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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 disease, 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. We discuss the impact of sweet tastes on the endogenous opioid system as well as clinical implications for analgesia and treating the opiate-dependent patient.

Keywords

opioid; sugar; weight gain; diabetes; analgesia; dental pathology

INTRODUCTION

Opioid dependence is significant public health concern. It is estimated that 1 million Americans are currently addicted to heroin in the United States (1). Morbidity and mortality are associated with intravenous administration (HIV, 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. The following article will review will explore some clinical implications of these relationships on the morbidity of opioid users, including those related to dental pathology, weight gain, and glycemic control. Literature describing the analgesic properties of sugar, and possible associations to the endogenous opioid system, will also be examined.

THE RELATIONSHIP BEWEEN OPIOID ADMINISTRATION AND SUGAR CONSUMPTION

Evidence from both preclinical and clinical studies demonstrates that chronic opioid exposure is associated with increased sugar intake. Preclinical research has attempted to refine the potential pathways and mechanisms of action through which opiates may regulate sugar intake, and how sugar consumption may affect the endogenous opiate system. Preclinical animal studies suggest that direct action of mu agonists at the nucleus accumbens shell, hypothalamus, and paraventricular nucleus is associated with development of sweet

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preference (2–7). This process possibly involves GABA-b activity in the ventral tegmental area (6). Consumption of palatable foods, especially on intermittent schedules, is associated with acute binding of the endogenous opiate B-endorphin in the hypothalamus, accumbens shell, cingulated, hippocampus, and locus ceruleus of rats (2, 8). Furthermore, in rats, intermittent access to sucrose leads to decreased enkephalin MRNA production (9). It is theorized that this down-regulation of enkephalin MRNA production may be associated with increased mu-opiate receptor agonism associated with the rats' sugar intake (10).

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 (11). It was noted that female methadone patients consumed fewer total calories, but maintained similar BMI to the national average (BMI 22.7) with sugar accounting for 31% of caloric intake. The authors speculated that weight was maintained with fewer calories because of the patients' "sedate lifestyles" (12). Clinical literature demonstrates that chronic exposure to mu-opiate agonists leads to heightened taste preference for high-sugar foods (12–15). Yet human subjects chronically exposed to opiates maintain their ability to distinguish various tastes compared with control subjects (15), indicating that taste preferences associated with opiate exposure are not related to an impaired taste sense.

Further, studies of mu-opiate antagonists (naloxone and naltrexone) in non-human opiate-dependent subjects, as well as clinical trials of binge eaters without opiate dependence, demonstrate decreased preference for high-sugar foods, with decreased caloric intake from those types of foods (3–6, 16–20). It has been found that the novelty of the diet may alter the effect of an opiate antagonist. With naltrexone, rats decreased both fat and carbohydrate intake from an established diet, but selectively decreased either fat or carbohydrate from a novel diet (17). In a study of normal human subjects who were administered a single 2.5mg oral dose of the opiate antagonist nalmefene, subjects described the same initial hunger ratings, and satiety with 22% less food intake than with placebo (16).

Buprenorphine, a partial mu-opiate agonist, appears to decrease saccharine consumption in non-opiate-dependent male Sprawg-Dawley rats, behaving like an opiate antagonist (21). Similarly, buprenorphine acutely decreased rhesus monkeys' consumption of sweetened fluid, but not of candy (22). However, this effect of buprenorphine becomes extinguished during chronic administration (23). In rats receiving their normal complement of food, while chronically administered 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 resulting from 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 "under-weight" likely as a consequence of spending money on 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 1988–2000 demonstrates that while 36% of heroin users were overweight (BMI>25), 43.1% of methadone users were overweight (27). Furthermore, when evaluating pre-obese IV drug abusers (BMI 30.0–39.9) by drugs of use, 27.5% were being treated with methadone, representing the largest portion of this subgroup (27). And among female

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methadone patients, sugar accounts for >30% of caloric intake(12). A recent study of methadone-maintained patients found higher BMI, and increased liking of sweet foods, over controls (13). Taken together, these findings suggest that opiate-dependent patients on methadone maintenance appear to develop increased BMI, with a greater proportion of them overweight and pre-obese than the average drug user.

Reviews of the preclinical and clinical literature demonstrate a trend of increased eating following opiate agonist intake, with decreased eating after opiate antagonist intake in animals under acute food deprivation or stress, but not those that are chronically food deprived (28–29). An earlier review concluded that mu agonists generally stimulate food intake, and may or may not be associated with increased BMI in humans (30). Conversely, intravenous administration of the mu 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, an opioid agonist with a relatively longer half life, was associated with zero to minimal weight loss in humans (30). Further studies are needed to explore whether long-term opioid antagonist maintenance is indeed a weight-neutral treatment strategy.

There are links between obesity and the mu-opiate receptor system in the absence of substance use pathology. When IV naloxone and methylnatrexone were administered to genetically obese mice over a 12-day period, food consumption and weight gain decreased compared to 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 OPRM1 (mu opiate receptor) gene (32).

Clinical investigations have demonstrated that B-endorphin appears in higher concentrations in the cerebrospinal fluid of obese adults and adolescents compared to 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).

In light of the growing body of evidence linking the opioid system to food intake and risk of obesity, clinicians should reinforce proper exercise and dietary habits with opioid-dependent patients. Opiate antagonists, like naltrexone, appear to be at least weight neutral, and possibly weight reducing, by decreasing preference for sweet foods. 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 extant cardiac risk factors, such as hypertension and elevated lipids.

OPIOID CONSUMPTION AND GLYCEMIC CONTROL

There is compelling evidence that chronic administration of mu-opiate agonists is associated with pathology clinically similar to non-insulin dependent diabetes mellitus. It has been demonstrated that use of heroin in humans is associated with increased resting insulin levels, as well as 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 (0.1mg/kg) demonstrated that while oral and intraduodenal glucose loads were associated with delayed insulin response, IV

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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 mu-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 mu-opiate administration (41).

Several other studies demonstrate a likely association between opioids and glycemic control that extends beyond mu-opiate agonist effects on gastric motility and emptying. In a preclinical study rats administered daily methadone over a 35-day period demonstrated increased resting serum 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). The authors concluded that methadone maintenance produces a metabolic state similar to non-insulin-dependent diabetes. However, the finding that opioid addicts, in addition to elevation of plasma glycosylated hemoglobin A1 and delayed insulin response to IV glucose loads, also demonstrated normal insulin responses to arginine, a hallmark of functional pancreatic beta cell function, implies pathology more similar to non-insulin-dependent diabetes mellitus (43).

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 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 (44). The authors noted that while the 9.6% of general population is diagnosed with diabetes mellitus, 18% of the VA methadone maintenance population bears this diagnosis (44). 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 (45). The hyperglycemia in these cases was noted to exceed what would have been expected from merely the ingestion of the syrup in which he methadone had been dissolved (45). And buprenorphine in the post-op period has shown divergent effects on glucose metabolism. In a study of patients receiving total hip replacements, an immediate post-operative dose of IV 0.3mg of buprenorphine was associated with hyperglycemia often seen with post-op analgesia. However, a sublingual buprenorphine 4mg dose administered 3 hours post-op was associated with an acute decrease in plasma glucose (46). This difference may suggest that with respect to effects on glycemic control, buprenorphine acts similarly to mu-agonists at low initial doses, and more like an antagonist at higher or later doses. Further research would need to be conducted to clarify the dose-response curve of buprenorphine regarding these effects.

SUGAR CONSUMPTION AND ANALGESIA VIA THE ENDOGENOUS OPIOID SYSTEM

Consumption of palatable foods is associated with acute binding of the endogenous opiate B-endorphin in the brain (2, 8), and decreased enkephalin MRNA production (9) which may be a consequence of mu opiate receptor down-regulation associated with increased mu-opiate receptor agonism (10). There is some evidence that mu-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

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compared to rats receiving water (47), an effect reversible by the mu-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 ICUs 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 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 this is likely because these infants are born with tolerance to mu-opiates because of chronic transplacental exposure to methadone (53).

Contrary to the theory that sweet-tasting solution leads to central mu-agonism in infants, resulting in analgesia, one study was not able to detect elevated levels of plasma B-endorphins in infants within 5 minutes of receiving a heel prick for drawing blood, during oral sucrose administration (54). Yet the analgesic effects of oral sucrose have also been demonstrated by significantly increased pain tolerance in the cold pressor test in pre-pubertal children of ages 8–11 (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, females reported that both water and soda increased their pain threshold, as compared to receiving no food (56). In this study water was considered palatable since the subjects had been somewhat water-deprived prior to the experiment. In a second experiment in well-hydrated female adults, comparing the analgesic effects of chocolate chip cookies (palatable), black olives (non-palatable), and rice cakes (neutral), only the sweet/palatable food led to increased pain tolerance in the pressure algometer (56).

Several studies have proposed limitations to the analgesic effect of sweet-tasting substances. We have reviewed evidence that both infants and pre-pubertal children experience significant analgesia from sweet solutions. In adults, there was an apparent gender bias, with only females experiencing analgesia. Studies in rats suggest that the analgesic effect of sweet solutions is limited to pre-weaning subjects, and is absent in adults (57). In children 7–12 years old exposed to routine vaccination injections, males tended to experience more pain while chewing sweet gum, but not while holding 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 a noxious stimulus (60). Thus, age, gender, blood pressure, and affective state may all influence the analgesia derived from sweet tasting substances.

DISCUSSION: CLINICAL IMPLICATIONS FOR TREATING OPIATE DEPENDENT PATIENTS

The preclinical and clinical literature provides strong evidence for associations among the following: opiate use and preference for sweets, weight gain, dental pathology and glycemic

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dysregulation. Several investigations have suggested a relationship between sweet or palatable tastes and analgesia through the endogenous opiate system. While heroin use, methadone administration, and experimental morphine administration are associated with hyperglycemia, there is additional evidence that centrally administered codeine produces the same effect (61). To date, no studies have been conducted to assess metabolic and weight changes, and dental pathology among opiate-dependent patients who abuse prescription opioid medications.

Clinicians are often concerned about prescribing opioid 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 from preclinical trials suggests that administration of sucrose solutions may either augment or attenuate morphine analgesia (61, 62). Further study of these phenomena is warranted and may support either the use of sweet solutions in opioid-dependent patients (e.g. methadone maintenance patients) to augment opioid analgesia and reduce the risks of tolerance or abuse or else withholding sweet substances from opioid-dependent patients as the sweet solutions if their consumption is found to accelerate tolerance to primary opiate treatment.

There is evidence that methadone maintenance is associated with poor dentition. Generally, drug and alcohol dependence give rise to 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 that attended a family practice clinic in Queensland, Australia. Among those patients with comorbid depression and anxiety, nearly 22% (R2 21.70%, $p<0.001$) of a model predicting dental pathology 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 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 vs, sugar-based solutions. 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. It would be useful to examine patterns of dental pathology in prescription opiate addicts, as well, but no such investigations have yet been carried out.

Obesity and glycemic dysregulation associated with chronic opiate administration manifest 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% of the patients reported having a primary care provider. Of that 53%, 45% used hospital-based clinics, 23% 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 illnesses frequently associated with the opioid-dependent population.

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Regarding treatment of opioid-dependent patients with comorbid obesity, one alternative for maintenance treatment may be the long-acting opioid antagonist naltrexone. Studies have demonstrated anorexic effects attributed to oral naltrexone in obese males with doses ranging from 25mg–200mg daily over 4 days (68). Gender influenced weight loss in obese subjects randomized to daily placebo, 50mg or 100mg of naltrexone. Female subjects lost a mean of 1.7kg by the end of the study, while no effect was found in male subjects; these results were significantly less than expected in light of prior animal studies. (69). Elevation of liver transaminases occurred in 6 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 daily naltrexone in doses of 100mg, 200mg, or 300mg did not demonstrate significantly reduced food intake or weight loss (70). In a study over 8 weeks, with 6 weeks of active medication at 300mg daily coupled to dietary counseling, not only was no difference found regarding weight loss, but significant hepatoxicity was noted (71). A double-blind 10- week trial demonstrated no significant difference in weight loss between naltrexone 200mg administered daily and placebo (72). Furthermore, elevated liver transaminases were noted in 3 of 41 subjects (72). A review of hepatoxicity associated with naltrexone maintenance found that it was asymptomatic, reversible with medication cessation, occurred more often in subjects over 40 years old, and at naltrexone doses of 300mg 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 SR and naltrexone SR 32mg, 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% of subjects in the 56-week studies lost at least 5% of body weight, compared to 16.4% and 17.1% of placebo controls ($p<0.001$). Furthermore, subjects on active drug demonstrated a reduction of 0.6% in HbA1C compared to a 0.1% reduction among subjects talking placebo ($p<0.001$) (74). Greater weight loss was noted in subjects on combination buproprion 300mg/naltrexone 50mg over 24 weeks (75) than subjects on placebo, naltrexone or buproprion alone (75). Similar results were obtained with combining buproprion 400mg and 48mg of naltrexone (76). These results may hold promise for the treatment of obesity in opioid-dependent patients following detoxification.

Lastly, opioid-dependent patients with diabetes mellitus, or metabolic syndrome and at risk for developing diabetes mellitus, may be at risk for further morbidity during methadone maintenance (44). Naltrexone maintenance may be a preferred alternative treatment for opioid dependence in this population as well. The pancreatic islet cells of genetically obese ob/ob mice, insulin secretion diminished upon exposure to naloxone, an opiate antagonist, whereas pancreatic cells of lean mice were unresponsive to the naloxone (77). In a clinical trial of obese adult females using a within-subjects design, administered daily naltrexone, basal insulin levels decreased without impairing response to an oral glucose test (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 all associated with hyperglycemia, there is additional evidence that centrally administered codeine produces this same effect (79). To date, there are no studies of glycemic regulation, weight or dental pathology among opiate-dependent patients who exclusively abuse prescription pain medications.

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CONCLUSION

Activation of the mu-opiate receptor is associated with several effects on glucose intake and glycemic control. These include inducing sweet, or palatable, taste preference; hyperglycemia induced by direct action on pancreatic islet cells, likely insulin resistance caused by dietary preference for sugary foods; weight gain and tooth decay likely 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 such 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. While some evidence exists that buprenorphine behaves like naltrexone, with respect to the above syndromes, further research is indicated. Lastly, given the rapidly rising rates of prescription opiate abuse and dependence, future research should determine whether such opioid maintenance carries similar public health risks of obesity, tooth decay, and metabolic pathology.

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