CRH immunoreactivity in discrete hypothalamic nuclei are altered in ob/ob mice, and whether dopaminergic treatment reverses this alteration [95]. Such dopaminergic treatment, while normalizing body weight gain and hyperglycemia, also significantly reduced elevated brain levels of NPY and CRH. These findings suggest that dopaminergic D1 /D2 coactivation may improve hyperphagia, hyperglycemia, and obesity in the ob/ob mouse, in part by normalizing elevated levels of both NPY and CRH in obese mice. Additionally, the work of Kuo

revealed that injection of NPY anti-sense unto brain could modify the anorectic action of repeated S1/S2 agonists, indicating the involvement of NPY. Taken together the present knowledge suggests that both subtypes of D1 and D2 receptors and cerebral NPY are involved in the anorectic action of the dopamine releasing agent amphetamine [96].

Scislowski and associates reported that a two week treatment with SKF 38393 (a dopamine D1 receptor agonists) plus bromocryptine (a D2 agonist) [BC] acted synergistically to normalize overeating, body fat, hyperglycemia and hyperlipidaemia in ob/ob mice. In a more recent study they found that the BC/SKF treatment also increased serum dehydroepiandrosterone (DHEA) sulfate concentrations, an inhibitor of body fat store accumulation. The authors conclude that their findings demonstrate that dopaminergic treatment not only normalizes overeating (hyperphagia) of ob/ob mice, but also redirects several metabolic and endocrine activities, independent of its effects on feeding to improve the obese –diabetic syndrome in ob/ob mice [97, 98].

Long term administration of the antipsychotic drugs known to block D2 receptors such as sulpiride, haloperodol, etc increased body weight in rats. This effect was found to be sex dependent that is, while female rats were prone to gain weight, male rats did not. In a study conducted by Baptista et al. a linear relationship between dose of sulpiride and body weight gain was found. Also sulpiride increased caloric intake, and both actions were counteracted by the specific D2 agonist bromocriptine. These results confirm that antipsychotic drugs affect feeding and body weight and suggest that hyperphagia and body weight gain might be mediated by blockade of dopamine D2 type receptors [99]. More recently, Freeman et al. studied the effect of glucose on anti-psychotic drug-induced changes in dopamine neuronal activity and suggested that caloric intake may influence antipsychotic drug-induced changes in the population activity of midbrain dopaminergoc neurons. In fact, glucose significantly reduced the number of spontaneously active A9 and A10 dopaminergic cells per track in control rats, but significantly attenuated the chronic haloperidol- and clozapine –induced reductions in dopaminergic cells per track [100]. For a review of animal models of food addiction see Blum et al. [101].

Brain hypodopaminergic function and the self-healing process

Since deficits have been found in neurotransmitter functions underlying craving behavior, and since these deficits may be alleviated by facilitated dopamine release consequent to the use of drugs, nicotine, alcohol, and food, the studies mentioned above indicate enkephalinase inhibition may similarly compensate for neurotransmitter imbalance (*i.e.*, opioids, thereby attenuating craving behavior).

In an attempt to understand that carbohydrate craving is a subset of generalized craving behavior ("Reward Deficiency Syndrome"), due to hypodopaminergic function (an impaired "reward cascade"), scientists believe individuals *self-heal* through biochemical (licit or non-ilicit) attempts to alleviate the low dopaminergic brain activity *via* drug-receptor activation (alcohol, heroin, cocaine, and glucose). It is conjectured this will subsitute for the lack of reward and yield a temporary sense of well-being. In order to help explain this so called *self-healing process*, it is germane that the reinforcing properties of many drugs of abuse may be mediated through activation of common neurochemical pathways, particularly with regard to the *meso-limbic*

dopamine system. In this regard, glucose, opiates, nicotine, cocaine, tetrahydracannabinol (THC), and ethanol have been shown to directly or indirectly enhance release or block re-uptake of dopamine in at least one of the primary terminal sites for the limbic dopamine neurons, the *nucleus accumbens* [31,102-104].

A number of studies of genetically bred animal models support the D_2 dopamine receptor involvement in substance-seeking behavior due to lower D_2 receptor sites in preferring compared to non-preferring animals [38,105,106-108].One inference from these observations is that ethanol intake, as well as the self-administration of other substances (i.e., glucose), might be altered by manipulation of dopamine receptors. Of interest is that further confirmation of the "Reward Deficiency Syndrome" in generalized substance-behavior involving slow dopamine release in the nucleus accumbens in polysubstance seeking Lewis animals has been observed recently by Gardner (1997)[17, 18].

Reward Deficiency Syndrome: Human studies

Human support for the ***Reward Deficiency Syndrome*** can be derived from a series of clinical trials with neuronutrients (precursor amino acid loading technique and enkephalinase inhibition) indicating :

- reduced alcohol and cocaine craving
- reduced stress rates
- reduction of leaving treatment against medical advice (AMA)
- facilitated recovery
- reduced relapse rates
- reduction in carbohydrate bingeing
- loss of body weight
- prevention of weight regain
- reduction of glucose craving
- enhancement of insulin sensitivity
- reduction of cholesterol
- enhancement of memory and focus

There are a number of studies using precursor amino-acids and enkephalinase inhibition which have been shown to affect various aspects of RDS [109- 119, 23] [see Table 1 and below].

Most recently, the notion of dopamine as the "final common pathway" for a number of diverse drugs of abuse such as cocaine, morphine, and alcohol [as well as glucose] is supported by Ortiz and associates at Yale University School of Medicine and the University of Connecticut Health Services Center. This support demonstrates that chronic treatment of cocaine, morphine, or alcohol similarly results in several biochemical adaptations in the *meso-limbic* dopamine system, which may "underlie prominent changes in the structural and functional properties of the neuronal pathway" related to the above. [120,121].

The brain reward cascade schematic (Figure 3), since then, became the blueprint for the search for "reward genes". We propose that the ***Reward Deficiency Syndrome*** gives rise to a wide range of disorders that can be classified as impulsive-addictive-compulsive diseases.

Impulsive diseases include attention deficit disorder and Tourette's Disorder. Addictive diseases include substance-seeking behavior involving alcohol, drugs, nicotine, and most importantly food. Compulsive diseases include pathological gambling and excessive sexual activity. In terms of personality disorders it includes conduct disorder, oppositional defiant disorder, antisocial personality disorder, schizoid/avoidant behavior, violent aggressive behaviors (See Figure 1) [122-125].

Compulsive Bingeing Dopamine & Other Genes

Obesity is a disease that comes in many forms. Once thought to be primarily environmental, it now is considered to have both genetic and environmental components. In a Swedish adoption study, for example, the weight of the adult adoptees was strongly related to the BMI of the biological parents and to the BMI of the adoptive parents. Other studies of adoptees and twins suggest heredity is an important contributor to the development of obesity, whereas childhood environment has little or no influence. Moreover, the distribution of fat around the body also has been found to have heritable elements. The inheritance of subcutaneous fat distribution is genetically separable from body fat stored in other compartments (among the viscera in the abdomen, for example). It has been suggested there is evidence for both single and multiple gene anomalies [126]. In fact according to our laboratory, in conjunction with David Comings of the City of Hope National Medical Center, at least twelve different genes have been associated with obesity providing a 33 per cent contribution to the overall variance.

Given the complex array of metabolic systems that contribute to overeating and obesity, it is not surprising that a number of neurochemical defects have been implicated. Indeed at least three such genes have been found: one associated with cholesterol production, one with fat transport and one related to insulin production [126]. Other genes include human chromosome 2, uncoupling protein 2 and the APO-D genes. The *ob* gene and its product the leptin protein have also been implicated in regulating long-term eating behavior [127]. Another protein, glucagon-like peptide 1(GLP-1) has been found to be involved in the regulation of short-term eating behavior [128]. The regulation between leptin and GLP-1 is not known. The *ob* gene may be involved in the animal's selection of fat. But perhaps not in the ingestion of carbohydrates, which appears to be regulated by the dopaminergic system. It may be that the *ob* gene is functionally linked to the opioid peptodergic system involved in reward.

Whatever the relation between these systems the complexity of compulsive eating disorders suggests that more than one defective gene is involved. Indeed, the relation between compulsive overeating and drug and alcohol addiction is well documented [129, 130, 91]. Neurochemical studies show that pleasure-seeking behavior is a common denominator of addiction to alcohol, drugs, and carbohydrates [8].

Variants of the dopamine D_2 receptor gene appear to be risk factors in obesity. The A_1 allele was present in 45 percent of overweight subjects as compared to 19 percent of non-overweight subjects [131]. Furthermore, the A_1 allele was not associated with a number of other metabolic and cardiovascular risks, including elevated levels of cholesterol, and high blood pressure. In contrast, when the subject's profile included factors such as parental obesity, a later onset of obesity and carbohydrate preference, the prevalence of the A_1 allele rose to 85 percent.

There also is an increased prevalence of the A_1 allele in overweight subjects who have severe alcohol and drug dependence [91]. When obesity, alcoholism, and drug addiction were found in a patient, the incidence of the A_1 allele rose to 82 percent. In contrast, the allele had an incidence of zero percent in non-overweight patients who also were not substance abusers and did not have a family history of substance abuse. In an unpublished study Blum and associates also found the A_1 allele of the dopamine D_2 receptor gene significantly contributes to percent body fat in morbidly overweight subjects. The percent contribution was found to be as much as 45.9 percent of the overall variance, when compared with "super" controls (highly assessed controls-no "reward deficiency" behaviors). Additionally, Comings *et al* (1996) found that the Dopamine D_2 receptor A_1 allele also associated with overweight young females [132]. Both the *ob* and the Dopamine D_2 receptor gene are additive in contributing to the overall variance of obesity (22 per cent in young females). Thus, the presence of the dopamine D_2 receptor gene variants increase the risk of obesity and related behaviors along with other polymorphic genes, some of which have not as yet been identified. In order to investigate the prevalence of the Taq1A1 allele of the dopamine receptor gene in obesity with and without comorbid SUD, a total of 40 patients, from an outpatient clinic were studied. In this sample with a mean BMI of 32, the A1 allele of the DRD2 gene was present in 52% of these obese subjects. Furthermore, it was found that in the 23 obese subjects possessing comorbid SUD, the prevalence of the DRD2 A1 allele was present in 73.9% of the obese subjects compared to only 23.5 % in obese subjects without comorbid SUD.

Moreover, when they assessed severity of substance usage (alcoholism, cocaine dependence, etc.) increasing severity of drug use increased the prevalence of the *Taq1* DRD2 A1 allele: where 66.7% of less severe probands possessed the A1 allele compared to 82% of the most severe cases. Linear trend analyses showed that increasing use of drugs was positively and significantly associated with A1 allelic classification.

Dopaminergic genes and obesity

In a study by F. Yasuna from Japan, personality is a behavioral pattern, which differs among individuals. E. Kretchmer (see Yasuna) categorized personality variants according to the concept of fundamental body types. Several lines of evidence suggest that the central dopamine system may underlie the regulation of weight and personality trait. In this study, the authors examined the dopamine D2 receptor (D2R) binding together with body mass index (BMI) and personality trait on the temperament and character inventory in 16 subjects. The data demonstrates a significant relation among the D2R binding in the amygdala, BMI and personality trait of harm avoidance (this is in agreement with other work by Blum et al. showing significant association with D2RA1 variants and harm avoidance). The authors conclude that variation of dopaminergic activity in the amygdala underlies the personality variants related to body type [133].

In a study by Jenkinson and associates, the association of the dopamine D2 receptor polymorphisms Ser311cys and Taq1A with obesity or type diabetes mellitus in Pima Indians was evaluated. They found that heterozygotes at the Ser311CysDRD2 polymorphism had a higher BMI than homozygotes. [134]

Moreover, the atypical antipsychotics have been shown to have superior efficacy compared with typical antipsychotics such as haloperidol, particularly in the treatment of negative symptoms of schizophrenia. However, following clinical use, marked bodyweight gain has been frequently observed with some of the atypical antipychotic drugs. A careful review of the literature from 1966- 2000, revealed that relative receptor affinities of the atypical antipsychotics for 5-HT2 and dopamine D2 receptors appear to be most robust correlate of body weight gain. This makes sense because if one blocks dopaminergic sites at the receptor it will increase carbohydrate bingeing. Wetterling suggests that if obesity is a problem in a patient other modalities must be considered for the long term treatment [135].

In a study, G.N. Thomas evaluated the potential relationship between blood pressure and obesity and dopamine D2 receptor *Taq1* polymorphism. Pharmacological data suggest that obesity and blood pressure (BP) may be modulated through the dopamine D2 receptor (DR2R), which may represent and underlying mechanism that links these conditions. Thomas et al. found that the A1 was decreased in hypertensives compared with controls. In the combined population, systolic, diastolic, and mean arterial BP's were lower in subjects with the A1A1 genotype relative to the A2A2 genotype. However, the DRD2A1 allele frequency increased with increased markers of "gynoidal" or peripheral subcutaneous obesity [136].

Brain dopamine receptors and obesity risk

Moreover, dopamine plays a major in the regulation of appetite and growth hormone. Dopaminergic agonists are known to suppress appetite and dopamine D2 receptor antagonists enhance it. Comings found that DRD2 polymorphisms significantly associated with high BMI as well as height [137].

In another study, Wang and associates found that striatal dopamine D2 receptor availability was significantly lower in ten obese individuals than in lean controls. The availability of the D2 receptors was decreased in obese individuals in proportion to their BMI. Dopamine modulates motivation and reward circuits and hence dopamine deficiency in obese subjects may perpetuate pathological eating as a means to compensate for decreased activation of these circuits. The authors conclude that strategies aimed at improving dopamine function may be beneficial in the treatment of obese individuals [138]**.**

Other dopaminergic reward gene risk taking behavior and overeating

Although we believe the gene for the D_2 receptor plays a critical role in Reward Deficiency Syndrome behaviors, other dopaminergic receptor genes (such as the dopamine transporter genes, dopamine-beta-hydroxylase genes and the D3 and D4 dopaminergic receptor genes) undoubtedly are involved in the different manifestations of the syndrome, but, for example, both the dopaminergic transporter and the dopamine-beta-hydroxylase genes are not associated with obesity. It is noteworthy, that some have suggested one type of overeating might reside in individuals who are high-risk takers and switch their addictive risk taking dopamine-linked neuronal release to carbohydrate bingeing. This is not surprising in light of recent molecular genetic findings.

George Koob and Associates from Scripts Institute in La Jolla, California found evidence for the D_3 locus and suggested it as a primary site of cocaine effects [31]. The exact effect of cocaine is unknown regarding gene expression; however, we do know that D_2 receptors are decreased by chronic cocaine administration and this may induce severe cocaine craving and possibly cocaine dreams [139] and the dopamine D_2 receptor gene has been associated with severe cocaine addicts [14]. The likelihood of carrying the A_1 allele increases as the number of risk factors increases among cocaine-dependent people. Three risk factors are especially significant: parental alcoholism and drug abuse, the potency of the cocaine used by the addict and early childhood deviant behavior, such as conduct disorder.

Most recently scientists from Israel and the National Institutes of Mental Health confirmed a genetic variation of the dopamine D_4 receptor gene to associate with novelty (or sensation) seekers. Both of these studies set out to test the hypothesis advanced by Cloninger of Washington University that novelty seeking behavior is affected by the way brain cells process dopamine. Epstein and his colleagues at the Herzog Memorial Hospital in Jerusalem found this association in 124 unrelated Israeli subjects. Specifically he found that subjects who scored highest on novelty seeking tended to be compulsive, exploratory, fickle, excitable, quick tempered, and extravagant. They were much more likely to have the longer version of the receptor gene than other subjects. Subjects with the shorter version of the gene scored lower and tended to be reflective, rigid, loyal, stoic, slow tempered, and frugal. In the second study conducted by Benjamin of the laboratory of clinical science, National Institute of Mental Health found similar results in his sample of 315 American subjects, most of them male siblings and other family members [140, 141]. The D_2 receptor gene and the D_4 receptor gene are fairly close in gene homology and may have similar physiological functions.

In an unpublished work scientists at UCLA found an association between the DRD_2 A_1 allele and agitation marked by impulsivity, excitability, "hot temper". These subjects were classified as "sensation seekers." The recent work of Benjamin and Epstein provide additional confirmation of the relationship between the Reward Deficiency Syndrome behaviors characterized by Blum and associates and the dopaminergic system. Additionally Benjamin and Epstein provide support of the earlier work of Susan George and associates (1993) at the University of Toronto who found a strong association between the D_4 gene variance and alcoholism and nicotine dependence again showing the interchangeable nature of this syndrome [13]. Therefore adding another element to the *"binge or not to binge?"* equation.

In this regard, Poston et al. carried out an association study of the D4 dopamine receptor and obesity risk. Many genes have been identified that may play a role in increasing susceptibility to obesity. Reduced dopamine function appears to play a role in dysfunctional eating patterns and may predispose some individuals to obesity. The long version of the D4 dopamine receptor gene (D4DR) has been shown to alter receptor function and reduce intracellular response to dopamine. It also has been associated with novelty-seeking – related personality traits that are found with greater frequency in obese individuals. Poston and associates examined the association between the D4DR and obesity in 115 obese patients participating in a weight management program. They constructed four models of increased obesity that included combinations of traditional risk factors (*i.e. history of obesity, parental*

obesity, a body mass index > 40) and novelty elevations on the Karolinska Scales of Personality. There was a significant increase in the frequency of the D4DR long alleles in individuals defined as high risktaking using the combination of novelty –seeking – related personality traits, severe obesity (*i.e. BMI > 40),* and any other traditional risk factor, but not with the traditional risk factors alone. These preliminary data suggest a potential role for the DR4D gene in increasing obesity susceptibility [142].

What is the neuronal inter-relationship between glucose and dopamine release mechanisms: Are there close ties?

To understand the important relationship between dopamine and glucose, it is of utmost importance to realize that in the meso-limbisc system the glucose receptor is in close proximity with the enkephalinergic neurons. There are also other important connections in the substania nigra (SN), tuberoinfundibular neurons, globus pallidus, and other important brain regions.

It is well known that glucose modulates SN dopamine neuronal activity and GABA terminal transmitter release by the actions of an ATP-sensitive potassium channel. In a study by Levin et al. the effect, on striatal dopamine release, of altering SN glucose levels was assessed by placing microdialysis probes into both the SN and striatum of male rats. During 50 mM glucose infusion, striatal DA efflux increased transiently by 50% and returned to baseline after 60 minutes. Moreover, efflux increased by a further 30% when GABA (A) antagonist bicuculline was added. Furthermore, at basal glucose levels, nigral bicuculline alone raised striatal dopamine efflux by 31% suggesting the well-known tonic GABA inhibitory input to the DA neurons. Thus striatal dopamine release is affected by changing SN glucose levels. According to Levin and associates, this response may reflect the known effect of glucose on K(ATP) channel activity on both SN Dopamine neurons and GABA axon terminals in the SN. These interactions could provide a mechanism whereby glucose modulates motor activity involved in food intake [143].

Koshimura et al. found that long –term incubation with high concentration of glucose increased the capacity of calcium uptake to enhance depolarization-induced dopamine release from Pheochromocytoma –12 cells. These data taken together suggest that a high concentration of glucose induced activation of the calcium channel to stimulate dopamine release from P12 cells [144].

Bello et al. found that restricted feeding with scheduled sucrose access results in an upregulation of the rat dopamine transporter in the n. accumbens and ventral tegmental area of the brain [145]. Moreover, Lee et al. (1998) found that dopamine can activate B_3 adrenoreceptor$_s$ to lower glucose uptake into rat white adipocytes which lack dopaminergic receptors [146]. It is of interest that intrastriatal injection of D_1 and D_2 dopamine agonists affects glucose utilization in both the direct and indirect pathways of the rat basal ganglia [147]. Moreover, dopamine receptor antagonism can influence fat intake in rats dependent upon dosage and time after treatment. In this regard, both $D_1$and D_2 receptor co-activation significantly reduced body weight, body fat, food consumption and serim concentrations of glucose, triglycerides, free fatty acid and insulin while increasing protein mass [99]. Furthermore, studies on blood glucose found blood glucose concentrations to be significantly correlated with cerebrospinal fluid concentrations if the dopamine metabolite, homovanillic acid [148].

With regard to the concept that within the RDS concept genetic commonality exist between a number of dopaminergic activating substances such as alcohol and opiates and possibly even glucose, evidence now exists that intermittent, excessive sugar intake causes endogenous opioid dependence. In rats, repeated, excessive intake of sugar created a state in which an opioid antagonist caused behavioral and neurochemical signs of opioid withdrawal. The indices of anxiety and DA/Ach imbalance were qualitatively similar to withdrawal from morphine or nicotine, suggesting that rats have become sugar-dependent [149]. In terms of understanding the brain reward cascade, there is evidence that serotonergic activation may also influence dopamine D2 receptor function. This is important when we consider the so called "sweet tooth" which has been associated with serotonin predominantly. Therefore the work by Kogan et al. confirms that the drug DR4004, a putative 5-HT_7 receptor antagonist, also has functional activity at the dopamine D2 receptor [150]. It is of interest that neuroanatomical data suggest a potentially interactive role between accumbens acetylcholine and dopamine. There is evidence that nucleous accumbens. Acetylcholine is apparently related to neural processes underlying not only psychostimulant reward but also natural consummatory behavior i.e. feeding. In this regard, Hajnal et al. found that accumbens cholinergic interneurons play a role in the regulation of body weight and metabolism. In this context both stress and the role of dopamine play an important part in the Ach response [151].

It is well known well known that pharmacologic doses of the glucose analogue, 2-deoxyglucose (2DG) cause acute glucoprivation and are associated with enhanced dopamine turnover in preclinical studies. In fact, lines of evidence indicate that a variety of metabolic stressors, including acute glucose deprivation are associated with dopamine release. Using PET Adler et al. found that 2DG administration enhanced synaptic dopamine concentrations [152]. The administration of 2DG is associated with significant striatal dopamine release even in healthy volunteers. These data are important because it further closely ties glucose levels to dopaminergic activity. Moreover, there is even a relationship between insulin levels and dopamine release in the tuberonfundibular neurons. The insulin effect is dependent on CA++ ions, protein kinase C Na (+) – H + exchange system. Additionally when there is lowered glucose in the brain leading to cerebral global transient ischemia, monamine release especially dopamine is inhibited. In this regard, Trugman et al. showed D1 antagonists lowered glucose utilization by 24-28% in the globus pallidus, entopeduncular nucleus, subthalmic nucleus, substania nigra, and even the motor cortex, suggesting that stimulation of the D1 receptor by endogenous dopamine contributes to basal metabolism in these regions [153]. In contrast both D1 and D2 agonists increase glucose utilization. These results suggest that feeding behavior is tied into the stimulation of both D1 and D2 receptors and provides metabolic evidence for the importance of D1 and D2 functional linkage in the brain, which relates to hyperphagia or overeating.

The direct effect of dopamine on glucose release from primary cultured rat hepatocytes were studied in Japan by Shiroyama et al. [154]. In this regard, dopamine is known to induce hyperglycemia in both animals and man. The authors investigated whether dopamine has any direct effect on glucose release from hepatocytes through the glcogenlytic and/or gluconeogenic pathways, and at the same time determined the main type of adrenergic receptor involved in

glucose release. The notion, increasing glucose release from tissue would reduce cravings for glucose and carbohydrates. Glycogen –rich and gluconeogenic –depleted hepatocytes were prepared in order to study glycogenolytic and gluconeogenic –depleted glucose release, respectively. Dopamine caused release of glucose which was inhibited by the beta blocker propranolol. The authors conclude that dopamine has a direct effect on heptocytes, increasing glucose release via both glycogenolytic and gluconeogenic pathways and mediated by beta adrenergic receptors.

Other obesity genes

Twin and family studies suggest that genetic factors potentially influence energy and nutrient intake. In this regard, the Heritage Group utilizing a genome-wide scan for dietary energy and nutrient intakes have determined that in whites, the strongest evidence of linkage appeared for dietary energy and nutrient intakes on chromosomes Ip21.2 and 20q14.1. The linkage evidence on chromosomes 20 related to total energy intake rather than to the intake of specific macronutrients. In blacks, promising linkages for macronutient intakes occurred on chromosomes 12q23-q24.21, Oq32.1, and 7q11.1. Several potential candidate genes are encoded in and around the linkage regions on chromosomes Op21.2, 12q14.1 and 20q13.13 [155].

Pharmacologic mechanisms of the drug Meridia: Comparison to proposed KB220 anti-craving formula.

Meridia is an approved FDA drug for "weight loss" and weight management. The major effect of this drug is an anti-craving action derived from its effect to inhibit the reuptake of serotonin (5HT), dopamine (DA) and norepinephrine (NE). This inhibition of neurotransmitter reuptake results in an increase in the length of time 5HT, DA, and NE are available to act in the synaptic junction, and ultimately in an amplification of the neurotransmitter effects to reduce sugar /glucose cravings.

In its simplest form, the ingredients in the patented composition proposed for anti-craving effects mirrors the Meridia mechanism and should produce similar anti-craving effects. In this section we will point out the potential of the ingredients in the proposed formula, based on a large body of neurochemical evidence concerning precursor amino-acids; the role of chromium as a tryptophan enhancing substance; D-amino acid inhibition of enkephalinase; Rhodiola as a suspected inhibitor of catechol-O-methyl transferase (COMT) as well as Synephrine, a substance that can minic some of the effects of catecholamines. Thus it is anticipated that since the same three neurotransmitters affected by Meridia® (sibutramine) could potentially be affected by certain ingredients, it should produce similar effects. It could be hypothesized that by increasing precursor (i.e. phenylalanine, tyrosine, and chromium and or 5-hydroxytryptophane or any other neurotransmitter enhancer even via transport blockers) intake and inhibiting enzymatic degradation by COMT, greater levels of 5HT, DA would be available at the synapse. The availability of the synapse is also increased since the D-phenylalnine causes preferential release of dopamine via opioid peptide breakdown inhibition. Thus the sum total effect is very much like Meridia and the following information will assure the scientific potential of this novel natural formula.

Most recently, Balcioglu and Wurtman measured the effects of sibutramine given intravenously, on brain dopamine and serotonin flux intostriatal and hypothalamic dialysates of freely moving rats. While low doses of the drug had no effect, higher doses increased both serotonin and dopamine concentrations in the striatal and hypotalmic brain regions. These findings further support the neurochemical effects of sibutramine, and suggest that the drug's anti-obesity action may result from changes it produces in brain dopamine as well as serotonin metabolism [156]. The importance here is that it provides further support for the KB220 variant formula and both serotonergic and dopaminergic anti-obesity actions.

There are known limitations which will be addressed:

- *Competition for uptake of precursors across the blood brain barrier*

While it is well known that the ability of phenylalanine, tyrosine and tryptophan to penetrate the blood brain barrier is mediated by a shared active transport system, it is also well known that the use of Chromium could significantly assist in enhancing or concentrating blood tryptophan into the brain by its effect on insulin release and subsequent enhance glucose utulization due to increase glucose receptor sensitivity [61]. In addition, glucose has the concurent effect of increasing muscle absorption of large amino acids like leucine, valine and isomeric forms, into muscle (see below). This all works in concert to help tryptophan cross into the brain and there increase serotonin synthesis. This is the exact reason for the inclusion of chromium at a dose of 1000 mcg's rather than the usual lower dosage of between 200-400mcgs. Moreover, even if this was not effective to increase the synthesis of serotonin, with the formula it could bypass serotonin and work through its enkephalinase activity of D-phenylalanine. This would cause dopamine release via its inhibition of SN GABA. In Earlier work by Wurtman's group, they showed that by reducing blood glucose the brain will concentrate up to 33% more blood borne tryptophan [157]. Furthermore, it is well known that if you reduce typtophan levels in the hypothalamus you will reduce brain serotonin levels and its neuronal release. Conversely, elevating tissue tryptophan levels (accomplished by adding natural 5-hydroxytryptophan or chromium) could increase both serotonin levels and serotonin release. According to Schaechter and Wurtman, these observations demonstrate for the first time that both precursor –dependent elevations and reductions in brain serotonin levels produce proportionate changes in serotonin release, and the magnitude of the tryptophan effect is unrelated to neuronal firing frequency, suggesting the importance of precursor administration to increase serotonin levels. In essence, the data support the hypothesis that serotonin release is proportionate to intracellular serotonin levels [157].

- *Nutrient –Dependent Control Of Brain Catecholamine Synthesis & Release*

While brain serotonin synthesis is affected by availability of tryptophan or 5-hydroxytryptophan under control conditions, precursor dependency of catecholamine synthesis in the brain is coupled to the firing rate of the tyrosine hydroxylase containing neuron. It has been

demonstrated in a number of studies that a supplementation of l-tyrosine does not augment the synthesis of catecholamines under resting non-stressed condition, while an enhanced neuronal activity will increase the synthesis and release of catecholamines, especially dopamine following tyrosine application. Of these physiological stress is the most important, in terms of enhancing neuronal activity. In essence stress is mandatory for l-tyrosne administration to affect catecholamine synthesis. While it is well known research has demonstrated that catecholamines such as norepinephrine and dopamine can act as feedback inhibitors of tyrosine hydroxylase, the enzyme that converts tyrosine into the immediate precursor for dopamine or norepinephrine under physiological stress this mechanism is obliterated [158]. The reason for this is that the mechanisms that couple catecholaminergic neuron's firing frequency to its precursor responsiveness involve the phosphorylation of the tyrosine hydroxylase enzyme portion [159]. This enzyme's affinity for its cofactor is thereby enhanced and it becomes independent of end - product inhibition, yet dependent on the availability of its precursor substrate. In essence under stress l-tyrosine supplementation becomes similar to the l-tryptophan (5-hydroxytryptophan) type of precursor responsiveness. Moreover, it is important to realize that this enzyme activation occurs under enhanced neuronal activity and is calcium – and calmodulin dependent. In addition, the phosphorylation of tyrosine hydroxylase can be catalyzed by several protein kinases that selectively act on different amino acids of the enzyme protein. The protein kinase enhances the enzyme activity without affecting end-product inhibition or the affinity to tyrosine or the tetrahydrobiopterin cofactor. In addition, it is well known that a different, cAMP –dependent protein kinase can also phosphorylate tyrosine hydroxylae, enhancing the affinity to the cofactor (but not to tyrosine) and reducing the regulation by end –product inhibition. In summary, these changes allow the enzyme activity to become dependent on the extent to which it is saturated with its substrate l-tyrosine.

Stress & obesity

The effect of excessive stress in modern life can lead to chronic states of fatique –related depression. This is an unfortunate fact yet true that about 80% of all illness can be traced back to stress and depression. According to the American Academy of Family Physicians, these factors account for about 2/3 of all office visits.

The importance here is to understand that it is our position that indeed an obese individual or a carbohydrate binger is definitely subject to a stressful condition and therefore there is increased neuronal firing. There are numerous examples in the literature to support this contention. Furthermore, if an obese individual has the DRD2A1 variant, numerous studies have shown that resultant low dopamine D2 receptors caused an inability to cope with stress in the family and as an individual [160, 131,132]. In this regard, it is known that stress could even reduce D2 receptor mRNA message in the substania nigra, the lateral part of the VTA, basal ganglia especially in the "reward site" the nucleus accumbens [161].This work supports the concept that forebrain dopamine systems are involved in mediating the behavioral effects of chronic mild stress. It further supports the view that in obese subjects, with chronic mild to moderate stress, a compromised number of D2 receptor sites and reduced mRNA message, the firing frequency of a catecholaminergic neuron is enhanced and would be quite receptive to l-

tyrosine supplementation as proposed in the formula. Moreover, it is also known that neuronal depletion of dopamine could also induce an independent end-product inhibitory state for TOH, which will also respond to l-tyrosine supplementation**.** With a slow release formula, there is constant dopamine release because of the effect of enhanced opioidergic activity via D-phenylalanine on substania nigra GABA neurons.

Treatment: Role of nutrients and pharmacogenomics in obesity and overeating

In the eating game we must first appreciate the importance of brain neurochemistry and how certain nutrients such as amino-acids could effect brain neurotransmitter status and how this could effect macro-selection. In this regard we must be cognizant of how a nutritionally unbalanced diet may lead to neurochemical processes that now induce the intake and aberrant craving for, high carbohydrate meals. The intake of macro – and micronutrients leads to characteristic changes in the serum concentration of amino –acids, in particular large neutral amino acids. The consensus of the literature suggests that changes in the concentration of large neutral amino acids lead to parallel changes in their brain concentration that, in turn, specifically influence the synthesis of their respective neurotransmitters.

While the functional impact of these neurotransmitters differs markedly, the basic metabolic processes are comparable. Most of these substances are metabolized within nerve cells from their precursor molecules that have been taken up from the extracellular brain fluid. They are stored in intraneuronal vesicles and are released following a depolarization of the neuron. They interact with either pre-or postsynaptic receptors within the synaptic cleft and are inactivated either through enzymatic degradation or through neuronal uptake. Central nervous system functions clearly depend on those mechanisms that guarantee the stability of precursor amino acid concentration. It also follows that a marked reduction in the concentration of these amino acids impairs physiological functions that are regulated and /or modulated by a respective neurotransmitter. The regulation of the synthesis of metabolic products from large neutral amino acids appears to be specific for neurotransmitters such as monamines. It is noteworthy that a similar impact on the synthesis of neurohormones (*i.e opioid peptides)* does not exist, since ribosomal protein synthesis does not depend on the fluctuation of amino acid concentrations. It may thus be speculated that a coupling of nutrient intake (amino-acid precursors), transmitter synthesis, and neuronal function reflects a phylogenetically relevant process.

When we consider that there are shared genes and RDS is an encompassing term which includes a number of impulsive, compulsive and addictive behaviors, we should not be surprised of the vast numbers involved in RDS. We know that at least one-third of the US alone carries the DRD2 A1 variant. This has been linked to multiple addictions including carbohydrate bingeing and other drugs of abuse (*i.e. alcohol, cocaine, nicotine)* and its presence at birth predicts future problems with food, drugs and certain destructive behaviors at the predictive value of 74% [43].

In the United States alone there are 60 million persons who are at least 20 percent overweight, 18 million alcoholics, 28 million children of alcoholics, six to ten million cocaine addicts, 14.9 million who abuse other substances, 25 million people addicted to nicotine, 3.5 milion school age children with attention-deficit disorder or Tourette Syndrome and about a half million compulsive gamblers. Utilizing a natural approach to attenuate compromised

neurochemistry will ultimately lead us to a better modality that is potentially without side – effects.

While we believe natural nutritional therapy could offer an important approach to prevent as well as treat reward deficit problems, especially as it relates to obesity, there is reason to believe a pharmacological approach can not be ignored. In an attempt to show the power of a new emerging field of "*Pharmacogenomics"* we provide the following example.

It is tempting to speculate that the pharmacological sensitivity of overeaters to dopaminergic agonists (bromocriptine, bupropion, n-propylnor-apomorphine, phentermine, and dopamine) may be determined partly by the individuals D_2 genotype. We predict that A_1 carriers should be more responsive to D_2 agonists (including naturaly released dopamine), especially in stimulant-dependent people. At least one study already has shown that direct microinjection of the D_2 agonist n-propylnor-apomorphine into the rat *nucleus accumbens* significantly suppresses the animals symptoms after withdrawal of opiates [162]. A double-blind study demonstrates the utility of this approach in human subjects [15]. The D_2 agonist bromocriptine or a placebo was administered to alcoholics who were carriers of the A_1 allele (A_1/A_1 and A_1/A_2 genotypes) or who carried only the A_2 allele (A_2/A_2). The greatest improvement in the reduction of craving and anxiety was found among the A_1 carriers who were treated with bromocriptine. The attrition rate (relapse) was highest among the A_1 carriers who were treated with the placebo. It is noteworthy, that as expected, dopamine receptor occupancy by a dopamine agonist or by dopamine itself, initiates a feedback system that produces more dopamine receptors even in A_1 carriers (low dopamine receptors) after a period of time. This is supported by the fact that the greatest effect occurred after a period of six weeks. In support of this, since 1993, Molinoff and associates using transfected kidney cells consistently showed that occupancy of D_2 receptors by dopamine agonists over time results in proliferation of dopamine D_2 receptors [163, 164].

Similar evidence for the role of genes in physiological response even with nutritional supplements has been accomplished with chromium picolinate by Blum et al. [165]. While there still is controversy regarding the effects of chromium salts (picolinate and nicotinate) on body composition and fat loss in general, recent unpublished work seems to support the positive change in body composition in humans (see Table 2). In consideration of the above study, Chen and Blum and others decided to genotype 130 overweight subjects for the dopamine D_2 receptor gene [166]. The subjects were assessed for scale weight and for percent body fat using dual energy X-ray absorptionmetry (DEXA ^{R}). The subjects were divided into matched placebo and chromium picolinate groups (400 μg. per day). The sample was separated into two independent groups; those with either an A_1/A_1 or A_1/A_2 allele and those with only the A_2/A_2 pattern. In the A_2/A_2 carriers, the measures of change in fat weight, change in body weight, the percent change in weight, and the body weight change in kilograms were all significant, whereas no significance was found for any parameter for those subjects possessing a dopamine D_2 receptor A_1 allele. These results suggest the dopaminergic system, specifically the density of the D_2 receptors, confers a significant differential therapeutic effect of chromium picolinate in terms of improved body mass and change in body fat. Moreover, we propose for the first time that mixed effects now observed with chromium picolinate in terms of body composition, may be resolved by

typing the patient via dopamine D_2 receptor genotyping prior to treatment with not only chromium salts, but with other nutritional supplements as well.

Brain nutrition and behavior

A detailed account of this subject is treated in the books *Alcohol and the Addictive Brain* [34], and *To Binge or Not to Binge?* [23]. In short, if genetic anomalies result in neurotransmitter imbalance, then how could we help to restore balance?

At the functional level, it seems clear that neurotransmitter imbalance may be a problem of brain nutrition: more specifically, a deficiency or excess of amino acids. In the healthy body, amino acids are in balance; if there is an excess or shortage, distortions of brain function can result [167].

As we know the brain cannot synthesize all of the amino acids involved in the formation of neurotransmitters; some are derived from food metabolism, and come to the brain *via* the blood supply. There are two categories of amino acids: *essential* and *nonessential.* There are five essential amino acids necessary for the manufacture of neurotransmitters, thought to play a role in obesity: methionine, leucine, phenylalanine, tyrosine, and trytophan (see above for more detail). Among the nonessential amino acids manufactured in the body, Glutamine probably plays a significant role, because it is involved in the manufacture of GABA. Two forms of amino acids are found in nature. The amino acids in the brain that make up the neurotransmitters, and the enzymes that regulate them, are all derived from the L-form. The D-form (as in D-phenylalanine) is found in a few microorganisms and in multi-cellular organisms like frog skin.

Single Versus Multiple Amino acid Neuronutrients

- First, although a single amino acid may be involved in the formation of a given neurotransmitter, it does not act alone. It needs the help of co-factors such as vitamins and minerals before the formation can take place. For example, vitamin B6 (in the alcoholic, pyridoxal –5-phosphae form is required) is needed for the manufacture of dopamine.
- Second, obesity is the result of a complex disorder that involves processes taking place in the neuron, at the synapse, and at receptors.
- Third, we cannot determine (until we use DNA tests) the specific defect that is producing a particular part of the problem. Therefore, in the effort to offset neurotransmitter deficits, it is not feasible to depend on single amino acids. This is why we include both serotonergic and dopaminergic precursors.
- Fourth, an odd characteristic of the blood/brain barrier actually makes treatment easier. Most overweight individuals have compounded stress and may have comorbid addictions like alcohol, smoking, and other drugs; it is known that all of these weaken the barrier facilitating the passage of restorative substances such as amino acids into the brain. This is particular important when you consider large neutral amino carrier system and competition of tryptophan, phenylalanine and tyrosine. It is equally important when you consider, as mentioned earlier, that the rate-limiting enzyme Tyrosine Hydroxylase works best under stressful conditions and the precursor tyrosine will indeed be converted to dopamine and will be subsequently released into the synapse of the n.accumbens.

- Fifth, it is well known that the degradation of catecholamines by COMT plays a role, albeit only partial, in clearing these neurotransmitters from synaptic cleft. Dopamine, norepinephrine and serotonin reuptake into nerve terminals via membrane transporter is thought to play a more significant role [158].

  However, it is our position that any enhancement of the neurotransmitters in the synapse is positive. In this regard, the effects of synephrine on norepinephrine receptors [168] plus the central nervous system effects of *Rhodiola rosea* [169, 170] could contribute to a sibutramine/D-fenfluromine–like effect. The amount of *Rhodiola rosea* recommended in the prposed formula herein is 240 mg per day (based on a 3% extract standardized to rosavin) which is somewhat higher than the recommended dose for use of *Rhodiola rosea* as an antidepressant (200mg/day, [171], see below). Moreover, the proposed formula may also contain synephrine, derived from citrus aurantium (6% synephrine) at a daily dose of 50mg. This amounts to only 6 mg per day. While this is less than normal recommended dose as s sympathiomimetic agent, when it is combined with caffeine thermogenesis could be achieved without the stimulatory effects seen with much higher doses (104mg/day).

Studies showing anti-craving efficacy of precursor amino-acids and Enkephalinase inhibitor activity

- It is our contention that with the proposed formula as designed for anti-craving, synergistic outcomes for other comorbid addictions might be observed since the ingredients are included that could act through several different mechanisms (see above) to enhance the activity of the neurotransmitters.
- In a number of experiments we have shown brain changes of enkephalins using D-phenylalanine (500mg/kg/day for 18 days) and or its metabolite hydrocinnamic acid (intracerebral ventricular injection of 25 micrograms) in mice [88]. Using the same doses these known enkephalinase inhibitors significantly reduced alcohol preference in both *acceptance* and *14 day preference* test [17].
- We have shown in healthy volunteers electrophysiological changes (enhanced memory and focus) with the combination of DL-phenylalanine (1500mg/day), L-tyrosine (900mg/day), L-glutamine (300mg/day), chromium picolinate (360 micrograms /day) and other co-factors [117].
- Positive effects in alcoholics in an in-patient hospital including lower building up to drink scores, required no PRN benzodiazepines (0% vs. 94%), ceased tremoring at 72 hours, had no severe depression on the MMPI, in contrast to 245 of control group. The ingredients included Dl-phenylalanine (2760mg/kg/day), L-tryptophan (150mg/day), L-glutamine (150mg/day), and pyridoxal -5-phosphate (30mg/day) [110].
- in a double –blind placebo controlled study of polysubstance abusers in an in -patient hospital, the combination of Dl-phenylalanine (2760mg/day), L-tryptophan (150mg/day) , L-glutamine (150mg/day), and pyridoxal-5 –phosphate (30mg/day), significantly reduced stress, improved physical and emotional scores, a six –fold reduction in AMA rates, enhanced treatment recovery [111].

- Utilizing DL-phenylalanine (1500mg/day), L-tyrosine (900mg/day), L-glutamine (300mg/day), L –tryptophan (400mg/day) and pyridoxal –phosphate (20mg/day) in inpatient treatment of cocaine abusers over a 30 day period compared to controls significantly reduced drug hunger and withdrawal against advice rate (AMA), reduced need for benzodiazepines, and facilitated retention in the treatment program [172].
- In an outpatient clinic DUI offenders (alcoholics and/or cocaine addicts) were treated with a combination of dl-phenylalanine, L-tyrosine, L-glutamine, Chromium, pyidoxyl-5-phosphate over a ten-month period. Compared to a vitamin control (only B-complex and vitamin c), the experimental group significantly reduced relapse rates and enhanced recovery in these DUI outpatient offenders. The retention rates obtained for alcoholics was 87% for the experimental group compared to only 47% of the control patients and for cocaine abusers the numbers are 80% vs. only 13% [108] . For alcoholics: DL-phenylalanine (2760mg/day), L-Glutamine (150mg/day), chromium picolinate (360 micrograms/day), pyridoxal –5-phosphate; For cocaine abusers: DL-phenylalanine (1500mg/day), L-Tyrosine (900mg/day), L-glutamine (300mg/day), pyridoxal –5-phosphate (20mg/day).
- Utilizing amino acid and enkephalinase inhibitory therapy, J.A. Cold found significant improvement in both cocaine craving and withdrawal symptoms in out patient cocaine addicts [114]. The ingredients included DL-phenylalanine (1500mg/day), L-Tyrosine (900mg/day), L-glutamine (300mg/day), and pyridoxal–5-phosphate (20mg/day).
- With only chromium picolinate it was found in two double – blind placebo controlled studies that doses of either 200 mcg or 400 mcg resulted in a body composition improvement, loss of body fat, gain in nonfat mass [115,116];
- With DL-phenylalanine (2700mg/day), L-tryptophan (150mg/day), L-glutamine (150mg/day) and pyridoxal –5 phosphate (30mg/day) it was also found that 27 outpatients with high carbohydrate bingeing behavior where females were assigned 800 calories total intake per day and males were assigned 1,000 to 1,200 calories per day and all withdrew from sugar use attending a supervised diet- controlled treatment program, the supplement group over a 90 day period lost an average of 26.96 pounds compared to the control group (no supplement) lost only 10 pounds. In fact, only 18.2 % of the experimental group relapsed (lost less than 15 pounds over the 90 day period) compared to 80.% in the control group [112];
- In another study where the supplement contained dl-phenylalanine (2760mg/day), L-tryptophan (150mg/day), L-glutamine (150mg/day), pyridoxal –5 phosphate (30mg/day), chromium Picolinate (200 micrograms/day), and carnitine (60mg/day) over a 2-year period in 247 obese patients the following results were obtained in a dual blind non-randomized open trial utilizing Centrum vitamin as a control. Compared with the Non-Phencal / Centrum group the experimental Phencal/Centrum group showed a two-fold decrease in percent overweight for both males and females; a 70 % decrease in food cravings for females and a 63% decrease for males; and a 66% decrease in binge eating for females and a 41 % decrease for males. Most importantly, the experimental group regained only 14.7% of the lost weight, and multiple regression modeling revealed that with Phencal treatment, morbid obesity and binge eating score were significant predictors of weight gain after 2 years. In contrast, family

history of chemical dependence was most closely associated, although not statistically significant, with improved results with Phencal [116].

- Blum decided to test the hypothesis that possibly that, the combination of a narcotic antagonist and amino acid therapy consisting of an enkephalinase inhibitor (D-Phenylalanine) and neurotransmitter precursors (L-amino –acids) to promote neuronal dopamine release, might enhance compliance in methadone patients rapidly detoxified with the narcotic antagonist Trexan®. In this regard, Thanos et al. and associates found increases in the dopamine D2 receptors (DRD2) via adenoviral vector delivery of the DRD2 gene into the nucleus accumbens, significantly reduced both ethanol preference (43%) and alcohol intake (64%) of ethanol preferring rats, which recovered as the DRD2, returned to baseline levels [21]. This DRD2 overexpression similarly produced significant reductions in ethanol non-preferring rats, in both alcohol preference (16%) and alcohol intake (75%). This work further suggests that high levels of DRD2 may be protective against alcohol abuse [24, 173]. The DRD2 A1 allele has also been shown to associate with heroin addicts in a number of studies. In addition, other dopaminergic receptor gene polymorphisms have also associated with opioid dependence. For example, Kotler et al. showed that the 7 repeat allele of the DRD4 receptor is significantly overpresented in the opioid dependent cohort and confers a relative risk of 2.46 [174]. This has been confirmed by Li et al. for both the 5 and 7 repeat alleles in Han Chinese case control sample of heroin addicts [175]. Similarly Duaux et al. found a significant association with homozygotes alleles of the DRD3-Bal 1 in French Heroin addicts [176]. A study from NIAAA, provided evidence which strongly suggests that DRD2 is a susceptibility gene for substance abusers across multiple populations [177]. Moreover, there are a number of studies utilizing amino –acid and enkephalinase inhibition therapy showing reduction of alcohol, opiate, cocaine and sugar craving behavior in human trials. Over the last decade, a new rapid method to detoxify either methadone or heroin addicts utilizing Trexan^{R} sparked interest in many treatment centers throughout the United States, Canada, as well as many countries on a worldwide basis. In using the combination of Trexan^{R} and amino-acids, results were dramatic in terms of significantly enhancing compliance to continue taking Trexan®. The average number of days of compliance calculated on 1,000 patients, without amino-acid therapy, using this rapid detoxification method is only 37 days. In contrast, the 12 subjects tested, receiving both the Trexan® and amino-acid therapy was relapse-free or reported taking the combination for an average of 262 days ($P<0.0001$). Thus coupling amino-acid therapy and enkephalinase inhibition while blocking the delta receptors with a pure narcotic antagonist may be quite promising as a novel method to induce rapid detox in chronic methadone patients. This may also have important ramifications in the treatment of both opiate and alcohol dependent individuals, especially as a relapse prevention tool. .It may also be interesting too further test this hypothesis with the sublingual combination of the partial opiate mu receptor agonist buprenorphrine. The ingredients tested included DL-phenylalanine (2760mg/day), L-Glutamine (150mg/day), chromium picolinate (360 micrograms/day), pyridoxal –5-phosphate(30mg/day). [34].

- Most recently a study was performed by Julia Ross best selling author of *The Diet Cure* [178], in an outpatient clinic in Mill Valley, California involving amino-acid therapy and enkephalinase inhibition based on Blum's work. At Recovery Systems, Ross has successfully utilized this approach to treat a number of RDS behaviors, especially eating disorders. In a preliminary evaluation, utilizing the following ingredients tailored made for each client, *dl-phenylalaine, 5-hydroxytryptophan, l-tryptophan, l-tyrosine, l-glutamine, chromium , vitamin B6,* follow –up interviews of six randomly selected former eating disordered female clients (three were also chemically dependent), were contracted nine months to three years post – treatment to evaluate efficacy of combining targeted nutritional elements (amino-acids, vitamins, digestive enzymes, a diet low in refined carbohydrates but adequate in calories and other nutrients) with conventional counseling, education, and peer support. Follow-up confirmed significant initial benefits in mood and freedom from compulsive behavior and ideation in 100% tested. While one subject relapsed within six months, the remaining five subjects all sustained, and in some cases exceeded expectations. Following this preliminary evaluation, we also evaluated an additional 100 patients and the data collected revealed 98% significant improvement in both mood and reduced craving for not only carbohydrates but other abusable substances as well. According to Ross this work further suggests the positive potential of adding targeted nutritional protocols to conventional treatment elements to improve outcome in an RDS intransigent population [179].
- The following results from a study in Las Vegas at an outpatient clinic has been evaluated and presented herein. Relapse rates: Clark County District:-Out of 15 patients only 2 patients dropped out, while the other 13 patients remained in the program for 12 months. Therefore, the percent relapse for this group is 13.33; County Court(Las Vegas) – Out of 43 patients 11 patients dropped out, while the other 32 patients remained in the program for 12 months. Therefore, the percent relapse for this group is 23.2.; Federal Court Sustem- Out of 10 patients only 2 dropped out, while the other 8 patients remained in the program for 12 months. Therefore, the percent relapse for this group is 20.0.; Self Referral- Out of 8 patients none dropped out, thus 8 patients remained in the program for 12 months. Therefore, the percent relapse for this group is 0.0. If we calculate the percent relapse of the entire program which included a total of 76 patients with a total of 15 patients that dropped out it is a remarkable 19.9 % relapse. The majority of drop outs (11 out of 15 or 73.3 %) were methamphetamine abusers.-the ingredients include DL-phenylalanine (2700mg/day), 5 – hydroxytryptophane (20mg/day), L-Tyrosine (750mg/day), L-glutamine (350mg/day), Rhodiola *rosea (3% rosavin) (*66mg/day), Chromium dinicotinate glycerate 1000 micrograms/day), DMAE (40mg/day), Hiperzine A (150 micrograms/day). Combination of vitamins (C, E, Niacin, Riboflavin, Thiamin, B6 [20% Pyridoxal –5 phosphate and 80% Pyridoxine], folic acid, B12, Biotin, Pantothenic acid, Calcium, Magnesium, Zinc, Manganese and a herbal calming blend, focus blend or mood enhancing blend. The ingredients and dosage was dependent on type of abusers including diagnosis of ADHD [180].

We have categorized the various benefits observed by individuals according to the following:

- Stress Reduction

- Enhancement of Sleep
- Increased Energy Levels
- Generalized Well –Being
- Craving Behavior Reduction (sweets/carbs)
- Mental Focus/Memory
- Blood Sugar Levels
- Food Consumption Reduction
- Loss Of Inches
- Loss Of Fat
- Blood Pressure Reduction
- Improvement of Workout Performance
- Reduction of drug seeking behavior (Alcohol, nicotine, cocaine, marijuana, opiates, etc)
- Reduction of Hyperactivity
- Reduction of Cholesterol

Fortunately, if a broad menu of amino acids is available in sufficient quantity, the brain appears to have the ability to choose from the menu the one or ones needed to manufacture more of the neurotransmitter that is deficient. Based on consistent positive research outcomes and technology, the following nutrients are scientifically formulated and have been clinically tested for over 25 years[34] and have relevance to the problem defined as Reward Deficiency Syndrome**,** more specifically-overeating and carbohydrate bingeing. However, the work to date supports a generalized anti-craving claim utilizing a number of important ingredients:.

- **D-Phenylalanine,** to inhibit enkephalinase, the enzyme that metabolizes or breakdown enkephalins, thereby increasing the availability of enkephalins and, presumably, making more dopamine available at the reward sites especially under stressful conditions.
- **L-Phenylalanine,** to stimulate the production of dopamine, and/ or increase norepinephrine levels in the reward area of the brain. The major problem with this amino acid is that it could compete with other amino-acids such as blood borne l- tryptophan and l-tyrosine at the large neutral amino –acid brain carrier system [159]. However, other data demonstrates for the first time that the synthesis and release responses to some dopaminergic agents may be elicited from synaptosomal dopamine which is formed by the hydroxylation of phenylalanine. Amphetamine and Cogentin increased the release of dopamine formed from 14C –phenylalanine in rat caudate nucleus synaptosomal preparation and concomitantly stimulated the synthesis. Amfoelic acid also caused a net release of that dopamine. In conclusion, the results suggest that synaptosomal particles represent a unit capable of synthesizing dopamine from l-phenylalanine and that synthesis from this precursor may be under the regulatory control of the particles [181].
- **L-glutamine,** to increase brain GABA levels at receptors associated with anxiety. Its major use is to maintain balance in case of over inhibition by D- phenylalanine.
- **L-5-hydroxytryptophan (or its natural form) –** The effect of systemic administration of 5-hydroxy-l-tryptophan on the release of serotonin in the lateral hypothalamus of the rat in vivo as examined utilizing brain microdialysis. Administration of 5-HTP caused an

immediate increase of the 5-HT in dialysates, which was long lasting and dose dependent. When calcium was omitted from the perfusion medium, thereby limiting exocytosis, levels of basal 5-HT were significantly decreased and the 5-HTP– induced response of 5-HT was markedly attenuated [182].

- **Pyridoxal-5-phosphate,** the active ingredient of vitamin B_6 to serve as a co-factor in the production of neurotransmitters and to enhance the gastrointestinal absorption of amino acids.
- **Chromium Salts (Nicotinate and Picolinate),** have a number of metabolic effects including : increase of insulin sensitivity; reduction of cholesterol; reduction of percent body fat; net reduction of weight; maintaining muscle mass promoting lean; enhancing body composition; promotes brain serotonin production (see above)
- **Carnitine (optional ingredient),** promotes fat metabolism [183].
- **Calcium,** promotes neurotransmitter release based on many studies [182, 159].
- **Rhodiola rosea –** Several clinical trials with double –blind placebo controls in Russia provide evidence that R. rosea possess positive mood enhancing and anti-stress properties with no detectable levels of toxicity. Generally, R. rosea extract has been shown to have a positive influence on the higher nervous system, increasing attention span, memory, strength and mobility of the human body, and weight management. It is believed that R. rosea can act as a COMT inhibitor where brain levels of serotonin and dopamine has been observed. Studies by Saratikov and Marina suggest that R. rosea can increase the level of neurotransmitters by 30 percent and decrease COMT activity by 60 percent. In the weight management area there are double –blind studies with regard to "weight loss" and fat mobilization and central nervous system effects [184-192]. Scientists explain that Rhodiola rosea likely affects multiple body systems to promote emotional well-being, physical endurance, and mental sharpness. Pharmacological studies in vitro and in vivo have demonstrated that Rhodiola rosea stimulates neurotransmitter activity in the Central Nervous System (CNS) and may positively influence Serotonin, Norepinephrine, Dopamine and Acetylcholine availability in neuropathways that regulate mood. Further laboratory analysis has shown that Rhodiola Rosea also enhances permeability of the blood-brain barrier to specific neurotransmitter precursors of Serotonin and Dopamine. Although the exact mechanism of action is not yet fully understood, clinical and laboratory research indicate that Rhodiola rosea may help to promote a healthy neurotransmitter balance and provide positive support for a occasional nervousness, nervous tension, and anxiety as well as a depressed mood and mild to moderate mood changes caused by everyday stress.
- ***Gymnea Syveste (Optional Ingredient)*** helps to reduce undesirable fat formation by its ability to reduce cravings for sweets and control blood sugar levels. A peptide isolated from *Gymnema,* gurmarin, has also been shown to block the sweet taste of glucose and sucrose in animals. Gurmarin temporarily binds the sweet and bitter receptors on the tongue, thereby blocking the taste sensation and reducing sweet cravings. It is very important to consider a recent study by Preuss et al regarding the efficacy of a novel, natural extract of (-) hydroxycitric acid and a combination of niacin-bound chromium and *Gymnema sylvetre* extract in weight management in human volunteers. In a double blinded study, in 30 obese

subjects for eight weeks the combination compared to controls resulted in reduction of weight loss, and reduction in BMI. Food intake was also reduced. The daily dosage of the HCA-SX was 4,667 mg, ChromeMate provided 400mcg of elemental chromium , and *Gymnema sylvetre* was 400mg (providing 100mg gymnemic acid) [193].

- ***Passiflora incarnate*** or passionflower is a name that has been given to several members of the genus Passiflora. There are more than 40 species in the genus whose origins are in both the tropical and subtropical regions of the western hemisphere. Passionflower was first brought to Europe from Mexico in the sixteenth century by Spanish conquerors. Its main medicinal purpose was that of a calming tea. It is now part of the medicinal herbarium in many countries throughout the world. Passion flower's long history in herbal medicine includes its use as a treatment for colic, diarrhea, dysentery, menstrual pain, skin eruptions, conjunctivitis, hemorrhoids, and myscle spasms. However, the inclusion in NAAT involves its central nervous system effects.It is well known that substances that alter meso-limbic function will ultimately influence metabolic X syndrome [194-197].

  One of the problems with this subtropical plant is its identity. While there are a number of alkaloids which have been sold under the rubric of Passionflower, the most important and consistently effective candidate is Passiflora incarnata. The ethnobotanical database on the U.S. Agricultural Research Service's Web site lists the total alkaloid content P. incarnata as 100 to 900 ppm and the total flavinoid content as 1.2 –3.9 percent which ahs been further tested by others [198]. Twenty –six components fall into two categories: 20 flavonoids (including a cyanogenic glycoside and gynocardine) and 6 alkaloids. Some researchers have ascribed the sedative effects of p. incarnata ip indole alkaloids such as Harmane and its relatives; harmaline and harmol. However, others have suggested that P. incarnata's alkaloid content is too small to cause this and other CNS effects and that flavonoids-such as apigenin, luteolin, or their glycosides-are more likely to account for CNS bioactivity. Most recently, scientists have isolated a highly anxiolytic, trisubstituted benzoflavone moiety from a P. incarnata extract. Reports from the literture reveal that this extract has the ability to restore libido on aging male rats [199], and those who are addicted to tetrahydrocannibinol [200] to restore fertility and libido that has been reduced by alcohol or nicotine use [201], and to reduce the anxiety arising from alcohol withdrawal [202]. There are also double –blind randomized studies which suggest that Passiflora extract is as effective substance for the management of generalized anxiety disorder comparative to the drug Oxazepam [203]. There is even evidence that Passiflora in a double –blind randomized controlled trial may be an effect adjuvant in the management of opiate withdrawal of opiates [204]. In addition Passoflora reduced benzodiazepone dependence in mice [201]. In fact, many pharmacological investigations confirm the sedative effects of Passoflora, especially in the P. incarnata form [205]. We have formulated NAAT with the knowledge afforded EuroMed (source of the fragmented or cut, dried aerial parts of P. incarnata). According to Dhawan et al. the separated leaves afford the best possible CNS results, and in fact, the selected of the entire aerial parts excluding the flowers may prove to be the optimum approach for pocking up the bioactive plant parts of P. incarnata. The importance of standardization of preparations of Passoflora has been actively studied especially as it relates to the anxiolytic activity [205].

Why Passoflora in NAAT?

In the early 70's one of us (KB) showed the importance of the brain neurotransmitter serotonin as a biological substrate of stress [206]. In fact, induction of stress in rodents was attenuated by injections of the serotonin chemical synthesis depleator Para –Chlora-Phenylalanine (PCA). Others have also shown the involvement of serotonin and dopamine in stress production in both animals and humans. Moreover, work by Blum et. al. also showed that amino-acid and enkepkalinase inhibition therapy reduced stress in polysubstance abusers as measured in a double –blind –placebo randomized controlled trial in humans using skin conductance levels. These studies seem to dove tail the work reported on the anxiolytic effects of Passoflora. In fact it is very interesting that at least one phytoconstituent is indeed an indole similar to the chemical makeup of serotonin [109, 110].

Combining KB220 Variants [NAAT] with Neuroadaptagens and Neuro-metabolic Optimizers

There are at least four important factors that can effect weight gain; *genetics, environment, diet composition and lifestlye and family society and culture.* In this regard, an individual's genetic code can determine basal metabolic rate, neurotransmitter function, regulatory peptide levels, and other variables that may put someone at greater risk of increased, excessive and aberrant fat storage. There is another even more important facet to the genetic tendency for aberrant fat storage than genes that control fat storage or metabolic rates. This is in the genes that control our desire "to binge or not to binge". These are the "reward genes'. The understanding of neurochemistry, genetics, metabolic rates and energy expenditure, carbohydrate bingeing, body types, lipid anabolism and catabolism, caloric intakes and Syndrome X will provide the basis for polygenetic diagnosis and treatment of obesity [194-197].

NAAT™ is a unique, patented scientifically advanced product that provides a multi-nutritional approach to normal brain function. We are proposing herein that combining Synaptose (KB220Z) an example of NAAT with other ingredients known to optimize metabolic function (SEP711CG) through neurophysiolgical processes will ultimately provide a clinically effective novel approach to obesity.

Neurometablic Optimizer (SEP711CG)

Based on consistent positive research outcomes and technology, the following nutrients are scientifically formulated (following meticulous ingredient selections and dosage determinations), have been clinically tested, and have demonstrated profound efficacy at supporting optimal brain health; improving craving management; enhancing energy expenditure, neuroendocrine function, memory, focus, and cognition; immune competence; stress reduction; and body composition and weight management.

- **Synaptose™** – A patented and patent-pending KB220/KB220Z neuroadaptogen nutraceutical complex has 24 clinical studies (at the time of this writing) demonstrating its ability to correct gene expression; help maintain dopamine in the normal range, promote optimal brain health, regulate cravings, and support focus, cognition, and neurotransmitter balance; reduce the impact of stress; enhance energy regulation,

neuroendocrine function, immune competence, and healthy mood; and support a leaner body composition and healthy weight management (see below for benefits)..

- **Cognitrim™-** Comprised of l-alpha-Acetyl-phosporylcholine and is a semi-synthetic derivative of Lecithin.
- **CurQFen™** – Superior to other curcumin products by up to 125 times, CurQFen is a fully reacted patent pending BR213 Curcuma galactomannosides compound that promotes: cognition, healthy cardiac function, immune competence, and a healthy gut; reduces the need to activate inflammatory cytokines; helps maintain blood sugar and blood lipid levels within the normal range; and slows the absorption of carbohydrates, cholesterol, bile acids, and improves gastric emptying.
- **Phospho*Lean*™** NOPE2G2 is a patented, advanced, appetite regulating and weight management compound that is clinically proven to help people control binge eating, and lower depressed feelings - all keys to successful, long-term weight loss. In a recent study, Phospho*Lean*™ increased satiety, decreased depressive symptoms, decreased binge eating severity, and provided favorable changes in insulin resistance and lipids. The EGCG polyphenols in Phospho*Lean*™ NOPE2G2 act synergistically via spathetic activation of thermogenesis and increased fat oxidation, thus enhancing the compound's weight management effects. Phospho*Lean* also significantly improved diet compliance in a group of healthy, overweight or obese subjects, as demonstrated by reduced dropout rate.
- **SH1028 Choline alphoscerate** – After consumption, SH1028 Choline alphoscerate is converted to the metabolically active form of choline able to reach cholinergic synaptic endings, thus increasing acetylcholine release. Metabolically active choline prevents fat deposits in the liver and facilitates the movement of fats into the cells. SH1028 promotes significant improvement in cognition, memory, and other neuro-chemical and -psychological cholinergic-dependent structures and functions, such as parasympathetic and sympathetic nervous system functions, neuromuscular junctions, basal forebrain function (considered to be the major cholinergic output of the central nervous system (CNS)), and important for healthy brain stem complexes.
  In addition, acute supplementation augments growth hormone response to, and peak force production during, resistance exercise.
- **GlucodOX™** is a proprietary nutraceutical ingredient complex comprised of a supercritical Commiphora mukul extract and a medium chain triglyceride (MCT) oil composed of C8 and C10 fatty acids. GlucodOX™ contains guggulsterones (standardized to 2.0% by HPLC analysis), which have been linked to several mechanisms that support lipid metabolism, glucose metabolism and cellular energy.
  GlucodOX™ is a unique blend whose properties are enhanced by MCTs, which can gain rapid access to the mitochondria (energy producing organelle in cells). Given their high energy density, rapid rate of absorption, and quick metabolic conversion into cellular energy, MCTs can be used for fueling physical exertion.

SEP711C3G is designed to:

1. Improve the efficiency of energy metabolism and fat burning
2. Improve tolerance to stress (reduce the impact of stress on the body)
3. Promote learning, memory, cognition, healthy brain function, and longevity (anti-aging)
4. Support a happier mood
5. Promote healthy cravings
6. Reduce the time needed for and improve the quality of satiety or the satisfaction from pleasurable experiences (like eating)
7. Improve brain, nerve and glandular (neuro-endocrine) function
8. Promote competent immune function
9. Promote healthy blood sugar and blood lipid levels within the normal range
10. Promote healthy fat loss and weight management.

Table 2 *SEP711CG:* Proposed new set of important ingredients that have never been combined into one anti-obesity product

*Ingredient**	*Description*	*Benefits*	*Protection /patents*	*References by claim number*
CurQFen™	**Novel result of curcuminoids fully reacted with galactomannans from Curcumin and Fenugreek.** **Provides 13 times more absorption of powerful curcumninods than regular 95% curcuminoid supplements.** **Delivers and maintains a 10-fold greater blood serum level**	**1.Healthy blood flow** **2.Healthy cardiac function** **3. Joint health** **4.Immune competence** **5. A healthy gut** **6.Blood sugar management** **7.Healthy cell structure & function** **8. Reduce the need to activate inflammatory cytokines** **9.Cognitive performance** **10.Hypoglycemic effects** **11.Hypolipidemic effects** **12.slow down the absorption of carbohydrates, cholesterol, bile acids**	**Fully reacted patent pending BR213 Curcuma galactomannosides compound.** **LifeGen Inc has exclusive to the combination for "My Secret Formula".**	**1.[207]** 2. **[208]** **3. [209]** **4. [210]** **5. [211]** **6. [212]** **7.[213], [214], [215]** **8. [216]** **9. [217]** **10. [218]** **11. [219]** **12. [220]**

	consistency of curcuminoids (bound with galactomannans) than regular curcuminoid supplements. **Provides a 125-fold increase in the concentration of curcuminoids in animal blood after 24 hours.** **Results in a 125-fold increase in the concentration of curcuminoids in human blood.** **The Galactose to Mannose Ratio is 1:1 and offers a more uniform arrangement of the monomers that prevents molecular breakage and maintains stability.**	**and improves gastric emptying**		
GlucodOX™	**Gugul + Triheptanoin 7 product (GU-TC7)**	**13.potent inhibitor of HMG-CoA reductase (beneficial for promoting healthy**	**GlucodOX™** is a proprietary GU-TC7 extract of Commiphora	**13.[221],[222]** **14. [223], [224]**

	The extract is standardized for its naturally occurring triheptanoin, a triglyceride composed of three 7-carbon fatty acids that support efficacy, bioavailability and is known to improve energy production from fatty acid oxidation.	**cholesterol levels within the normal range).** 14.. **Inhibit transformation of pre-adipocytes to adipocytes (i.e. fat cells) and inhibit triglyceride storage** **15. Significantly promote insulin sensitivity in adipocytes as measured by enhanced glucose uptake** **16. Increased glucose uptake** **17. Stimulate AMPK (nutrient/energy sensor), which is an important target that also helps to naturally reduce blood sugar levels within the normal range.** **18. Increase the NAD/NADH ratio via increased NAD** **19. Healthy glucose metabolism** **20. Mitochondrial biogenesis (creation of new energy-producing mitochondria)** **21. Primary energy production** **22. Increased catabolism (breakdown of larger molecules into simpler molecules thereby**	mukul (Guggul GU-TC7). **LifeGen Inc has exclusive to the combination for "My Secret Formula".**	**15.[225], [226], [227], [228], [229]** **16. [230], [231].** **[232], [233], [234], [235], [236], [237], [234]** **17. [238], [239], [240]** **18. [241]** **19. [242], [243], [244]** **20. [245], [246], [247], [231]** **21. [248], [249], [250], [251], [252], [253]** **22. [254], [255], [256]** **23. [257]**

		releasing energy…secondary energy production) 23. Reduced lipid production &8. Healthy blood lipid metabolism		
PHOSPHOLEAN™ NOPE+EGCG	**PhosphoLean™ is a patented, natural, compound of N-oleoyl-phosphatidyl-ethanolamine (NOPE) and EGCG, and it has been clinically proven to help dieters stay on their diets.** **Recent research has shown that OEA, the active compound liberated from PhosphoLean™, binds to a cell receptor class called peroxisome-proliferator-activated receptor-alpha (PPAR-α) found in the intestinal tract. This signal is "hard-wired" to the brain,**	24. **PhosphoLean™ significantly improved diet compliance in a group of healthy, overweight or obese subjects, as demonstrated by drop out rate. It also increased satiety, decreased depressive symptoms, decreased binge eating severity, and provided favorable changes in insulin resistance and lipids.**	**Protected under US Patent Application: US 2010/0179107 A1; Filed September 19, 2007; Publication Date, July 15, 2010. Pistolesi et al.; "N-Acyl-Phosphatidyl-Ethanolamines And / Or Mixtures Of N-Acyl-Ethanolamines With Phosphatidic Acids Or Lysophosphatidic Acids** **LifeGen Inc has exclusive to the combination for "My Secret Formula".**	**24. [258]**

	where appetite suppression is switched on. The EGCG polyphenols in PhosphoLean™ NOPE+EGCG act synergistically with OEA via sympathetic activation of thermogenesis and increased fat oxidation, thus enhancing the compound's weight management effects.			
Cognitrim™	l-alpha-Acetyl-phosporylholine is a semi-synthetic derivative of Lecithin. After oral administration, it is converted to phosphorylcholine, which is ametabolically active form of choline able to reach	25. Significant improvement in neuropsychological parameters associated with dementia. 26. Acute supplementation with alpha-glycerylphosphorylcholine augments growth hormone response to, and peak force production during, resistance exercise	LifeGen Inc has exclusive to the combination for "My Secret Formula".	25. [259] 26. [260]

	cholinergic synaptic endings, thus increasing acetylcholine and reelase. L-Alpha-Acetyl-phosporylholine contributes to anabolic processes responsible for membrane phospholipid and glycerolipid synthesis positively influencing membrane fluidity and integrity.			

Benefits and Features

In summary, **NAAT™** provides a unique combination of diet ingredients which include the *Synapatamine™* composition and other natural substances like potassium glycerophosphate, citrus aurantum, and gymnema sylvestre among others helps normalize the "Reward System" in the brain by maintaining normal levels of neurotransmitters involved eating behaviors. When normal neurotransmitter function is maintained food intake, especially of carbohydrates is controlled. Potassium glycerophosphate is a compound that helps the body maintain metabolic and enhance function and increase energy levels. The product also contains thermogenic and energy supporting ingredients that will help one lose weight and increase lean muscle. To review of the clinical outcomes of many trials go to the reference Chen et al. [181].

In terms of craving behavior each neutraceuitical developed will address a specific brain dysfunction. In this regard, **NAAT™** has been designed to significantly reduce carbohydrate bingeing. The mechanism for this effect involves the pharmacological principal -like treats like. In this case, the common release of dopamine at the reward site by glucose is linked to aberrant glucose seeking behavior. This compulsive drive for dopamine is affected by the use of the patented (US # 6.132.724) *Synaptose ™* composition which works on the brain reward system to mimic the action of glucose on nucleus accumbens neurons to release dopamine. Dopamine when released activates dopamine D_2 receptors. When these receptors are activated by dopamine the system is driven to attain pleasure and well-being. In general, since deficits have been found

in brain chemical functions underlying craving behavior, and since these deficits may be alleviated by facilitated dopamine release consequent to the use of substances such as glucose, combining amino- acid precursors and enkephalinase inhibition may stimulate the brain's reward system and compensate for neurotransmitter imbalance (thereby attenuating glucose craving behavior). In an attempt to understand that carbohydrate seeking behavior, is a subset of generalized craving behavior (Reward Deficiency Syndrome) due in part to low dopamine function (an impaired reward cascade), scientists believe individuals self-heal through biochemical attempts to alleviate hypodopaminergic activity *via* glucose - reward site interaction. Since the brain is made up of 200 billion cells and these cells require good nutrition, which includes minerals, vitamins, trace metals and amino acids, **NAAT™** is a special blend with brain stabilizing and metabolic properties. It is noteworthy, that since it is known that dopamine D_2 occupancy by dopamine D_2 agonists increase D_2 receptors, it is the contention that the use of this product would induce a constant release of dopamine, to occupy dopamine D_2 receptors, and ultimately reduce craving behavior due to a genetic deficiency of carrying the Dopamine D_2 Receptor A1 allelle (expression of low D_2 receptor number).

Imaging studies: Genes and weight gain.

We decided to test the acute oral **NAAT™**on reward circuitry during uprotracted abstinence following psychostimulant dependence in ten subjects associated with G & G Holistic Addiction Treatment Center of North Miami Beach, Florida. These subjects were diagnosed as having severe psychostimulant dependence and have been in recovery for at least two years. As part of the inclusion criteria, each patient was urine tested to determine the absence or presence of any psychoactive drug (illicit). None of the subjects tested showed a positive drug tested urine. Therefore, they were subsequently admitted to the study.

We found that a comparison of the FFT absolute Power (uVSq) of alpha (8-12Hz) demonstrated higher activity in the **NAAT™**group compared to the placebo group. Similarly observing the FFT absolute Power (uVSq) of low beta (12.0 15hz), the activity is considerably larger in the **NAAT™**group compared to the placebo group. Finally, there was a consistent effect of **NAAT™**on frontal regions when compared to placebo. The p values for group 1 (**NAAT™**) versus Group 2 (Placebo) for a between-group analysis of week 1 and week 2 whereby group comparisons utilizing T-tests were performed resulted in significant differences. This study is still in progress whereby we are increasing the subject population.

To date, as observed there are numerous clinical trials showing various recovery benefits from RDS behaviors using **NAAT™**. However, prior to the imaging studies, a measurable magnitude of effect and the mechanism of action have been elusive. The results of these preliminary qEEG studies suggest an interaction of NAAT and meso-limbic activation leading to "normalization" of abnormal dopaminergic function in anticipation of patients carrying a number of reward gene polymorphisms [261, 100].

While **NAAT™**appears to be a D2 natural non-addicting agonist, cautious interpretation must await future fMRI and PET scan analysis to determine chronic induction of D2/D3 receptors, especially in DRD2 A1 allele carriers and direct interaction at D2 receptor NAc interaction.

Further confirmation and study expansion results of the qEEG analyses and continued demonstration that **NAAT™** in the oral form leads to activation of the Parietal and Frontal regions of the brain, will be important. Moreover, increasing both alpha and low Beta activity will have important clinical outcomes. If confirmed it will suggest that **NAAT™** "normalizes" brain abnormalities associated with drug dependence (alcohol, heroin and psycho stimulants) induced by dopaminergic deficiency by acting as a Dopaminergic receptor agonists during protracted abstinence in polydrug abusers. This notion is supported by other studies showing enhanced treatment response in only A1 vs. A2 carriers we anticipate, that the greatest effect will have occurred with those individuals possessing the DRD2 TAq A1 allele [15,262,263].

We cautiously suggest that long-term activation of dopaminergic receptors (i.e., DRD2 receptors) will proliferate D2 receptors, leading to enhanced "dopamine sensitivity" and an increased sense of happiness. Even in carriers of DRD2 A1 allele, in psychostimulant abusers this is supported by numerous clinical trials and awaits PET scanning results to determine chronic effects of **NAAT™** on numbers of D2 receptors [15]. Positive outcomes will provide important information that could ultimately lead to significant improvement of recovery for victims of RDS having dopamine deficiency [264- 267].

Our laboratory has now published three papers on utilizing these nutrigenomic principles to target certain gene polymorphisms including but not limited to 5HT2a receptors, PPAR – Gamma, MTHFMR, LEP-OB and DRD2 genes (figure 4)with significant reductions in both weight (see figure 5) and BMI (see figure 6) [267, 268]. In these studies we also found that there was a 2 fold better compliance with carriers of the DRD2 A1 allele compared to carriers of the DRD2 A2 allele. (see figure 7) [269].

Figure 6 Happiness gene map as proposed whereby five gene polymorphic genes (circles) were utilized for obesity nutrigenomic therapeutic targets.

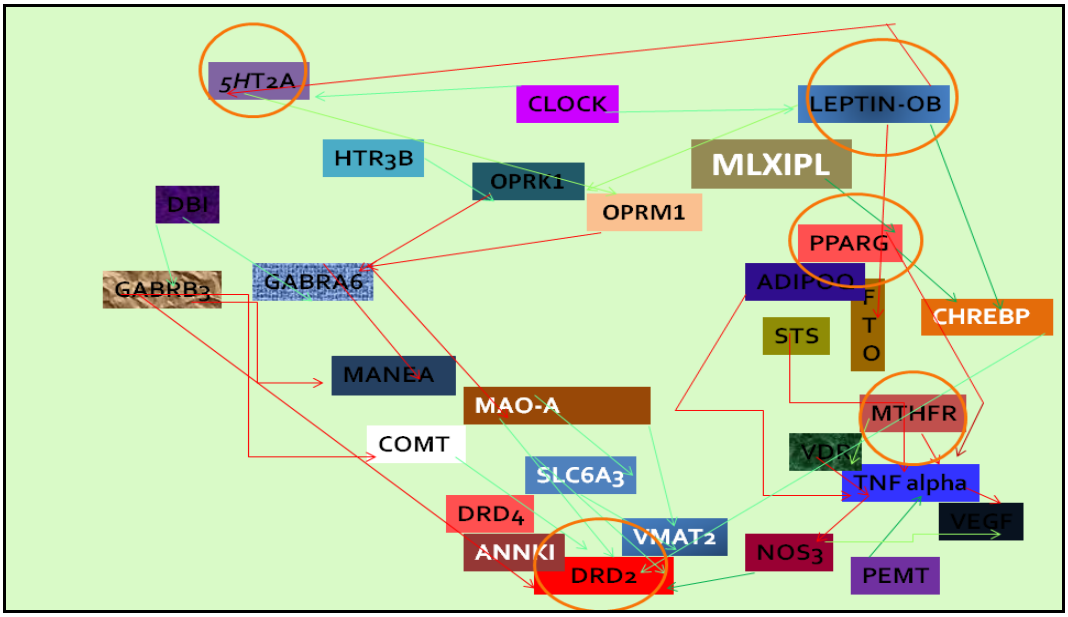


Figure 7. DNA directed KB220 (LG839 in experiment) reducs weight.Taken from reference 268 (with permission)

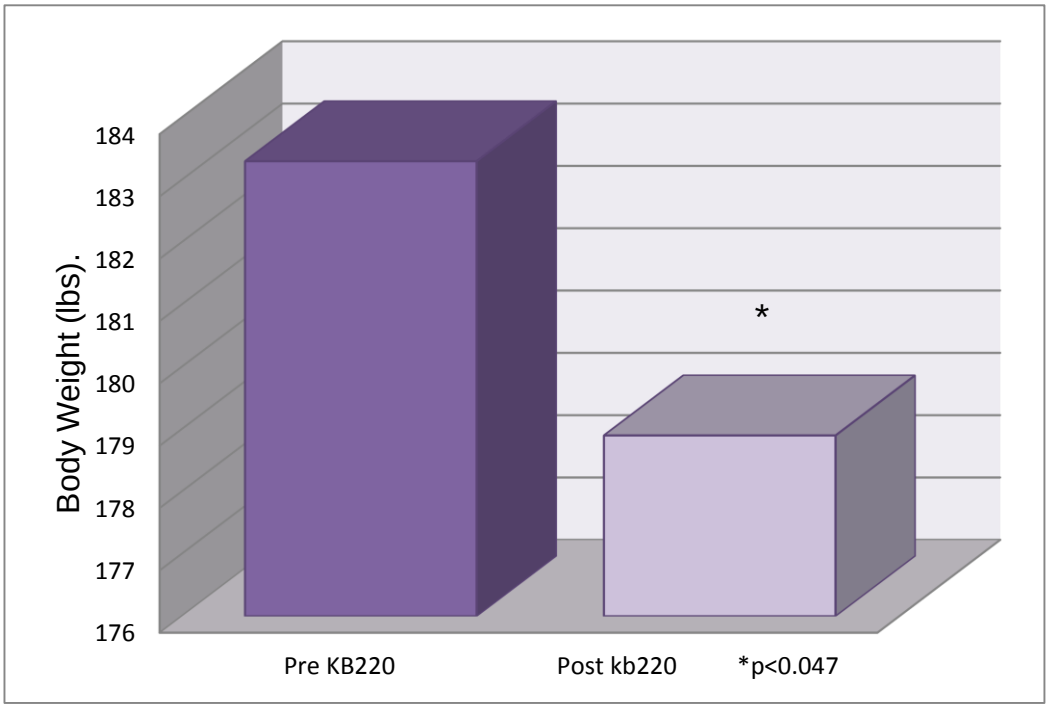


Figure 8. DNA directed KB220 reducs (LG839 in experiment) BMI. Taken from reference 268 (with permission)

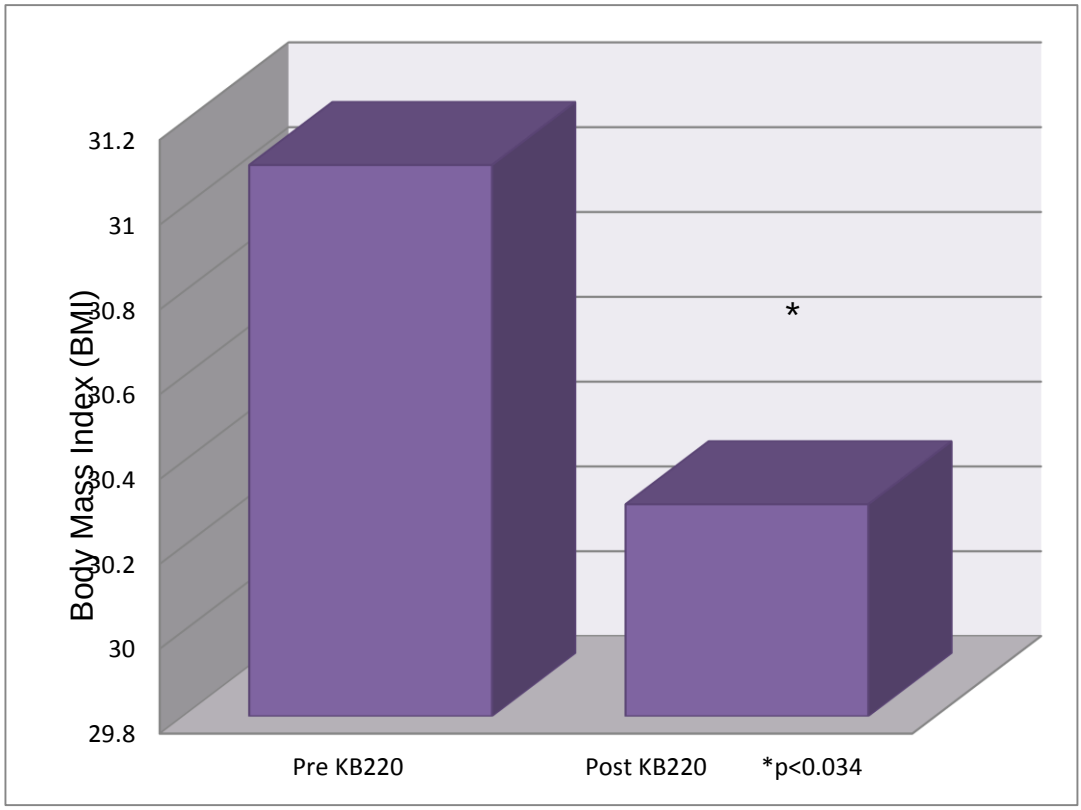
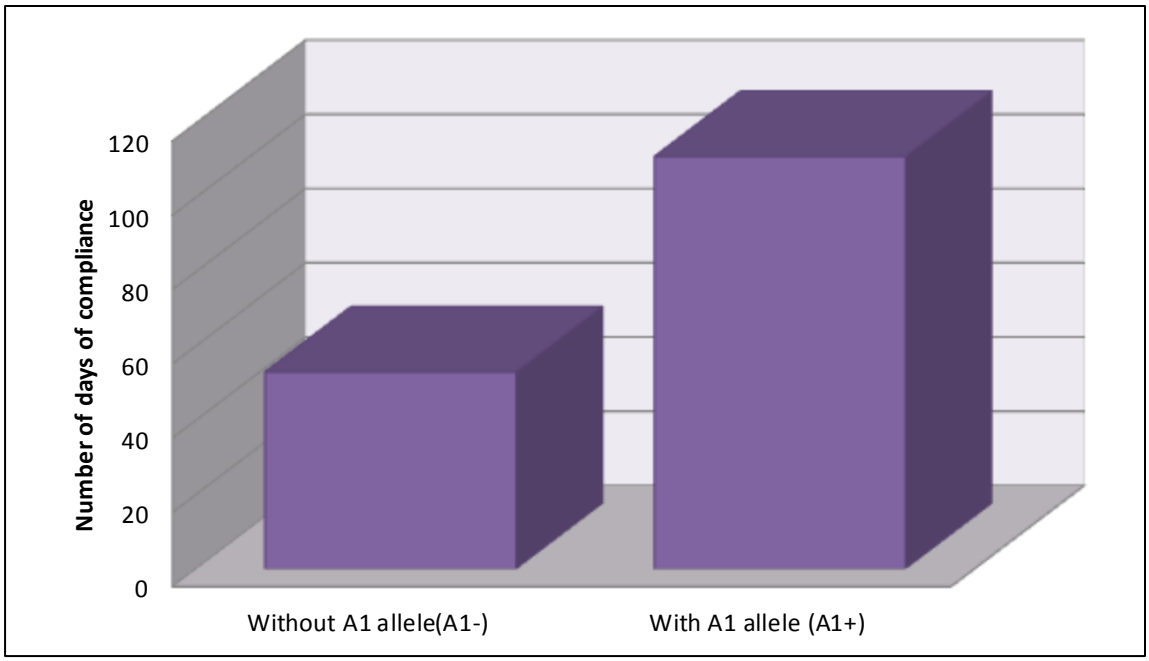


Figure 9. Treatment Compliance: Data on DNA directed KB220 (LG839 in experiment). Taken from reference 269 (with permission)



Conclusion

While we have attempted to provide a detailed comprehensive account of the need to develop nutrigenomic solutions to treat obesity and especially sugar craving behavior, a subtype of Reward Deficiency Syndrome, we are cognizant that additional large randomized double –blinded –placebo studies are needed to firmly confirm these novel ideas prior to any final conclusions could be ascertained. The intent herein is to encourage our scientific peers to consider additional studies utilizing nutrigenomic solutions such as proposed with NAAT [267-269].

It is well know that stress induces the preferential release of the circularitory hormone cortisol in humans [270]. It is well know that lipolysis is the major activity that is involved in the burning of fat in adipose tissue. Ottosson et al. [*271*] clearly showed that cortisol significantly reduced the basal rate of lipolysis ($p < 0.01$) and the catecholamine lipoysis stimulators isoprenaline and noradreanline *in vitro* [270]. Thus, cortisol will increase rather than decrease fat burning. In addition, the patogenesis of obesity has been suggested to be intimately linked to the catechoalminegic regulation of lipolysis and the function of the sympathetic nervous system. Norepinephrine and epinephrine activate lipolysis via B_1 and B_2 and B_3 – adrenoreceptors and inhibit it via $alpha_2$ adrenoreceptors, and these neurotransmitters are the most important lipolytic substances on vivo [271]. Defects of the catecholamine –induced lipolysis have been observed in a number of obese subjects, and polymorphisms of the B2- and B 3 receptors [272, 273].

By adding both *Passoflora and KB220BZ* (for a detailed description see [180]) a combination heretofore never combined we propose a synergistic effect on stress production and enhanced catecholamine synthesis. We further believe that these ingredients coupled together

would induce a reduction of plasma cortisol on humans. This will indeed then enhance lipolysis and increase fat burning.

In essence, this novel formulation will promote the synthesis of the brain reward neurotransmitters like serotonin and catecholamines and through its effect on the natural opioids will by virtue of inhibiting GABA cause a significant release of dopamine at the *nucleus accumbens*. This constant release of possibly therapeutic amounts of dopamine (anti-stress substance) occupies dopamine D_2 receptors, especially in carriers of the A_1 allele (low D_2 receptors and high glucose craving), and over time (possibly 6-8 weeks) effects RNA transcription leading to a proliferation of D_2 receptors, thereby, reducing craving for carbohydrates. Evidence for anorectic actions of dopaminergic stimulators like Amphetamines I (ephedra) have been found to work via activation of both D1 ands D2 dopamine receptors [40,44]. In addition, elucidation of the composition, characteristics and properties of stabilized (-) HCA compounds of GcEs is essential to differentiate effective sources from ineffective and substantiate the actual active ingredients in such mineral-based complexes. Recent research demonstrates intake of 4500 mg/d of a novel IH464 GcE containing 720 mg of K and 495 mg of Ca bound by (-) HCA for 8 weeks, while consuming a 2000 Kcal/d diet, produced safe and effective loss of body fat and improved BMI without stimulating the central nervous system. Other ingredients as listed in the example will also provide important benefits such as anti-craving, anti-sress, enhancement of serotonin, energy and metabolism induction, appetite suppression, starch blocking, glucose stabilization, fat burning, and general nutrition. as well as neurotransmitter rebalancing. Collateral benefits of lowered food intake and improved serotonin, insulin, lipid and leptin metabolism provide valuable evidence that this compound addresses multiple pathways in achieving sustainable healthy fat loss and improvements in body mass index while averting the consequences of rapid "weight loss" induced by CNS stimulation and/or calorie deprivation impacting many obesity genes [274,275].

Through a series of both neurogenetic and clinical experiments it is becoming increasingly clear that this novel formulation is the first neuroadaptagen known to activate the brain reward circuitry. Ongoing research repeatedly confirms the numerous clinical effects ultimately result in significant benefits for victims having genetic antecedents for all addictive, compulsive and impulsive behaviors. These behaviors are all correctly classified under the rubric of "Reward Deficiency Syndrome" (RDS). Preliminary findings in United States using qEGG and China using fMRI regarding the effects of oral **NAAT™** in addicts on activation of brain reward circuitry provides potentially exciting results. It seems from this preliminary data, utilizing an fMRI 2X2 design at resting state, **NAAT™** in comparison to placebo shows activation of the caudate brain region and potentially a smoothing out of heroin induced putamen abnormal connectivity. If further confirmed in the ongoing studies in China coupled with the qEEG results showing an increase in alpha and increase in low beta may have important treatment outcomes. Cautiously these remarkable results are in progress and must await final analysis. For a very recent review on Neuroadaptagen –Amino-Acid Therapy [**NAAT™**] see Chen et al. [275].

Understanding that we have a worldwide epidemic of obesity coupled with substance use disorder described under the rubric of Reward Deficiency Syndrome one of us (KB) as early as 1991 sumerized it up in his book "Alcohol and the Addictive Brain"[276]

"*In the remainder of this century and the early decades of the centeury to come, I think that we will see neurobiokogy, neuropharmacology, biogenetics, psychiatry, and medicine moving forward in close coordination to reduce the devasting behavioral and social costs of faulty brain function. My vision of the future is a world in which the chemical and electrical functions of the brain are understood; the problem of chemical imbalences as they affect behavior has been solved; the role of genetic anomalies in defective brain chemistry is understood; pharmaceutical and nutrional intervention as an adjunct to twelve-step programs and professional treatment is precise and effective; and the technique of defective-gene replacement has been perfected, enabling us to break the genetic chain of inherited addiction. In this world, each individual will be able to enjoy the inborn legacy of reward and pleasure without having the need for an addictive substance [sugar], without having to pay the price of addiction and pain."*

Competing Interest

Kenenth Blum, B. William Downs, Margaret A. Madigan all own stock in LifeGen, Inc. John Giordano is apartner of LifeGen, Inc. The various nutriceuticals discussed in this manuscript are based on US and foreign patents issued, awarded and pending to Blum et al.These patents have been exclusively licensed to LifeGen, Inc. There are no other conflicts of interest by any other author.

Authors Contributors

KB wrote the manuscript; AB developed the figures; BWD, RW, JG, MM, ERB, JMD, and TS contributed to the writing of the manuscript; JG and SM provided case studies; MAM edited the entire manuscript.

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