Chronological Summary of Studies of KB220(Z) Neuroadaptogen Therapy (NAT) & Active Ingredients of NAT Using Both Animal Models (Phase 1) & Humans Studies (Phase 2).

Phase 1

1973

L-DOPA: effect on ethanol narcosis and brain biogenic amines in mice.

Blum K, Calhoun W, Merritt J, Wallace JE.

Nature. 242: 407-409.

Abstract

L-DOPA augments ethanol-induced narcosis in mice. Determination of brain biogenic amines suggested that the enhancement effect may be due in part to the marked increase in brain dopamine following L-DOPA administration. Here we provide further evidence to implicate dopamine in L-DOPA-induced augmentation of ethanol narcosis.

Key Points:

- **Increased brain L-DOPA increases brain dopamine in mice and causes alcohol induced inebriated mice to sleep longer.**
- **Dopamine, l-tryptophan and alcohol work similarly in the brain.**

1974

Ethanol narcosis in mice: serotonergic involvement.

Blum, K.; Wallace, J.E.; Calhoun, W.; Tabor, R.G. & Eubanks, J.D.

Experientia 30:1053-1054.

Abstract

The role of serotonin in the sleep-time effects of ethanol was evaluated in mice. The administration of l-tryptophan (I.P.) compared to saline resulted in a significant increase in the soporific effects of ethanol in mice supporting the role of serotonin in ethanol mechanism of action.

Key Points:

- **When mice were given alcohol and 1-tryptophan compared to saline the L-tryptophan plus alcohol group slept longer than saline plus alcohol group.**
- **l-tryptophan and alcohol work similarly in the brain.**

Chronological Summary of Studies of KB220(Z) Neuroadaptogen

1987

Enkephalinase inhibition: Regulation of ethanol intake in mice.

Blum K, Wallace JE, Trachtenberg MC. Briggs AH, Dellallo L.

Alcohol: 4; 449-456.

Abstract

This is the first report of alteration in alcohol intake in mice with a genetic predisposition to alcohol preference and known to have innate brain enkephalin deficiencies. We have been able to significantly attenuate both volitional and forced ethanol intake respectively by acute and chronic treatment with hydrocinnamic acid and D-phenylalanine, known carboxypeptidase (enkephalinase) inhibitors. Since these agents, through their enkephalinase inhibitory activity, raise brain enkephalin levels, we propose that excessive alcohol intake can be regulated by alteration of endogenous brain opioid peptides.

Key Points:

- **Mice genetically predisposed to like alcohol have a measured deficiency in enkephalin.**
- **D-phenylalanine and its metabolite hydrocinnamic acid are substances known to stop the breakdown of enkephalin in the brain -the amount of enkephalin available in the brain increases.**
- **When the amount of enkephalin available in the brain increases both voluntary and forced intake of alcohol decreases.**
- **D-phenylalanine is one of the ingredients in NAAT.**

Phase 2

Chronological Summary of Studies of KB220(Z) Neuroadaptogen

1988

Improvement of inpatient treatment of the alcoholic as a function of neurotransmitter restoration: a pilot study.

Blum K, Trachtenberg MC, Ramsey JC.

The International journal of the addictions 23(9): 991-998.

Abstract

We report results of a double-blind evaluation of the nutritional supplement SAAVE for facilitating improvement in a 30-day inpatient alcohol and drug rehabilitation center. SAAVE is uniquely designed to elevate levels of enkephalin(s), serotonin, catecholamines, and GABA, which are believed to be functionally deficient in alcoholics. Twenty-two patients were studied. The SAAVE patients, as compared to the control group (a) had a lower BUD (building up to drink) score, 1 vs 2; (b) required no PRN benzodiazepines, 0% vs 94%; (c) ceased having tremors at 72 h, as compared to 96 h; and (d) had no severe depression on the MMPI, in contrast to 24% of control group. These preliminary data suggest that SAAVE is a valuable adjunct to therapy by aiding the patient's physical adjustment to a detoxified state while facilitating a more positive response to behavioral therapy.

Key Points:

- **First small clinical trial of SAAVE (precursor amino acid loading and enkephalinase inhibition -earliest version of NAAT).**
- **Designed to elevate levels of enkephalin(s), serotonin, catecholamines, and regulate GABA, thought to be deficient in alcoholics.**
- **Compared to controls those who took SAAVE had:**
  - **lower building up to drink score,**
  - **required no PRN benzodiazepines,**
  - **ceased having tremors 24 hrs earlier**
  - **had less depression.**

1988

Enkephalinase inhibition and precursor amino acid loading improves inpatient treatment of alcohol and polydrug abusers: double-blind placebo-controlled study of the nutritional adjunct SAAVE.

Blum K, Trachtenberg MC, Elliott CE, Dingler ML, Sexton RL, Samuels AI, Cataldie L.

Alcohol. 5(6): 481-93.

Abstract

We investigated the effects of the amino acid and vitamin mixture SAAVE in inpatient, chemically-dependent subjects to evaluate the role of neurotransmitters in facilitating recovery and adjustment to a detoxified, sober state. SAAVE is formulated from amino acids that are precursors for

neurotransmitters and neuromodulators thought to be involved in alcohol and drug seeking behavior. In a double-blind, placebo-controlled, randomized study of 62 alcoholics and polydrug abusers, SAAVE patients had a significantly reduced stress response as measured by the skin conductance level (SCL), and significantly improved Physical Scores and BESS Scores (behavioral, emotional, social and spiritual). After detoxification there was a six-fold decrease in AMA rates when comparing SAAVE vs. placebo groups. In this inpatient treatment experience SAAVE facilitated the rate of recovery and allowed patients to respond more fully and more quickly to the behavioral goals of the program, for example as measured by the BESS Score. The use of SAAVE to achieve enkephalinase inhibition and precursor amino acid loading in the acute inpatient treatment environment provides the practitioner with the potential ability to restore the neurochemical changes inherent to alcoholism and drug abuse. These findings increase our understanding of the clinically relevant neurobiological mechanisms which underlie compulsive disease.

Key Points:

- **Double blind placebo controlled clinical trial of SAAVE of 62 people with Substance Use Disorder (SUD).**
- **Results:**
  - reduced stress as measured by skin conductance,
  - improved Physical and BESS (behavioral, emotional, social and spiritual) Scores,
  - six fold decrease in leaving Against Medical Advice (AMA) rates.

1988

Reduction of both drug hunger and withdrawal against advice rate of cocaine abusers in a 30 day inpatient treatment program by the neuronutrient Tropamine.

Blum, K.; Allison, D.; Trachtenberg, M.C.; Williams, R.W. & Loeblich, L.A.

Current Therapeutic Research 43: 1204-1214.

Abstract

Tropamine®, an amino acid and vitamin supplement designed to re- store catecholaminergic, serotonergic, opioidergic, and GABAergic deficits observed in stimulant abusers (primarily cocaine), significantly reduces both the withdrawal against medical advice (AMA) rate and drug hunger of inpatients at a 30-day hospital treatment program when compared with patients receiving either the neuronutrient SAAVE® or with controls who had no supplement added to treatment regimen. The AMA rate for controls was 37.5% (6/16), and that for the SAAVE® group was 28.6% (4/14) yielding no significant differences. In sharp contrast, for the Tropamine® group, the AMA rate was significantly ($P < 0.014$) less than for controls, being only 4.2% (1/24) almost a nine fold improvement. For this study a drug hunger index was devised utilizing various behavioral observations, requests, and/or need for benzodiazepines, threats, or actual leaving AMA. Patients were rated throughout the 30-day program and were found to have significantly

reduced drug hunger with Tropamine® compared with SAAVE® and control groups. These results suggest that Tropamine®, which contains specific neuronutrients, vitamins, and minerals, accelerates recovery during withdrawal of serious cocaine abusers by facilitating retention in a treatment program and by reducing drug hunger.

Key Points:

- **Comparison of the effects of Tropamine [T] – (amino acid and vitamin supplement), SAAVE [S]-(a neuronutrient supplement) and no supplement [C] on a group of cocaine abusers in a 30 day hospital treatment program.**
- **AMA rate: - [C] 37.5%**
  - [S] 26.6%
  - [T] 4.2 %
- **Tropamine decreased the AMA rate by significant reduction of drug hunger.**

1990

Neurodynamics of relapse prevention: a neuronutrient approach to outpatient DUI offenders.

Brown, R.J.; Blum, K. & Trachtenberg, M.C.

Psychoactive Drugs 22: 173-187.

Abstract

The central nervous system rewarding properties of ethanol, cocaine, and heroin may activate a common catecholaminergic reward system in the mesolimbic circuitry of the brain. Driving-under-the-influence (DUI) offenders with either alcohol- or cocaine-related problems were studied. The neuronutrients SAAVE and Tropamine significantly reduced relapse rates and enhanced recovery in these DUI outpatient offenders over a 10-week period. Follow-up on both the SAAVE and Tropamine groups after 10 months revealed a 73% and a 53% overall recovery rate, respectively. These clinical results favor the use of these neuronutrients as adjuncts to psychological therapeutic modalities.

Key Points:

- **Relapse prevention using neuronutrients SAAVE and Tropamine in DUI offenders; either alcohol or cocaine.**
- **Reduced relapse rates and enhanced recovery in 10 week outpatient setting.**
- **After 10 months recovery rate was SAAVE 73% and Tropamine 53%.**
- **These recovery rates are significantly better than the literature**

average for both alcoholism and cocaine dependence.

1990

Neuronutrient effects on weight loss in carbohydrate bingers; an open clinical trial.

Blum K, Trachtenberg MC, Cook DW.

*Curr Ther Res.*48: 217-233.

Abstract

In as much as neurotransmitters and neuromodulators are known to stimulate or inhibit eating behavior, we elected to examine the effects of precursor amino acid loading and enkephalinase inhibition on compulsive eating and weight loss in a controlled-diet clinical setting. In the present 90 day open trial, we investigated the effect of the experimental neuronutrient PCAL-103 on weight loss, uncontrollable carbohydrate binging, and relapse rates in 27 outpatients attending a supervised diet-controlled treatment program. The patients were assigned, retrospectively, to two matched treatment groups: those receiving the neuronutrient (experimental group [E]; n = 16) and those not receiving the neuronutrient (control group [C]; n = 11). E patients exhibited facilitated withdrawal from carbohydrates compared with the C patients. The E group lost an average of 26.96 ± 2.7 pounds; the C group only 10.0 ± 2.1 pounds. Only 18.2% of the E group relapsed in contrast to 81.8% of the C group. Use of the amino acid supplement PCAL-103 by chronic carbohydrate bingers allowed overweight individuals to lose 2.7 times as much weight as patients without benefit of this product.

Key Points:

- **Examine the effects of PCAL-103 (NAAT) on compulsive eating and weight loss in 27 outpatients attending a supervised diet-controlled treatment program.**
- **The PCAL-103 average weight loss was 26.96 lbs vs 10.2 lbs in the control group.**
- **Relapse 18.2% in the PCAL-103 group vs 81.8% in the control group.**

1996

NeuRecover-SATM in the Treatment of Cocaine Withdrawal and Craving: A Pilot Study

Cold, Julie A.

Clinical Drug Investigation. 12(1):1-7,

Chronological Summary of Studies of KB220(Z) Neuroadaptogen

Abstract

Summary: The efficacy of NeuRecover-SATM (formerly called Tropamine+™, and TropaGen™) in the treatment of cocaine withdrawal and craving was evaluated at a state psychiatric hospital. This double-blind, placebo-controlled study was conducted in hospitalized patients with a DSM-III-R diagnosis of cocaine dependence. Eight patients received NeuRecover-SATM and 4 patients received placebo. No significant difference in patient demographics was found. The mean number of abstinent symptoms (+/- SEM) declined over the first 4 days of treatment, 10.63 +/- 1.32 on day 1 vs 4 +/- 1.65 on day 4 in the NeuRecover-SATM group compared with 7.25 +/- 2.93 on day 1 vs 4.25 +/- 3.61 on day 4 in the placebo group. Cocaine craving in the NeuRecover-SATM group on day 1 was 7.88 +/- 1.22 vs 2.71 +/- 1.22 on day 4 and 5 +/- 2.89 on day 1 vs 2 +/- 1.68 on day 4 in the placebo group. A Mann-Whitney U test showed no statistically significant differences in abstinent symptomatology between or within treatment groups, or treatment effect in the placebo group. However, a significant decrease ($p < 0.05$) in cocaine craving occurred in the NeuRecover-SATM group.

In conclusion, these preliminary results suggest that NeuRecover-SATM reduces cocaine craving, and larger, longer term studies are warranted.

Key Points:

- **Small preliminary double-blind, placebo-controlled study of efficacy of NeuRecover-SATM (formerly Tropamine+™) in the treatment of cocaine withdrawal and craving.**
- **Cocaine craving decreased significantly in the NeuRecover-SATM group compared to placebo.**

1997

Enhancement of attention processing by Kantroll in healthy humans: a pilot study.

DeFrance, J.F.; Hymel, C.; Trachtenberg, M.C.; Ginsberg, L.D.; Schweitzer, F.C.; Estes, S.; Chen, T.J.; Braverman, E.R.; Cull, J.G. & Blum, K.

Clinical Electroencephalography 28: 68-75.

Abstract

This is the first report in humans of the effects of daily ingestion of a specific amino acid mixture, Kantroll, on cognitive event-related potentials (ERPs) associated with performance. Cognitive ERPs were generated by two computerized visual attention tasks, the Spatial Orientation Task (SOT) and Contingent Continuous Performance Task (CCPT), in normal young adult volunteers, where each subject acted as his own control for testing before and after 28-30 days of amino acid ingestion. A statistically significant amplitude enhancement of the P300 component of the ERPs was seen after Kantroll for both tasks, as well as improvement with respect to cognitive processing speeds. The enhancement of neurophysiologic function observed in this study

on normal controls is consistent with the facilitation of recovery of individuals with RDS (i.e., substance use disorder, ADHD, carbohydrate bingeing) following the ingestion of the amino acid supplement, Kantroll, and warrants additional placebo-controlled, double-blind, studies to confirm and extend these results.

Key Points:

- **Cognitive processing speeds in normal young adult volunteers were measured before and after 28-30 days of supplementation with a combination of amino acids-enkephalinase inhibition (NAAT), vitamins and minerals.**
- **Cognitive processing speeds were enhanced by a statistically significant amplitude of the P300 component of the Event Related Potentials (ERPs). FOCUS IMPROVED**
- **These findings have relevance to relapse prevention because the resultant enhanced effect following NAAT as measured by the Contingent Continuous Performance Task (CCPT); Spatial Orientation Task (SOT) and focus reflects better judgment and thus decision making.**

1997

Clinical evidence for effectiveness of Phencal™ in maintaining weight loss in an open-label, controlled, 2-year study.

Blum K, Cull JG, Chen TJH, Swan SG, Holder JM, Wood R, Braverman ER, Bucci LR, Trachenberg MG.

Current Therapeutic Research 55(10) 745-763.

Abstract

Over a 2-year period we carried out a prospective analysis of 247 outpatients in a very-low-calorie fasting program. Subjects having difficulty attaining their desired weight or maintaining their desired weight constituted the experimental group. At 2 years, the experimental group that took the amino acid regimen of PhenCal™ compared with the non-PhenCal/Centrum™ vitamin control group showed a twofold decrease in percent overweight for both males and females; a 70% decrease in food cravings for females and 63% decrease for males; and a 66% decrease in binge eating for females and 41% decrease for males. Most importantly, the experimental group (PhenCal group) regained only 14.7% of the weight the lost during fasting while the control group (non-PhenCal group) regained 41.7% 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 significantly, with improved results with PhenCal. These data suggest that PhenCal may be an anti-obesity adjunct.

Key Points:

Chronological Summary of Studies of KB220(Z) Neuroadaptogen

- **In a two –year study, of 247 Outpatients in a very-low-calorie fasting program 130 who were having difficulty attaining their desired weight or maintaining their desired weight constituted the experimental group who took PhenCal™ plus Centrum Vitamins and the rest 117 took only vitamins (Centrum) 117 were the control group.**
- **The PhenCal™ group compared to the control:**
  - **lost twice as much weight,**
  - **regained 14.7% of the weight while the control group regained 41.7%,**
  - **decrease in food cravings (sugar) for females 70% and males 63%,**
  - **decrease in binge eating for females 66% and males 41%.**

2001

1st Conference on Reward Deficiency Syndrome: Genetic Antecedents and Clinical Pathways. San Francisco, California, USA. November 12-13, 2000. Abstracts. Amino-acid precursor and enkephalinase inhibition therapy: evidence for effectiveness in treatment of "Reward Deficiency Syndrome (RDS) with particular emphasis on eating disorders.

Julia Ross**.**

Mol Psychiatry. Feb; 6(1 Suppl 1):S1-8.

Abstract

Earlier work discovered that neurotransmitter restoration via synthesis occurs by oral feeding of certain precursor amino acids to both animals and humans. These amino acid include but are not limited to L-tryptophane, L-5-hydroxytryptophane (serotonin restoration), d-phenylalanine (enkephalin restoration), L-phenylalanine and L-tyrosine (dopamine restoration), L-glutamine (GABA restoration). Moreover, work from the laboratory of Blum and associates found evidence for the use of D- phenylalanine in significantly reducing alcohol preference in enkephalin deficient alcohol preferring C57bl mice. Following this work, numerous studies in both animals and humans confirmed the anti-craving properties of not only d-phenylalanine but a combination of the aforementioned amino acids in a number of "reward" behaviors such as alcohol abuse, opiate dependence, cocaine addiction, polysubstance abusers and carbohydrate bingeing among others (Blum; Mathews-Larsen; and Tennant). In a one year follow-up study on DWI offenders, a similar combination caused a prevention of relapse in both alcoholics and cocaine abusers (Brown et al. 1990). Moreover, in a two year study of obese subjects, similar neuro-nutrients reduced weight regain, decreased bingeing behavior and eliminated sugar cravings (Blum et al.1997). At Recovery Systems, we have successfully utilized this approach to treat a number of RDS behaviors, especially eating disorders. In a preliminary evaluation, follow-up interviews of six randomly selected former eating disordered female clients (three were also chemically dependent), were contacted 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 evaluated an additional 100 patients and the data collected revealed 98% significant improvement in both mood and reduced substance craving. This work further suggests the positive potential of adding targeted nutritional protocols to conventional treatment elements to improve outcome in an RDS intransigent population. Reference: Julia Ross, The Diet Cure (Viking Press, USA 1999; Penguin UK, AU, and USA, 2000).

Key Points:

- **Preliminary evaluation of six randomly selected former eating disordered female clients (three were also chemically dependent), contacted at 9 months and 3 years of treatment with amino-acid precursor and enkephalinase inhibition therapy.**
- **All 6 reported initial benefit, one relapsed at 6 months the other 5 all sustained, and in some cases exceeded expectations.**
- **98% of 100 patients similarly treated and evaluated reported significant improvement in both mood and reduced substance craving.**

2004

Narcotic antagonists in drug dependence: pilot study showing enhancement of compliance with SYN-10, amino-acid precursors and enkephalinase inhibition therapy.

Chen, T.J.; Blum, K.; Payte, J.T.; Schoolfield, J.; Hopper, D.; Stanford, M. & Braverman, E.R.

Medical Hypotheses 63 (3): 538-48.

Abstract

We decided to test the hypothesis that possibly by combining 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 (Dupont, Delaware). In this regard, Thanos et al. [J. Neurochem. 78 (2001) 1094] 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. 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 [JAMA 263 (1990) 2055; Arch, Gen. Psychiatr. 48 (1991) 648].

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. [Mol. Phychiatr. 3 (1997) 251] showed that the 7 repeat allele of the DRD4 receptor is significantly over represented in the opioid-dependent cohort and confers a relative risk of 2.46. This has been confirmed by Li et al. [Mol. Psychiatry 2 (1997) 413] for both the 5 and 7 repeat alleles in Han Chinese case control sample of heroin addicts. Similarly Duaux et al. [Mol. Psychiatry 3 (1998) 333] in French Heroin addicts, found a significant association with homozygotes alleles of the DRD3-Bal 1. A study from NIAAA provided evidence which strongly suggests that DRD2 is a susceptibility gene for substance abusers across multiple populations (2003). 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 (see Table 1). Over the last decade, a new rapid method to detoxify either methadone or heroin addicts utilizing Trexan 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 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 1000 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 ($p < 0.0001F$). 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 to further test this hypothesis with the sublingual combination of the partial opiate mu receptor agonist buprenorphine.

Key Points:

- **A combination of Trexan (a narcotic antagonist) and amino-acids was use to detoxify either methadone or heroin addicts.**
- **Results were dramatic in terms of significantly enhancing compliance to continued taking of Trexan:**
  -Trexan alone for rapid detoxification the average number of days of compliance calculated on 1000 patients is 37 days.
  -12 subjects tested, receiving both the Trexan and amino-acid therapy continued to take the combination for an average of 262 days.
- **Suggests:**
  -coupling amino-acid therapy and enkephalinase inhibition, while blocking the delta-receptors with a pure narcotic antagonist as a novel method to induce rapid detox in chronic methadone patients and prevent relapse.
  - testing this hypothesis with the sublingual combination

of the partial opiate mu receptor agonist buprenorphine.

2006

Reward deficiency syndrome in obesity: a preliminary cross-sectional trial with a Genotrim variant.

Blum K, Chen TJ, Meshkin B, Downs BW, Gordon CA, Blum S, Mengucci JF, Braverman ER, Arcuri V, Varshavskiy M, Deutsch R, Martinez-Pons M.

Adv Ther. 2006 Nov-Dec;23(6):1040-51.

Abstract

Obesity is the second largest preventable cause of death in the United States. Even though it was classified as a disease in 1985, traditionally, obesity has been treated primarily as a behavioral problem that requires only modifications in diet and exercise. Similar to research on obesity, clinical studies have elucidated the role of biologic and genetic factors in alcoholism and other conditions previously classified as behavioral. These studies showed that behavioral adjustments alone may not address underlying genetic causes. We hypothesize that biologic and genetic factors must be addressed synergistically while behavioral modifications are implemented to adequately treat obese patients. We hypothesize that a predisposition to glucose craving and obesity is due to inadequate dopaminergic activity in the reward center of the brain. This defect drives individuals to engage in activities of behavioral excess, which, in turn, enhance brain dopamine function. Consumption of large quantities of alcohol or carbohydrates (carbohydrate bingeing) stimulates production and usage of dopamine within the brain; the term reward deficiency syndrome (RDS) may be used to categorize such biologic influences on behavior. We propose that a novel approach to nutritional supplementation may be required to target the role of RDS in obesity. In this regard, GenoTrim, a DNA-customized nutritional solution, has been developed and is currently under investigation in several clinical studies. Through its mechanism of action, GenoTrim addresses the genetic influence of RDS on obesity. In this cross-sectional study, 24 subjects were studied after they had completed a case report format questionnaire. For this assessment, we used a novel assessment tool-a path analysis. This statistical regression model is used to (1) examine the effectual relationships between various systems within a multisystem matrix, and (2) measure the contributory roles of those relationships in obesity, enabling the development of targeted and effective therapeutic interventions.

Key Points:

- **Consumption of large quantities of alcohol or carbohydrates (carbohydrate bingeing) stimulates production and usage of dopamine within the brain.**
- **Obesity is due to the need to make up for inadequate dopaminergic activity in the reward center of the brain.**
- **This has been called reward deficiency syndrome (RDS) used to**

categorize such genetic biologic influences on behavior.

- **RDS must be addressed at the same time as behavioral modifications are implemented to adequately treat obese patients.**
- **In this small observational trial; 24 individuals completed a survey on which they documented 15 categories of benefit during their experience with a GenoTrim a NAAT formulation customized to DNA.**
- **Statistical analysis of the survey results demonstrated that stress reduction lead to:**
  -(1) improved sleep, enhanced energy, and improved focus and performance;
  -(2) reduced appetite, loss of unwanted weight, decreased body inches, and enhanced well-being.

2007

Gene \Narcotic Attenuation Program attenuates substance use disorder, a clinical subtype of reward deficiency syndrome.

Chen, T.J.; Blum, K.; Waite, R.L.; Meshkin, B.; Schoolfield, J.; Downs, B.W.; Braverman, E.E.; Arcuri, V.; Varshavskiy, M,; Blum, S.H.; Mengucci, J.; Reuben, C. & Palomo, T.

Advances in Therapy 24: 402-414.

Abstract

This study evaluated the effects of a putative activator of brain reward circuitry on outcomes in a 1-y prospective comprehensive outpatient clinical program. As part of the Gene Narcotic Attenuation Program, Haveos (Synaptamine™) was administered for the treatment of substance use disorder. Seventy-six patients (45 males and 31 females; mean age, 33 y [standard deviation, 7.0]) who had been given a diagnosis of serious substance use disorder were recruited. After exclusion of 15 patients who dropped out before the end of the study, self-reported craving decreased from program entrance to 12 wk (visual analog scale whereby 0 represents no craving and 5, the strongest craving) for 61 compliant patients (mean decrease, 2.85, 95% confidence interval [CI], 2.65, 3.05); this improvement was significant (P<.001). Building up to relapse scores (each of 5 individual items and summary value) showed similar improvement after 1 y of treatment; the mean decrease in scores was significant for stress (t=3.3; P=.002), depression (t=4.0; P<.001), anger (t=4.4; P<.001), anxiety (t=4.5, P<.001), drug craving (t=5.4, P<.001), and summary building up to relapse (t=4.1; P<.001). Also, recovery score measures of energy level (t=8.4; P<.001) and ability to refrain from drug-seeking behavior (t=7.4; P<.001) showed significant mean increases from entry to 1 y. During the study, the alcoholic dropout rate was only 7% (4 of 57), which was significantly (Fisher's exact test, P<.001) lower than the 73% (11 of 15) dropout rate reported for psychostimulant users. Although these results are significant, any interpretation must await the performance of rigorous double-blind studies.

Chronological Summary of Studies of KB220(Z) Neuroadaptogen

Key Points:

- **1-year prospective study that evaluated the effects of taking Haveos (Synaptamine ™) on 61 compliant patients in a comprehensive outpatient clinical program.**
- **Results after 12 weeks:**
  - **Significant decrease in craving**
- **Results after 1 year:**
  - **Building up to relapse scores and ability to refrain from drug-seeking behavior both significantly improved.**
  - **Dropout rate: Alcohol users 7%**
    Psychostimulant users 73%

2007

Synaptamine (SG8839),TM An Amino-Acid Enkephalinase Inhibition Nutraceutical Improves Recovery of Alcoholics, A Subtype of Reward Deficiency Syndrome (RDS).

Blum, K.; Chen, T.J.H.; Downs, B.W.; Meshkin, B.; Blum, S.H.; Martinez Pons, M.; Mengucci, J.F.; Waite, R.L.; Arcuri, V.; Varshofsiky, M. & Braverman, E.R.

Trends in Applied Sciences Research 2 (3): 132-138.

Abstract

The present research was conducted to test the hypothesis that manipulation of the reward neural circuitry by utilization of oral and intravenous amino-acid–enkephalinase therapy would improve both the emotional and behavioral symptom logy of recovering 600 alcoholics in an open trial clinical study. Our findings suggest that the combination of both oral and intravenous administration of SG8839 significantly improved both the emotional and behavioral recovery of the alcoholic subjects when compared to pre and post administration scores, including reduction of craving ($p<0.001$), reduced depression ($p<0.001$), reduced anxiety ($p<0.001$), anger ($p<0.001$), fatigue ($p<0.001$), lack of energy ($p<0.001$) and crisis ($p<0.001$). Mean reductions for anxiety (53.8±10.2%), craving (76.3±3.1%), depression (61.0±6.3%), fatigue (76.9±3.1%) and crisis (53.8±5.5%) were all significantly greater than 50% ($p<0.001$). This is the first study combining both oral and intravenous solutions suggesting clinical improvement.

Key Points:

- **In an open clinical study Intravenous plus oral Amino-Acid Enkephalinase Inhibition Nutraceutical improved symptomatology of 600 recovering Alcoholics.**
- **Emotional and behavioral recovery scores significantly improved after administration of oral and intravenous Synaptamine.**
- **Mean reductions for craving, depression, anxiety, anger, fatigue, lack of energy and crisis were all significantly greater**

than 50% (p<0.001).

2007

Chromium Picolinate (Crp) A putative Anti-Obesity Nutrient Induces Changes In Body Composition As Function Of The Taq1 Dopamine D2 Receptor Gene.

Chen TJH , Blum K, Kaats G, Braverman ER, Eisenberg A, Arcuri V, Varshavsky M, Mengucci JF, Blum AH, Downs BW, Meshkin B, Williams L, Schoolfield J, Whitel L.

Gene Ther Mol Biol 11; 161-170.

Abstract

There is controversy regarding the effects and safety of chromium salts (picolinate and nicotinate) on body composition and weight loss in humans. Thus, we decided to test the hypothesis that typing the obese patients by genotyping the dopamine D2 receptor (DRD2) gene prior to treatment with Chromium Picolinate (CrP) would result in a differential treatment outcome. We genotyped obese subjects for the DRD2 gene utilizing standard PCR techniques. The subjects were assessed for scale weight and for percent body fat using dual energy X-ray absorptiometry (DEXAR). The subjects were divided into matched placebo and CrP groups (400 mg. per day) accordingly. The sample was separated into two independent groups. Those with either an A1/A1 or A1/A2 allele or those with only the A2/A2 allelic pattern. Each of these groups were tested separately for differences between placebo and treatment means for a variety of measures of weight change. The measures of the change in fat weight ($p<0.041$), change in body weight ($p<0.017$), the percent change in weight ($p<0.044$), and the body weight change in kilograms ($p<0.012$) were all significant for carriers of the DRD2 A2 genotype, whereas no significance was found for any parameter for those subjects possessing a DRD2 A1 allele. These results suggest that the dopaminergic system, specifically the density of the D2 receptors, confers a significant differential therapeutic effect of CrP in terms of weight loss and change in body fat, thereby strengthening the need for DNA testing.

Key Points:

- **Chromium Picolinate (CrP) was tested against placebo in groups of obese patients tested for the Taq1 Dopamine D2 Receptor Gene.**
- **In carriers of the DRD2 A2 genotype weight loss and other changes in body composition were significant.**
- **They were not significant for patients with the A1/A1 or A1/A2 allele.**
- **These results suggest that the dopaminergic system, specifically the density of the D2 receptors, confers a significant differential therapeutic effect of CrP in terms of weight loss and**

change in body fat.

- **It is speculated that carriers of the DRD2 A1 allele had aberrant sugar cravings which masked the effects of CRP.**

2007

A short term pilot open label study to evaluate efficacy and safety of LG839, a customized DNA directed nutraceutical in obesity: Exploring Nutrigenomics.

Blum K, Chen TJH, Williams L, Chen ALC, Downs WB, Waite RL, Huntington T, Sim S, Prihoda T, Rhoads P, Reinking J, Braverman D, Kerner M, Blum SH, Quirk B, Eric R Braverman ER.

Gene Therapy and Molecular Biology Vol 12, page 371-382.

Abstract

Activated Receptor gamma (PPAR-γ), and Leptin (OB) genes. In the present study, we systematically evaluated the impact of polymorphisms of these five candidate genes as important targets for the development of a DNA-customized nutraceutical LG839 [dl-phenylalanine, chromium, l-tyrosine other select amino-acids and adaptogens]) to combat obesity with special emphasis on body recomposition as measured by Body Mass Index (BMI). A total of 21 individuals were evaluated in a preliminary investigational study of LG839. Based on the results of buccal swab genotyping of each subject, an individualized customized nutraceutical formula was provided as a function of measured gene polymorphisms of the five gene candidates assessed. At the inception of the study and every two weeks subsequently, each subject completed a modified Blum-Downs OPAQuE Scale™ [Overweight Patient Assessment Questionnaire]. The alleles included the DRD2 A1; MTHFR C 677T; 5HT2a1438G/A; PPAR-γPro12A1a and Leptin Ob1875<208bp. Pre- and post ad hoc analysis revealed a significant difference between the starting BMI and the BMI following an average of 41 days (28-70d) of LG839 intake in the 21 individuals. The pre- BMI was 31.2 (weight/Ht2) compared to the post BMI of 30.4 (weight/Ht2) with a significance value of $P < 0.034$ (one tailed). Similarly the pre -weight in pounds (lb) was 183.52 compared to the post weight of 179 lb with a significance value of $P<(0.047)$. We also found trends for reduction of late night snacking, carbohydrate craving reduction, reduction of stress, reduction of waist circumference. Moreover, in the 41 day period we found a trend in weight loss whereby 71.4% of subjects lost weight. Thus 15 out of 21 subjects lost weight with a z score of 2.4 and significance value of $P <(0.02)$. In this group 53% lost on average over 2.5% of their starting weight. Further confirmation of these preliminary results (ongoing) warrants investigation and should ultimately provide novel DNA directed "omic" therapeutic targets of novel anti-obesity agents especially in diabetes and other related diseases.

Key Points:

- **Preliminary investigational study to evaluate the impact of polymorphisms of five candidate genes on treatment for obesity with NAAT.**
- **The formula for each patient was customized based on their**

genetic results.

- **Pre- NAAT compared to Post-NAAT had significantly lower BMI.**
- **Pre- NAAT compared to Post-NAAT had significantly lower pounds.**
- **Pre- NAAT compared to Post-NAAT had trends for reduced late night snacking, carbohydrate craving reduction, reduction of stress, reduction of waist circumference.**

2008

LG839: anti-obesity effects and polymorphic gene correlates of reward deficiency syndrome.

Blum, K.; Chen, A.L.; Chen, T.J.; Rhoades, P.; Prihoda, T.J.; Downs, B.W.; Waite, R.L.; Williams, L.; Braverman, E.R.; Braverman, D.; Arcuri, V.; Kerner, M.; Blum, S.H. & Palomo, T.

Advances in Therapy 25 (9): 894-913.

Abstract

Introduction: This study systematically assessed the weight management effects of a novel experimental DNA-customized nutraceutical, LG839 (LifeGen, Inc., La Jolla, CA, USA).

METHODS: A total of 1058 subjects who participated in the overall D.I.E.T. study were genotyped and administered an LG839 variant based on polymorphic outcomes. A subset of 27 self-identified obese subjects of Dutch descent, having the same DNA pattern of four out of the five candidate genes tested (chi-square analysis) as the entire data set, was subsequently evaluated. Simple t tests comparing a number of weight management parameters before and after 80 days of treatment with LG839 were performed.

Results: Significant results were observed for weight loss, sugar craving reduction, appetite suppression, snack reduction, reduction of late night eating (all $P<0.01$), increased perception of overeating, enhanced quality of sleep, increased happiness (all $P<0.05$), and increased energy ($P<0.001$). Polymorphic correlates were obtained for a number of genes (LEP, PPAR-gamma2, MTHFR, 5-HT2A, and DRD2 genes) with positive clinical parameters tested in this study. Of all the outcomes and gene polymorphisms, only the DRD2 gene polymorphism (A1 allele) had a significant Pearson correlation with days on treatment ($r=0.42$, $P=0.045$).

Conclusion: If these results are confirmed in additional rigorous, controlled studies, we carefully suggest that DNA-directed targeting of certain regulator genes, along with customized nutraceutical intervention, provides a unique framework and strategic modality to combat obesity.

Key Points:

- **First DNA Customized analysis of LG839 for weight management effects.**
- **Out of 1058 Dutch participants a subset of 27 self –reported**

obese subjects were genotyped and based on their polymorphisms each subject utilized a customized LG839 variant assessed for pre –and post for after 80 days of usage.

- **Significant results were observed for weight loss, sugar craving reduction, appetite suppression, snack reduction, reduction of late night eating (all P<0.01), increased perception of overeating, enhanced quality of sleep, increased happiness (all P<0.05), and increased energy (P<0.001).**
- **The study points to the importance of genotyping patients and providing DNA customized nutraceutical intervention to combat obesity.**

2008

Dopamine D2 Receptor Taq A1 allele predicts treatment compliance of LG839 in a subset analysis of pilot study in the Netherlands.

Blum K, Chen, TJH, Chen ALC, Rhodes P, Prihoda TJ, Downs BW, Bachi D, Bachi M, Blum SH, Williams L, Braverman ER, Kerner M, Waite RL, Quirk B, White L & Reinking J.

Gene Therapy Molecular Biology 12, 129-140.

Abstract

Various types of individuals having "Reward Deficiency Syndrome (RDS)" related behaviors including sugar craving (*e.g.* obesity) have been described and heredity has been shown to be involved in some of these types. An important role of the mesolimbic dopamine system has been suggested in the reinforcing effects of a number of addictive substances (*i.e.* alcohol, nicotine, sugar etc.) and recent molecular genetic studies are implicating the gene for the dopamine receptor (DRD2) as well as other genes in RDS and in particular obesity. We genotyped 1,058 Dutch subjects for polymorphisms of four candidate genes (PPAR gamma 2, MTHFR, 5-HT2a, and DRD2) receiving the experimental DNA- customized nutraceutical LG839. In a subset of 27 subjects having a similar genotype pattern of the entire sample, and of all the outcomes and gene polymorphisms, only the DRD2 gene polymorphisms (A1 allele vs. A2 allele) had a significant Pearson correlations with days on treatment (r=0.42, p=).045). Compared to the DRD2 $A1^-$ carriers the number of days in treatment with LG839 was 51.9±9.9 SE (95% CI, 30.8 to73.0) and for the DRD2 A^+ carriers the number of days on treatment with LG839 was 110.6±31.1 (95% CI, 38.9 to 182.3). Thus the attrition was highest in the $A1^-$ genotype group. Thus, the genotype may be a predictor of treatment persistency and compliance. The feasibility of a pharmacogenetic approach in treating certain types of obesity related behaviors is cautiously suggested and warrants rigorous larger studies for confirmation.

Key Points:

- **This study evaluated the importance of carrying the dopamine D2 receptor A1 allele and treatment compliance in an Obese**

Dutch population nutraceutical intervention to combat obesity.

- **Candidate genes to be associated with obesity include amongst others the dopamine D2 receptor (DRD2), methylenetetrahydrofolate reductase (MTHFR), serotonin receptor (5-HT2a), Peroxisome Proliferator Activated Receptor gamma (PPAR-γ), and Leptin (OB) genes.**
- **Compliance 2 fold better in carriers of DRD2 A1 allele compared to DRD2 A2 allele.**

2009

Putative targeting of Dopamine D2 receptor function in Reward Deficiency Syndrome (RDS) by Synaptamine Complex™ Variant (KB220): Clinical trial showing anti-anxiety effects.

Blum K, Chen ALC, Chen TJH, Bowirrat A, Waite RL, Kerner M, Blum SH, Downs BW, Savarimuthu S, Rhoades P, Reinking J, Braverman ER, DiNubile N, Braverman D, Oscar-Berman M.

Gene Therapy Molecular Biology 13, 214-230.

Abstract

Since 1990, researchers have proposed that genetic variants of dopaminergic genes and other "reward genes" are important common determinants of Reward Deficiency Syndrome (RDS). RDS refers to the breakdown of a cascade of neurotransmitters in the brain in which one reaction triggers another — the reward cascade — and resultant aberrant conduct. Association studies have amassed strong evidence implicating the D (2) dopamine receptor (DRD2) gene in harmful conditions such as alcoholism, and the DRD2 gene also has been found to be involved in other substance use disorders including cocaine, nicotine, and opioid dependence, as well as obesity. Brain dopamine has been implicated as the so-called "anti-stress molecule." The present study investigated anti-anxiety effects of Synaptamine Complex [KB220], a dopaminergic activator, in a randomized double-blind placebo controlled study in alcoholics and in polydrug abusers attending an in-patient chemical dependency program. In this randomized double-blind placebo controlled study of 62 alcoholic and polydrug abusers, we utilized skin conductance level (SCL) to evaluate stress responses. Patients receiving Synaptamine Complex [KB220] had a significantly reduced stress response as measured by SCL, compared to patients receiving placebo. Two factor ANOVA yielded significant differences as a function of Time ($p<0.001$), and Treatment ($p<0.025$) as well as a Time–by-Treatment interaction ($p< 0.01$). The results of this study suggest that the Synaptamine Complex™ [KB220] may improve treatment response in an in-patient treatment setting by reducing stress related behaviors and warrants further investigation.

Key Points:

- **Double-blind-placebo controlled study to determine anti-anxiety effects of KB220 (Synaptamine Variant) in 62 alcoholic and poly-drug abusers**
- **This was an objective test not subjective because antianxiety**

effect evaluated by skin conductance level (SCL).

- **Significant reduction of stress in the KB220 group compared to placebo including a Time by-treatment interaction. Positive anti-anxiety effect as monitored throughout a 28 day treatment period is most significant at the 7th day (a time with the most severe anxiety).**
- **These findings may be relevant to prevention of relapse.**

2010

Sustainable Weight Loss and Muscle Gain Utilizing the Rainbow Diet™: Targeting Noradrenergic and dopaminergic Mechanistic Sites, Hormonal Deficiency Repletion Therapy and Exercise: A case report.

Braverman ER, Braverman D, Acrui V, Kerner M, Downs B.W., Blum K.

The American Journal of Bariatric Medicine. 25 (2)18-28, 2010.

Abstract

Background: There is an ongoing obesity epidemic, and for many, weight loss and sustained weight mainte-nance is difficult. We have proposed that, in order to effectively treat obesity, a multifaceted approach must be utilized.

Case Presentation: In this regard we report on the potential of attaining sustainable weight loss over a 12-month period in a male subject following a protocol that included: administration of anti-carbohydrate craving agents, Diethypropion (Tenuate®), and Synaptamine Complex (KB22Q)fM; hormonal repletion therapy; use of the Rainbow Diet® and light exercise. After one year, the 58 year old patient's BMT decreased from 32 to 25.4kg/m2 representing a 6.9kg/m2 reduction. His body fat composition decreased from 36.91% to 17.8% as measured by the Hologic DEXA scanner. EKG remained unchanged. Echocardiography demonstrated unimproved diastolic dysfunction and less impaired cardiac relaxation with an ejection fraction of 55%. Fasting glucose levels declined with resultant improvement in Glycated hemoglobin (HbA1c). Prostate Specific Antigen (PSA) levels tripled to 3.54 from 1.25 ng/mL. Memory functions (as measured via Wechsler Memory Scale) also showed improvement.

Mood and temperament similarly demonstrated improvement as shown by a decrease in subjective reporting of anxiety/depression. Low-density lipoprotein (LDL) remained constant. Testosterone levels increased to 1043 ng/dL despite intervention (normal is 560 ng/dL, but patient refused to adjust dose of testosterone). Insulin-like growth factor-1 (IGF-1) levels were maintained to average of 200 ng/ml. Patient self-reported gain in tolerating low- impact exercise.

Conclusion: While others have shown sustainable weight loss utilizing both pharmacological and nutraceutical therapies enhanced by DNA analysis, we have now shown the potential for improving obesity treatment, at least in males, by utilizing a multifaceted approach that includes evaluating hormonal deficiencies and providing repletion therapy. These results should be

cautiously interpreted and must be confirmed by systematic stringent trials. Weight loss with repair hormones may prevent the usual muscle atrophy associated with dieting.

Key Points:

- **Case study of 58 Y old male identified as being obese utilized a special Rainbow Diet.**
- **Patient received Noradrenergic drug; NAAT (a natural D2 agonist); hormonal deficiency replacement therapy and light exercise.**
- **After one year BMI decreased; Percent body fat decreased; improved cardiac function; fasting glucose level declined; Prostate Specific Antigen (PSA) tripled; memory improved; testosterone levels increased.**
- **There was sustainable weight loss and muscle gain.**

2010

Acute intravenous synaptamine complex variant KB220™ "normalizes" neurological dysregulation in patients during protracted abstinence from alcohol and opiates as observed using quantitative electroencephalographic and genetic analysis for reward polymorphisms: part 1, pilot study with 2 case reports.

Miller DK, Bowirrat A, Manka M, Miller M, Stokes S, Manka D, Allen C, Gant C, Downs BW, Smolen A, Stevens E, Yeldandi S, Blum K.

Postgrad Med. Nov; 122(6):188-213.

Abstract

It is well established that in both food- and drug-addicted individuals, there is dopamine resistance due to an association with the DRD2 gene A1 allele. Evidence is emerging whereby the potential of utilizing a natural, nonaddicting, safe, putative D2 agonist may find its place in recovery from reward deficiency syndrome (RDS) in patients addicted to psychoactive chemicals. Utilizing quantitative electroencephalography (qEEG) as an imaging tool, we show the impact of Synaptamine Complex Variant KB220™ as a putative activator of the mesolimbic system. We demonstrate for the first time that its intravenous administration reduces or "normalizes" aberrant electrophysiological parameters of the reward circuitry site. For this pilot study, we report that the qEEGs of an alcoholic and a heroin abuser with existing abnormalities (i.e., widespread theta and widespread alpha activity, respectively) during protracted abstinence are significantly normalized by the administration of 1 intravenous dose of Synaptamine Complex Variant KB220™. Both patients were genotyped for a number of neurotransmitter reward genes to determine to what extent they carry putative dopaminergic risk alleles that may predispose them for alcohol or heroin dependence, respectively. The genes tested included the dopamine transporter (DAT1, locus

symbol SLC6A3), dopamine D4 receptor exon 3 VNTR (DRD4), DRD2 TaqIA (rs1800497), COMT val158 met SNP (rs4680), monoamine oxidase A upstream VNTR (MAOA-uVNTR), and serotonin transporter-linked polymorphic region (5HTTLPR, locus symbol SLC6A4). We emphasize that these are case studies, and it would be unlikely for all individuals to carry all putative risk alleles. Based on previous research and our qEEG studies (parts 1 and 2 of this study), we cautiously suggest that long-term activation of dopaminergic receptors (i.e., DRD2 receptors) will result in their proliferation and lead to enhanced "dopamine sensitivity" and an increased sense of happiness, particularly in carriers of the DRD2 A1 allele. This is supported by a clinical trial on Synaptamine Complex Variant KB220™ using intravenous administration in > 600 alcoholic patients, resulting in significant reductions in RDS behaviors. It is also confirmed by the expanded oral study on Synaptose Complex KB220Z™, published as part 2 of this study. Future studies must await both functional magnetic resonance imaging and positron emission tomography scanning to determine the acute and chronic effects of oral KB220™ on numbers of D2 receptors and direct interaction at the nucleus accumbens. Confirmation of these results in large, population-based, case-controlled experiments is necessary. These studies would provide important information that could ultimately lead to significant improvement in recovery for those with RDS and dopamine deficiency as a result of a multiple neurotransmitter signal transduction breakdown in the brain reward cascade.

Key Points:

- **Pilot study: Combination of both IV –NAAT and oral forms**
- **Two case reports of an alcoholic and heroin addict**
- **Both patients were genotyped for a number of neurotransmitter reward genes to determine to what extent they carry putative dopaminergic risk alleles that may predispose them for alcohol or heroin dependence, respectively.**
- **The genes tested included the dopamine transporter (DAT1, locus symbol SLC6A3), dopamine D4 receptor exon 3 VNTR (DRD4), DRD2 TaqIA (rs1800497), COMT val158 met SNP (rs4680), monoamine oxidase A upstream VNTR (MAOA-uVNTR), and serotonin transporter-linked polymorphic region (5HTTLPR, locus symbol SLC6A4).**
- **Both patients showed prevalence of at least one risk allele.**
- **qEEG analysis revealed dys-regulation in the PFC-Cingulate Gyrus in both addicts.**
- **IV-NAAT and oral produced a regulation of widespread theta activity**
- **These results have relevance for relapse prevention because of its effect on the part of brain involved in relapse (PFC-Cingulate Gyrus).**

Chronological Summary of Studies of KB220(Z) Neuroadaptogen

2010

Overcoming qEEG abnormalities and reward gene deficits during protracted abstinence in male psychostimulant and polydrug abusers utilizing putative dopamine D_2 agonist therapy: part 2.

Blum K, Chen TJ, Morse S, Giordano J, Chen AL, Thompson J, Allen C, Smolen A, Lubar J, Stice E, Downs BW, Waite RL, Madigan MA, Kerner M, Fornari F, Braverman ER.

Postgrad. Med. Nov; 122(6):214-26.

Abstract

Background: It is well established that in both food- and drug-addicted individuals there is "dopamine resistance" associated with the DRD2 gene A1 allele. Based on earlier studies, evidence is emerging wherein the potential of utilizing a natural, nonaddicting, safe, putative D2 agonist may play a significant role in the recovery of individuals with reward deficiency syndrome, including those addicted to psychoactive chemicals.

Findings: Positive outcomes demonstrated by quantitative electroencephalographic (qEEG) imaging in a randomized, triple-blind, placebo-controlled, crossover study involving oral Synaptose Complex KB220Z™ showed an increase of alpha waves and low beta wave activity in the parietal brain region. Using t statistics, significant differences observed between placebo and Synaptose Complex KB220Z™ consistently occurred in the frontal regions after week 1 and then again after week 2 of analyses (P = 0.03). This is the first report to demonstrate involvement of the prefrontal cortex in the qEEG response to a natural putative D2 agonist (Synaptose Complex KB220Z™), especially evident in dopamine D2 A1 allele subjects. Independently, we have further supported this finding with an additional study of 3 serious polydrug abusers undergoing protracted abstinence who carried the DRD2 A1 allele. Significant qEEG differences were found between those who received 1 dose of placebo compared with those who were administered Synaptose Complex KB220Z™. Synaptose Complex KB220Z™ induced positive regulation of the dysregulated electrical activity of the brain in these addicts. The results are indicative of a phase change from low amplitude or low power in the brain to a more regulated state by increasing an average of 6.169 mV(2) across the prefrontal cortical region. In the first experiment we found that while 50% of the subjects carried the DRD2 A1 allele, 100% carried ≥ 1 risk allele. Specifically, based on the proposed addiction risk score for these 14 subjects, 72% had moderate-to-severe addiction risk. Similar findings were obtained by repeating the experiment in 3 additional currently abstinent polydrug abusers carrying the DRD2 A1 allele.

Conclusion: This seminal work will provide important information that may ultimately lead to significant improvement in the recovery of individuals with psychostimulant and polydrug abuse problems, specifically those with genetically induced dopamine deficiency. Based on this small sample size, we are proposing that with necessary large populations supporting these initial results, and possibly even additional candidate genes and single nucleotide polymorphisms, we may eventually have the clinical ability to classify severity according to genotype and possession of risk alleles, along with offering a safe, nonaddicting, natural dopaminergic receptor agonist that potentially up-

regulates instead of downregulates dopaminergic receptors, preferably the D2 subtype.

Key Points:

- **In a cross over study a total of 10 abstinent Psychostimulant dependent patients were randomized in a triple –blind –placebo controlled study.**
- **Each patient was genotyped for a number of reward genes for addiction risk assessment.**
- **100% of the patient carried a least on risk allele.**
- **qEEG analysis was performed on each patient one-hour after administration of KB220Z powder.**
- **KB220Z™ showed an increase of alpha waves and low beta wave activity in the parietal brain region (relapse area).**
- **Authors propose that utilization of KB220Z may up-regulate dopamine receptors in patients having moderate to high genetic addiction risk.**

2011

"Dopamine Resistance" in brain reward circuitry as a function of DRD2 gene receptor polymorphisms in RDS: Synaptamine complex variant (KB220) induced "Dopamine Sensitivity" and enhancement of happiness.

Blum, K.; Stice, E.; Liu, Y.; Giordano, J.; Morse, S.; Downs, B.W.; Waite, R.L.; Madigan, M.; Braverman, E.R.; Kerner, M.; Oscar-Berman. M.; Miller, D.; Stokes, S.; Gant, C.; Thompson, T.; Allen, C.; Smolen, A., Bowirrat, A. & Gold, M.

XIX World Congress of Psychiatric Genetics, September 10-14th. Washington DC.

Abstract

Explorations of brain function in terms of both physiology and behavioral traits have resulted in a plethora of studies linking these activities to neurotransmitter functions having a genetic basis. We address the age-old question of "Nature vs. Nurture" as it relates to the question of happiness and to the larger question relating to human nature as an emerging science. Attempts to identify key "vector influences" that link genes, the brain, and social behaviors to a so-called state of "happiness" are important areas for developing a new science of human nature. It is well established that in both food and drug addicted individuals there is "dopamine resistance" due to an association with the DRD2 gene A1 allele. Based on these and earlier studies evidence is emerging whereby the potential of utilizing a natural non-addicting , safe putative D2 agonist may find its place in recovery of Reward Deficiency Syndrome (RDS) including addiction to psychoactive chemicals. Utilizing qEEG and fMRI as imaging tools will show the impact of Synaptamine Complex Variant [KB220] ™ as an activator of the meso-limbic system and

administration significantly reduces or "normalizes" aberrant electrophysiological parameters of the reward circuitry site. Based on our QEEG studies presented herein we cautiously suggest that long-term activation of dopaminergic receptors (i.e., DRD2 receptors) will result in proliferation of D2 receptors leading to enhanced "dopamine sensitivity" and an increased sense of happiness. Even in carriers of DRD2 A1 allele. This is supported by numerous clinical trials on KB220 and awaits both fMRI and n PET scanning to determine chronic effects of KB220 on numbers of D2 receptors and direct interaction at N. Accumbens (NAc). Positive outcome as seen with the QEEG randomized double-blind placebo controlled study involving oral KB220 showing an increase of Alpha activity and an increase low Beta activity along with similar findings with the IV therapy will provide important information that could ultimately lead to significant improvement of recovery for victims of RDS having dopamine deficiency. Utilization of this new finding will bridge the gap whereby for the first time "science will meet recovery".

Key Points:

- **In a cross over triple–blind–placebo controlled study on ten Chinese abstinent (16.9 months) heroin dependent patients, fMRI was utilized to assess dopaminergic BOLD activation in the brain.**
- **KB220Z was administered to each patient and after one hour it was found that the complex induced BOLD activation of caudate-accumbens dopaminergic activation.**
- **The BOLD activation was significantly different compared to placebo.**
- **In addition KB220Z also reduced the hyper-excitability of putamen.**
- **The authors suggest that KB220Z induces "dopamine sensitivity" in genetically prone "dopamine resistant "patients genotyped for various reward gene polymorphisms.**

2012

Neurotransmitter-precursor-supplement Intervention for Detoxified Heroin Addicts.

CHEN D, LIU Y, HE W, WANG H, WANG Z#

Huazhong University of Science and Technology and Springer-Verlag Berlin Heidelberg [Med Sci 32(3):422-427,2012

Abstract

Summary: This study examined the effects of combined administration of tyrosine, lecithin, L-glutamine and L-5-hydroxytryptophan (5-HTP) on heroin withdrawal syndromes and mental symptoms in detoxified heroin addicts. In the cluster-randomized placebo-controlled trial, 83 detoxified heroin addicts were recruited from a detoxification treatment center in Wuhan, China.

Patients in the intervention group (n=41) were given the combined treatment with tyrosine, lecithin, L-glutamine and 5-HTP and those in the control group (n=42) were administered the placebo. The sleep status and the withdrawal symptoms were observed daily throughout the study, and the mood states were monitored pre- and post-intervention. The results showed that the insomnia and withdrawal scores were significantly improved over time in participants in the intervention group as compared with those in the control group. A greater reduction in tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia and total mood disturbance, and a greater increase in their vigor-activity symptoms were found at day 6 in the intervention group than in the control group (all $P<0.05$). It was concluded that the neurotransmitter-precursor-supplement intervention is effective in alleviating the withdrawal and mood symptoms and it may become a supplementary method for patients' recovery from heroin addiction.

Key Points:

- **In the cluster-randomized placebo-controlled trial, 83 detoxified heroin addicts were evaluated during withdrawal.**
- **This study examined the effects of combined administration of tyrosine, lecithin, L-glutamine and L-5-hydroxytryptophan (5-HTP) on heroin withdrawal syndromes and mental symptoms.**
- **The experimental group compared to placebo had reduced insomnia, and reduced withdrawal scores.**
- **After 6 days of treatment compared to placebo the experimental group had a significant reduction in tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia and total mood disturbance, and a greater increase in their vigor-activity symptoms (all $P<0.05$).**

2012

Early Intervention of Intravenous KB220IV- Neuroadaptagen Amino-Acid Therapy (NAAT)™ Improves Behavioral Outcomes in a Residential Addiction Treatment Program: A Pilot Study

Merlene Miller, Amanda LC Chen, Stan D. Stokes, Susan Silverman , Abdalla Bowirrat, Matthew Manka, Debra Manka[a] (NHD), David K Miller[a,l] (PhD), Kenneth Perrine[f] (PhD), Thomas JH Chen, John A Bailey, B William Downs, Roger L Waite, Margaret A Madigan, Eric R Braverman, Uma Damle, Mallory Kerner, John Giordano, Siobhan Morse, Marlene Oscar-Berman, Debmayla Barh, Kenneth Blum.

Journal of Psychoactive Drugs (in press December issue 2012).

Abstract

Dopamine plays an important role in drug seeking behaviors. It is well established that Substance Use Disorder (SUD) runs in families and is inheritable. Hypodopaminergic function is a major culprit in multiple addictive behaviors and is regulated by a number of reward genes. In this study we evaluated a known natural dopaminergic agonist KB220IV along with oral

variants directed toward overcoming hypodopaminergic function. In our first pilot experiment, we found a significant reduction of chronic symptoms as measured by the Chronic Abstinence Symptom Severity (CASS) Scale for both intravenous (IV) and oral compared to only oral administration. Specifically, the IV and oral group did significantly better than the oral only group over the first week, as well as over the following 30-day period. In the second experiment consisting of 129 subjects receiving both IV and orals, three factors with eigenvalues greater than one were extracted for the baseline CASS-R (CASS-Revised) variables. Three scales were constructed based on this factor analysis: Emotion, Somatic, and Cognitive. Paired sample t-tests between the pre-treatment scales and the post-treatment scales were calculated. All three scales showed significant declines (p=.00001) from pre- to post-treatment: t=19.1 for Emotion, t=16.1 for Somatic, and t=14.9 for poor - Cognitive. In a two year follow-up of 23 subjects who underwent KB220IV therapy (at least five IV treatments over a 7 day period) plus orals for at least 30 days: 21 (91%) were sober at 6 months with 19 (82%) having no relapse; 19 (82%) were sober at one year with 18 (78%) having no relapse; 21 (91%) were sober at two-years post-treatment with 16 (70%) having no relapse. Awaiting additional required research, due to limitations and sampling analysis, we cautiously propose that KB220IV therapy (a putative dopaminergic agonist) may provide important therapeutic outcomes in residential treatment programs.

Key Points:

- **In 129 patients a combination of IV and oral NAAT therapy (generic KB220) were assessed for Chronic Abstinence Symptom Severity (CASS) Scale over a 30 day period.**
- **Three scales were constructed based on this factor analysis: Emotion, Somatic, and Cognitive.**
- **All three scales showed significant improvement (p=.00001) from pre- to post-treatment: t=19.1 for Emotion, t=16.1 for Somatic, and t=14.9 for impaired - Cognitive.**
- **A two year follow-up in a subset of 23 patients showed: 21 (91%) were sober at 6 months with 19 (82%) having no relapse; 19 (82%) were sober at one year with 18 (78%) having no relapse; 21 (91%) were sober at two-years post-treatment with 16 (70%) having no relapse.**

In Review

Neurogenetics and Nutrigenomics of Neuro-Nutrient Therapy for Reward Deficiency Syndrome: Clinical Ramifications and Pitfalls.

Kenneth Blum, Merlene Miller, David Miller, John Giordano, Siobhan Morse, Lee McCormick, B.William Downs, Roger L. Waite, Margaret A. Madigan, Elizabeth Stuller , Charles Parker, Debmalya Barh, Girish G Yajnik, Dennis Neal, Eric R. Braverman, Raquel Lohmann, Carolyn Coker Ross, Joan Borsten, Mary Hauser, David Han, Manya Heyman, Thomas Simpatico.

Chronological Summary of Studies of KB220(Z) Neuroadaptogen

Theoretical Biology & Medical Modeling

Abstract

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

Key Points:

- **In one case report of a heroin addict targeted treated using high amounts of GABA and /or L-Glutamine showed serious complications as measured by SPECT.**
- **In a case report of an alcoholic utilizing appropriate and careful administration of balanced amounts of precursor amino-acid and inhibitors of neurotransmitter catabolic enzymes showed significant improvement as measured by SPECT.**
- **The authors caution clinicians to incorporate known appropriate neuro-therapy by adhering to basic neuro-genetic and nutrigenomic principles.**

To be submitted

Neuroadaptagen Amino-Acid Dopaminergic Agonist Facilitates Withdrawal From Long –Term Buprenorphine and Naloxone Combination: Have we found a natural opioid substitution weaning therapeutic agent?

Blum K, Femino J, Borsten J, Benya L, Waite RL, Giordano J, Downs B.W. Madigan M, Rector C, Braverman ER, Thomas Simpatico, M Hauser, Baily JA.

Journal of Addiction (to be submitted).

Abstract

While numerous studies support the efficacy of methadone and buprenorphine for the stabilization and maintenance of opioid dependence, clinically significant opioid withdrawal symptoms occur upon tapering and cessation of dosage. We present a case study of a 35 year old Caucasian female who was prescribed increasing dosages of prescription opioids after carpel tunnel

surgery secondary to chronic pain from reflex sympathetic dystrophy and fibromyalgia. Over the next 5 years, daily dosage requirements increased to over 80 mg of Methadone and 300 ug/hr Fentanyl transdermal patches, along with combinations of 12-14 1600 mcg Actig lollipop and oral 100 mg Morphine and 30 mg oxycodone 1-2 tabs q4-6hr PRN for breakthrough pain. Total monthly prescription costs including supplemental benzodiazepines, hypnotics and stimulants exceeded $53,000. The patient was subsequently transferred to Suboxone in 2008, and gradually tapered the dosage until admission for inpatient detoxification with the use of KB220Z a natural dopaminergic agonist. We carefully documented her withdrawal symptoms when she precipitously stopped taking buprenorphine/naloxone and during follow-up while taking KB220Z daily. At 432 days post Suboxone® withdrawal the patient is being maintained on KB220Z, has been urine tested and is opioid free. This preliminary case data suggest that the daily use of KB220Z could provide a cost effective alternative substitution adjunctive modality for Suboxone®. We encourage double-blind randomized –placebo controlled studies to test the proposition that KB220Z may act as a putative natural opioid substitution maintenance adjunct.

Key Points:

- **A report of a Workers Compensation case of a female who received pain medication and Suboxone.**
- **Total monthly prescription costs including supplemental benzodiazepines, hypnotics and stimulants exceeded $53,000.**
- **The patient subsequently was placed on Suboxone for 2.5 years.**
- **The authors carefully documented very severe withdrawal symptoms when she precipitously stopped taking buprenorphine/naloxone and during follow-up while taking KB220Z daily.**
- **At 432 days post Suboxone® withdrawal the patient is being maintained on KB220Z has been urine tested and is opioid free. The patient reports a very positive quality of life.**