Neurotransmitters as predictive biomarkers of responsiveness to substance abuse treatment

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ABSTRACT

Evidence-based practices are becoming ever more important for the effective treatment of substance abuse disorders. Substance abuse places a substantial burden on society, as it can cause adverse health effects and contribute to destructive social behavior. Traditional treatment for substance abuse relies on pharmacological interventions and counseling, but new strategies are being explored. Of interest is the use of complementary and alternative medicine (CAM) approaches that target neurological functioning. Amino acid supplementation is one modality that may show promise as an adjunctive therapy in substance abuse programs. The purpose of this study was twofold; to examine the effects of amino acid supplementation in substance abuse patients and to identify novel predictive biomarkers that may aid in detecting 'responders' and 'non-responders' prior to beginning treatment. Patients at a residential rehabilitation facility provided urine specimens to monitor neurotransmitter levels before and three weeks following amino acid supplementation. Several amino acids demonstrated an increase in serotonin and taurine and a decrease in phenylethylamine (PEA) following three weeks of treatment. This study further demonstrated significantly higher baseline norepinephrine, serotonin, and PEA levels in the patients that managed to abstain from substance use following amino acid supplementation. Overall, results demonstrated that amino acid supplementation may be a promising addition to current substance abuse programs and that urinary neurotransmitters may serve as biomarkers to predict treatment responses in substance abuse patients.

INTRODUCTION

The abuse of alcohol and illegal substances poses a substantial economic burden to society. Research suggests that substance abuse leads to extensive economic costs due to increases in crime, violence, and institutionalization/hospitalization (Conover, Arno, Weaver, Ang, & Ettner, 2006; Miller, Levy, Cohen, & Cox, 2006). For example, the abuse of alcohol cost between 210-665 billion US dollars in 2002 for both medical and legal fees (Baumberg, 2006). Due to this tremendous economic burden, evidence-based practices in traditional and complementary and alternative medicine (CAM) are being explored as a means to improve treatment regimens and outcomes for patients with addictions (O'Brien, 2008).

Traditionally, pharmacological and support groups have been the primary treatments for substance abuse, however, non-traditional methods are being explored. For instance, acupuncture has been examined as an adjunct therapy to existing treatments for cocaine addiction (Kim, Schiff, Waalen, & Hovell, 2005). Other CAM modalities, such as herbal therapy, continue to appear more frequently in psychiatric settings. In one survey, 63% of respondents, of which 26% had a diagnosed substance abuse disorder, used at least one CAM modality in the previous 12 months (Elkins, Rajab, & Marcus, 2005). The most frequently used CAM modality was herbal therapy, followed by mind-body therapies such as relaxation or mental imagery, hypnosis, meditation, and biofeedback (Elkins et al., 2005).

There is strong evidence supporting the use of amino acid supplements to alter specific brain regions that are related to substance abuse, such as the nucleus accumbens (Blaiss & Janak, 2008). Morphine, heroine, cocaine, alcohol, and other stimulants have been shown to cause alterations in neurotransmitter signaling in the nucleus accumbens, thereby reinforcing pleasure responses and increasing the likelihood of persistent drug use (Floresco, McLaughlin, & Haluk, 2008).

Research has shown that amino acid supplementation can alter levels of neurotransmitters implicated in addiction, making this a promising approach in substance abuse programs (Kiefer & Mann, 2005). Specifically, intravenous administration of L-tryptophan was found to attenuate the cocaine-induced increase in forebrain dopamine, as well as decrease the cocaine-induced locomotor activity in rats (Molina, Ahmed, Gatley, Volkow, & Abumrad, 2001). Similarly, the co-administration of 5-hydroxytryptophan (5-HTP), the direct precursor to serotonin, with phentermine, a dopamine agonist, reduced alcohol intake and suppressed alcohol withdrawal seizures in rats (Molina et al., 2001). These therapeutic actions may be related to elevations in synaptic dopamine and serotonin in critical brain regions involved in addiction such as the nucleus accumbens (Molina et al., 2001).

Another example of the effects of amino acid supplementation on drug effects is N-acetylcysteine. Cocaine produces a persistent reduction in cystine/glutamate exchange in the nucleus accumbens, a region of the forebrain that plays an important role in reward, pleasure, fear, and addiction (Schwienbacher, Schnitzler, Westbrook, Richardson, & Fendt, 2006). N-acetylcysteine has been shown to prevent cocaine-induced changes in cystine transport (LaRowe et al., 2007) (Grant, Kim, & Odlaug, 2007; Madayag et al., 2007) and to reduce the

desire for an abused substance in the presence of drug cues (LaRowe et al., 2007).

A limitation to substance abuse treatment has been the inability to target therapy due to the lack of available biomarkers (Elkashef & Vocci, 2003). Determining the neurobiological effects of addiction, combined with the known mechanisms of medications and supplements may prove useful for discovering biomarkers. This will help target specific pharmacological agents to responder patient segments, predict responses to medication(s), and identify patient types more prone to relapse (Elkashef & Vocci, 2003). In this way, biomarkers may allow patients to overcome substance abuse more quickly and with greater long-term success.

The purpose of this study was two-fold. First, we wished to determine whether amino acid treatment would lead to a decrease in relapse rates for subjects at a residential rehabilitation facility. Second, the study evaluated the applicability of urinary neurotransmitters as biomarkers to identify individuals at-risk for relapse, and to monitor treatment responses. We hypothesized that amino acid supplementation would decrease relapse rates and that urinary neurotransmitter analysis may be used to predict relapse susceptibility and assist in monitoring treatment responses.

METHODS

Subjects were enrolled in a residential rehabilitation facility at the Courage to Change Ranch Addiction Recovery Program in Simla, Colorado. Upon arrival to the facility, subjects were asked to sign a consent form and provide a detailed patient history. Various surveys were filled out by each subject to determine their degree of drug dependency and to help reveal the potential chance of relapse. A urine specimen was collected by each subject following enrollment into the facility to establish baseline levels of the neurotransmitters epinephrine, norepinephrine, dopamine, serotonin, glycine, taurine, gamma-aminobutyric acid (GABA), glutamate, phenylethylamine (PEA), and histamine. Urine specimens were analyzed by Pharmasan Labs, Inc. (Osceola, WI) by enzyme-linked immunosorbent assay (ELISA).

After collecting baseline urine specimens, subjects were placed on an amino acid supplement protocol, which included a proprietary blend of 5-HTP, taurine, L-theanine, N-acetyltyrosine, L-histidine, L-methionine, *Rhodiola rosea* extract, N-acetylcysteine, alpha-lipoic acid, and coenzyme Q10. A total of 173 subjects were initially enrolled in the study, of which 64 subjects submitted urine specimens after 3 weeks of treatment. Of these, 43 subjects provided information as to whether they stayed sober or relapsed back into substance abuse.

Three types of drug dependencies were characterized across subjects: “alcohol dependence”, “methamphetamine dependence”, and “other”, which included heroin, cocaine, and polysubstance abuse and for which there were an insufficient number of subjects to warrant individual categorization.

Paired t-tests were used to determine statistical significance between baseline neurotransmitter values compared to follow-up values after 3 weeks of treatment with amino acid supplementation. Chi-squared analysis was used to determine if sobriety was related to the type of drug dependence. Finally, a two-way ANOVA was conducted to determine whether differences existed in baseline and follow-up neurotransmitter levels to evaluate sobriety following treatment.

RESULTS

Among the 64 subjects who completed a neurotransmitter assessment following 3 weeks of amino acid supplementation, levels of serotonin ($p<0.01$) and taurine ($p<0.05$) were significantly greater compared to baseline (Figure 1). Conversely, levels of PEA ($p<0.05$) were statistically lower following 3 weeks of supplementation (Figure 1).

Amino acid supplementation included taurine as well as 5-HTP, which acts as a precursor to serotonin (Lynn-Bullock, Welshhans, Pallas, & Katz, 2004). Accordingly, we observed increased urinary taurine and serotonin in substance abuse patients after three weeks of supplementation. PEA was found to be highest at baseline, and levels decreased following 3 weeks of amino acid supplementation.

We next assessed whether there were any differences between individuals who achieved sobriety (n= 27) after three weeks of supplementation, and those who had relapsed (n=16). Chi-squared analysis did not show any relationship between the type of drug dependency and sobriety following 3 weeks of supplementation. However, two-way ANOVA revealed significantly different baseline norepinephrine, serotonin, and PEA levels in subjects who remained sober versus those who relapsed. The average norepinephrine values for those who remained sober were significantly higher than for those who relapsed ($p<0.05$) (Figure 2). Bonferroni post-tests revealed a significantly higher mean baseline norepinephrine value for subjects who remained sober compared to those who relapsed ($p<0.05$) (Figure 2). A two-way ANOVA determined that the average serotonin values of those that remained sober were significantly higher than those who relapsed ($p<0.01$) (Figure 2). Finally, average PEA values of those that remained sober were significantly higher than in patients who had relapsed ($p<0.01$; Figure 2).

DISCUSSION

This study examined the effects of amino acid supplementation in subjects enrolled in a residential substance-abuse rehabilitation program.

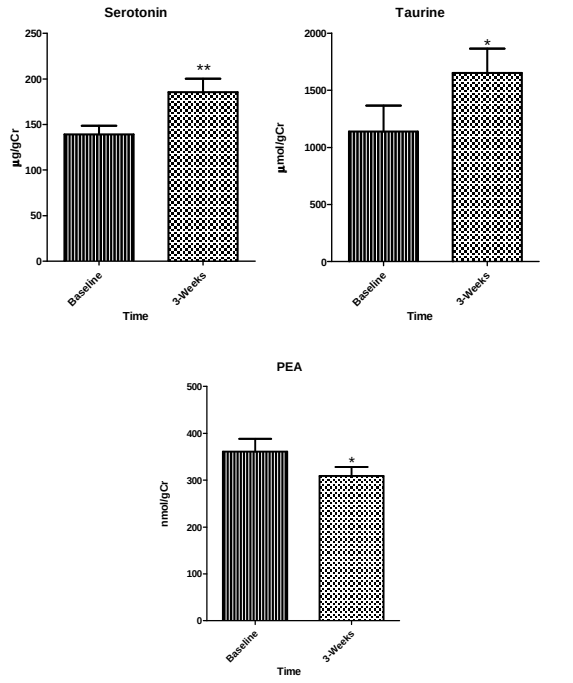

Figure 1. Following 3 weeks of amino acid supplementation, substance abuse patients had significant increases in serotonin and taurine with decreases in PEA. N=63; ** = $p<0.01$, * = $p<0.05$.

Urinary serotonin and taurine levels increased in subjects after 3 weeks of supplementation, while PEA levels decreased. Each of these changes may have clinical impacts. For example, oral administration of 5-HTP may play a role, via increasing serotonin levels, in reducing drug-seeking behaviors. Taurine supplementation has been shown to be neuroprotective and may improve cardiovascular health (Nittynen, Nurminen, Korpela, & Vapaatalo, 1999), possibly by mitigating the effects of alcohol consumption on sulfur-containing amino acid (SCAA) metabolism that can lead to elevated homocysteine (Yang et al., 2009), an independent risk factor for cardiovascular disease, cerebrovascular disease, dementia-type disorders, and osteoporosis-associated fractures (Maron & Loscalzo, 2008). Oral administration of taurine may therefore reduce the risk of cardiovascular disease by decreasing homocysteine levels (Yang et al., 2009).

The decrease in PEA from baseline that we observed after 3 weeks of amino acid supplementation may have resulted from subjects discontinuing the use of stimulant drugs such as methamphetamine, based on findings by Kusaga and colleagues (2002) that PEA levels increase following the administration of methylphenidate and amphetamines.

We observed interesting correlations between baseline neurotransmitter levels and whether patients relapsed or remained sober after three weeks of amino acid supplementation. Baseline serotonin was significantly higher in sober individuals compared to those who relapsed. In addition, relapsing individuals did not have the same magnitude of serotonin increase. Our findings suggest that lower baseline serotonin values may serve as a predictive marker for relapse, possibly warranting a more aggressive 5-HTP regimen. The benefits of 5-HTP observed in this study are in agreement with earlier reports showing that 5-HTP enhances serotonin concentrations in the nucleus accumbens in cocaine-dependent rats, reducing the desire for cocaine following drug withdrawal (Harris, Altomare, & ston-Jones, 2001).

Subjects who remained sober also had higher baseline norepinephrine and PEA levels compared to those who relapsed. The lower baseline neurotransmitter values observed in individuals who relapsed may suggest the need to "self-medicate". Markou and colleagues (1998) proposed a hypothesis suggesting that individuals with depression share biochemical similarities to those with drug dependence. The authors proposed that individuals with depression may experiment with several types of drugs and depressed individuals were able to determine the drug or drug combinations that best normalized their neurochemical imbalances based on their symptomatology (Markou, Kosten, & Koob, 1998). Thus, baseline urinary neurotransmitters such as serotonin, norepinephrine, and PEA may be useful as a Type 0 (baseline) biomarkers that can help predict treatment responders and guide the therapeutic regimen.

Stimulant medications may have enhanced monoaminergic neurotransmission by reversing deficits in serotonin, dopamine, and norepinephrine in depressed individuals (Jayanthi & Ramamoorthy, 2005; Paterson & Markou, 2007). Substances such as alcohol, morphine, and nicotine may also have enhanced monoaminergic mechanisms, which can lead to an antidepressant-like effect (Heinz, Schafer, Higley, Krystal, & Goldman, 2003; Nowakowska, Kus, Florek, Czubak, & Jodynis-Liebert, 2006; Rowlett, Platt, & Spealman, 2004). Evidence indicates that antidepressant medication appears to be more effective in the reduction of drug use in depressed drug abusers versus non-depressed drug abusers, suggesting that antidepressants may have replaced the need for drugs of abuse (Moeller et al., 2007; Shoptaw et al., 2008). Therefore, biochemical imbalances may contribute to drug-seeking behavior in an effort to normalize an individual's biochemistry, and the severity of the biochemical

abnormality may be correlated with the severity of elicit drug use (Belknap, Metten, Beckley, & Crabbe, 2008).

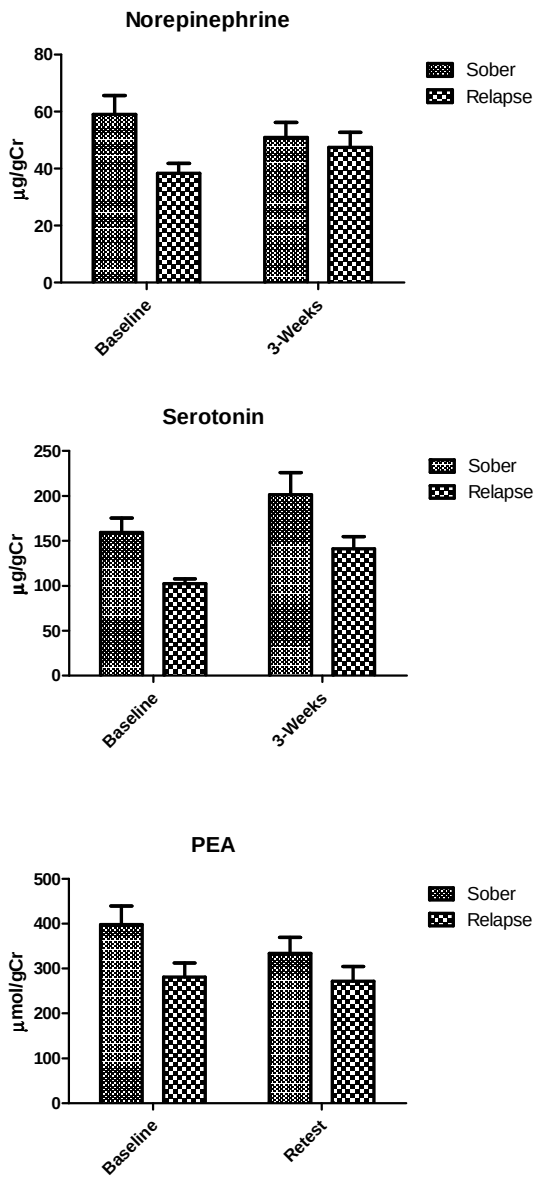

Figure 2. Norepinephrine, serotonin, and PEA were significantly higher for the sober group (n= 27) than the relapsed group (n=16). There were no significant differences from baseline to 3 weeks and no significant interactions for any of the parameters. N= 43.

CONCLUSIONS

This study shows that successful achievement of sobriety following amino acid supplementation correlates significantly with higher baseline neurotransmitter levels. One limitation of the study was the lack of a control population where subjects did not utilize amino acid supplementation. Without the control population, the efficacy of amino acid supplementation was difficult to interpret as a means to assist in the treatment of substance abuse. However, the study revealed how neurotransmitter analysis may predict treatment responses to pharmacological agents, as observed in a residential rehabilitation facility for drug and alcohol abuse. Future studies should examine neurotransmitter fluctuations to treatments other than amino acid supplementation for substance abuse. In addition, it will be critical to determine whether relapse rates are dependent on the dose of amino acid supplementation in subjects with significant neurotransmitter deficiencies.

The potential for using neurotransmitters as biomarkers to predict treatment responses could substantially decrease economic costs associated with substance abuse. Urinary neurotransmitter assessment may help identify individuals at greater risk of relapse and thus warrant a more aggressive or extended therapy to increase the chance of achieving sobriety and ultimately maintaining a drug-free status.

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