REVIEW ARTICLE

The relationship between opioid and sugar intake: Review of evidence and clinical applications

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ABSTRACT

Opioid dependence poses significant public health risks arising from associated morbidity and mortality caused by accidents, infectious diseases, and social ramifications of crime and unemployment, among other complications. Opioid use, acute and chronic, is also associated with weight gain, glycemic dysregulation, and dental pathology. The literature supporting the connection between opiate use and development of preference for sweet tastes is reviewed, and further association with dental pathology, weight gain, and loss of glycemic control are considered. Additionally, the impact of sweet tastes on the endogenous opioid system, as pertaining to analgesia, is also discussed. The authors discuss the clinical implications in relation to the aforementioned conditions while treating the opiate-dependent patient.

INTRODUCTION

Opioid dependence is a significant public health concern. It is estimated that one million Americans are currently addicted to heroin in the United States.[1] Morbidity and mortality are associated with administration (human immunodeficiency virus, hepatitis C), intoxication (accidents, overdose), and chronic use (dependence) of opiates. Research has demonstrated associations between opioid consumption and sugar intake and metabolism in human and nonhuman subjects. This article will review and explore some clinical implications of these relationships on the morbidity of opioid users, including those related to weight gain and glycemic control. Literature describing the analgesic properties of sugar will also be examined, as they may act through the endogenous opioid system.

THE RELATIONSHIP BETWEEN OPIOID ADMINISTRATION AND SUGAR CONSUMPTION

There is an apparent association between intake of μ-opiate agonists and increased sugar consumption. Methadone-maintained patients assessed at entry to treatment, 9 months and 4 years into treatment demonstrate increased consumption of sugary food, fewer complex carbohydrates, less fruits, vegetables, and fats from fish or vegetables.[2] It was noted that while female methadone patients consumed fewer total calories in a given amount of time than the national average, they still maintained similar body mass index (BMI) to the national average (BMI 22.7), with sugar accounting for 31 percent of caloric intake. The authors speculated that weight was maintained with fewer calories because of the patients' "sedate lifestyles."[3] Clinical literature demonstrates that chronic exposure to μ-opiate agonists leads to heightened taste preference for high-sugar foods.[3-6]

Preclinical research has attempted to refine the potential pathways and mechanisms of action through which opiates may regulate sugar intake and has attempted to explain how sugar consumption may affect the endogenous opiate system. Preclinical animal studies suggest that direct action of μ-agonists at the nucleus accumbens shell, hypothalamus, and paraventricular nucleus is associated with development of sweet preference.[7-12] This process possibly involves γ-aminobutyric acid type B activity in the ventral tegmental area.[11] Consumption of palatable

foods, especially on intermittent schedules, is associated with acute binding of the endogenous opiate β-endorphin in the hypothalamus, accumbens shell, cingulated, hippocampus, and locus ceruleus of rats.[7,13] Furthermore, in rats, intermittent access to sucrose leads to decreased enkephalin messenger RNA (mRNA) production.[14] It is theorized that this downregulation of enkephalin mRNA production may be associated with increased μ-opiate receptor agonism associated with the rats' sugar intake.[15] Notably, human subjects chronically exposed to opiates maintain their ability to distinguish various tastes when compared with control subjects,[6] indicating that taste preferences associated with opiate exposure are not related to an impaired taste sense.

Although there is compelling evidence of an association between μ-opiate agonism and increased sugar consumption, studies of μ-opiate antagonists (naloxone and naltrexone) in nonhuman opiate-dependent subjects and in human binge eaters without opiate dependence demonstrate decreased preference for high-sugar foods, with decreased caloric intake from those types of foods.[8-11,16-20] It has been demonstrated that the novelty of the diet may alter the effect of an opiate antagonist. With naltrexone, rats would decrease fat and carbohydrate intake from an established diet, but would selectively decrease either fat or carbohydrate from a novel diet.[17] In a study of normal human subjects who were administered with a single 2.5 mg oral dose of the opiate antagonist nalmefene, subjects described the same initial hunger ratings and described satiety with 22 percent less food intake than with placebo.[16]

Buprenorphine, a partial μ-opiate agonist, appears to decrease saccharine consumption in nonopiate-dependent male Sprawg-Dawley rats, behaving like an opiate antagonist.[21] Similarly, buprenorphine acutely decreased Rhesus monkeys' consumption of sweetened fluid, but not candy.[22] However, this effect of buprenorphine becomes extinguished over chronic administration.[23] In rats receiving their normal complement of food, while chronically administered with buprenorphine, decreased sucrose intake in reward situations was noted; however, the rats would generally consume their overall expected quantity of food.[24]

OPIOID INTAKE AND ASSOCIATED WEIGHT GAIN

The preference for sugary foods associated with opiate administration may lead to increased consumption of such foods and possibly accumulation of excess body fat and weight gain. In a review of the medical treatment of heroin addicts, it was noted that these patients were generally "underweight" likely secondarily to diverting resources to drugs rather than food.[25] Heroin addicts who initiated methadone maintenance treatment typically demonstrated significant weight gain, possibly related to their expressed strong cravings for sweets during protracted abstinence.[25] The rats in acute opiate withdrawal also express a similar increased craving for sweets.[26] A study of autopsies of Swedish IV drug users recorded between 1988 and 2000 demonstrates that while 36 percent of heroin users were overweight (BMI > 25), 43.1 percent of methadone users were overweight.[27] Furthermore, when evaluating preobese IV drug abusers (BMI 30.0-39.9) by drugs of use, 27.5 percent were being treated with methadone, representing the largest portion of this subgroup.[27] As stated previously, female methadone patients were observed to consume fewer total calories, but maintained similar BMI to the national average (BMI 22.7) with sugar accounting for 31 percent of caloric intake.[3] A more recent study of methadone-maintained patients found higher BMI and increased liking of sweet foods over controls.[4] Opiate-dependent patients on methadone maintenance appear to develop increased BMI, with a greater proportion of them overweight and preobese than the average drug user.

Reviews of the literature regarding preclinical animal studies demonstrate a trend of increased eating following opiate agonist intake, with decreased eating after opiate antagonist intake in animals that are under acute food deprivation or stress, but not those that are chronically food deprived.[28,29] Atkinson's review concluded that μ-agonists generally stimulate food intake and may or may not be associated with increased BMI in humans.[30] The IV administration of the μ-antagonist naloxone, a drug with a relatively short half-life, was associated with short-term single-meal decreased oral intake in lean and obese humans; however, the daily oral administration of naltrexone, a drug with a relatively longer half-life, was associated with zero to minimal weight loss in humans.[30] The evidence for acute appetite suppression via short-acting μ-opiate antagonists appears more compelling than evidence for prolonged appetite suppression, with associated weight loss, under the chronic administration of long-acting μ-opiate antagonists.

Activity at the μ-opiate receptor is associated with development of obesity, even outside the context of opioid abuse and dependence. When IV naloxone and methylnatrexone were administered to genetically obese mice for a 12-day period, food consumption and weight gain decreased when compared with control obese mice.[31] It has been shown that obese humans with binge eating disorder are more likely to have a particular A118G "gain of function" polymorphism at the μ-opiate receptor gene.[32] The authors speculate that binge eating behavior may derive from excessive hedonic sensation caused by food in the context of an overactive μ-opiate receptor.[32] β-Endorphin appears in larger concentrations in the cerebrospinal fluid of obese adults and adolescents when compared with lean human subjects.[30] There are emerging neurochemical similarities between regulation of substance use and food intake. Leptin, a protein produced by adipose tissue and associated with food satiety, appears to decrease heroin relapse in food-restricted rats when infused into the hypothalamus.[33,34] Melanocortin is another protein involved in brain signaling related to appetite. Melanocortin agonists have been associated with inhibition of food intake in obese animal models, as well as decreased alcohol and food intake in alcohol-dependent mice.[35,36] Opiate antagonists, like naltrexone, appear to be at least weight neutral (and possibly weight reducing) by decreasing preference for sweet foods. Opiate antagonists appear more likely to decrease consumption of palatable foods in obese individuals with comorbid binge eating pathology when compared with obese individuals without this trait. Further study and clinical use of these agents for treatment of opiate dependence may be warranted in overweight patients, those at risk of gaining excessive weight, and those with current cardiac risk factors, like hypertension and elevated lipids. However, clinicians should reinforce proper exercise and dietary habits with these patients.

OPIOID CONSUMPTION AND GLYCEMIC CONTROL

There is compelling evidence that chronic administration of μ-opiate agonists is associated with pathology clinically similar to noninsulin-dependent diabetes mellitus. It has been demonstrated that use of heroin in humans is associated with increased resting insulin levels, with delayed and increased insulin response to glucose loads.[37] Similarly, methadone-maintained patients have clinically evident delayed insulin response to food ingestion with associated mild hyperglycemia.[38] Furthermore, increased fasting insulin levels have been noted in both heroin addicts and methadone patients.[39] An earlier study in healthy adults given a single dose of IV morphine (0.1 mg/kg) demonstrated that while oral and intraduodenal glucose loads were associated with delayed insulin response, IV glucose was associated with a normal insulin response.[40] The authors concluded that morphine has no direct impact on insulin activity, but rather the slowing of gastric motility associated with μ-agonists causes delayed absorption of glucose, and therefore a delayed insulin response.[40] Inhibited gastric motility and delayed gastric emptying, with associated ileus and constipation, are known sequelae of μ-opiate administration.[41]

Several other studies demonstrate a likely association between opioids and glycemic control that goes beyond μ-opiate agonist effects on gastric motility and emptying. In a preclinical study involving rats administered with methadone daily for a 35-day period, the authors demonstrated increased resting blood glucose and impaired oral glucose tolerance tests during methadone exposure, as expected. However, the rats also demonstrated impairment in key enzymes related to glucose metabolism: the glycolytic activity of hexokinase and phosphofructokinase-1 activity was diminished, leading to less breakdown of plasma glucose. Meanwhile, the gluconeogenic activity of glucose-6-phosphatase and fructose-1,6-biphosphatase was increased, leading to augmented production of plasma glucose.[42] In a review of glucose metabolism in opioid addicts, elevation of plasma glycosylated hemoglobin A1 was generally found in this population, as well as delayed insulin response to IV glucose loads, contrary to the aforementioned study.[43] Notably, opioid-dependent subjects demonstrated normal insulin responses to arginine, in evidence with functional pancreatic beta cell function. This implied pathology more similar to noninsulin-dependent, as opposed to insulin-dependent, diabetes mellitus.[43] In a study of patients who received total hip replacements, an immediate postoperative dose of IV 0.3 mg of buprenorphine was associated with hyperglycemia often seen with postoperative analgesia. However, a sublingual buprenorphine 4 mg dose administered 3 hours postoperation was associated with an acute decrease in plasma glucose.[44] This may suggest that in relation to the effects on glycemic control, buprenorphine acts similarly to μ-agonists at low

initial doses and more like an antagonist at higher or later doses. Further research should be conducted to clarify the dose-response curve of buprenorphine regarding these effects.

There may be significant clinical implications inherent in the potential derangement of glycemic control in opioid-dependent patients. A retrospective chart review of 91 methadone-maintained patients in the Atlanta Veterans Medical Center system revealed that an odds ratio of 30.79 ($p = 0.008$) of dying before the age of 65 was associated with a comorbid diagnosis of diabetes mellitus.[45] The authors noted that while the 9.6 percent of general population is diagnosed with diabetes mellitus, 18 percent of the VA methadone-maintenance population bears this diagnosis.[45] Several case studies have been reported of toddlers presented to emergency rooms in nonketotic hyperglycemic coma following accidental ingestion of their parents' weekend "take-home" methadone doses.[46] The hyperglycemia in these cases was noted to exceed, which would have been expected from merely the ingestion of the syrup in which the methadone had been dissolved.[46]

SUGAR CONSUMPTION AND ANALGESIA VIA THE ENDOGENOUS OPIOID SYSTEM

As described earlier, consumption of palatable foods is associated with acute binding of the endogenous opiate β-endorphin in the brain[7,13] and with decreased enkephalin MRNA production,[14] which may be a consequence of downregulation associated with increased μ-opiate receptor agonism.[15] There is some theoretical evidence that μ-opiate agonism associated with palatable food ingestion may have clinically relevant analgesic properties. Preclinical studies demonstrate significant increased pain tolerance in rats receiving oral sucrose when compared with rats receiving water,[47] an effect reversible by the μ-opiate antagonist naloxone.[47]

Sweet and palatable food intake has been associated with clinically significant analgesia in humans. Clinically, sucrose is often administered to preterm infants in neonatal intensive care units to provide analgesia for routine heel sticks for blood sampling.[48] This practice is grounded in evidence that orally administered sucrose solutions[49] and artificial sweeteners[50] decrease crying and heart rate in infants subjected to heel pricks. Sucrose administered via nasogastric tube does not appear to reduce pain response in infants.[51] It is postulated that the sweet taste of the sucrose or sweetener, not the substance itself, causes the analgesia.[52] Further evidence that this effect of sweeteners occurs through the opiate system is that infants born to methadone-dependent mothers did not have the expected analgesic response.[53] The authors surmise that this is likely because these infants are born with tolerance to μ-opiates because of chronic transplacental exposure to methadone.[53] One study was not able to detect elevated levels of plasma β-endorphins in infants within 5 minutes of receiving a heel prick for drawing blood, during oral sucrose administration.[54] This is contrary to the theory that sweet-tasting solution leads to central μ-agonism in infants by increasing release of β-endorphin, resulting in analgesia. Intraoral exposure to sucrose led to significantly increased pain tolerance in the cold pressor test in prepubertal children of age 8-11 years.[55] A study in healthy adults using a pressure algometer to apply painful pressure to the subjects' fingers detected a gender difference in pain tolerance derived from palatable food. While male subjects did not report increased pain tolerance, female subjects reported that both water and soda increased their pain threshold, as compared with receiving no food.[56] The authors concluded that water was considered palatable as the subjects had been somewhat water deprived prior to the experiment. Therefore in a second experiment in well-hydrated female adults, while comparing the analgesic effects of chocolate chip cookies (palatable), black olives (nonpalatable), and rice cakes (neutral), only the cookies led to increased pain tolerance in the pressure algometer.[56]

Several studies have proposed limitations to the analgesic effect of sweet-tasting substances. As described earlier, there is evidence that infants and prepubertal children experience significant analgesia from sweet solutions. In adults, there was an apparent gender bias, with only female adults experiencing analgesia. Studies in rats suggest that the analgesic effect of sweet solutions is limited to preweaning subjects and is absent in adults.[57] Of children 7-12 years old exposed to routine vaccination injections while chewing sweet gum, males tended to experience more pain during while chewing the gum, but not while holding the gum in their mouths without chewing. Female subjects experienced decreased pain sensitivity while chewing sweet gum, without any effect when not chewing the gum.[58] High diastolic blood pressure may be correlated to analgesia from sweet solution during a cold pressor test.[59] Mood state may impact the analgesia experienced from taste sensations. Rats

under normal conditions experienced expected analgesia from tasting sweet solution, determined by increased tail-flick latency; however, rats that underwent daily stress from brief forced immobilization did not experience analgesia from sweet solution. In fact, the stressed rats experienced increased latency in the tail-flick test after tasting ascetic acid, generally considered as a noxious stimulus.[60] Age, gender, blood pressure, and affective state may all influence the analgesia derived from sweet-tasting substances.

DISCUSSION

The clinical implications of opiate administration and associated sugar consumption in relation to (1) analgesia, (2) dental pathology, (3) obesity, and (4) glycemic control are discussed.

Clinicians are often concerned about prescribing opiate pain medication for analgesia in known, or suspected, opiate abusers. Furthermore, clinicians may be reluctant to prescribe opiate analgesics in higher than usual doses in patients already tolerant to opiates, such as patients in methadone maintenance. Evidence in rats suggests that sucrose solution administered with daily meals for 3 weeks augmented the analgesic effect of morphine, as measured by increased tail-flick latency.[61] However, in a separate rat study, subjects provided sucrose-saccharine mixed solution before receiving morphine had attenuated morphine analgesia.[62] Further study of these phenomena may support the use of sweet solutions in opioid-dependent patients (eg, methadone maintenance patients) to augment opioid analgesia in situations where tolerance or abuse may be the considerations. However, studies may support withholding sweet substances from opioid-dependent patients as the sweet solutions may accelerate tolerance to primary opiate treatment.

There is evidence that methadone maintenance is associated with poor dentition. Generally, drug and alcohol dependence are associated with increased dental pathology.[63] Specifically, opiate use, both methadone and heroin, has been independently associated with dental pathology after controlling for quality and frequency of dental care.[64] Regression analyses were conducted on dental patients who attended a family practice clinic in Queensland, Australia. It concluded that among those patients with comorbid depression and anxiety, nearly 22 percent (R^2 21.70 percent, $p < 0.001$) of a model predicting dental pathology in patients could be derived from age, overall severity of mental illness, the cumulative dose of tobacco and morphine, and the use (regardless of cumulative dose) of methadone.[65] While a compelling case can be made that chronic opioid use predisposes individuals to increased consumption of sugary foods, thereby causing increased dental decay, dentists surmise that perhaps the sugary syrup in which methadone is often dissolved and the generally poor oral hygiene associated with a lifestyle of drug dependence may also promote dental pathology.[66] Dentists now recommend sugar-free syrups in which the methadone may be dissolved to mask the medicine's bitter taste.[66] No studies have been conducted to date comparing dental pathology between patients using the sugar-free solution and those who are not. Furthermore, the propensity to prefer sweet-tasting foods associated with chronic opiate agonism may be more likely the cause of generalized dental pathology rather than the single daily dose of methadone syrup regardless of its sugar content. There have been no studies to date that examine dental pathology in prescription opiate addicts.

Obesity and glycemic dysregulation associated with chronic opiate administration manifests clinically in the methadone-maintained population. In a study of methadone-maintained patients at a single methadone maintenance treatment facility with an onsite primary care clinic, only 53 percent of the patients reported having a primary care provider. Of that 53 percent, 45 percent used hospital-based clinics, 23 percent used the methadone program's primary care clinic, and the remainder used private physicians or other sources.[67] Considering the propensity to develop chronic disease, such as obesity and glycemic dysregulation, an area of further research should be enhancing this patient population's use of primary care. This would be especially beneficial within the methadone maintenance milieu, as clinicians there may be more astute regarding medical illness particularly associated with the opioid-dependent population.

Regarding treatment of opioid-dependent patients with comorbid obesity, one alternative for maintenance treatment may be the antagonist naltrexone. Studies have demonstrated anorexic effects attributed to oral naltrexone in obese males with doses ranging from 25 mg to 200 mg daily for 4 days.[68] Gender-influenced weight loss in obese subjects randomized to daily placebo, 50 mg or 100 mg of naltrexone. Female subjects lost a mean of 1.7 kg by the end of the study, whereas no effect was found in male subjects.[69] The authors described the result as "significantly less than

expected in light of prior animal studies."[69] There was also noted elevation of liver transaminases in six of 60 subjects, with one subject reaching elevations deemed clinically significant.[69]

However, the data are not conclusive regarding weight loss. In a 28-day study, obese men administered with naltrexone daily in doses of 100, 200, or 300 mg did not demonstrate significantly reduced food intake or weight loss.[70] In an 8-week study, with 6 weeks of oral naltrexone 300 mg taken daily coupled with dietary counseling, not only was no difference found regarding weight loss compared to subjects not on naltrexone, but significant hepatotoxicity was noted.[71] A 10-week trial demonstrated no significant difference in weight loss between naltrexone 200 mg administered daily and placebo.[72] Furthermore, elevated liver transaminases were noted in three of 41 subjects.[72] A review of hepatotoxicity associated with naltrexone maintenance found that it was asymptomatic, reversible with medication cessation, occurred more often in subjects older than 40 years, and at naltrexone doses of 300 mg daily, a dose significantly larger that that used for treatment of opiate dependence.[73]

Recently, Orexigen® Therapeutics, Inc. submitted a press release documenting results of their completed phase III trials of Contrave®, a combination of buproprion sustained-release and naltrexone SR 32 mg, marketed for treatment of obesity.[74] Buproprion is a purported activator of melanocortin pathways in the hypothalamus,[75] thereby decreasing appetite.[35,36] They note that 48.0 to 56.3 percent of subjects in the 56-week studies lost at least 5 percent of body weight when compared with 16.4 percent and 17.1 percent of placebo controls ($p < 0.001$). Furthermore, subjects on active drug demonstrated a reduction of 0.6 percent in HbA1C when compared with a 0.1 percent reduction among subjects taking placebo ($p < 0.001$).[74] Greater weight loss was noted in subjects on combination of buproprion 300 mg/naltrexone 50 mg for 24 weeks[75] than subjects on placebo, naltrexone or buproprion alone.[75] Similar results were obtained when combining buproprion 400 mg and 48 mg of naltrexone.[76]

Lastly, opioid-dependent patients with diabetes mellitus, metabolic syndrome, and at risk for developing diabetes mellitus may be at risk for further morbidity during methadone maintenance.[45] Naltrexone maintenance may be preferred as an alternative treatment for opioid dependence in this population as well. Insulin secretion diminished on exposure of the pancreatic islet cells of genetically obese ob/ob mice to naloxone, an opiate antagonist, whereas lean mice's pancreatic cells were unresponsive to the naloxone.[77] In obese adult females administered daily with naltrexone, basal insulin levels were noted to decrease without impairing response to an oral glucose test when compared with the same subjects prior to naltrexone administration in a within-subject design.[78] The evidence may suggest a decrease in HbA1c with daily naltrexone administration for over 50 weeks.[74] While heroin use, methadone maintenance, and experimental morphine administration are associated with hyperglycemia, there is additional evidence that centrally administered codeine is as well.[79] To date, there are no studies of glycemic regulation, weight, or dental pathology among opiate-dependent patients who strictly abuse prescription pain medications.

CONCLUSIONS

Activation of the μ-opiate receptor is associated with inducing sweet, or palatable, taste preference; hyperglycemia (induced by direct action on pancreatic islet cells and likely from insulin resistance from dietary preference for sugary foods); weight gain; and possibly tooth decay (also associated with preference for sweet foods). Furthermore, sweet-tasting substances are associated with activation of the endogenous opiate system, leading to clinically significant analgesia that may augment opiate treatment, or hinder it through tolerance. Opiate antagonists, like naltrexone, are not associated with the weight gain and glycemic dysregulation. Further research may determine that opiate antagonist maintenance treatment may be preferable in opiate-dependent patients at risk for weight gain and diabetes. Methadone-maintained patients are especially susceptible to weight gain and diabetes and have poor follow-up with primary care treatment, thereby making them an especially vulnerable population. Although some evidence exists that buprenorphine behaves like naltrexone, in relation to the aforementioned syndromes, further research is indicated. Lastly, as prescription opiate abuse and dependence are growing problems, research is needed to determine whether obesity, tooth decay, and metabolic pathology are also associated with those phenomena.

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