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

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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 symptomology 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 words: Enkephalinase-inhibition, Synapatmine™, dopamine, reward deficiency syndrome, alcoholism, nutraceutical

INTRODUCTION

Despite approval by the US. FDA of two drugs for the treatment of alcoholism, the narcotic antagonist Naltrexone and the glutamate receptor agonist, Acamprosate®, the rate of recovery following these two drugs has been only moderate.

We believe that these drugs fall short because they only affect either the opioid receptor or glutamate receptor systems. While it is well established that addictive behavior, such as alcoholism, is a multi-factorial disease that has both genetic and environmental antecedents, it would be more prudent to provide treatment that couple these multiple systems. Previous literature suggested that alteration of the brain reward cascade (Blum and Kozlowski, 1990) by utilization of oral precursor

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amino-acids and enkephalinase inhibition therapy produced significant reductions in alcohol withdrawal symptomology and alcohol/drug/glucose craving behavior in a number of controlled studies (Blum *et al*., 1988a-c, 1990b, 1997; Brown *et al*., 1990; Defrance *et al*., 1997; Cold, 1996; Chen *et al*., 2004).

In 1996, our laboratory first described Reward Deficiency Syndrome (RDS) to define a common genetic variant involving dopamine D2 receptor gene (DRD2) polymorphisms as a putative predictor of impulsive, compulsive and addictive behaviors (Blum *et al*., 1996a). The D_2 receptor has been associated with pleasure and the DRD2 A1 allele has been referred to as the reward gene (Blum *et al*., 1990a, 1996a; Blum and Braverman, 2000).

The dopamine D2 (DRD2) gene and especially its allele Taq1 A1 and its receptor, also may be involved in co-morbid antisocial personality disorder symptoms (Ponce *et al*., 2003), high novelty seeking (Noble *et al*., 1998) and related traits (Hill *et al*., 1999). The mesocorticolimbic dopaminergic pathway system plays an especially important role in mediating reinforcement by abusable drugs and it may be a common denominator for multiple addictions and a number of psychiatric disorders (Comings *et al*., 1991).

When the mesocorticolimbic system dopamine reward system dysfunctions (potentially caused by certain genetic variants), the end result is Reward Deficiency Syndrome (RDS) and subsequent drug-seeking behavior (Blum *et al*., 1996a, b). RDS refers to the breakdown of the reward cascade (Blum and Koslowski, 1990) and resultant aberrant conduct due to specific genetic and environmental influences (Rowe, 1986).

It is well known that alcohol and other drugs of abuse, as well as most positive re-inforcers (i.e., sex, food, gambling, aggression) cause activation and neuronal release of brain dopamine, which can decrease negative feelings and satisfy abnormal cravings (Gessa *et al*., 1985; Dichiara and Impereto, 1988; Blum, 1991; Noble *et al*., 1994; Adler *et al*., 2000). A deficiency or absence of the D_2 receptors then predisposes individuals to a high risk for multiple addictive, impulsive and compulsive behaviors (Comings and Blum, 2000). Although other neurotransmitters (e.g., glutamate, gamma-aminobutyric acid (GABA), serotonin and enkephalins) may be important in determining the rewarding and stimulating effects of ethanol, dopamine may be critical for initiating drug use and for reinstating drug use during protracted abstinence (Gardner, 1997; Connor *et al*., 2002).

A number of studies have observed that the Taq1 A1 allele is associated with low dopamine D_2 densities in alcoholics (Noble *et al*., 1992; Hietala *et al*., 1994; Tihonen *et al*., 1995; Little *et al*., 1998; Repo *et al*., 1999; Kuilkka *et al*., 1998). Moreover, other studies have confirmed that the striatal post-synaptic D_2-receptor densities are low among alcoholics (Volkow *et al*., 1996).

In light of these and other findings involving the role of dopaminergic activity and alcoholism (Volkow *et al*., 1996, 1993, 2000, 2001, 2002; Thanos *et al*., 2005; Noble, 2003), we decided to test the hypothesis that manipulation of the reward neural circuitry and potential NAC dopamine release by utilization of oral and intravenous amino-acid-enkephalinase therapy would improve both the emotional and behavioral symptomology of recovering alcoholics in an open trial clinical study.

MATERIALS AND METHODS

Participants

The study protocol was approved by the PATH Foundation IRB (registration No. IRB00002334) and Ethics Committee and each participant signed an informed consent. In an outpatient drug educational program and clinic which was linked to the judicial system of Denver, Colorado, we evaluated 600 moderate to severe alcoholics (360 males and 240 females) ranging in age from 17 to 65 years. The period of evaluation was from April 2000 until June 2005. Each subject had a history of

past treatment and multiple relapse failures. During the intake interview (one-hour structured), an extensive psychosocial history developed by RDS founder, Dr. Kenneth Blum, [both written and verbal] was taken for each subject. This evaluation along with the standardized DSM-1V inventory determined each subject's level of addiction and explored past treatment modalities that appeared to be ineffective. Utilizing a Visual Analog Scale (VAS 1-10 cm), as well as self reporting scores (time of entering the treatment clinic and ten weeks later) concerning a number of emotional (anxiety, depression and anger) and behavioral (cravings, fatigue, concentration, energy, crisis) parameters, the intensity of feelings were evaluated. A number of patients were experiencing typical alcohol induced withdrawal symptoms at the initiation of the treatment. The collection of data was accomplished by personnel at a treatment program in Denver, Colorado. The overall program was directed by Dr. Kenneth Blum and all data was blinded to all other investigators.

Intravenous Solution and Orals

Each patient was treated with a patented intravenous solution containing certain neurotransmitter precursor amino-acids (DL-Phenylalanine, L-tyrosine, L-Tryptophan, L-Glutamine) and enkephalinase inhibitors, chromium and other trace metals (SG8839-exclusively by Salugen, Inc, San Diego, California), for ten weekly treatments (Fig. 1). Each patient was also asked to take SG8839 in an oral form as well. Compliance for the orals was determined by the receipt of at least three monthly bottles of the product. Substance abuse counseling was also provided to each subject at least 2 times a week and educational videos were played during IV infusion. Our educational focus was strategically designed to assist each patient in understanding the RDS theory and how it has worked in their personal lives. The patients also attended a drug and alcohol didactic seminar on a weekly basis.

Statistical Analysis

Paired Student's t-tests were performed to identify any statistically significant differences between the pre- and post-treatment values among the parameters tested, with $p<0.01$ considered significant.

RESULTS

The following Intensity of Feeling score means and standard deviations were observed for each parameter tested: anxiety (pre: 6.5±0.84 vs. post: 3.0±0.68) ($p<0.001$]); craving (pre: 5.7±0.57 vs. post: 1.35±0.16) ($p<0.001$); depression (pre: 5.0±0.35 vs. post: 1.95±0.31) ($p<0.001$]); fatigue (pre: 5.2±0.57 vs. post: 1.2±0.14) ($p<0.001$); concentration (pre: 4.9±0.98 vs. post: 4.18±0.54) ($p<0.001$); anger (pre: 4.24 vs. post: 1.9± 0.36) ($p<0.001$]; lack of energy (pre: 5.85±0.64 vs. post 3.5±0.47) ($p<0.001$); and crisis (pre: 6.5±0.65 vs. post: 3.0±0.30) ($p<0.001$). Further statistical testing using one-sample Student's t-tests was done to determine if the average reduction in mean scores due to treatment exceeded 50%, suggesting clinical improvement. 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% ($p<0.001$). It is noteworthy that, in the 600 alcoholics tested, the only parameters that did not result in clinical improvement after treatment were concentration (14.7±20.2%) and lack of energy (40.2±8.4%) (Fig. 1).

DISCUSSION

While we are not able to emphatically prove that the improvement in both emotional and behavioral parameters found in this clinical trial are solely due to the oral and intravenous amino-acid-

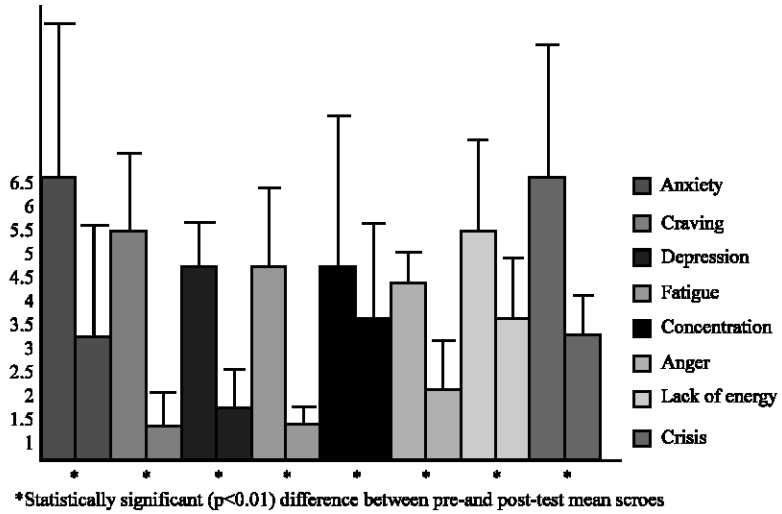

Fig. 1: Pre- and post intensity of feeling score means of each parameter tested. For each parameter, the bar represents the pre-test mean and the right bar displays the post-test mean. The wisker above each bar represents the standard error of the mean

enkephalinase therapy (cannot eliminate the positive affect of drug abuse counseling), these results strongly suggest the potential significant effects of this novel therapeutic modality.

The notion that the oral and intravenous amino-acid therapy actually paves the way for the patient to intellectually accept RDS as a lifelong condition she/he must face seems to be the key to successful substance abuse treatment. This dual therapeutic approach allows the brain to say No to substance abuse and provides the body with a softer, gentler way. Thus it has become apparent that positive mind-body interaction actually creates the feeling of well-being necessary for successful recovery.

We further hypothesize that SG8839, increases dopamine release at the NAC, thereby activating D_2 receptors and reduces alcohol craving behavior (Thanos *et al*., 2001).

Based on this well-studied foundation, whereby the deficiency or absence of DRD2 receptors then leads to a high risk for multiple addictive, impulsive and compulsive behavioral propensities called Reward Deficiency Syndrome (Blum *et al*., 1996a, b; Gardner, 1997; Xu *et al*., 2004), we propose that SG8839, because of its potential induction of a slow, natural, neuronal release of dopamine may indeed be an important treatment modality. This premise warrants further investigation including a double-blinded, randomized, placebo controlled study for both the intravenous and oral forms of delivery of this novel modality.

While there are no controls in this open label study, the strength of the experiment resides in the large sample size (n = 600) and the high levels of significant differences between pre and post measurements.

We further hypothesize that coupling certain gene polymorphisms involved in dopaminergic, serotonergic, gabaergic and catecholamine catabolism enzymes (e.g., Catechol-O-Methyl-Transferase COMT) function to guide customized formulations based on solid nutrigenomic principles may indeed enhance treatment outcomes in the future (Blum *et al*., 2006).

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