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Links between Nutrition, Drug Abuse, and the Metabolic Syndrome

ASHRAF VIRMANI,[a] ZBIGNIEW BINIENDA,[b] SYED ALI,[c] AND FRANCO GAETANI[a]

[a]*Research and Development, Sigma tau-HealthScience, Pomezia 00040, Italy*

[b]*Neurophysiology Laboratory, Division of Neurotoxicology, National Center for Toxicological Research, Food and Drug Administration, Jefferson, Arkansas 72079, USA*

[c]*Neurochemistry Laboratory, Division of Neurotoxicology, National Center for Toxicological Research, Food and Drug Administration, Jefferson, Arkansas 72079, USA*

ABSTRACT: Nutritional deficiency in combination with drug abuse may increase risk of developing the metabolic syndrome by augmenting cell damage, excitotoxicity, reducing energy production, and lowering the antioxidant potential of the cells. We have reviewed here the following points: effects of drugs of abuse on nutrition and brain metabolism; effects of nutrition on actions of the drugs of abuse; drug abuse and probability of developing metabolic syndrome; role of genetic vulnerability in nutrition/drug abuse and brain damage; and the role of neuroprotective supplements in drug abuse. Nutrition education is an essential component of substance abuse treatment programs and can enhance substance abuse treatment outcomes. The strategies available, in particular the nutritional approach to protect the drug abusers from the metabolic syndrome and other diseases are discussed.

KEYWORDS: nutrition; drug abuse; metabolic syndrome; L-carnitine; acetyl-L-carnitine; creatine; selenium; cocaine; ecstasy; methamphetamine; alcohol; brain; liver; metabolic compromise; metabolic modifier; glycolysis; free radicals; reactive oxygen species (ROS); vitamins; minerals; zinc; thiamine; supplements; diabetes; metabolic compensation

INTRODUCTION

The role of nutrition as a risk factor during drug abuse in provoking disease pathogenesis, e.g., alcohol abuse associated with liver injury, is well known. Nutritional deficiency may increase potential for cell damage by augmenting

Address for correspondence: Dr. Ashraf Virmani, Sigma tau-HealthScience, Via Treviso 4, Pomezia, 00040, Italy. Voice: + 39-06-916-19721; fax: + 39-06-916-12631.
e-mail: ashraf.virmani@st-hs.it

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excitotoxicity, reducing energy production, and lowering the antioxidant potential of the cells. One of the risk factors for brain developmental disorders is nutritional deficiency.[1] Role of nutrition in drug abuse is well studied for alcohol abuse but not for other drugs of abuse.

Alcohol abuse is generally associated with steatohepatitis but already in the early 1980s it was recognized that there was a population subgroup that developed this condition despite not using alcohol (non-alcoholic steatohepatitis).[2–4] This subgroup typically suffered from insulin resistance syndrome, synonymous with the metabolic syndrome (syndrome X, dysmetabolic syndrome), which is characterized by obesity, diabetes, hyperlipidemia, and hypertension.[5] The triggers of the non-alcoholic steatohepatitis include drugs, such as tamoxifen, and certain industrial toxins together with steatosis associated with inflammation, fibrosis, or necrosis. It is the interactions of nutritional abnormalities, cytokines, oxidative stress, and mitochondrial dysfunction that may underlie the induction of steatohepatitis, both alcoholic and non-alcoholic in origin.[2]

Although designer drugs, such as the amphetamine and its analogs, are popular and considered safe by the abusers, a variety of adverse effects have been associated with their use, such as the serotonin syndrome, hepatotoxicity, neurotoxicity, and psychopathology.[6] In this article, we examine the possibility that there is an increased probability of developing the metabolic syndrome in drug-abuse subjects. Treatment with antipsychotics has been associated with increased risk of developing diabetes and ketoacidosis.[7–9]

The role of nutrition together with other risk factors such as level of education, poverty, heredity, and environmental factors must be taken into account in assessing whether a drug abuser will develop the metabolic syndrome. The strategies available, in particular, the nutritional approach to protect the drug abusers from the metabolic syndrome and other diseases are discussed.

Effects of Drug Abuse on Nutrition

Abused drugs have adverse effects on the mind and on the body itself. They weaken the immune system and affect nutrition.[10] The effects on nutrition are related to behavioral changes as well as direct effects on the energy balance-related signaling systems. Alcohol-and drug-dependent subjects have distorted eating behavior that predisposes them to eating disorders (anorexia, bulimia, obesity, habitual eating). Many alcoholics are malnourished since alcohol and its metabolism prevents the body from properly absorbing, digesting, and using those nutrients. These nutritional deficiencies are not as well studied in other types of drug abuse. Drug addicts suffer from calorie and protein malnutrition with over 90% being underweight[11] and 74% of them showing clinical signs of nutrient deficiency with significantly lower hemoglobin and serum total protein levels.[12]

Effects of Drug of Abuse on Brain Metabolism

Drugs of abuse affect brain activity mainly at the level of neurotransmitter signaling and concomitantly brain metabolism in specific regions. Brain energy requirements and in particular glucose metabolism is affected. Metabolism of amino acids and fatty acids may be affected as well. Many of the studies have used positron emission tomography (PET) and an analog of glucose, 2-deoxy-2-[18F]fluoro-D-glucose, to measure regional brain glucose metabolism during drug abuse. These studies show that each drug has its own pattern of brain stimulation, inducing therefore, unique changes in brain metabolism.[13] Thus, psilocybin (hallucinogen) increases cerebral glucose metabolism in distinct right hemispheric frontotemporal cortical regions and decreases it in the thalamus.[14] The widely abused drugs like the analog of "ecstasy," 3,4-methylenedioxyethamphetamine (MDE) and methamphetamine (METH) induce cortical hypometabolism and cerebellar hypermetabolism.[14,15] Abuse of "ecstasy" (3,4-methylenedioxymethamphetamine or MDMA) reduces glucose metabolism globally in the brain but mainly in the striatum.[16] Drugs of abuse cause metabolic changes even in healthy volunteers, for example MDE significantly decreased glucose metabolism in the frontal cortex and increased it in the cerebellum and the right putamen.[17] The action of cocaine on brain is associated with metabolic changes in the prefrontal cortex.[18]

Many studies have also examined the scenario underlying these metabolic changes, such as the neurotransmission changes, i.e., dopamine and other neurotransmitters, as well as associated receptors, transporters, and enzymes.[13] Drug abusers have abnormalities in brain regions implicated in mood disorders. It is interesting to note that in METH users, PET scans of brain metabolic activity have shown that the glucose metabolism is lower in brain regions linked to depressive disorders, depressed mood, and sadness, but higher in brain regions linked to anxiety and drug cravings.[19] Chronic cocaine administration to rats results in upregulation of cytochrome *c* oxidase and therefore metabolic activity in brain reward regions such as the nucleus accumbens.[20] In the case of alcohol abuse, it has been shown by PET studies that the abuse of alcohol produces a global brain depression and that the long-term effects of alcohol abuse require several weeks of abstinence to subside.

Effect of Nutrition on Actions of the Drugs of Abuse

Several environmental factors including the individual's feeding habits will affect the reaction to the abused drug. Studies have shown that chronic food restriction increases the systemic self-administration and locomotor-stimulating effect of abused drugs (FIG. 1).[21] These nutritional effects via metabolic changes are transformed into behavioral changes and may reflect enhanced rewarding potency or a central nervous system (CNS)-based modulatory process. Differences in the amounts of macronutrients in the diet also cause different

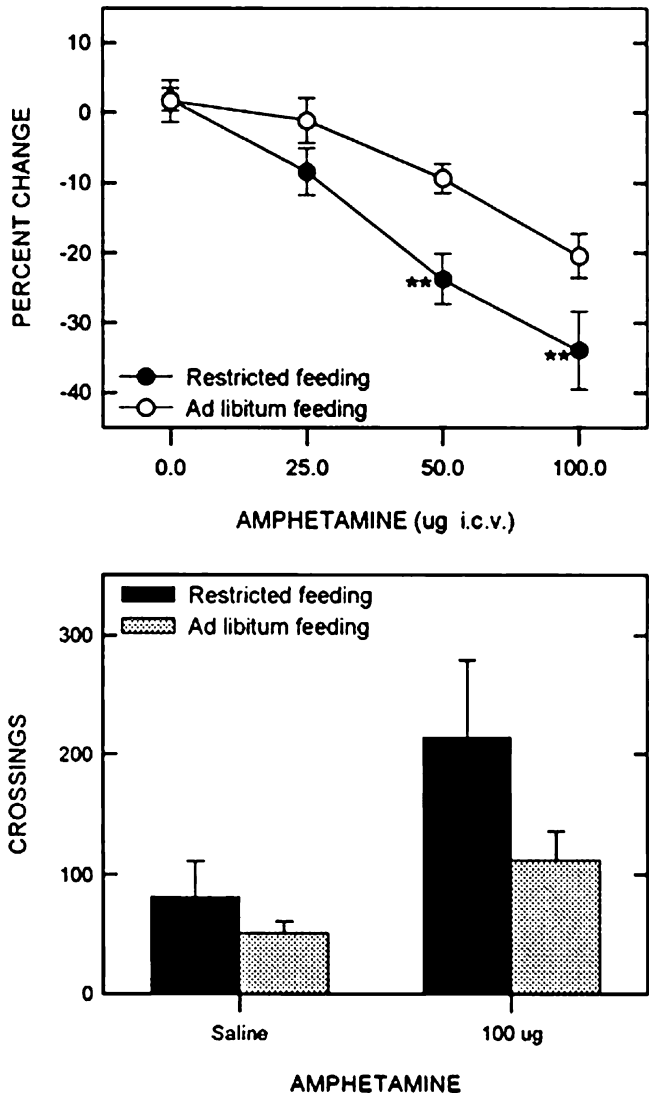

FIGURE 1. Chronic food restriction increases the systemic self-administration and locomotor-stimulating effect of amphetamine. *Top*: percentage of change in reward threshold as a function of D-amphetamine dose for food-restricted (*filled circles*) and *ad libitum* fed (*open circles*) rats. Reward thresholds were derived from lateral hypothalamic self-stimulation (LHSS) rate-frequency curves obtained immediately before and 5 min after intracerebroventricular injection of D-amphetamine. Mean ± SEM. *Bottom*: number of crossings in a shuttle box during two 30 min tests: (*a*) 5 min after intracerebroventricular injection of saline, and (*b*) 5 min after intracerebroventricular injection of 100.0 μg of D-amphetamine. Mean ± SEM. (Reprinted from Cabeza de Vaca and Carr[21] with permission from *The Journal of Neuroscience.*)

TABLE 1. Nutritional deficiency may affect cellular defenses and increase susceptibility to the metabolic syndrome during drug abuse via following pathways

- Decreased energy production
- Decreased cellular antioxidant potential
- Increased excitotoxicity
- Increased genetic susceptibility
- Reduced insulin sensitivity
- Increased susceptibility to inflammation/fibrosis
- Other?

behavioral outcomes. For instance, after cocaine withdrawal, rats were more immobile if fed a high-fat diet and were less immobile if fed a high-protein or high-carbohydrate diet.[22]

Drug Abuse May Increase Probability of Developing Metabolic Syndrome

The metabolic syndrome represents a cluster of interrelated risk factors that identify individuals at increased risk for the development of type-2 diabetes mellitus and cardiovascular events.[23] The metabolic syndrome is triggered by initial imbalances at the cellular level in various metabolic pathways (TABLE 1). These initially small metabolic imbalances cascade with time and lead to the larger problems in body functions and finally to what has been termed the *metabolic syndrome* and is generally characterized by hyperinsulinemia (impaired glucose metabolism), obesity, dyslipidemia, and hypertension.

Are drug abusers at higher risk of metabolic syndrome? The problem as to whether drug abuse is a risk factor for developing the metabolic syndrome has not been well studied but there are some indications that would suggest that drug abuse is linked with the metabolic syndrome.

First, drug-abusing patients have higher rates of diabetes complications. A study in the United Kingdom indicated that street drug use in young adults with diabetes may contribute to poor glycemic control and serious complications of diabetes.[24] The metabolic disturbances such as diabetic ketoacidosis and poor glycemic control may be further exacerbated by MDMA abuse during prolonged exercise.[25]

Second, substance abuse is a significant contributing factor for treatment non-compliance in diabetes and other diseases. A significant number of adults admitted to hospital with diabetic ketoacidosis were found to use cocaine use. Further, these individuals were associated with more frequent omission of insulin therapy in the absence of precipitating systemic illness.[26] In another study, adolescents with diabetes who reported alcohol and drug use or who reported they live in an environment of substance abuse had poorer diabetes control than patients who did not.[27]

Although more studies are needed in this area, it appears that drug abuse is indeed a risk factor for metabolic syndrome. Thus, as part of the strategy aimed at the prevention of drug abuse by drug-naïve adolescents and young adults, the detrimental effects on health and risk of developing metabolic syndrome should also be pointed out. For those drug abusers attempting abstinence and recovery from their addictions, a special treatment strategy to prevent the metabolic syndrome is advisable, possibly focusing on aerobic exercise, weight loss, and adequate nutrition with the right supplements (as discussed below). To tackle the insulin resistance, treatment with insulin sensitizers, such as metformin and thiazolidinediones, may improve both metabolic and hormonal patterns.[28] Stopping drug abuse early and following such a broad approach may delay or prevent the development of the metabolic syndrome.

Role of Genetic Vulnerability in Nutrition/Drug Abuse and Brain Damage

Another risk factor that must be mentioned here is the role of genetic susceptibility, especially in combination with nutrition and drug abuse in the development of the metabolic syndrome. Genetic polymorphism in individuals may contribute in a positive or negative manner depending on the circumstances. From affecting the drug metabolizing enzyme activities, to transport and excretion up to the level of the individual's behavior, the genetic influence should be considerable on the overall effects to the abused drug response/toxicity.[29,30] The presence or absence of certain alleles in the subjects, or the presence of defective alleles, will change drastically the behavior of that subject to the effects of drug abuse. The actual efficacy/toxicity will be affected, for example, by the rate of metabolism of the drug caused by multiple genes or by induction of gene expression.

The individual's susceptibility may already be affected even earlier by the imprinted genes which play key roles in controlling feto–placental nutrient supply and demand and their epigenetic liability in response to nutrients.[31] The maternal nutritional imbalance and resulting metabolic disturbances during critical phases of development may predispose the offspring to the adverse effects of drug abuse and development of the metabolic syndrome and may even be transmitted to the next generation.

Alcohol dependence is associated with specific genetic markers.[32] Chronic alcohol abuse causes well localized damage in the brain, mainly in the superior frontal cortex. The study conducted by Dodd and collaborators in alcoholic versus non-alcoholic subjects, revealed that alcohol dehydrogenase (ADH)3 genotype interacted significantly with NMDA receptor efficacy and affinity in a region-specific manner. Furthermore, the EAAT2 genotype was associated with local $GABA_A$ receptor β subunit mRNA expression, and GABB2 and DRD2B genotypes. They, therefore, concluded that the genotype modulated amino acid transmission locally and influenced neuronal vulnerability.[29]

Role of Neuroprotective Supplements in Drug Abuse

Alcohol abuse is linked with marked steatosis and liver injury, and malnutrition is common associated with vitamin (B1, B2, B6, B12, C, K, A, and D) and mineral deficiencies (selenium, zinc, magnesium, iron, and phosphorus). Many alcoholics suffer from a deficiency of zinc which is necessary for the body to manufacture the enzymes essential for the detoxification of alcohol.[33,34] But the most important and common deficiency in alcoholics is in the B vitamins. Thiamine (B1) deficiency in alcoholics causes neurological damage leading to Wernicke–Korsakoff syndrome.[35] Antioxidants have been proposed to counteract liver damage and vitamin E may decrease damage in cirrhotic livers,[36] but another study reported that vitamin E supplementation (500 IU per day) for 1 year did not influence liver function, survival, or hospitalization rates in people with alcoholic cirrhosis.[37] This could be related to differences in ingested doses, bioavailability, and the ability of the liver to accumulate the various antioxidant compounds.[38] On the basis of the studies reviewed, these authors suggested that lycopene-rich foods should be considered as therapeutic treatment of some liver pathologies.

The amount of alcohol that can injure the liver varies greatly from person to person as well as the gender. Alcohol seems to injure the liver by blocking the normal metabolism of protein, fats, and carbohydrates. Mechanisms involving cellular energy failure and mitochondrial dysfunction have also been implicated.[39]

There is some suggestion that alcohol in moderate amounts may infer cardioprotective effects. The "French Paradox," where diet is high in saturated fat accompanied by regular consumption of red wine is associated with such effects. However, it must be noted that it is probably the antioxidant effect of the grape polyphenols, e.g., resveratrol, found in the wine and not the actual alcohol that provide these benefits.[40] Strategies to limit the processes leading to the induction of alcoholic and non-alcoholic steatohepatitis, such as modulation of insulin resistance, normalizing lipoprotein metabolism, and down regulating inflammatory mediators, have been suggested.[3]

Compounds such as L-carnitine have been shown to protect against the alcohol toxicity. L-carnitine is a naturally occurring quaternary ammonium compound (trimethylamino-β-hydroxybutyrate) and is a vital cofactor for the mitochondrial oxidation of fatty acids, and is an endogenous compound in all mammalian species.[41] L-Carnitine exists in the body primarily in its unesterified form, but also as a number of esters (acylcarnitines) including acetyl-L-carnitine, propionyl-L-carnitine, and palmitoyl-L-carnitine. Humans take in carnitine primarily from diet 75% with the remaining 25% coming from endogenous synthesis. Supplementation with L-carnitine alleviated alcohol-induced liver damage possibly by reducing hepatic concentrations of thiobarbituric acid reactive substances, an indicator of lipid peroxidation.[42] Part of this action of L-carnitine may be related to restoration of normal transport of

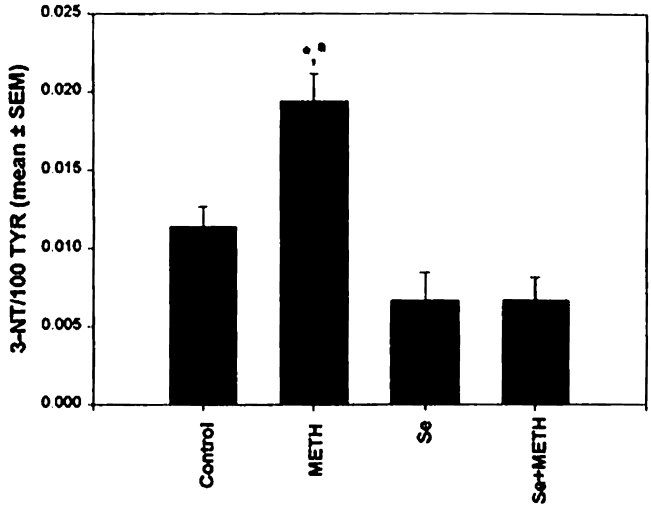

FIGURE 2. Selenium supplementation protects striatum in mouse against METH-toxicity. Effects of METH (4 × 10 mg/kg, i.p.) on 3-nitrotyrosine in the striatum of adult male C57BL/6N mice. Animals received selenium for 1 week before the first injection of METH and 1 week after the last injection of METH. Each value is mean and SEM from eight animals per group. $^{*}P < 0.05$ significantly different from control. $^{a}P < 0.05$ significantly different from Se and Se + METH groups. (Reprinted from Imam and Ali[47] with permission from Elsevier.)

fatty acids from the liver. It helps us to reduce free fatty acid load produced by ingestion of alcohol, and it also reduces elevated triglycerides and liver enzymes.[43,44] The administration of its ester, acetyl-L-carnitine has been reported to reduce cognitive deficits in chronic alcoholics.[45] A protective action of L-carnitine against METH neurotoxicity has also been found.[46]

Other supplements such as selenium also protect against METH toxicity in CNS (FIG. 2)[47] as well as against cocaine-induced myocardial oxidative stress.[48] Selenium is a well-known antioxidant that is also an essential component of several major metabolic pathways, which include not only the antioxidant defense systems but also thyroid hormone metabolism and immune function. Selenium is necessary for glutathione peroxidase action; this enzyme functions synergistically with the other antioxidants, e.g., vitamin E. Selenium deficiency has been linked to neurodegenerative and cardiovascular diseases.[49]

A number of other compounds could also be helpful against the damage induced by drug abuse. For example, creatine has been reported to have neuroprotective actions.[1,50] Creatine is a natural nutrient found in animal foods, and is commonly used as a nutritional ergogenic aid to enhance exercise performance. The creatine and its related creatine kinase enzymes are found in tissues with high-energy demand and energy production mainly muscle, where

creatine readily combines with phosphate to form creatine phosphate (PCr), a high-energy phosphagen.[51] Creatine deficiency syndromes manifesting as inborn errors of metabolism have been recently described.[52] These syndromes are characterized by a lack of creatine/phosphocreatine in the brain. Clinically, most of the patients develop a variable mental retardation and a severe speech delay associated with epilepsy, extra-pyramidal syndrome, and behavior disturbances. In animal experiments, the supplementation with creatine was reported recently to protect against the dopamine depleting effects of neurotoxic doses of METH.[53] They found that rats fed with 1% creatine in normal diet had greater striatal dopamine after 1 week of METH treatment. They also found that the indices of oxidative damage were reduced in the creatine fed compared to the animals on normal diet.

CONCLUSION

Apart from the compounds mentioned above, a number of dietary antioxidants, such as coenzyme Q10, lipoic acid, resveratrol, melatonin, polyphenols (green tea, curcumin), and flavonoids (quercetin, isoflanones, and catechins), as well as other compounds, such as omega 3 fatty acids, may also be useful in drug abuse and in the prevention of the metabolic syndrome; however, further studies are necessary.

There is a delicate balance between the metabolic systems producing energy and the intrinsic cellular protective mechanisms. Drug abuse can be detrimental to that balance. This may explain the higher risk of developing the metabolic syndrome in drug abuse condition. Such a link with the metabolic syndrome has also been found for antipsychotic medicines and tobacco.[54,55]

The correction of metabolism as well as the mineral, vitamin, specific metabolic cofactors, and supplemental compounds may reinforce the balance. Nutrition education is an essential component of substance abuse treatment programs and can enhance substance abuse treatment outcome.[56]

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