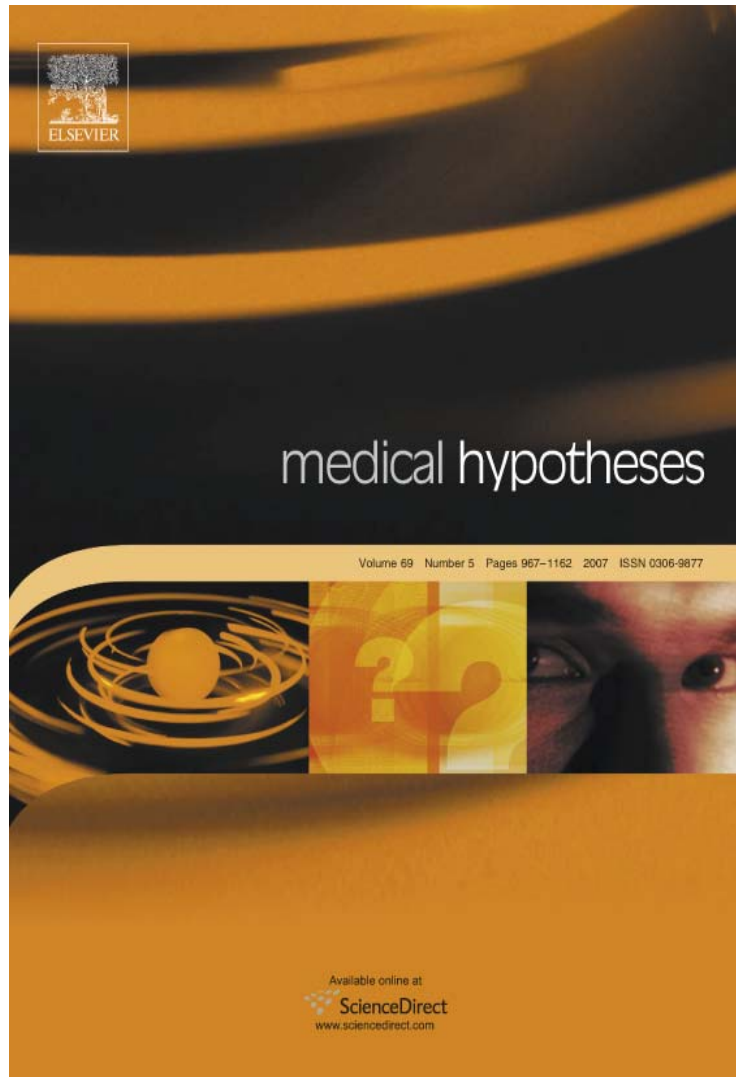


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Manipulation of catechol-*O*-methyl-transferase (COMT) activity to influence the attenuation of substance seeking behavior, a subtype of Reward Deficiency Syndrome (RDS), is dependent upon gene polymorphisms: A hypothesis

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Received 21 November 2006; accepted 6 December 2006

Summary There are common genetic mechanisms responsible for both drug effects and subsequent seeking behavior. In 1996, we coined the term Reward Deficiency Syndrome (RDS). Past and current treatment of substance seeking behavior, a subtype of Reward Deficiency Syndrome (RDS), is considered by most to be inadequate. Recently, we evaluated a complex named Synaptamine™ [Haveos™ (SG8839R)]. The main difference with an older studied variant and the latest variant is the inclusion of a proprietary form of *Rhodiola rosea*, a known catechol-*O*-methyl-transferase inhibitor (COMT) to potentially enhance the activity of presynaptic released dopamine. In this regard, based on the current literature we hypothesize that manipulation of catechol-*O*-methyl-transferase (COMT) activity to influence the attenuation of substance seeking behavior, is dependent upon gene polymorphisms. In this regard we hypothesize that carrying the LL genotype with low COMT activity should as theorized, increase the reward induced by substance-induced dopamine release and may indeed increase the propensity to type 1 alcoholism and possibly other drugs that

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activate the dopaminergic system. Thus when alcohol is present in low COMT LL genotype, increasing COMT activity, not inhibiting it should assist in the reduction of social consumption or abuse. Alternatively, under physiological conditions (no psychoactive substances present (e.g. alcohol) carrying the DRD2 A1 allele with associated low D2 receptors should, as theorized, increase craving behavior because of a low or hypodopaminergic state causing the individual to seek out substances that increase the release of dopamine for subsequent activation of unbound D2 sites in the nucleus accumbens. Thus, in the absence of alcohol or other psychoactive drugs (dopamine releasers), especially during recovery or rehabilitation, decreasing, not increasing COMT activity, should result in enhanced synaptic dopamine as physiologically released, thereby proliferating D2 receptors while reducing stress, increasing well-being, reducing craving behavior and preventing relapse. Based on this hypothesis, we believe that adding the COMT inhibitor *R. rosea* (as Rhodimin™) to our amino-acid and chromium combination in DUI offenders and other illegal drug-related crimes, increases the potential for more targeted neurochemical rebalancing and enhanced relapse prevention. Finally, we hypothesize that these data coupled together provide evidence that the combination of enkephalinase inhibition, neurotransmitter precursor loading, brain tryptophan enhancing and COMT inhibition as well as DNA analysis of the individual's genome, may be useful as an adjunct to therapy when used in outpatient recovery, specifically to assist in reducing craving behavior and preventing relapse.

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Introduction

A global problem

Alcohol dependence is one of the most pervasive diseases of the Western world and is increasing world wide. However, less than 5% of all patients receive proper treatment. Each year in the United States alone, about 30% of all alcohol-dependent patients are admitted to general hospitals, usually to treat alcohol-related physical diseases. It is known that if adequate treatment is available, relapse rates are as high as 50% in those follow-up studies that examined treatment periods of up to a 2 year period [1]. In accordance, several neuroendocrinological and brain imaging studies have observed that subjects with a high relapse risk show increased dopamine turnover and a prolonged recovery of post-synaptic dopamine D2 receptor dysfunction after detoxification [2–6].

Associative learning may transform neutral emotional or environmental stimuli into alcohol-associated cues that induce a conditioned compensatory response to alcohol, conditioned withdrawal and craving [7]. Acamprosate, an FDA approved drug used to reduce cravings in abstinent alcoholics, effects the glutaminergic-NMDA receptors and may ultimately affect dopamine release. However, in one trial, about 80% of all patients who received placebo relapsed, while 60% of patients who received Acamprosate resumed alcohol intake within the first year after detoxification, and this result has been confirmed by others [8–10]. While the results were significant, its use is only adjunctive and thus we hypothesize that Acamprosate should be combined with other dopamine activating compounds, such as certain precursor amino-acids. Moreover, alcohol craving involves the so-called

dopaminergic reward system and its opioidergic stimulation via mu-opiate receptors [11].

A national survey reported that across three treatment programs evaluating 1605 patients, combining measures of weekly psychostimulant use with return to treatment shows that 41.5% had evidence of further drug related problems [12]. The authors even admit that their basic findings rest on comparative outcomes however, rather than the accuracy of relapse estimates per se. While there is some data to support the role of a mixed D1 and D2 receptor antagonist such as Flupenthixol in reducing psychostimulant craving [12], its long term use seems counter to the role of low D2 receptors and craving behavior as shown in a number of studies both genetic and non-genetic [12].

Synaptamine™ [Haveos™ (SG8839R)]

Past and current treatment of substance use disorder (SUD), a subtype of Reward Deficiency Syndrome (RDS), is considered by most to be inadequate [16]. The search for better treatment prompted our intensive investigations over a 30 year period. We realize that any approach utilizing a single pharmacological target, while having some effect, may not be the end all to SUD treatment especially for the alcoholic. We therefore embarked on a number of studies over the years that utilized the conceptual framework of a reward cascade involving multiple neurotransmitters and genes which control and regulate these neurotransmitters [13–20]. Our group further realized that there are common genetic mechanisms responsible for both drug effects and subsequent seeking behavior [21–43]. Thus we coined the term Reward Deficiency Syndrome (RDS). Utilizing these principles we systematically evaluated novel

nutraceuticals having impact on reward dependence mechanisms including dopaminergic [44–62]. Moreover, we evaluated a complex named Synaptamine™ (SG8839). The main difference with an older studied variant and the latest variant is the inclusion of *Rhodiola rosea* (as Rhodimin™ supplied by Salugen, Inc.), a known catechol-*O*-methyltransferase inhibitor (COMT) to potentially enhance the activity of presynaptic release of dopamine.

Similar to the first DUI study [19] utilizing a variant of Synaptamine (SG8839) (no rhodiola), in subsequent studies from our laboratory we also found that relapse rates during the first 10 weeks were not statistically significant at the end of 10 months [63]. In both studies, relapse rates usually occurred early on and primarily prior to the 12th week of the program, and was sustainable over the entire 12-month period. In a clinical program in Las Vegas Nevada, whereby *Rhodiola rosea* (as Rhodimin™) was added, we observed a 79.1% recovery. In this regard, the court system considered these results significant. The main observation is that unlike all other treatments tried by the court system these patients after a 3 month period showed great improvement in all levels physiological, psychological and even spiritual [63].

When we compare relapse rates obtained from the literature: 56% for alcoholics and 90% for cocaine or stimulant dependent subjects [64,65], both our earlier results in DUI offenders [19] and other results are quite significant [63]; suggesting a potentially new mode of adjunctive treatment in alcohol, heroin and psychostimulant dependence (the program included a mix of polysubstance abusers having multiple relapses).

The COMT gene hypothesis

Based on the current literature, we hypothesize that there are two opposing theories regarding the involvement of catechol-*O*-methyltransferase (COMT) genes and their role in Substance Use Disorder (SUD). Dependent upon an individual's COMT genotype, differential treatment outcomes could be explained. It is further conjectured that there are two different mechanisms involved in high alcohol risk. At first look, they appear to be diametrically opposed and even paradoxical.

The *first mechanism* of carrying the LL genotype with low COMT activity should as theorized, increase the reward caused by substance-induced dopamine release and may indeed increase the propensity to type 1 alcoholism and possibly other drugs that activate the dopaminergic system. Thus when

alcohol is present in low COMT LL genotype, increasing COMT activity, not inhibiting it should assist in the reduction of social consumption or abuse [1].

As stated earlier, catecholamine-*O*-methyltransferase (COMT) is an enzyme that has a crucial role in dopamine metabolism. The variability of COMT enzyme activity in humans is substantially regulated by a common functional polymorphism [66–71]. A low activity variant of the enzyme contains a methionine residue at amino acid 158 of membrane-bound COMT protein, whereas the high activity variant has a valine molecule at this site. Homozygosity for the low activity allele (LL genotype) is found in approximately 25% of Whites. The high activity homozygosity (HH genotype) results in a 3–4 fold increase in activity of dopamine metabolism. This variant is also found in about 25% Whites [71]. Heterozygotes (LH genotype) have intermediate levels of COMT activity.

Evidence shows that this functional polymorphism in the COMT gene is associated with certain mental disorders such as obsessive-compulsive disorder and substance abuse [66], rapid cycling bipolar disorder [67], and schizophrenia with increased violent behavior [69]. It has been conjectured that the allelic variants at the COMT locus are candidates in the etiology of SUD. Ethanol-induced euphoria is associated with rapid increase in the release of dopamine in the limbic areas [68]. While others have postulated that individuals homozygous for low activity COMT alleles (resulting in a low dopamine inactivation rate) may be at an increased risk of developing alcohol abuse or dependence as compared to heterozygotes and high activity homozygotes, this hypothesis has not been confirmed. In this theory, individuals with a low activity (LL) COMT genotype may experience a longer lasting and more effective dopamine release in the brain. This might increase the reward of alcohol drinking and lower the threshold of pleasure-seeking behavior. There are studies and others [72] which support this notion including the work of Long et al. [32] in alcohol dependence in an American Indian population; Tiihonen et al. [73], in type 1 alcoholism in a Finish population and in Finish social drinkers. However, there are studies which do not support this hypothesis including the work of Kohnke et al. [68], who found an association with plasma homovanillic acid (HVA), an indicator of central dopaminergic activity, independent of a functional polymorphism of human COMT; and the work of others who could not find an association of heroin dependence and COMT 108 val/met polymorphism in a Chinese population. This is in contrast to the very high association (1.4×10^{-22} OR = 52.8) of the dopamine D2

receptor A1 allele in a Chinese population [74] conferring low dopamine D2 receptors.

The *second mechanism* of carrying the DRD2 A1 allele with associated low D2 receptors should, as theorized, increase craving behavior because of a low or hypodopaminergic state causing the individual to seek out substances that increase the release of dopamine for subsequent activation of unbound D2 sites in the nucleus accumbens. Thus, in the absence of alcohol or other psychoactive drugs (dopamine releasers), especially during recovery or rehabilitation, decreasing, not increasing COMT activity, should result in enhanced synaptic dopamine as physiologically released, thereby proliferating D2 receptors while reducing stress, increasing well-being, reducing craving behavior and preventing relapse.

There is evidence [75] in alcoholics that low dopamine D2 receptors are responsive to bromocriptine, a D2 agonist compared to carriers of the normal complement of D2 receptors (DRD2 A2 allele). Moreover, prolonged D2 receptor activation increases D2 receptors in transfected kidney cells with bromocriptine [44]. These two studies prompted an opposite theory that suggests instead of decreasing COMT activity as seen with the LL genotype inhibition of the COMT enzyme, thereby increasing synaptically released dopamine might induce a proliferation of D2 receptors especially in DRD2 A1 carriers and reduce aberrant cravings or substance seeking behavior (see reviews [20,22,38]). Thus it is not obvious that inhibiting the activity of COMT in individuals having a high risk for alcoholism or other drug seeking behavior is beneficial.

In terms of inhibiting the COMT enzyme we decided to incorporate a proprietary form of *R. rosea*. Several clinical trials with double-blind placebo controls in Russia provide evidence that *R. rosea* possesses positive mood enhancing and anti-stress properties with no detectable levels of toxicity [76]. Generally, *R. rosea* extract has been shown to have a positive influence on the central nervous system, increasing attention span, memory, strength and mobility of the human body, and weight management. It is believed that *R. rosea* can act as a COMT inhibitor where higher brain levels of serotonin and dopamine have been observed. We have no explanation for increases in the serotonin levels since COMT is for catecholamine, and not indole, catabolism. Studies by Saratikov and Marina [77] suggest that *R. rosea* can increase the level of neurotransmitters (i.e. dopamine) by 30% and decrease COMT activity by 60%.

The finding of significantly reduced relapse rates in our studies utilizing one of three reward products

or the major active ingredients called Synaptamine™ [SG8839R] (DL-phenylalanine [78], elemental chromium [79–81], a proprietary form of rhodiola and/or Huperzine A) as governed by US patent number 6,132,724, for either alcohol and heroin recovery; psychostimulant recovery, and/or Attention Deficit Hyperactivity Disorder (ADHD), certainly requires replication. Somewhat similar results have been obtained in an unpublished (very small sample size ($n = 20$)), double-blind placebo randomized controlled study in Drug Court Participants in Sacramento Biochemical Recovery Program over a three month period. Outcome measures included cravings and symptoms of psychostimulant dependence. While the number of participants was too small to detect statistically significant differences between those participants who received placebo and those who received SG8839R, the results suggest a potential benefit of SG8839R during the initial one-month period as the supplement group had greater decrease in symptoms and levels of cravings compared to the placebo group. Similar but less profound results have been obtained in a double-blind placebo controlled study with an earlier version of this complex [82].

Hypothesis

We therefore hypothesize that manipulation of catechol-*O*-methyl-transferase (COMT) activity to influence the attenuation of substance seeking behavior, a subtype of Reward Deficiency Syndrome (RDS), is dependent upon gene polymorphisms. In this regard, we hypothesize that carrying the LL genotype with low COMT activity should as theorized, increase the reward caused by substance-induced dopamine release and may indeed increase the propensity to type 1 alcoholism (genetic induced) and possibly other drugs that activate the dopaminergic system. Thus when alcohol is present in low COMT LL genotype, increasing COMT activity, not inhibiting it should assist in the reduction of social consumption or abuse.

Alternatively, under physiological conditions (no psychoactive substances present [e.g. alcohol]) carrying the DRD2 A1 allele with associated low D2 receptors should, as theorized, increase craving behavior because of a low or hypodopaminergic state causing the individual to seek out substances that increase the release of dopamine for subsequent activation of unbound D2 sites in the nucleus accumbens. Thus, in the absence of alcohol or other psychoactive drugs (dopamine releasers), especially during recovery or rehabilitation, decreasing, not increasing COMT activity, should result in enhanced synaptic dopamine as physiologically

released, thereby proliferating D2 receptors while reducing stress, increasing well-being, reducing craving behavior and preventing relapse. Based on this hypothesis, we believe that adding the COMT inhibitor *R. rosea* (as RhodiMet™) to our amino-acid and chromium combination in DUI offenders and other illegal drug related crimes, increases the potential for more targeted neurochemical rebalancing and enhanced relapse prevention.

Summary

Finally we believe that adding the COMT inhibitor *R. rosea* to our amino-acid and chromium combination in DUI offenders and other illegal drug related crimes, increases the potential for more targeted neurochemical rebalancing and enhanced relapse prevention. Earlier studies from our laboratory showed that using amino-acid precursor loading and enkephalinase inhibition [82], but not chromium or rhodiola in outpatient DUI offenders with either alcohol-or cocaine-related problems resulted in significant reduced relapse rates. However, after 10 months, especially for the psychostimulant group, approximately half of the participants dropped out of the program. With the addition of both chromium and a proprietary form of rhodiola in a more recent study [63], out of 76 patients (alcohol and methamphetamine related) attending a 12 month program the recovery rate was 79.1%. We hypothesize that data gleaned from the literature provide evidence that the combination of enkephalinase inhibition, neurotransmitter precursor loading, brain tryptophan enhancing and COMT inhibition, as discussed with regard to the second mechanism, may be useful as an adjunct to therapy when used in outpatient recovery. This combination in conjunction with other known approved pharmacological treatments such as narcotic antagonists and the partial opiate mu receptor agonist buprenorphine may become a front-line modality to assist in reducing craving behavior and preventing relapse. We further propose that DNA analysis prior to treatment of SUD with either a pharmacological or nutraceutical dopaminergic activator/agonist will significantly enhance outcome, especially as it relates to COMT polymorphisms [83].

Declaration of conflict of interest

Kenneth Blum and Brian Meshkin are officers and own stock in Salugen, inc.

Acknowledgements

We want to thank the financial support of Salugen, Inc, San Diego, California, Electricwaveform Laboratories, Inc., Huntington Beach, California, and Path Medical Research Foundation, New York, NY. We want to especially thank Rein Norma for his financial contribution to the Path Medical Research Foundation.

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