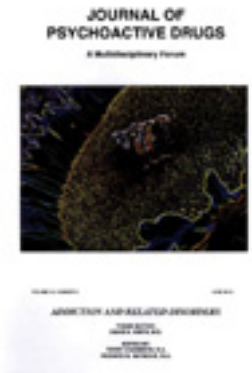

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Sweet Preference, Sugar Addiction and the Familial History of Alcohol Dependence: Shared Neural Pathways and Genes

Jeffrey L. Fortuna [a]
[a] Department of Health Science, California State University, Fullerton
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Sweet Preference, Sugar Addiction and the Familial History of Alcohol Dependence: Shared Neural Pathways and Genes

Jeffrey L. Fortuna, Dr.P.H.*

Abstract—Contemporary research has shown that a high number of alcohol-dependent and other drug-dependent individuals have a sweet preference, specifically for foods with a high sucrose concentration. Moreover, both human and animal studies have demonstrated that in some brains the consumption of sugar-rich foods or drinks primes the release of euphoric endorphins and dopamine within the nucleus accumbens, in a manner similar to some drugs of abuse. The neurobiological pathways of drug and "sugar addiction" involve similar neural receptors, neurotransmitters, and hedonic regions in the brain. Craving, tolerance, withdrawal and sensitization have been documented in both human and animal studies. In addition, there appears to be cross sensitization between sugar addiction and narcotic dependence in some individuals. It has also been observed that the biological children of alcoholic parents, particularly alcoholic fathers, are at greater risk to have a strong sweet preference, and this may manifest in some with an eating disorder. In the last two decades research has noted that specific genes may underlie the sweet preference in alcohol- and drug-dependent individuals, as well as in biological children of paternal alcoholics. There also appears to be some common genetic markers between alcohol dependence, bulimia, and obesity, such as the A1 allele gene and the dopamine 2 receptor gene.

Keywords—A1 allele, cross sensitization, dopamine 2 receptor, nucleus accumbens, sucrose concentration, sweet preference

This article will analyze the complex association between carbohydrate craving, or "sugar addiction," and familial history of alcohol dependence. One initial question, from a clinical perspective, is whether sugar addiction is synonymous with carbohydrate craving. Ingestion of carbohydrates, including simple sugars, leads to increased central production of serotonin, the calming and mood elevating neurotransmitter. Clearly in some individuals sugar-rich foods and meals act as powerful comfort foods.

*Faculty, Department of Health Science, California State University, Fullerton.

Please address correspondence and reprint requests to Jeffrey L. Fortuna, Dr.P.H., Department of Health Science, KHS-121, California State University Fullerton, 800 N. State College Blvd., Fullerton, Ca. 92831; email: jfortuna@fullerton.edu

Recent research has identified an association between parental or family history of alcohol dependence and sugar addiction in some of their biological children. There are specific areas of the brain that are activated when some individuals consume sugar-rich foods or meals. An in depth examination of these important issues is warranted.

NEUROBIOLOGY OF SUGAR ADDICTION

The Dopamine Turnover Pathway

It is well established that the drugs of abuse (cocaine, heroin, methamphetamine, etc.) cause increased dopamine turnover, that is, elevated extracellular dopamine levels in the nucleus accumbens (Wise et al. 1995; DiChiara & Imperato

1988). The pharmacologic actions of these drugs are quite different yet the effect of increasing dopamine turnover is the same.

Likewise in some animals, ingestion of sugar-rich foods can prime the release of dopamine. For example, rats with intermittent access to sugar will drink a sucrose solution in a binge-like manner that stimulates the release of dopamine within the nucleus accumbens (Avena et al. 2006; Rada, Avena & Hoebel 2005). Moreover, rats that are food deprived and then given 12-hour access to a sugar solution show a bingeing behavior. Specifically, the rats consume copious amounts of sucrose solution in the first hour (Colantuoni et al. 2002, 2001). After 30 days, receptor binding was analyzed in the rats that binged on the sugar solution and compared to chow fed controls. Dopamine-1 receptor binding increased significantly in the dorsal striatum. This is similar to the down regulation of dopamine-2 receptors that occurs in stimulant drug-dependent and alcohol-dependent individuals (Wang et al. 2004; Koob et al. 2004). This is sometimes referred to as reward deficiency syndrome (Fortuna & Smelson 2008).

Of some interest, intermittent, excessive sugar intake sensitized dopamine-1 and also mu-1 receptors, similar to the drugs of abuse. In addition, the researchers reported a "withdrawal" from sugar including depression and irritability (Colantuoni et al. 2002, 2001). Other research has even documented signs of cross sensitization from sugar to drugs of abuse (Avena et al. 2004; Avena & Hoebel 2003).

In a separate study, rats that were fed daily intermittent sugar (with chow) had a consistent release of dopamine every day as measured on days 1, 2, and 21 of the sugar access or "opportunity" (Rada, Avena & Hoebel 2005).

Even more fascinating, still another study found that when rats binged on sugar, the amount of dopamine release was proportional to the *sucrose concentration*, not the volume of sucrose consumption. (Hajnal, Smith & Norgren 2004).

THE ENDORPHIN (OPIOID) PATHWAY

In addition to the effect of sugar rich meals on dopamine release and receptor activity, recent research has uncovered the effects of sugar intake on the endorphin system. To begin with, injection of mu agonists into the nucleus accumbens increases the intake of palatable foods rich in sugar and fat (Kelley et al. 2002; Zhang, Gosnell & Kelley 1998). In addition, opioid antagonists decrease the ingestion of sweet food and decrease the feed time of palatable and preferred foods (Kelley et al. 2002).

Over time, intermittent sugar access causes decreased enkephalin mRNA expression within the nucleus accumbens (Spangler et al. 2004). This is a clinical marker that the production of central endorphin is decreased via reduced transcription of enkephalin RNA.

What is probably most intriguing is that following a period of intermittent access to sugar, and the subsequent sugar addiction, withdrawal can be precipitated with an opioid antagonist or when sugar and/or food is removed. After rats are injected with the antagonist naloxone, withdrawal symptoms include: teeth chattering, forepaw tremor, head shakes, and anxiety (in a maze) (Colantuoni et al. 2002).

So, in summary, food deprivation can induce opiate-like withdrawal; or, an opiate-like withdrawal can be obtained through the administration of the opioid antagonist naloxone. Of some interest, "food withdrawal," like opiate withdrawal, has two similar neurochemical manifestations. They are: (1) a decrease in extracellular dopamine in the nucleus accumbens, and (2) an increase in acetylcholine release from accumbens interneurons.

THE SEROTONIN OR CARBOHYDRATE CRAVING PHENOMENON

Carbohydrate craving may really be a serotonin or tryptophan craving. Serotonin (5-HT) is the primary antidepressant neurotransmitter, but also plays a critical role in the modulation of pain. In addition, serotonin regulates sleep and the circadian rhythm. No wonder so many individuals crave "comfort foods" in the evening. Such foods as cookies and milk, ice cream, cakes and sweet rolls elevate serotonin levels and thereby lift one's mood, modulate pain, and help one disengage from the trials and tribulations of the day.

Over the past 30 years significant progress has been made in the understanding of carbohydrate craving in humans. Again, carbohydrate craving may be a craving for tryptophan, the amino acid precursor or substrate of serotonin. In the 1970s, researchers at MIT (Fernstrom & Wurtman 1979) discovered that seven specific amino acids, including tryptophan, compete for entry into the brain through the LNAA (Large Neutral Amino Acid) carrier complex within the blood brain barrier. The key word here is *compete*. Whichever of these seven amino acids is most abundant in the blood, following a given meal or snack, will dominate entry into the brain for a period of four to five hours or longer. Every time we eat a meal or snack the balance of these seven amino acids is changed, based upon the constituent amino acids present in the food consumed.

Unfortunately, tryptophan is very scarce in food and thereby has a very difficult time entering the brain. Nonetheless, nature has provided one primary mechanism by which tryptophan can enter the brain through the LNAA. That mechanism is through the consumption of a carbohydrate-rich meal or snack (Fortuna 2009). For example, if one consumes a pasta dinner, without meat in the sauce, along with broccoli and carrots, a dinner salad and garlic bread—nearly a pure carbohydrate meal—one can expect to become nonfocused and sleepy as tryptophan enters the brain and dominates the LNAA for hours. This is because a carbohydrate-rich meal causes blood glucose levels to rise. In response to a moderate rise in blood glucose, the pancreas releases the hormone insulin. As it turns out, all

of the amino acids that compete with tryptophan for entry through the LNAA are sensitized to insulin. So, these six amino acids evacuate or partially evacuate the blood. When this happens the ordinarily scarce tryptophan becomes the most abundant of the seven competing amino acids and dominates entry into the brain (Fortuna 2009).

Research has clarified that there are several sets of patients who exhibit a chronic carbohydrate craving. These include individuals with bulimia, binge eating disorder, obesity, alcohol dependence, stimulant drug dependence and many smokers. There is also some research showing that patients with chronic pain states such as multiple sclerosis and diabetic neuropathy have notable carbohydrate craving.

An interesting side note to all of this is the issue of acquisition of specific palatable textures and tastes. For example, one of the reasons that nonfat ice cream has not been a major success in the United States is the fact that it is not creamy. Most people who like ice cream, and even those who enjoy it on occasion, like the creamy sensation when they eat it. It is just not the same without some creamy texture. Again, it is a texture (e.g., creamy) craving.

One could argue that chocolate has an irreplaceable taste and texture. Both the unique creamy texture and multiple tastes (e.g. over 400 distinct flavors) make chocolate a cherished food among many people all over the world. Indeed, in a number of countries cacao seeds have been used as currency.

LINK BETWEEN SUGAR ADDICTION & FAMILIAL (PATERNAL) ALCOHOL DEPENDENCE

Recent research has identified an association between paternal history of alcohol dependence and a sweet preference, or "sugar addiction" in some children who are substance dependent. For example, Janowsky and colleagues (2003) noted a greater sweet preference in cocaine-dependent patients when compared to nonaddicted controls. Kampov-Polevoy and colleagues (1998, 1997) also found a greater sweet preference in alcoholic patients when compared to nonalcoholic controls. Similarly, Kampov-Polevoy and colleagues (2001) compared a sample of alcohol-dependent men and nondependent men and noted that individuals with a paternal history of alcoholism were three times more likely to prefer stronger sweet solutions, regardless of their present alcohol status.

Previous research going back to the 1940s (Williams, Berry & Beerstecher 1949; Richter 1941) has suggested a higher consumption of sweets or a greater "sweet liking" in alcohol-dependent individuals. A similar association has been noted in rats that had a genetic history of alcohol dependence (Sinclair et al. 1992).

A number of neurobiological markers in various types of addictive behavior including bulimia, binge eating disorder, some forms of obesity and alcohol dependence are now beginning to be uncovered. All of these disorders may involve a faulty endorphin system.

It is now well established that in some individuals food primes the release of beta-endorphin within the nucleus accumbens (Gianokolakis et al. 1990). For example, multiple studies have shown that the addition of sucrose solutions for neonates who are in acute pain notably modulates pain levels (Gradin & Schollin 2005; Stevens, Yamada & Ohlsson 2004). Moreover, if the infants are then given a narcotic antagonist, the sucrose-induced analgesia is then reversed (Taddio et al. 2003; Blass, Fitzgerald & Kehoe 1987). This is similar to the naloxone challenge, which induces opiate withdrawal in narcotic dependent individuals.

So, sweet preference or "sugar addiction" may be a compensatory behavior for a latent or deficient beta-endorphin system. As such, it may be another form of self medication to correct a neurobiological deficiency.

In another investigation, Kampov-Polevoy and colleagues (2003) noted a major differential in sweet preference among alcoholics and nonalcoholic controls. The preference for sweets was found in 65% of alcoholic subjects, compared with only 16% of nonalcoholic controls. In a separate study, cocaine-dependent patients were found to prefer stronger sweet solutions when compared with psychiatric patients without a genetic history of alcohol or other drug dependence in their family of origin.

So, the hypothesis that there is a genetic association between sweet preference and familial alcohol dependence appears to be supported by the findings showing that individuals with a paternal history of alcohol dependence were three times more likely to prefer sweets than individuals with no paternal history of alcoholism, regardless of their own alcoholism status.

ARE GENES INVOLVED IN SWEET PREFERENCE?

Research is just beginning to clarify that polymorphisms of specific genes and alleles may underlie the sweet preference in a similar way that specific polymorphisms underlie the risk for alcohol dependence. A couple of interesting research questions arise. First, can the sweet preference genes be inherited from either paternal or maternal history of alcohol dependence? Also, are they the same genes that place one at risk for being alcohol dependent? Moreover, are the same or similar genes involved in specific forms of obesity and bulimia?

Let's review what is known so far. As might be expected, many bulimic and obese individuals have a sweet preference and self-medicate with a variety of sweets and sugars to activate reward pathways (i.e., dopamine, beta-endorphin) like many alcohol- or drug-dependent individuals. In these individuals, food triggers the release of dopamine and beta-endorphin within the nucleus accumbens and ventral tegmental area.

Numerous studies have elucidated that the dopamine 2 receptor gene is a critical determinant of the ability to experience pleasure from "normal" life events (i.e., reading a good book, watching a funny movie, exercise, music, fun activities with friends and family) (Fortuna & Smelson 2008; Wang et al. 2001). A deficiency in the number of dopamine 2 receptors or "pleasure" receptors is a common marker for increased risk to abuse alcohol and other drugs. This phenomenon has sometimes been referred to as the reward deficiency syndrome and involves a deficiency in the number of dopamine 2 receptors in the striatum (Blum et al. 1996).

The A1 allele of the dopamine 2 receptor (DRD2) has been implicated in a wide variety of addictive disorders including: alcohol abuse and dependence, cocaine dependence, methamphetamine dependence, bulimia, binge eating disorder, and obesity. The presence of the A1 allele is strongly correlated with reduced dopamine 2 receptor density (Davis et al. 2008; Nisoli & Brunani 2007).

There are a number of important arguments in play in this discussion of the dopamine 2 receptor. For example, is having an underactive D2 receptor system strictly a result of genes or could that condition be caused and/or exacerbated by drugs of abuse, binge eating, bulimia, and other specific behaviors? This is certainly an open-ended question that only years of further research will answer.

One study evaluated the association of the D2 receptor gene in individuals with binge eating disorder and obesity. In that study, individuals who carried the A1 allele self-reported greater reward sensitivity from food than normal weight controls. The investigators also found that the presence of the A1 allele predicted reduced receptor density (Davis et al. 2008).

Still another study evaluated the presence of the dopamine 2 receptor gene A1 allele in persons diagnosed with eating disorders, specifically: anorexia, bulimia, and obesity. The researchers found a strong association between having the A1 allele gene and having an eating disorder, albeit quite variant. Moreover, the researchers suggested that the presence of the A1 allele was not simply related to body weight, but that it might also be a strong predictor of psychological traits involving a drive for "thinness" and a belief in "ineffectiveness." So, the presence of this allele might manifest in some very different psychological disorders (Nisoli & Brunani 2007).

In yet a different study the presence of the dopamine 2 receptor A1 allele confirmed a greater risk for obesity as well as related addictive disorders (Blum et al. 1996). For example, in a group of 40 obese patients, the 23 individuals who had a comorbid substance abuse disorder had a notably greater prevalence of the A1 allele when compared with the 17 obese subjects without a substance abuse disorder.

The genetic associations regarding the presence of the A1 allele on a wide range of addictive behaviors provide significant credibility to the neurobiological basis of addiction. Much of this research is tentative and was only evaluated in animals. Nonetheless, this research paves the road for future investigations in humans.

CONCLUSION

There is no doubt that when some individuals eat sweets the ingestion of such food dramatically changes their blood chemistry. In addition, in some individuals carbohydrate or sweet food intake has a drug-like effect. That is, such foods profoundly change brain chemistry. This phenomenon appears to have some genetic associations with paternal history of alcohol dependence. Indeed, some individuals may be "self-medicating" with food. It may be like what Hippocrates said: "food is the oldest drug."

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