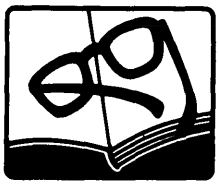
Review



Morphine, Opioid Peptides, and Pancreatic Islet Function

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Since the isolation of enkephalins 7 yr ago, there has been an explosive increase in knowledge and an enormous interest in the action of both exogenous and endogenous opiates. This review deals with the interaction of opiates with the endocrine pancreas. The results of animal studies performed in vitro do not allow any conclusion to be drawn, because the effects of opioid peptides on pancreatic hormone release seem dependent on many variables, including the agent investigated, dose administered, concentration of glucose in the medium, and experimental procedure used. The results of in vivo animal studies suggest that central administration of opiates and opioid peptides acts indirectly via the sympathetic nervous system to cause hyperglycemia and impaired insulin secretion, while peripheral administration tends to stimulate insulin and glucagon secretion. This last statement seems also to be true for studies performed in human beings. The narcotic addict offers a model to evaluate the hormonal and metabolic effects of a chronically administered agent that binds and activates endogenous receptors. In these subjects, it is possible to find increased concentrations of glycosylated hemoglobin A_1 and a marked reduction of the acute insulin response to intravenous glucose, but not to arginine, which suggests a state of defective glucose recognition by pancreatic β-cells during narcotic addiction. Thus, the heroin addict, like patients with non-insulin-dependent diabetes, does not respond appropriately to glucose signals. Moreover, naloxone, an opiate-receptor blocking agent, can cause a partial restoration of the acute insulin response to i.v. glucose in some subjects with non-insulin-dependent diabetes. An increased sensitivity to endogenous opiates—enkephalins—might be important in the pathogenesis of non-insulin-dependent diabetes in human beings. DIABETES CARE 7: 92–98, JANUARY–FEBRUARY 1984.

More than a century ago, Claude Bernard was able to induce diabetes by placing a trocar in the brain stem of a rabbit;[1] this "piqûre" diabetes led to the theory that diabetes was centrally mediated. Because of his piqûre experiments, he was convinced that glucose flux rates were regulated by the central nervous system through a balance of opposing forces: "nerfs deassimilateurs" that stimulate hepatic glucose production and "nerfs assimilateurs" that stimulate glucose uptake.[2] During the current century, glucagon and insulin have replaced "nerfs deassimilateurs" and "assimilateurs," respectively.[3] Since then, morphine has been acknowledged to induce hyperglycemia.[4] Intraventricular injection of morphine leads to a rapid and sustained elevation of blood sugar in cats and rats.[5,6] Because this effect is reduced by section of the sympathetic ganglia or adrenal ablation, it has been suggested that morphine-induced hyperglycemia is a centrally innervated, sympathetically mediated effect.

The characterization of a specific receptor for opiates in the central nervous system[7,8] and the evidence provided by Terenius and Wahlström[9,10] and Hughes[11] for the existence of endogenous opiate-like substances in the brain created an enormous interest in the action of both exogenous and endogenous opiates. The two pentapeptide enkephalins (Tyr-Gly-Gly-Phe-Met and Tyr-Gly-Gly-Phe-Leu) were isolated from porcine brain in 1975 and shown to have opiate-like activity.[12] The sequence of one of these peptides (met-enkephalin) is contained within a larger peptide, β-endorphin, which in turn is identical to the last 31 amino acid sequence of the peptide hormone β-lipotropin.[13] Guillemin et al.[14,15] isolated two opiate-like peptides from porcine hypothalamus and posterior pituitary, termed α-endorphin and

γ-endorphin, respectively (Figure 1). The mechanism of action of the opioid peptides is similar to that of many other hormones: the binding of the peptides with the specific receptor leads to the activation of the second messenger responsible for their actions at the cellular level. The complex opioid peptide-receptor decreases intracellular cAMP levels while increasing cGMP; these effects can be blocked by naloxone, an opiate-receptor blocker.[16] Recent evidence exists indicating heterogeneity of opiate receptors.[17] Using different pharmacologic approaches, it has been possible to postulate the existence of at least five types of opiate receptors, namely, μ, κ, σ, δ, and ε. Morphine is believed to behave as a typical μ-agonist and naloxone as a typical μ-receptor antagonist.

OPIATES AND CARBOHYDRATE METABOLISM

The recent demonstration of immunoreactive enkephalin[18] and β-endorphin[19,20] in the pancreatic islets has suggested the possibility that besides the central effects, opioid peptides may affect the endocrine pancreas by local as well as humoral pathways. The influences of the various opiates and opioid peptides on the secretion of the endocrine pancreas have been investigated using different experimental procedures.

In vitro studies. The results of in vitro studies are at present inconclusive, since the effects of opioid peptides on pancreatic hormone release seem dependent on the agent investigated, dose administered, concentration of glucose in the medium, and experimental procedure used. Morphine and β-endorphin invariably stimulate insulin and glucagon release,[21-23] while enkephalins have a dose-dependent effect on insulin release, low concentrations being stimulatory and high concentrations being inhibitory.[22,24,25] In every case, naloxone blockade of morphine and opioid peptide-induced changes in pancreatic hormone release argues in favor of an opiate mechanism of action by these agents.

In vivo studies. Peripheral administration of opioid peptides tends to increase insulin and glucagon plasma levels. Ipp et al.[26] showed in unstressed, conscious normal dogs that morphine, at a dose approximately twice that used in clinical situations, caused increases in circulating levels of insulin and glucagon without affecting glucose. However, similar doses of morphine caused plasma glucose to rise more than 120 mg/dl in alloxan-diabetic dogs as a consequence of opiate-induced glucagon release in the absence of accompanying insulin secretion. Although the plasma catecholamine response to similar doses of morphine in the dog has been reported to be inhibited,[27] or augmented,[28] it seems unlikely that circulating catecholamines might have played an important role in the mediation of morphine effects, since high catecholamine levels are associated with depression of insulin release.[29] In contrast to these apparent direct effects of opioid peptides at the pancreatic level, central administration of morphine and β-endorphin acts indirectly via the sympathetic nervous system to cause hyperglycemia and possibly impaired insulin secretion.[30,31]

Human studies. The limited number of studies that examined the influence of opioid peptides on islet function in human beings indicates that peripheral administration of these compounds exerts a stimulatory effect on insulin and glucagon circulating levels. While the intravenous infusion of the long-acting enkephalin analogue DAMME does not produce any significant change in insulin, glucagon, and glucose plasma levels,[32] the single intravenous bolus of β-endorphin (2.5 mg) elicits a rise in insulin and glucagon levels within 5 min and a parallel increase in plasma glucose.[33] The dose of β-endorphin used increases the plasma β-endorphin levels 1000-fold.[34] Feldman et al.[35] observed a near-maximal response of plasma glucose, insulin, and glucagon in normal subjects after the intravenous injection of 0.05 mg of synthetic human β-endorphin, which acutely increases plasma β-endorphin concentrations 100-fold or more. The six insulin-dependent diabetic patients studied by Feldman et al.[35] had glucose and glucagon increases after injection of 1 mg of β-endorphin similar to those of nondiabetic subjects. A quite surprising finding of that study was the failure of naloxone to block the effect of β-endorphin on islet cell function. It should be noted that the doses of naloxone used were sufficient to block the effects of β-endorphin in other systems,[36] which raises the possibility that the effects of β-endorphin in human endocrine pancreas are mediated by opiate receptors that are not sensitive or extremely resistant to naloxone. This possibility is supported by the observation that naloxone itself fails to alter insulin secretion in healthy people. Morley[37] found a small increase in basal insulin and

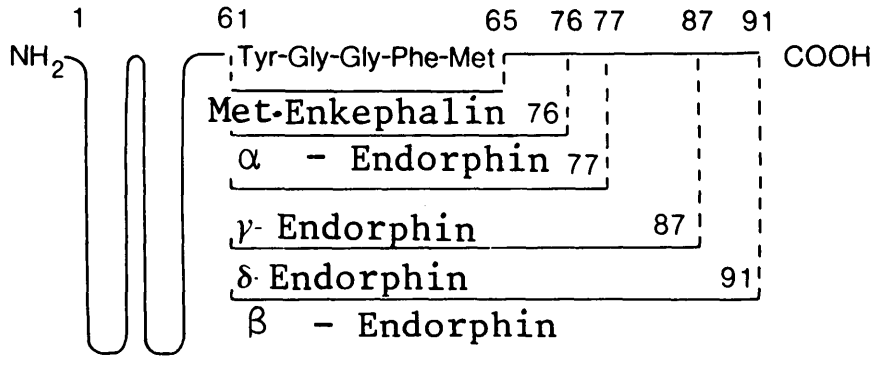

FIG. 1. Beta-lipotropin and related opioid peptides.

an increased glucose response to intravenous glucose administration after high doses of naloxone in human beings. Naloxone given intravenously as a single bolus or infusion does not alter insulin secretion in response to intravenous glucose in normal individuals[38,39] (Figure 2). These studies suggest that endogenous opiates do not play an important role in the modulation of insulin secretion in normal human beings. On the other hand, both opioid peptides and naloxone may influence carbohydrate metabolism indirectly, through an interaction with other hormones.[40] Moreover, evidence exists that indicates endogenous opiates may influence basal hepatic glucose production, since naloxone causes an immediate but transient decrease in both glucose production and utilization without affecting insulin.[41]

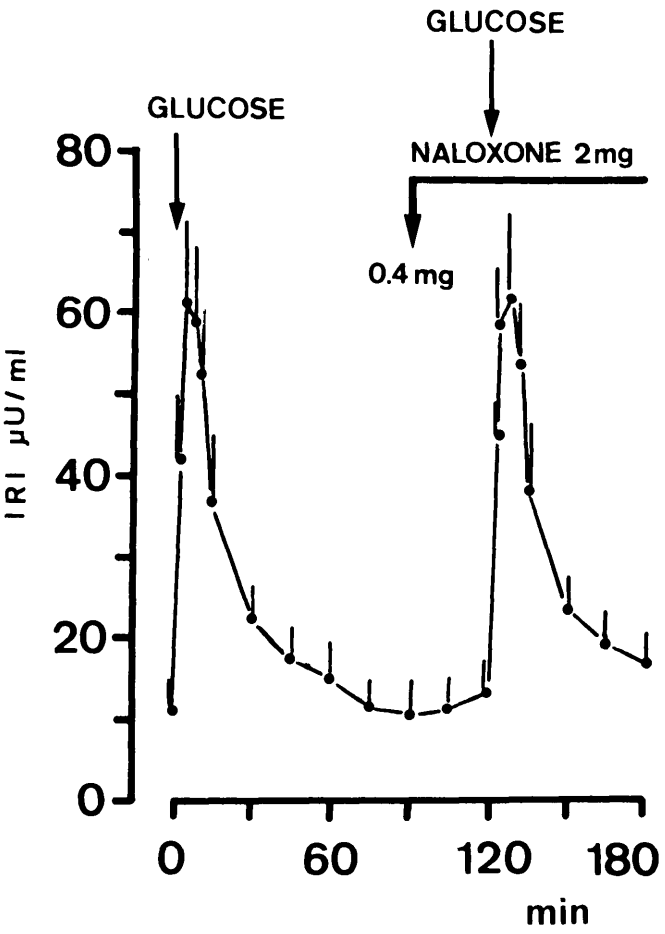

FIG. 2. Comparison of insulin responses to two consecutive intravenous glucose pulses (0.33 g/kg) given before and during an infusion of naloxone in normal subjects. No significant differences are observed between the two insulin responses. (Reproduced from ref. 38.)

NARCOTIC ADDICTION AND CARBOHYDRATE METABOLISM

The possible link between carbohydrate metabolism and narcotic addiction has not been extensively investigated, although the heroin addict may offer a model to investigate the impact of a chronically administered agent that binds and activates endogenous receptors. It is part of the folklore of narcotic addiction that an addict has a craving for sweet foods, and observation of the eating pattern of heroin-dependent patients attending a drug-dependency treatment unit suggested that they have a preference for foods containing a high proportion of carbohydrates. It seems also to be part of the mythology of addiction that diabetes mellitus is more frequent among heroin users than other people.[42] Although it is true that a single dose of morphine may produce a transient hyperglycemia, tolerance may develop with chronic administration, and a slight hypoglycemia may eventually occur afrer the injection.[43] Flat glucose tolerance test curves after narcotic administration have been reported in the old literature (for review see ref. 43). Reed and Ghodse[44] have confirmed the flat glucose tolerance curves in a group of heroin addicts and have reported an exaggerated and delayed insulin response after oral glucose load.

The results of some recent studies seem to throw new light on this interesting topic. Since the determination of fasting plasma glucose and the results of oral glucose tolerance curves may be influenced by the mode of living and the eating habits of heroin users, we decided to evaluate the concentration of glycosylated hemoglobin A_1, which represents a useful index of the glycemic control of the previous 3–4 wk.[45] The results (Figure 3) indicated that heroin users have concentrations of total hemoglobin A_1 significantly higher than those of control subjects matched for age, sex, and weight.[46] Subsequently, we have noted that the increased hemoglobin A_1 levels found in addicts are due to the higher proportion of the labile form, the concentration of which strictly depends on the plasma glucose level at any one time.[47] This probably reflects the transient hyperglycemic effect of repeated morphine administration.

Recent findings from this laboratory[48] have shown that heroin addicts have, with respect to control subjects, significantly higher fasting concentrations of insulin, glucagon, and growth hormone. However, the insulin responses to an intravenous glucose pulse (0.33 g/kg) are dramatically reduced, with low values of glucose utilization ($K_G < 1.2$). Interestingly enough, heroin addicts can have a satisfactory insulin response to oral glucose (via gut factors?) as herein reported[44] and to intravenous arginine infusion (Giugliano et al., unpublished results). These data are suggestive of a state of selective unresponsiveness or defective glucose recognition by pancreatic β-cells in heroin addiction. Although unlikely, the possibility that the impaired insulin response to intravenous glucose may represent a stress response in sick patients cannot be totally excluded.

Morley et al.[49] have recently reported that chronic high-dose administration of the exogenous opiate, morphine sulfate, in rats leads to significant alterations in the concentration of a number of endogenous brain peptides. In particular, thalamus somatostatin content increased during morphine

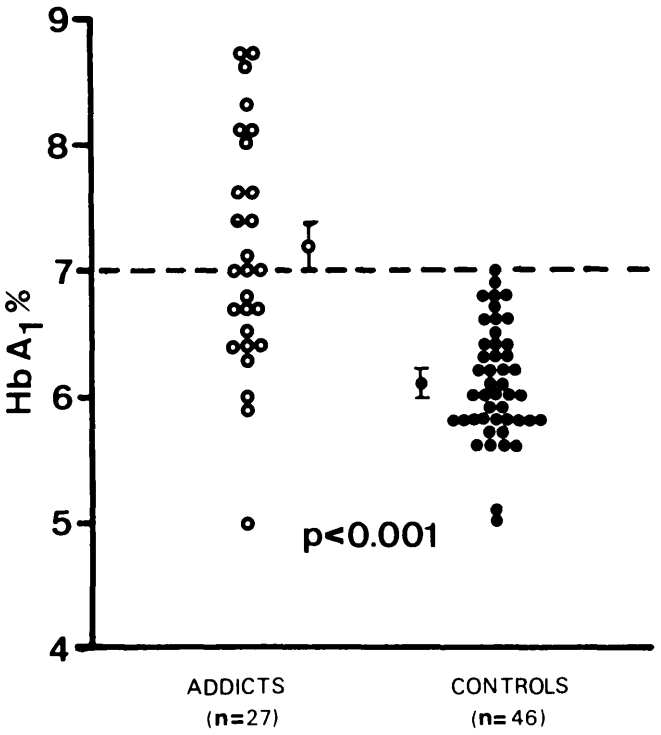

FIG. 3. Heroin addicts have HbA_1 concentrations (7.18 ± 0.17%, mean ± SE) significantly higher than those of matched control subjects (6.11 ± 0.66%). (Reproduced from ref. 46.)

addiction and fell during naloxone-induced withdrawal. This fall correlated well with the fall in circulating growth hormone, suggesting that this could be secondary to somatostatin release. These findings, together with those of Ipp et al.,[21] might offer a possible link between the reduced somatostatin release from endocrine pancreas and thalamus during narcotic addiction and the elevated insulin, glucagon, and growth hormone levels in heroin addicts.

ENDOGENOUS OPIATES AND HUMAN DIABETES

From the standpoint of physiopathology, it seems that heroin addicts, like patients with non-insulin-dependent diabetes mellitus (NIDDM), do not respond appropriately to glucose signals. Patients with NIDDM lack the acute insulin response to an intravenous glucose challenge but respond to a variety of other secretagogues, such as arginine,[50] isoproterenol,[51] glucagon,[52] and secretin.[53] In these patients, it has been possible to restore partially the acute insulin response to glucose by using drugs, such as phentolamine, an α-adrenergic blocker, and acetylsalicylic acid, an inhibitor of endogenous prostaglandin synthesis.[54-57] This has led to the suggestion that some endogenous and possibly pancreatically produced substances—perhaps prostaglandin E, catecholamine, and somatostatin—may play a part in the abnormal β-cell function of human diabetes.[58,59]

Endogenous opiates are present within the endocrine pancreas and sensitivity to enkephalins is thought to play some role in the pathogenesis of NIDDM. This statement is based on the observation that a proportion of patients with NIDDM who have taken the sulfonylurea chlorpropamide exhibit profound facial flushing when they drink alcohol.[60] This tendency to flush, which is inherited as an autosomic dominant trait, may be reproduced in susceptible subjects by the infusion of the met-enkephalin analogue DAMME and blocked by naloxone.[61] Moreover, Medbak et al.[62] have reported significant increases of met-enkephalin plasma levels in both normal and diabetic flushers during chlorpropamide and alcohol assumption. The observation that aspirin may also block chlorpropamide alcohol flushing (CPAF) in patients with NIDDM suggests that the CPAF (and perhaps the met-enkephalin flush) involve a prostaglandin step in their mechanism. Since met-enkephalin increases the prostaglandin content in the rat brain,[63] it seems safe to hypothesize that some of the metabolic and hormonal effects of this opioid peptide may be mediated by prostaglandin E, which induce vasodilation and inhibition of acute insulin response to glucose in human beings.[64]

Some recent studies have evaluated the influence of naloxone on glucose-induced insulin secretion in NIDDM.

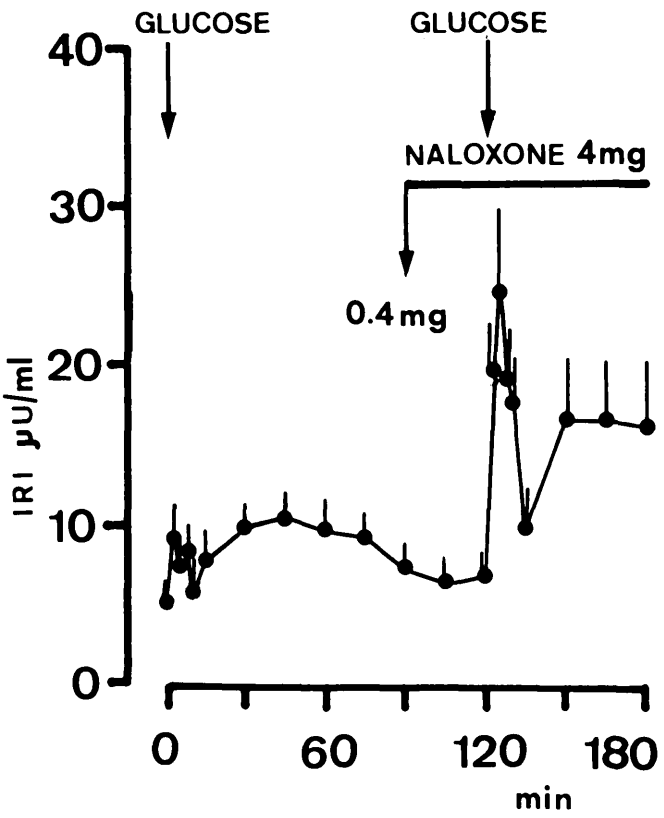

FIG. 4. Partial restoration of the acute insulin response to intravenous glucose in non-insulin-dependent diabetic patients with fasting hyperglycemia receiving an infusion of naloxone. (Reproduced from ref. 38.)

Giugliano et al.[38] found that the infusion of naloxone (0.4 mg as i.v. bolus plus 4 mg infused for 75 min) increased acute insulin responses to an intravenous glucose challenge and augmented glucose disappearance rates (Figure 4). In contrast, Hershon et al.[65] found no significant change in insulin response to intravenous glucose in both CPAF-positive and CPAF-negative diabetic patients receiving naloxone. The discrepancies between these two recently reported studies are not evident. Differences in the experimental protocol could be involved, since Hershon and co-workers used a much higher dose of naloxone (10 mg) injected as an intravenous bolus before the start of the glucose pulse. Different sensitivity of the opiate receptors to the different doses of naloxone might also be important. Finally, as it happens in neuroendocrine research, it would not be surprising if a neuroregulator or blocking agent shows a dose-dependent biphasic effect, thus giving rise to conflicting results. On the other hand, Mason and Herber[66] showed that naloxone (0.8 mg as bolus + 0.1 mg/min for 180 min) decreased by 50% the exaggerated plasma insulin response to oral glucose only in CPAF-positive diabetic patients. These effects of naloxone in NIDDM may happen at a central rather than peripheral level, since the observation by Feldman et al. that naloxone fails to block the stimulatory effect of β-endorphin on the human endocrine pancreas.

CONCLUSIONS

Morphine and opioid peptides may produce profound alterations in carbohydrate metabolism and pancreatic hormone secretion. It seems that β-endorphin stimulates insulin and glucagon secretion in normal human beings, while enkephalins are without apparent effects. On the other hand, heroin addicts have increased concentrations of glycosylated hemoglobin A_1 and, like patients with NIDDM, present a marked reduction of the acute insulin response to i.v. glucose with low K_G values, but can respond appropriately to other stimulants, like arginine. Sensitivity to enkephalins, thought to play some role in the pathogenesis of NIDDM, may offer a link between CPAF and the impaired insulin secretion—namely, that a concentration of enkephalin, which in normal people would stimulate or have no effects on insulin release, might in these patients inhibit it. The partial restoration of insulin secretion by naloxone in some NIDDM patients seems to support this speculation. On the light of the evidence presented, a discharge of endogenous opiates might have participated to the piqûre diabetes provoked by Claude Bernard in 1879. This view is also supported by the finding that β-endorphin is released in conjunction with ACTH and other hormones during stress[67] and by our recent observation that catecholamines, prostaglandin E, and endogenous opiates may act synergistically in impairing insulin secretion in NIDDM.[68]

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