Review Article

Opioid use and diabetes: An overview

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ABSTRACT

Illicit opioids have emerged as a major public health problem over the past century. It continues to remain so in the current times. From the studies conducted among the animals, it has been clear that there are acute as well as chronic effects of opioids on the endocrine system. Diabetes has been recognized as a major public health concern and is expected to be a major problem in the coming decades. In this article, we shall discuss the effects of opioids in the glucose homeostasis in both the animal population and human population and its relation to diabetes.

Key words: Buprenorphine, diabetes mellitus, methadone, naltrexone, opioids

Introduction

The history of use of opioids dates back to 9th BCE as described by Homer. The active ingredient of opium was extracted by Serturmer in 1806 and was named morphine after the god of dreams. Heroin was synthesized in 1898 and it was first thought to be free from abuse liability.[1] However, further evidence proved it to be otherwise. Stereospecific opiate binding sites were described by Pert and Snyder, and Terenius and Simon *et al.* in 1973.[2-4] The existence of different types of receptors was proved in 1976 by Martin *et al.*[5]

Illicit opioids have emerged as a major public health problem over the past century. It continues to remain so in the current times. According to the World Drug Report 2014, global estimation of the use of opioids in the past year, including heroin and prescription painkillers, is between 28.6 million people and 38 million people with a global average prevalence of 0.7%.[6] As per the findings of a national survey in India, opioids are the most common illicit drugs of abuse in patients presenting to the treatment settings with around 2 million heroin abusers.[7]

From the studies conducted among the animals, it has been clear that there are acute as well as chronic effects of opioids on the endocrine system.[8] The different endocrine effects in humans involves decreased hypothalamic gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and possibly follicle-stimulating hormone (FSH), decreased testosterone, estradiol, and testicular interstitial fluid leading to the loss of libido, impotence, and even infertility in both males and females. Depression, anxiety, fatigue loss of muscle mass and power, amenorrhea, menstrual irregularity, galactorrhea, osteoporosis, fractures, etc., are other clinical manifestations of opioid-induced endocrinopathies.[9]

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These endocrine effects may be caused as a result of opioid therapy as analgesics.[10] There is evidence that opioids play a role in feeding behavior such as food intake, food choice, and the reward; increased use of opioids leads to hyperglycemia and worsens diabetes.[11]

Diabetes, a group of metabolic disorder is characterized by hyperglycemia and results from defects in insulin secretion, insulin action, or both.[12] In 2013, 382 million people were living with diabetes around the world and this number is expected to increase every year. It has been estimated that the number of people with diabetes will reach 592 million by 2035. Most people having diabetes live in low- and middle-income countries. Moreover, these countries are expected to have the greatest increase in cases of diabetes over the next 22 years.[13] Diabetes has already been recognized as a major public health concern and is expected to be a major problem in the coming decades. In this article, we shall discuss the effects of opioids in the glucose homeostasis in both the animal population and human population and its relation to diabetes.

Animal Studies

There are multiple opioid receptor types in the central nervous system. Among them, the dynorphin/α-neo-endorphin kappa-opioid receptor is likely to be involved in the modulation of feeding behavior.[14] However, the effects of opioids in feeding are controversial. It has been suggested that food intake is increased in animal models after the administration of opioids such as morphine, which is modulated by the above mentioned receptors.[15,16] Similarly, studies have also reported the anorexic effect of morphine in the animal models.[17-19] Levine in his review has concluded that the effect is dose-dependent.[14] Similarly, it has also been shown that the effect of morphine seems to be triphasic in the animal feeding behavior.[20] In a study by Anghel *et al.*[21] it was seen that morphine pellet implantation in rats led to decreased food intake, along with a marked weight loss. Several genes involved in food intake such as agouti-related, neuropeptide Y, protein, and cocaine and amphetamine-regulated transcript were altered by morphine exposure in either the hypothalamus or pituitary gland, suggesting the anorexic role of opioids in food intake. Similarly, there are a few studies that highlight the higher level of β endorphin level and upregulation of δ and κ receptor activity in the genetically obese rats.[22,23]

The experiment conducted in lean and obese mice has shown that the encephalin agonist for δ and μ receptors led to increased glucose and insulin levels.[24] There was a rise in serum glucose levels and decrease in enzymatic activity of the glycolytic enzymes in female mice when oral methadone was given for 35 days. This metabolic state mimics the insulin-resistant diabetes.[25] There is a reduced analgesic effect of opioids in diabetic rats. The mechanism could be reduced numbers of μ receptors in the spinal dorsal horn. This highlights the interaction between anesthetic effects of opioids and diabetes.[26] So in animals, there could be a possibility of diabetes being associated with opioids and that diabetic animal models needed more opioids for analgesia.

Human Studies

There is an increased risk of metabolic syndrome and diabetes in people with substance use. The contributory factors for this increased risk could be nutritional deficiencies, increased cell damage, augmented excitotoxicity, reduced energy production, lowered antioxidant potential of the cells, etc.[27] Most of the prevalence studies of diabetes in the substance use population has been conducted for alcohol and nicotine. When reviewing the literature, only a single study from North India has highlighted the higher prevalence of metabolic syndrome in the opioid-dependent individual. The study reported an incidence of 29.3% patients with opioid-dependent syndrome.[28]

In a study among 49 patients with noninsulin dependent diabetes, it was observed that opium in the form of smoking increased serum glucose, adding to the complications of the diabetes.[29] In the patients with opioid addiction, islet cells responsible for the production of insulin do not respond in an appropriate manner to the glucose signals. This state is similar to the state of diabetes as evidenced by increased concentration of hemoglobin A1c (HbA1c) and reduction of acute insulin to glucose given intravenously.[30] However, in a study conducted by Sood *et al.* it was seen that the HbA1c level was not different in opioid-dependent individuals when compared with the controls. This study indicated no long-term effect on glucose tolerance.[31] There are studies that have looked into the effect of opioids on humans indirectly with the help of opioid antagonists. A study among 60 obese people had shown decreased weight when naltrexone was administered. This effect was more pronounced in female than in male patients.[32] However, studies with contrasting findings also exist.[33,34] The administration of naloxone (opioid-antagonist) in obese subjects inhibited the responses of insulin and C-peptide to glucose administration. This suggests that endogenous β-endorphins increase the

responsiveness of pancreatic β cells. This may suggest that exogenous opioid administration may contribute to hyperinsulinemia.[35] On the other hand, it has also been shown that chronic naltrexone administration leads to lower basal concentration of insulin and C-peptide.[36] It has also been seen that in methadone-maintained patients, there is an increased consumption of food with sugar, fewer carbohydrates that are complex, less fruits, vegetables, and fats that come from fish or vegetables.[37] Similarly, in another study it was noted that female patients on methadone consumed more total calories but maintained body mass index (BMI) similar to the national average. In this study, sugar accounted for 31% of the caloric intake. The authors explained that weight was maintained with fewer calories because of the sedentary lifestyle of patients.[38]

An autopsy study on Swedish intravenous drug users between 1988 and 2000 demonstrated that 36% of heroin users were overweight with a BMI >25. Similarly, among methadone users 43.1% were overweight. Furthermore, when preobese intravenous drug users were evaluated, 27.5% were being treated with methadone.[39]

The fasting concentrations of insulin is significantly higher in those with heroin addiction and they have markedly reduced plasma insulin responses to intravenous glucose, highlighting the fact that heroin administration produces a state of hyperinsulinemia during fasting even in the absence of obesity and glucose intolerance. There is a marked reduction of insulin secretion in the first phase.[40] Similarly, in opioid-dependent patients when glucose load is given, the glycemic response shows a delayed peak time. The insulin curves show an increase in insulin peaks, delay in peak time, and prolongation of hyperinsulinemia, and there is a possibility of influence of the opioids on the neurotransmitter regulation of insulin.[41,42] In the basal state, among opioid-dependent individuals it has been observed that insulin responses to intravenous glucose was markedly reduced and they had low glucose disappearance rates when compared to the controls.[43] There are case reports that suggest that accidental ingestion of methadone in children can lead to nonketotic hyperglycemic coma.[44] Hence, the evidence suggests that opioid-dependent individuals are in a metabolic state that resembles diabetes, albeit the causal hypothesis has not been established yet.

Giugliano has hypothesized that opioids and opioid peptides have a central effect through the sympathetic nervous system and cause hyperglycemia and impaired insulin secretion. Opioid-dependent individuals do not respond in an expected manner to insulin signals, thus causing a higher prevalence of glucose disorders.[30] Apart from this, there is evidence to suggest that opioid receptors are also involved in glucose homeostasis. It has been observed that increased sensitivity to endogenous opiates such as encephalin may give rise to noninsulin-dependent diabetes associated with chlorpropamide alcohol flushing.[45] Naloxone, an opioid antagonist when administered to diabetic individual leads to a sharp increase of the insulin level in response to glucose.[46,47] When nonopioid-dependent diabetic patients are compared with opioid-dependent individuals, the latter show a higher level of hemoglobin A1c. Similarly, increased serum glucose is also associated with increased risk of metabolic disorders.[29] However, there are contrasting reports as well where there is no significant change in the level of HbA1c in the diabetic individuals with or without opioid dependence as discussed earlier.[48]

There could be another path via which opioids might affect the sugar hemostasis causing insulin resistance, which in turn increases the risk of metabolic syndrome. When spontaneous or induced chronic hypogonadism is created in male patients, it leads to increased insulin resistance and risk for diabetes mellitus. However, it is not associated with frank hyperglycemia.[49] This state of hypogonadism when reversed with testosterone replacement may lead to improvement of insulin resistance.[50]

In human subjects, it has been found that the levels of endogenous opioids are altered when they have diabetes. It has been observed that there is an elevation (of up to 60%) of plasma β endorphins levels, along with a substantial increase in enkephalin-like immunoreactivity. It is suggested that the role of enkaphalin is to inhibit insulin secretion.[51] It has been seen that long-acting met-enkephalin analog FK 33824 administered in both normal individuals and type 2 diabetic individuals lead to the inhibition of insulin secretion.[52] Apart from this, when the effect of opioids are studied in diabetic individuals it is seen that the higher doses are needed for effective analgesia during the postoperative period. The anesthetic effects are lessened in these individuals.[53]

Summary and Future Research

The increasing evidence suggests that opioids play an important role in regulating food intake and the reward associated with the ingestion of foods. Similarly, the opioid receptors help in regulation of feeding *via* the central nervous system. However, the results of the studies looking at the role of chronic opioid use with the weight

gain are inconsistent. Nevertheless, the opioid antagonist, naltrexone, holds promise for weight loss in obese patients. In both humans and animal models, opioid administration leads to a metabolic state similar to diabetes as well as worsening diabetes by decreasing insulin secretion. So both the direct and indirect evidences point toward the role of opioids in glucose hemostasis as well as exogenous opioids, leading to higher chances of individuals having diabetes. It is not clear whether the association of diabetes in opioid-dependent individual is dose-dependent or route-dependent. There is a possibility of the occurrence of other confounders as multiple comorbidity is not an exception in these individuals. Apart from this, it is a matter of further discussion as to whether the evidence gathered by the studies on antagonists such as naltrexone and agonists such as buprenorphine and methadone can be directly or indirectly extrapolated into the opioids that are abused in the clinical setting. The question about the mechanism of acute versus chronic exposure and gender-related issues remain largely unanswered. Most of the studies are of a cross-sectional nature. There is a need of prospective studies to assess the effect of chronic opioid therapy on the glucose control.

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Conflicts of interest

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