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Neuro-Genetics of Reward Deficiency Syndrome (RDS) as the Root Cause of "Addiction Transfer": A New Phenomenon Common after Bariatric Surgery

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Abstract

Now after many years of successful bariatric (weight-loss) surgeries directed at the obesity epidemic clinicians are reporting that some patients are replacing compulsive overeating with newly acquired compulsive disorders such as alcoholism, gambling, drugs, and other addictions like compulsive shopping and exercise. This review article explores evidence from psychiatric genetic animal and human studies that link compulsive overeating and other compulsive disorders to explain the phenomenon of addiction transfer. Possibly due to neurochemical similarities, overeating and obesity may act as protective factors reducing drug reward and addictive behaviors. In animal models of addiction withdrawal from sugar induces imbalances in the neurotransmitters, acetylcholine and dopamine, similar to opiate withdrawal. Many human neuroimaging studies have supported the concept of linking food craving to drug craving behavior. Previously our laboratory coined the term Reward Deficiency Syndrome (RDS) for common genetic determinants in predicting addictive disorders and reported that the predictive value for future RDS behaviors in subjects carrying the DRD2 Taq A1 allele was 74%. While poly genes play a role in RDS, we have also inferred that disruptions in dopamine function may predispose certain individuals to addictive behaviors and obesity. It is now known that family history of alcoholism is a significant obesity risk factor. Therefore, we hypothesize here that RDS

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Conflict of Interest

Kenneth Blum, PhD owns patents related to KB220Z and has provided LifeGen, Inc, San Diego, California with worldwide exclusive rights. Kenneth Blum owns stock in LifeGen, Inc. John Giordano is a Lifegen, Inc partner. No other author claims any conflict of interest.

is the root cause of substituting food addiction for other dependencies and potentially explains this recently described Phenomenon (addiction transfer) common after bariatric surgery.

Keywords

Bariatric surgery; Addiction transfer; Cross tolerance; Reward Deficiency Syndrome; Dopamine; Reward genes

Introduction

Bariatric surgery**,** or weight loss surgery, includes a variety of procedures performed on people who are obese. Weight loss is achieved by reducing the size of the stomach with an implanted medical device (gastric banding) or through removal of a portion of the stomach (sleeve gastrectomy or biliopancreatic diversion with duodenal switch) or by resecting and re-routing the small intestines to a small stomach pouch (gastric bypass surgery). Long-term studies show the procedures cause significant long-term loss of weight, recovery from diabetes, improvement in cardiovascular risk factors, and a reduction in mortality of 23% from 40% [1].

Bariatric surgery is intended for subjects with BMI ≥ 40 kg/m(2) or ≥ 35 kg/m(2) with co-morbidities [2]. After 60 years, physiological age and co-morbidities need to be very carefully considered. In genetic obesity, surgery seems appropriate. Main contraindications consist in severe disorders in feeding behavior, non-stabilized psychiatric disorders, alcoholism, drug addiction and inability to participate in prolonged medical follow-up. The surgical process includes many important stages: assessment and preparation by a multidisciplinary team to identify contraindications, give optimal patient pre-operative education, diagnose and treat co morbidities such as sleep apnea syndrome, diabetes and cardiopulmonary disease and assess psychological and nutritional status and feeding behavior. The decision to intervene is also based on the need for lifelong followup including: screening for nutritional deficiencies and surgical complications, counseling to reinforce diet and physical activity and assist in adaptation to new situations (such as pregnancy), and referral for psychological care if necessary [3].

According to Odam et al. [3] predictors of significant postoperative weight regain after bariatric surgery include indicators of baseline increased food urges, decreased well-being, and concerns over addictive behaviors. Accordingly, when determining eligibility for bariatric surgery for extremely obese patients, psychiatric screening is crucial; it is also central to postoperative success. Half of bariatric surgery candidates are depressed and in patients with a body mass index of 40 kg/m^2 or greater, there is a fivefold risk of depression [4].

Reduced mortality and morbidity

Several recent studies report decrease in mortality and severity of medical conditions after bariatric surgery [4–7]. However, long term effects are not clear [8]. In the Swedish prospective matched controlled trial, patients with a BMI of 34 or more for men and 38 or more for women underwent various types of bariatric surgery and were followed for an average of 11 years. Surgery patients had a 23.7% reduction in mortality (5.0% vs. 6.3% control, adjusted hazard ratio 0.71). This means 75 patients must be treated to avoid one death after 11 years. In a Utah retrospective cohort study that followed patients for an average of 7 years after various types of gastric bypass, surgery patients had 0.4% mortality while control patients had 0.6% mortality [6]. However, death rates were lower in the gastric bypass patients for all diseases combined, as well as for diabetes, heart disease and cancer.

On the other hand, deaths from accident and suicide were 58% higher in the surgery group [9].

A randomized, controlled trial in Australia compared laparoscopic adjustable gastric banding ("lap banding") with non-surgical therapy in 80 moderately obese adults (BMI 30–35). At 2 years, the surgically-treated group lost more weight (21.6% of initial weight vs. 5.5%) and had statistically significant improvement in blood pressure, measures of diabetic control, and high density lipoprotein cholesterol [7]. Bariatric surgery in older patients has also been a topic of debate, centered on concerns for safety in this population. One study of elderly patients undergoing laparoscopic bariatric surgery at Mount Sinai Medical Center, however, reported 0% conversion to open surgery, 0% 30-day mortality, 7.3% complication rate, an average hospital stay of 2.8 days and post operative mortality from 0.1 – 2% [9]. Interestingly the rate of complications appears to be reduced when the procedure is performed by an experienced surgeon. Guidelines recommend that surgery be performed in dedicated or experienced units [10].

Bariatric surgery and addictive behaviors

The obesity epidemic is emerging as the most debilitating disease of modern times, as well as the leading cause of preventable death. For persons affected by morbid obesity, bariatric surgery is one intervention with proven effectiveness for long term significant weight loss. In addition, results of numerous scientific studies demonstrate that weight loss following bariatric surgery is accompanied by numerous other positive outcomes, including dramatic improvement in quality of life, reduction or even reversal of chronic medical conditions such as hypertension, sleep apnea and diabetes—and lengthening of life span [11]. In fact a 25-year mortality follow-up in The Program on the Surgical Control of the Hyperlipidemia (POSCH) shows statistically significant gains in: overall survival, cardiovascular disease-free survival, and life expectancy, in the surgery group compared with the control group [12]. Now following years of successful weight-loss surgeries, clinicians and researchers are observing that some patients stop overeating and instead acquire new compulsive disorders such as alcoholism, gambling or other addictions like compulsive shopping. While the suggestion has been made that patients adopt a new addictive habit as an exchange for their compulsive eating problem (addiction transfer), how frequently this type of phenomenon occurs and whether there is a true cause-and-effect relationship between the surgery and the appearance of these behaviors has not been established.

There are however number of PUBMED reports which suggest that this new phenomena is on the rise and is real. Numerous parallels exist between obesity and addictive behaviors, including genetic predisposition, personality, environmental risk factors, and common neurobiological pathways in the brain In fact, the indications for bariatric surgery as therapeutic procedure for morbidly obese patients requires the application of selection criteria which deal with the degree of obesity, associated complications and previous failure of conventional therapy. Alcohol or drug addiction and concomitant serious disease are contraindications for bariatric surgery [13]. Studies in this area have included narcotic withdrawal, alcohol abuse and other addictions but more empirical research is certainly needed [13–17]. Most importantly, the relationship between eating, overeating, and addiction have been discussed, debated and more recently investigated.

Gold's group and others have hypothesized that drugs of abuse compete with food for brain reward sites [18,19]. In their report on an inverse relationship between the presence of comorbid overweight/obesity and substance use disorders in bipolar I disorder, the McIntyre et al. [19] results suggest that comorbid addictive disorders (i.e., substance use and compulsive overeating) may compete for the same brain reward systems.

Overeating and obesity may act as protective factors reducing drug reward and addiction. In their study Kleiner et al. [20] examined 374 charts of all active weight management patients in a 12-month period. Demographic information, laboratory testing, psychiatric diagnostic interview, alcohol and drug history were reviewed. A detailed alcohol use, abuse, dependence history was present in 298 charts as part of the pre-bariatric evaluation. The relationship between BMI and alcohol use among female patients (n = 298) was then analyzed. They found a significant ($p < .05$) inverse relationship between BMI and alcohol consumption. The more obese the patient was, the less alcohol they consumed. The percentage of women who consumed alcohol in the past year decreased as BMI level increased. These results confirmed that the surgeons' perception that it is rare to find a morbidly obese patient excluded for bariatric surgery because of excessive alcohol consumption. Gold's group concluded that obese patients have lower rates of alcohol use than found in the general population of women. As BMI increases, lower rates of alcohol consumption are found. Overeating may compete with alcohol for brain reward sites, making alcohol ingestion less reinforcing [20]. Other research by Hagedorn et al. [21] concluded that alcohol metabolism was significantly different between the postgastric bypass and control subjects. The gastric bypass patients' had a greater peak alcohol level and a longer time for the alcohol level to reach 0 than the controls. These findings provide caution regarding alcohol use by gastric bypass patients with altered alcohol metabolism.

Substance-abuse centers, including the Betty Ford Center in Rancho Mirage, Calif., say they are seeing more bariatric-surgery patients checking in for help with new addictions. And alcohol use has become a topic of discussion on bariatric-surgery-support sites, such as Weight Loss Surgery Center, wlscenter.com. In an unpublished statement at the Betty Ford Center, about 25% of alcoholics who relapse switch to a new drug, such as opiates. While still controversial the conversion rate to other dependencies vary from only 5% to 30% [22].

To help us understand the nature of cross-tolerance and addiction transfer we are providing a number of case reports to illustrate this emerging new phenomena after bariatric surgery.

Case Reports

Case 1

Client H was a 27 year old, white female who entered treatment for polysubstance abuse and bipolar disorder November 2008. Her substances of choice were opiates (heroin), stimulants (crack) and benzos (xanax). She weighed 135 lbs, with a 61in height on a small frame, upon arriving in treatment. She entered treatment 2 years following a gastric bypass procedure.

Prior to surgery, Client H weighed 293 lbs. She admitted to abusing alcohol and occasional marijuana use prior to surgery in October of 2006. Client H underwent gastric bypass at 25 years of age. Following the surgery, she found that she could no longer drink sufficient quantities of alcohol to produce the results that she desired and became addicted to the pain medication that she was prescribed for post operative pain.

During the two years that followed her surgery, she progressed from prescription medications to street drugs. She began using cocaine because she found that she had no energy as a result of both the opiates and the probable malnutrition induced by the surgery. Crack was a natural progression from cocaine and heroin use supplemented then replaced prescription opiates.

As of December 2010, Client H has nearly 2 years clean and sober. She relapsed twice during the first 90 days after treatment. Currently, Client H has been using amino acids to manage her bipolar symptoms.

Case 2

Client M was a 47 year old, white female who entered treatment for polysubstance abuse, bipolar disorder and anxiety disorder. Her substances of choice were alcohol, pain pills and cocaine. Client M entered treatment in February of 2010 weighing 235 pounds three (3) years following lapband surgery in October of 2007.

Prior to surgery she weighed 285 pounds. She has been to treatment five times before and admits to abusing pain pills prior to surgery. Her lowest weight after surgery was 200 pounds.

She currently has 10 months clean and sober and is using amino acids to manager her bipolar symptoms and anxiety.

Case 3

J is a 44 year old morbidly obese female who suffers from hypertension, type 2 noninsulin dependent diabetes, obstructive sleep apnea and lower extremity venous stasis. In the past she has been hospitalized for recurrent cellulitis and received IV antibiotics. She also suffers from long term chronic low back and knee pain and had been a patient in our pain management program for several years. During this time her pain has been marginally controlled. Her physical examination and radiologic studies suggests degenerative disc disease, facet joint arthropathy and osteoarthritis. Her treatment plan included, weight loss, physical therapy, and interventional modalities. After trying several nonopioid medications and adjuncts, her regimen progressed to include chronic opioid therapy which provided moderate relief and improved function. Her medicinal regimen consisted of pregabalin 75 mg TID, duloxitine 60 mg/day, as well as time-release oxymorphone and one or two rapid onset short acting opioids for episodic breakthrough pain. Her compliance with this regimen had been exceptional with appropriate pill counts. It was common for her to have leftover breakthrough pain pills each month. She reported minimizing the use of breakthrough opioid analgesics because she did not like the way they made her feel. As a result, her breakthrough medications often required no refill. Her random drug screens were always appropriate.

J reported being overweight as far back as she could remember. She suffered from low self esteem which she attributed to being overweight. At the time of the bariatric surgery evaluation her weight was 348 lbs. In the past she had attempted numerous diets with limited success. She smoked tobacco and had seriously attempted to quit “on multiple occasions” without success. She admitted to worrying about the possibility of gaining weight with smoking cessation. Her sister, father and husband smoke cigarettes were all overweight. She has no history of compulsive behaviors other than overeating. J reported overeating especially when anxious or depressed and experienced significant guilt afterwards. She reported that she rarely felt satiated with normal proportions. She had a history of depression for which she was in remission. She had a stable marriage, no children and was employed as a registered nurse in a hospital cancer ward.

Because her weight was contributing significantly to her many medical as well as chronic pain problems, J was evaluated for bariatric surgery. After successfully completing the pre-surgery screening and educational program, J underwent successful gastric bypass surgery and had an uneventful postoperative course. When she followed up at our pain clinic approximately three weeks after her surgery she had already lost fourteen pounds. She continued to lose weight over the next 8 months and though we expected this weight loss to have a positive effect on pain control, J consistently complained of increased knee and back pain and insisted on continuing tid breakthrough medications. She called our clinic on several occasions requesting early appointments due to scheduling conflicts with her work

and family obligations. Unlike prior t surgery, J also forgot to bring her pill bottles with her to appointments for counting as is our practice.

Months later a random urine drug screen was repeated. This was appropriate for her controlled release medication, though her breakthrough was absent. Her explanation for this absence was she had not needed it for the several days prior to her appointment and therefore the drug levels must have dropped to undetectable. Several months later another point-of-contact random drug screen was positive for benzodiazepines. At first she insisted that this was an error. However, she finally admitted taking a single clonazepam several days prior to the appointment for anxiety. She said this pill was leftover from a very old prescription that she had failed to discard. Instead of clonazepam. GC/MS confirmation testing which returned several days later was positive for alprazolam metabolites, as well as ethyl glucuronide (ETG), a test indicative of alcohol consumption within the past several days. Though not precisely correlated with the degree of alcohol consumption, her level of 25,000 was well beyond our cutoff of 1000 ng/dl. Since the ingestion of controlled medications and alcohol consumption was a violation of her opioid agreement, J was called and told to come in immediately.

At first J denied the validity of the results, however when confronted with the possibility of clinic discharge she admitted to taking an occasional Xanax that she obtained from a “friend” and “ had an occasional drink” for anxiety. After a long discussion of the dangers of combining benzodiazepines with opioids, especially with coexisting obstructive sleep apnea and reviewing clinical policies with her, J agreed to follow-up ASAP with psychiatry for evaluation and appropriate treatment of her anxiety. She assured us that this would not happen again. She kept her psychiatry appointment the following week and her psychiatrist increased her duloxitine to 90 mg/day, her pregabalin to 100 mg tid, and arranged for her to receive counseling and begin cognitive behavioral therapy. Later that same week our clinic received a message from J stating that her medications had been stolen the previous evening and requesting a replacement prescription. She also reminded us that this had never happened in the past. She was told to bring in a police report. When she arrived, she requested the prescription and became angry when told that she needed to sign in for a full appointment and a discussion of events with her doctor. Her vital signs were significant for an increased heart rate and elevated blood pressure. Her pupils were dilated and she seemed agitated. When told that she needed to provide urine for a repeat drug screen, J became extremely angry, and stated that she had suffered from the flu and had been experiencing diarrhea and GI distress and was probably too dehydrated to provide a urine sample. We explained that this was an absolute requirement, and had her sit in the waiting room and drink water until she was able to do so. The urine she provided was noted to be very dilute, not much above room temperature and negative for all drugs. When confronted with these results, she became upset and finally admitted that her medications had not been stolen but that she had actually overused them and that she had run out early. Furthermore J confessed that she has been going to another pain clinic and obtaining additional opioid medications. She demanded that we just transfer her care there. When we stated that we needed to call them to discuss these events, she broke down and admitted that she felt that she had developed a problem with alcohol and opioids, and had been drinking heavily for the past six months and concealing it from her family. She stated that she tried to quit drinking alcohol after her recent positive urine drug screen but developed “jitters” and nausea. She also admitted that she had been taking Xanax several times a day for the past few months. She had also been overeating constantly. Finally, she confessed that her pain had actually improved along with her weight loss, however she had embellished her symptoms because the pain medications seemed to elevate her mood and she felt that she could not do without them. She admitted that she felt unhappy, that her life was out of control and was experiencing feelings of guilt surrounding her deceptive behavior and recently had been

experiencing suicidal ideation. J wanted help and agreed to be immediately admitted to our drug detoxification facility. While in detox, she also admitted that she had recently begun diverting dilaudid while at work and that one of her coworkers recently approached her asking if everything was OK. She felt that it was just a matter of time before she was discovered. She agreed to sign a contract with the state's recovering nurses program.

While in treatment, J was placed on buprenorphine for pain, embraced the diagnosis of addiction, began going to AA and NA meetings, and obtained a sponsor who is guiding her through the 12 steps of alcoholics anonymous. Her anxiety and depression has improved and she has continued to participate in outpatient cognitive/behavioral therapy. Her weight loss has been slow but steady, and her compliance in our pain clinic has been 100%. She has been participating several times a week in aqua therapy. At this time J continues to take sublingual buprenorphine at a dose of four milligrams every eight hours. Her weight is now 214 lbs and she has signed a five year contract with the impaired nurse monitoring program and is optimistic about being allowed to return to work.

Case 4

Fifty-five year old man who weighed 423 lbs prior to gastric bypass surgery. He had a BMI of 63. He has done well after surgery and now weighs 180 lbs. He has transferred his food addiction to exercise. He runs jogs and exercises religiously five times per week. He has already run 2 half marathons and plans to run a full marathon (26 miles) in a few months. This is an example of a positive transfer addiction.

Case 5

Forty year old female who had a lap gastric bypass for a BMI of 44 five months ago. Post operatively has been non compliant with her vitamins and has begun to smoke and drink coffee excessively. Despite smoking cessation counseling, she continues to use tobacco. She has been explained the increased risk of marginal ulcer in gastric bypass patients who smoke.

Because of these new phenomena it is generally agreed by bariatric surgeons across America that comprehensive physical and psychological pre-operative assessments combined with continued medical care and counseling post-operatively are critical for assuring the best possible outcome for patients who undergo bariatric surgery. Prospective patients may have a previous or current history of various mental health disorders, including binge eating or addictions to cigarettes, alcohol, drugs or other illegal substances; active substance abuse is generally considered a reason to exclude a patient from surgery. However, the pre-surgical screening programs such as genetic testing may in the not too distant future help identify persons affected by such problems [23] and allow them to receive treatment so that they can overcome the addiction and then be considered for bariatric surgery in the future.

Common dopaminergic mechanism of food and drug craving behavior

Certainly, overeating in obese individuals share similarities with the loss of control and compulsive drug taking behavior observed in drug-addicted subjects. The mechanism of these behaviors is not well understood. However, recent studies by Wang et al. [24] with positron emission tomography (PET) in drug-addicted subjects documented reductions in striatal dopamine (DA) D2 receptors. In pathologically obese subjects, the same researchers [25] found reductions in striatal DA D2 receptors similar to that in drug-addicted subjects. Moreover, DA D2 receptor levels were found to have an inverse relationship to the body mass index of the obese subjects. Wang et al [25] postulated that decreased levels of DA D2 receptors predisposed subjects to search for reinforcers; in the case of drug-addicted subjects, the drug and in the case of the obese subjects, food as a means to temporarily

compensate for a decreased sensitivity of DA D2 regulated reward circuits. Understanding the mechanisms involved in food intake will help to suggest strategies for the treatment of obesity. This understanding has been researched by Stice and associates revealing that carriers of the DRD2 A1 allele show a blunted reward circuitry response to palatable food and that carriers of the polymorphisms of the D2 and the D4 genes with a blunted response gain weight in a one-year follow –up [26–28].

Furthermore, diminished dopaminergic neurotransmission contributes to decreased reward and negative eating behaviors in obesity. While Bariatric surgery is the most effective therapy for obesity and rapidly reduces hunger and improves satiety through unknown mechanisms little is known about dopaminergic activity following this surgical procedure. Volkow et al [29] hypothesized that dopaminergic neurotransmission would be affected after Roux-en-Y-Gastric Bypass (RYGB) and Vertical Sleeve Gastrectomy (VSG) surgery and that these changes would influence eating behaviors and contribute to the positive outcomes from bariatric surgery. In their study, body weight decreased as expected after surgery. DA D2 receptor availability decreased after surgery. Regional decreases (mean+/–SEM) were caudate 10+/–3%, putamen 9+/–4%, ventral striatum 8+/–4%, hypothalamus 9+/–3%, substantia nigra 10+/–2%, medial thalamus 8+/–2%, and amygdala 9+/– 3%. These were accompanied by significant decreases in plasma insulin (62%) and leptin (41%).

Volkow et al. [29] points out that decreases in DA D2 receptor availability after RYGB and VSG most likely reflect increases in extracellular dopamine levels. Enhanced dopaminergic neurotransmission may contribute to improved eating behavior (e.g. reduced hunger and improved satiety) following these bariatric procedures. However, it might also reflect a decrease in brain D2/D3 receptor availability in the longer term which will enhance addiction liability and lead to aberrant drug seeking behavior as an addiction transfer or even cross tolerance. These findings may have real importance in explaining in part the increased risk for drug seeking behavior following bariatric surgery. However, it is our hypothesis herein that the real culprit may reside in a condition we have coined called RDS and the genetic antecedents thereof [30].

Neurogenetics of RDS as an antecedent to food and drug cravings

One new hypothesis for epidemic obesity is food addiction, which is associated with both substance-use and eating disorders. Emerging evidence has shown that there are many neural, hormonal and genetic pathways and antecedents that are shared. Functional neuroimaging studies have revealed that reinforcing food has characteristics similar to that of drugs of abuse. Moreover many of the brain changes reported for hedonic eating and obesity are also seen in various forms of addiction. A consensus of the literature suggests that overeating and obesity may have an acquired drive like drug addiction with regard to motivation and incentive, craving, wanting, and liking. These behavioral elements occur after early and repeated exposures to stimuli. Liu et al [31] concluded that the acquired drive for food and the relative weakness of the satiety signal would cause an imbalance between the drive and the hunger/reward centers in the brain and their regulation.

Warren and Gold [32] pointed out the relationship between obesity and drug abuse in response to a paper by Kalarchian et al. [33] who found that approximately 66% of the participants had a lifetime history of at least one axis I disorder, and 38% met diagnostic criteria at the time of preoperative bariatric surgery evaluation. In addition, 29% met criteria for one or more axis II disorders. Axis I psychopathology, but not axis II, was positively related to BMI, and both axis I and axis II psychopathology were associated with lower scores on the Medical Outcomes Study 36-item Short-Form Health Survey. It was concluded current and past DSM-IV psychiatric disorder (including a number of addictive behaviors) are prevalent among bariatric surgery candidates and are associated with greater obesity and

lower functional health status, highlighting the need to understand potential implications for surgery preparation and outcome.

Certainly, eating behaviors are similar to those of other addictions since both affect the levels of dopamine in the meso-limbic dopaminergic system [34]. It is well established that there is an increased prevalence in obese individuals carrying the DRD2 Taq A1 allele [35–39] and this allele has been linked to low levels of D2 receptors in obese individuals [40–43].

In order to investigate the prevalence of the Taq I A1 allele of the dopamine receptor gene (DRD2) in obesity with and without comorbid substance use disorder, Blum et al [44] investigated a total of 40 patients, from an outpatient neuropsychiatric clinic in Princeton, New Jersey, by genotyping for the presence or absence of the Taq I DRD2 A1 allele. The prevalence of the Taq I A1D2 dopamine receptor (DRD2) alleles was determined in 40 Caucasian obese females and males. In this sample with a mean BMI of 32.35 +/− 1.02, the A1 allele of the DRD2 gene was present in 52.5% of these obese subjects. Furthermore, they found that in the 23 obese subjects possessing comorbid substance use disorder, the prevalence of the DRD2 A1 allele significantly increased compared to the 17 obese subjects without comorbid substance use disorder. The DRD2 A1 allele was present in 73.9% of the obese subjects with comorbid substance use disorder compared to 23.5% in obese subjects without comorbid substance use disorder. Moreover, when we assessed severity of substance usage (alcoholism, cocaine dependence, etc.) increasing severity of drug use increased the prevalence of the Taq I DRD2 A1 allele; where 66.67% (8/12) of less severe probands possessed the A1 allele compared to 82% (9/11) of the most severe cases. Linear trend analyses showed that increasing use of drugs was positively and significantly associated with A1 allelic classification ($p < 0.00001$). These preliminary data suggest that the presence of the DRD2 A1 allele confirms increased risk not only for obesity, but also for other related addictive behaviors further supporting the commonality between food and drug addiction. Therefore, these individuals use food to raise their dopamine levels initially through positive reinforcement but secondary because of a blunted reward circuitry response to palatable food as pointed out by Stices group [26–28] which causes a weak satiety signal leading to weight gain. Certainly it has been shown that the activity of dopamine in the brain can be related to abnormal eating behavior, binge eating and other eating disorders including bulimia [45–47]. In terms of genetics and eating disorders there have been a number of association studies linking various type of eating disorders with candidate gene polymorphisms: serotonergic [48–51], opiate receptors and peptides [52–57] and GABA [58–60].

It is known that many genes are involved in complex behavioral disorders including addictive behaviors Li et al. [61] performed a meta-analysis of 396 genes that were supported by two or more independent items of evidence to identify 18 molecular pathways that were statistically significantly enriched, covering both upstream signaling events and downstream effects. Five molecular pathways significantly enriched for all four different types of addictive drugs were identified as common pathways which may underlie shared rewarding and addictive actions, including two new ones. In their gene map they found that all roads lead to two common neurotransmitters glutamate and dopamine.

Thus the key neurotransmitter of addiction, DA, has site specific action regulating the intake of food and it reinforces the effects of food [62]. As Stice et al. [63] and others [64] have suggested dopamine is necessary to begin the meal process. It acts upon the prefrontal area, ventral medial hypothalamus and the arcade nucleus to reduce the intake of food and prevent hyperphagia, which in turn is influenced by leptin, insulin and other hormones [64]. Blum

and Gold [65] have inferred that disruptions in DA function may predispose certain individuals to addictive behaviors and obesity.

Animal models of food addiction

Interestingly, animal models have shown that the predisposition to food addiction in offspring was caused by feeding rat mothers junk food consisting of fatty, sugary, and salty snacks during pregnancy and lactation [67]. Rat offspring showed increased weight gain and BMI compared to controls, while their mothers displayed bingeing and overeating junk food [67]. These observations may have relevance to pregnant mothers following Bariatric surgery in terms of diet in order for them to have healthy children with normal appetites and weight. While a healthy diet during pregnancy is advocated, the problem may be more complex. One must also consider the potential effect of hypodopaminergic genetics in the pregnant mother which could oppose the advocacy of a healthy diet in the long term. Avena et al. [68] found clear evidence that sugar has addictive attributes since it releases both opioids and dopamine, which are characteristic of addiction neurochemicals. Moreover, the same authors [68] classified sugar as an addictive substance because it follows the typical addiction pathway that according to Blumenthal and Gold [69] and Liu et al [31] consists of binging, withdrawal, craving and cross –sensitization. In fact cross-sensitization was observed in rats showing the movement from sugar to drugs [70]. Surprisingly recent work by Cantin et al. [71] found that cocaine is low on the value ladder of the large majority of rats, near the lowest concentrations of sweet water. In addition, a retrospective analysis of all experiments over the past 5 years revealed that no matter how heavy was past cocaine use most rats readily give up cocaine use in favor of the nondrug alternative (Saccharin). Only a minority, fewer than 15% at the heaviest level of past cocaine use, continued to take cocaine, even when hungry and offered a natural sugar that could relieve their need of calories. Most importantly Koob and Le Moal [72] suggest that sensitization and cross tolerance are necessary for the initiation of any form of addiction and as such sugar fits this model.

In terms of withdrawal it is of interest that the withdrawal from sugar induces imbalances in both acetylcholine and dopamine similar to opiate withdrawal. Specifically, Avena et al [73] found that rats undergoing withdrawal from sugar bingeing using microdialysis revealed a concomitant increase in extracellular acetylcholine and decrease in dopamine release in the nucleus accumbens shell. The findings suggest that a diet of bingeing on sucrose and chow followed by fasting creates a state that involves anxiety and altered accumbens dopamine and acetylcholine balance. This is similar to the effects of naloxone, suggesting opiate-like withdrawal. This may be a factor in some eating disorders.

While there are similarities between food and drugs in terms of addictiveness others have argued its validity as a model of obesity on the basis that food per se is not a psychoactive drug [74]. With that said, the Columbia University Seminar on Appetitive Behavior, the obesity epidemic proposed various causes, one of which is the concept of “food Addiction”. This concept has been vigorously debated in the media [75] as well as in the scientific community [76–77].

The criteria in the Diagnostic & Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) pertaining to substance abuse have been also applied to food addiction in humans by Gearhardt et al. [78]. In terms of sugar being considered a psychoactive substance there are clinical accounts in which self-identified food addicts use food to self-medicate; they often eat in order to escape a negative mood state [79]. The authors further assert that overeating can be described as an addiction to refined foods that conforms to the DSM-IV criteria for substance use disorders. Reports by self-identified food addicts illustrate behaviors that conform to the 7 DSM-IV criteria for substance use disorders [79]. This

commonality notion has been confirmed by studies showing that food craving in normal weight and obese patients activates areas of the brain similar to those indicated in drug seeking [25,80].

In a recent review by Nicole Avena [81] where she summarized evidence for "food addiction" using animal models of binge eating she adequately defined *bingeing, withdrawal and craving* by presenting evidence using an animal model of sucrose or glucose bingeing.

Avena et al [82] performed analysis using gene array expression and *PANTHER* on 152 unique genes resulting in a total of 193 assignments sorted into 20 categories. It is noteworthy that sucrose binge eating group compared to ad libitum sucrose group resulted in differential gene expression clusters. These findings seems to be convergent when one considers the neurotransmitters involved in the brain reward circuitry (e.g. serotonin; endorphins; GABA; Dopamine; Cannabinoids; Acetylcholine) specifically the brain reward cascade [83] and RDS [30]. Interestingly Avena et al found significant differences between binge and ad libitum sucrose groups in a number of neurotransmitter pathways for example: Cholinergic Receptor-CREB signaling($P < 0.001677$); Leptin Receptor –ELK-SRF signaling ($P < 0.001691$); Dopamine D2 Receptor –AP-1/CREB/ELK-SRF signaling ($P<0.003756$); Serotonin-Fos signaling ($P< 0.00673$); Cannabinoid –AP1/EGR signaling ($p<0.015588$) and Opioid receptor –CREB/ELK-SRF/Stat3 signaling ($P < 0.01823$). These findings of significant differences in neurotransmitter genes in the binge eating group compared to the ad libitum group provides important evidence to suggest involvement of brain reward circuitry in binge eating per se. These results in animals may have relevance to binge eating in humans which is a subtype of RDS.

Reward Deficiency and Food Addiction: Neurochemical Commonality to Drugs of Abuse

In 1996 my associates and I coined the term RDS which is emerging as an acceptable explanation of the interrelatedness of impulsive – compulsive and addictive behaviors [30]. At that time we utilized Bayes' theorem to predict future substance and deviant behavior seeking. The dopaminergic system, and in particular the dopamine D2 receptor, has been profoundly implicated in reward mechanisms in the meso-limbic circuitry of the brain. Dysfunction of the D2 dopamine receptors leads to aberrant substance (alcohol, drug, tobacco and food) seeking behavior. Decades of research indicate that genetics play an important role in vulnerability to severe substance seeking behavior. We proposed that variants of the D2 dopamine receptor gene (DRD2 A1 allele) are important common genetic determinants in predicting addictive disorders. In that study the predictive value for future RDS behaviors in subjects carrying the DRD2 Taq A1 allele was 74% [84]. Following this report many studies have supported this concept linking food craving to drug craving behavior using neuroimaging tools [85–86].

It is apparent that while many genes are involved in RDS behaviors the dopamine D2 receptor plays a major role [87]. Johnson and Kenney detected compulsive-like feeding behavior in obese but not lean rats, measured as palatable food consumption that was resistant to disruption by an aversive conditioned stimulus. Striatal dopamine D2 receptors were downregulated in obese rats, and has been reported in pathologically obese humans [25] and humans addicted to drugs. Moreover, lentivirus-mediated knockdown of striatal D2 receptors rapidly accelerated the development of addiction-like reward deficits and the onset of compulsive-like food seeking in rats with extended access to palatable high-fat food. These data demonstrate that overconsumption of palatable food triggers addiction-like neuroadaptive responses in brain reward circuits and drives the development of compulsive eating. The authors suggest that common hedonic mechanisms may therefore underlie

obesity and drug addiction. It is noteworthy that others found selective BDNF depletion in the ventromedial hypothalamus (VMH) of mice resulted in hyperphagic behavior and obesity. Specifically Cordeira et al. [88] found that expression of BDNF and TrkB mRNA in the ventral tegmental area of wild-type mice was influenced by consumption of palatable, high-fat food. Moreover, amperometric recordings in brain slices of mice depleted of central BDNF uncovered marked deficits in evoked release of dopamine in the nucleus accumbens (NAc) shell and dorsal striatum but normal secretion in the NAc core. Moreover Lobo et al [89] recently showed that activation of D2+ neurons, mimicking the loss of TrkB, suppresses cocaine reward, with opposite effects induced by activation of D1+ neurons. These results provide insight into the molecular control of D1+ and D2+ neuronal activity as well as the circuit-level contribution of these cell types to cocaine reward.

The D2 dopamine receptor has been associated with pleasure, and the DRD(2) A1 allele has been referred to as a reward gene [90]. Evidence suggests that there is a tripartite interaction involving dopamine receptor deficiency, a propensity to abuse alcohol, and reduced sensitivity to rewards. This interaction relies heavily on the genetic characteristics of the individual, with certain ethnic groups having a greater tendency toward alcoholism than others. The DRD(2) has been one of the most widely studied in neuropsychiatric disorders in general, and in alcoholism and other addictions in particular. The dopamine D2 gene, and especially its allele TaqI A1 allele may also be involved in comorbid antisocial personality disorder symptoms, high novelty seeking, obesity, gambling and related traits [91]. The mesocorticolimbic dopaminergic pathway system plays an especially important role in mediating reinforcement by abused drugs, and it may be a common denominator for addictions such as alcoholism [92].

When the mesocorticolimbic dopamine reward system dysfunctions (perhaps caused by certain genetic variants), the end result is RDS and subsequent drug-seeking behaviors. RDS refers to the breakdown of the reward cascade, and resultant aberrant conduct, due to genetic and environmental influences [30]. Alcohol and other drugs of abuse, as well as most positive reinforcers, cause activation and neuronal release of brain dopamine, which can decrease negative feelings and satisfy abnormal cravings. A deficiency or absence of D2 receptors then predisposes individuals to a high risk for multiple addictive, impulsive, and compulsive behaviors. Although other neurotransmitters (e.g., glutamate, gamma-aminobutyric acid (GABA), and serotonin) may be important in determining the rewarding and stimulating effects of ethanol, dopamine may be critical for initiating drug and food craving and for reinstating substance use during protracted abstinence [93].

Exploration of various treatment approaches for the most part reveal poor outcomes in terms of relapse prevention and continued drug hunger. Pharmacological therapies for drug addiction have had limited success because these powerful agents have focused on maintenance or interference with drug euphoria rather than correcting or compensating for pre-morbid dopamine system deficits. Blum and Gold [66] proposed a paradigm shift in residential, non-residential and aftercare involving the incorporation of genetic testing to identify risk alleles coupled with D2 receptor stimulation using neuroadatogen amino acid precursor enkephlinase -catecholamine –methyltransferase (COMT) inhibition therapy. Such a natural but therapeutic nutraceutical formulation potentially induces DA release could cause the induction of D2-directed mRNA and proliferation of D2 receptors in the human involving oral KB220Z. They further hypothesized that this proliferation of D2 receptors in turn will induce the attenuation of drug-like craving behavior. Finally, these concepts await required neuro-imaging studies for confirmation. Meanwhile very recent studies may shed some new light and potential therapeutic approaches [94].

Positive outcomes demonstrated by quantitative electroencephalographic (qEEG) imaging in a randomized, triple blind, placebo controlled cross-over study involving oral showed an increase in alpha waves and low beta activity in the parietal brain region. Using t statistics, significant differences observed between placebo vs KB220Z consistently occurred in the frontal regions at week one and then again at week two of analysis (Figure 1)

Perspectives of Bariatric Surgery in Response to Increase Addiction Transfer (Cross-Tolerance)

Comprehensive physical and psychological pre-operative assessments combined with continued medical care and counseling post-operatively are critical for assuring the best possible outcome for patients who undergo bariatric surgery. Prospective weight loss system patients may have a previous or current history of various mental health disorders, including binge eating or addictions to cigarettes, alcohol, drugs or other illegal substances; active substance abuse is generally considered a reason to exclude a patient from surgery. However, the pre-surgical screening program can help identify persons affected by such problems and allow them to receive treatment so that they can overcome the addiction and then be considered for weight loss surgery in the future.

The physical recovery process after bariatric surgery and the need to adapt to the major life changes that follow from the procedure create stress. Anstrom et al. [98] found that aggressive confrontations in defeated rats are associated with increases in phasic dopamine transmission in the mesolimbic pathway suggesting a role of stress in dopamine transmission [98]. Since it is well know that stress reduces neuronal dopamine [98] it is conceivable that patients may develop or redevelop compulsive behavior problems as a response to those pressures when overeating is no longer an option. In fact, there is also research to suggest that persons who have undergone previous psychotherapy or other counseling for addictive behaviors may do especially well after weight loss surgery since they have already learned positive coping techniques.

Anyone deciding on a bariatric surgery program should consider the availability of services focused on reinforcing mental health. Psychiatrists/psychologists dedicated to bariatric surgery patients are an integral part of a required clinical team. In addition to their role in pre-operative assessment, they maintain close contact with patients after surgery, which allows them to answer questions, provide therapy and support and identify any worrisome emerging habits and the need for intervention to prevent the evolution of a significant problem.

Bariatric surgery is a life modifying and potentially lifesaving procedure, but persons considering this surgical intervention for obesity need to become fully educated about the potential risks and ready themselves for the challenges they will face afterward. Continued counseling and participation in support group activities can help bolster emotional health and assist patients in developing positive coping strategies. Individuals who take advantage of these programs to make necessary changes in their lifestyle and dietary habits will be well served, not only reducing any risk for developing new compulsive behavior problems, but increasing their chances of an overall successful outcome after bariatric surgery.

Obesity–alcoholism link

It is not surprising that there is a link between obesity and alcoholism in the United States and around the world. Certainly the link resides in genetic antecedents in part leading to a hypodopaminergic function in the brain reward circuits. The inheritability of obesity [99] is between 40–70% and alcoholism [100] is between 30–47% respectively.

The prevalence of obesity in the United States has doubled in the past three decades, from 15% in 1976–1980 to 33% in 2003–2004 [101]. Correspondingly, there has been a marked increase in the risk of premature death due to obesity-related disease, and the relative contribution of obesity-attributable mortality to total US deaths rose substantially between 1990 and 2000 [102,103].

Among the factors that might contribute to differential vulnerability to overeating in an obesigenic environment is a deficiency in impulse control, possibly related to individual differences in sensitivity to neurochemical rewards. Impulsive, compulsive and addictive characteristics are properties of substance use disorders, and behavioral and neurobiological commonalities between overeating-associated obesity and substance use disorders have been documented in recent years and termed Reward Deficiency syndrome [30]. Substance use disorders and overeating-associated obesity are complex and moderately heritable; both are influenced by availability and access to highly reinforcing substances (like drugs or palatable foods), both are aggravated by stress, and both lead to dopamine-modulated neurobiological adaptations [104]. Observational and laboratory studies have detected links between impulsive characteristics and overeating, as well as a preference for highly palatable (eg, sweet, salty, or fatty) foods. Therefore, it is plausible that individuals at risk for substance use disorders have been differentially affected by the obesity epidemic in the United States [105,106].

Most recently, Grucza et al. [107] evaluated the link between obesity and alcoholism in the United States and found that in 2001–2002, women with a family history of alcoholism (defined as having a biological parent or sibling with a history of alcoholism or alcohol problems) had 49% higher odds of suffering from obesity than those without a family history (odds ratio, 1.48; 95% confidence interval, 1.36–1.61; $P < .001$), a highly significant increase ($P < .001$) from the odds ratio of 1.06 (95% confidence interval, 0.97–1.16) estimated for 1991–1992. For men in 2001–2002, the association was significant (odds ratio, 1.26; 95% confidence interval, 1.14–1.38; $P < .001$) but not as strong as for women. Grucza et al. [107] suggested that their results provide epidemiologic support for a link between familial alcoholism risk and obesity in women and possibly in men. This link has emerged in recent years and may result from an interaction between a changing food environment and predisposition to alcoholism and related disorders.

Conclusion

Obesity is a growing epidemic in the western world and is emerging as the most debilitating disease of modern times, as well as the leading cause of preventable death. Bariatric surgery, or weight loss surgery, includes a variety of procedures performed on people who are obese. Bariatric surgery is intended for subjects with BMI ≥ 40 kg/m(2) or ≥ 35 kg/m(2) with co-morbidities

Several recent studies report decrease in mortality and severity of medical conditions after bariatric surgery. Long-term studies show the procedures cause significant long-term loss of weight, recovery from diabetes, improvement in cardiovascular risk factors, and a reduction in mortality of 23% from 40%. Now however after many years of successful bariatric surgeries clinicians are observing and reporting a new phenomenon: that some patients are replacing compulsive overeating with new compulsive and addictive disorders.

Overeating and obesity may act as protective factors reducing drug reward, and addictive behaviors possibly due to common neurochemical similarities. In animal models of addiction the withdrawal from sugar induces imbalances in both acetylcholine and dopamine

similar to opiate withdrawal. Many neuroimaging human studies have supported the concept of linking food craving to drug craving behavior.

Previously our laboratory coined the term RDS and reported that the predictive value for future RDS behaviors in subjects carrying the DRD2 Taq A1 allele was 74%. While poly genes play a role in RDS, we have also inferred that disruptions in dopamine function may predispose certain individuals to addictive behaviors and obesity. It is now known that family history of alcoholism is a significant risk factor for obesity. Therefore, we are hypothesizing that RDS is the root cause of transferring food addiction for other dependencies and potentially explains this new phenomena common after bariatric surgery.

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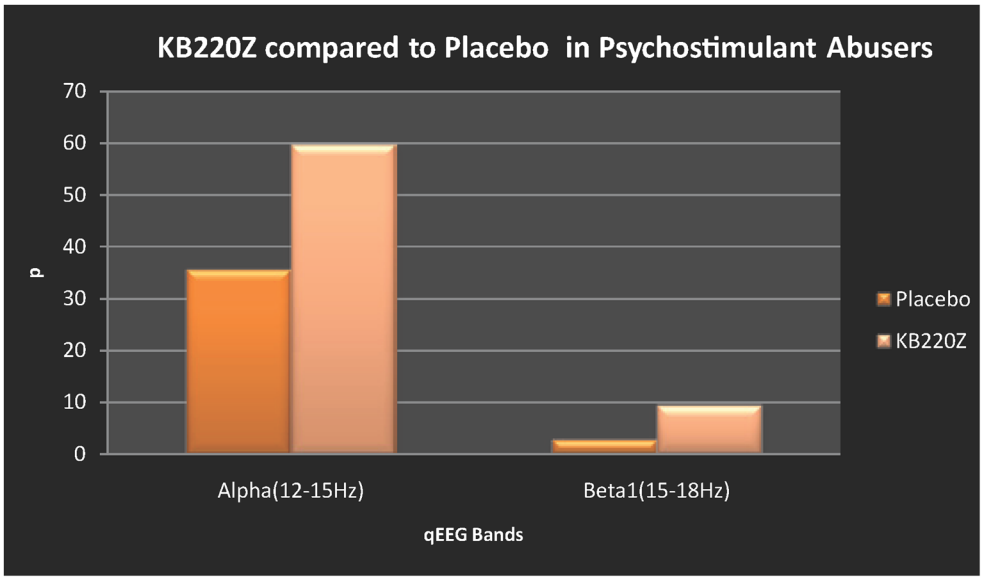

Figure 1. Illustrates a positive response to KB220Z compared to placebo in triple blind randomized placebo controlled study in psychostimulant abusers undergoing protracted abstinence (modified from Blum et al. [94]

This is the first report to demonstrate involvement of the prefrontal cortex in the qEEG response to a natural putative D2 agonist, especially evident in dopamine D2 A1 allele subjects in agreement with NIDA scientists as well as others in terms of the use of D2 agonist therapy to treat additive behaviors [95,96]. These authors concluded that DA/5-HT releasers and D2 agonists might be useful therapeutic adjuncts for the treatment of cocaine and alcohol addiction, obesity, and even attention deficit disorder and depression [95]. Of particular interest germane to bariatric surgery Brandacher et al. [97] reported that Tryptophan depletion in morbidly obese patients due to chronic immune activation persists in spite of significant weight reduction following bariatric surgery. They suggest that this finding might be responsible for diminished serotonin functions, leading to unchanged satiety dysregulation and play a role in reward-deficiency-syndrome.