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Research Article

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Effects of Morphine on Glucose Homeostasis in the Conscious Dog

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Abstract. This study was designed to assess the effects of morphine sulfate on glucose kinetics and on glucoregulatory hormones in conscious overnight fasted dogs. One group of experiments established a dose-response range. We studied the mechanisms of morphine-induced hyperglycemia in a second group. We also examined the effect of low dose morphine on glucose kinetics independent of changes in the endocrine pancreas by the use of somatostatin plus intraportal replacement of basal insulin and glucagon.

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Also, we report the effect of a 2 mg/h infusion of morphine on glucose kinetics when the endocrine pancreas is clamped at basal levels. Under these conditions, morphine exerts a hypoglycemic effect (25% fall in plasma glucose, $P < 0.05$) that is due to inhibition of glucose production (by 25–43%, $P < 0.05$). The hypoglycemia was independent of detectable changes in insulin, glucagon, epinephrine and cortisol, and was not reversed by concurrent infusion of a slight molar excess of naloxone. Therefore, we postulate that the hypoglycemic effect of morphine results from the interaction of the opiate with non-mu receptors either in the liver or the central nervous system.

Introduction

The hyperglycemic effect of morphine has been well known for decades (1, 2), but the mechanisms and significance of this phenomenon are unclear. Since the discovery of opiate receptors and endorphins, the effects of opioids on glucose metabolism have received much attention. Opiates may act as both physiologic and pharmacologic modulators of glucoregulation but the mechanisms and importance of these roles are not settled.

Studies by Vassalle (3), Feldberg et al. (4, 5, 6), and Van Loon et al. (7) have shown that morphine and β-endorphin can cause hyperglycemia by increasing circulating epinephrine via what appears to be a centrally-mediated mechanism. Reid and Yen (8) and Unger and colleagues (9, 10, 11) have suggested that opioids can cause hyperglycemia by direct stimulation of pancreatic secretion of glucagon, and to a lesser extent, insulin. All of these studies have been narrow in that they have failed to account for simultaneous changes in glucoregulatory hormones and potential interactions between them. Thus, the overall hormonal response to opioids has not been clearly defined. In addition, the hyperglycemic response to opioids has not been explained mechanistically with regard to the components of glucose turnover. Finally, the possibility that opioids can affect glucose homeostasis independent of changes in other hormones, has not been investigated. Therefore, the present studies were undertaken; (*a*) to establish a dose-response range for the effects of morphine on glucose kinetics and circulating levels of catecholamines, glucagon,

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and insulin; (*b*) to examine the nature of the hyperglycemic response to morphine; (*c*) to examine the effects of morphine on glucose homeostasis at a time when changes in other glucoregulatory hormones do not occur.

Methods

Animals. Experiments were carried out on 28 overnight (18 h) fasted mongrel dogs (18–23 kg) of either sex that had been fed a meat and chow diet containing 30% crude protein, 44% carbohydrate, 12% moisture, 9% fat, and 5% crude fiber (Wayne Dog Food, Allied Mills, Chicago, IL) for 3 wk prior to their use in an experiment. 14–21 d before the study, silastic catheters were implanted under general anesthesia in the femoral artery and in a splenic vein as previously described (12). All catheters were filled with heparinized saline (200 U/ml), knotted, and placed in a subcutaneous pouch to allow complete closure of skin incisions. Animals were used for experiments only if they had an hematocrit >38%, a white cell count of <14,000 cells/mm^3, consumed >⅔ of their daily rations, and had normal stools.

On the day of the study, the catheters were removed from their pouches through skin incisions made under local anesthesia (1% Lidocaine, Astra Pharmaceutical Products, Worcester, MA). The arterial catheter was used for blood sampling, and when needed, the splenic vein was used for hormone replacement. Angiocaths (No. 18 gauge) were inserted percutaneously into the left cephalic vein for infusion of [3-^{3}H]glucose; the right cephalic vein for infusion of morphine and naloxone; and when needed, the right saphenous vein for infusion of somatostatin (SRIF)[1]. After completion of these preexperimental preparations, the conscious dogs were placed in a Pavlov harness and allowed to rest ~1 h prior to the beginning of the experiments.

Experimental design. Each experiment consisted of an 80 min tracer equilibration period (from −120 to −40 min), followed by a 40 min basal period (from −40 to 0 min), and a 180-min experimental period (0 to 180 min). A primed (116×10^6 dpm in 20 ml saline), constant (mean = 807×10^3 dpm/min) infusion of [3-^{3}H]glucose was started at −120 min and continued throughout the study.

Five types of experiments were performed: in group 1 (n = 5), morphine was infused in a series of increasing doses to establish morphine dose responsiveness. In this protocol, morphine sulfate was infused at 2 mg/h for the first hour, 8 mg/h for the second hour, and 16 mg/h for the third hour. In group 2 (n = 5), the effects of morphine (16 mg/h for 3 h) on glucose turnover and the multiple systems that regulate it were studied. In groups 3, 4, and 5, endocrine pancreatic function was fixed at basal levels by infusion of SRIF with intraportal replacement of insulin and glucagon. SRIF (0.8 μg/kg per min) was started at −90 min. 2 min later, intraportal replacement of basal glucagon (0.65 ng/kg per min) and insulin (175–250 μU/kg per min) was begun via the splenic vein catheter. During the equilibration period, adjustments were made in the insulin delivery rate so that dogs remained euglycemic. When a dog had maintained euglycemia for 40 min past an adjustment in the insulin delivery rate, no further changes were made and the basal sampling period was begun. Group 3 (n = 7) received saline for 3 h to determine the stability of glucose kinetics with insulin and glucagon fixed at basal circulating levels. This group served as controls for groups 4 and 5. Group 4 (n = 7) received a continuous infusion of low-dose morphine (2 mg/h) for 3 h to assess the effects of the opiate on glucose homeostasis independent of changes in insulin and glucagon. During the last hour, the dogs also received naloxone hydrochloride (Narcan, Dupont Pharmaceuticals, Manati, PR) at 2 mg/h intravenously to determine whether morphine's effect on glucose homeostasis could be reversed with this opiate antagonist. Group 5 (n = 4) also received morphine at 2 mg/h intravenously for 3 h. In addition, euglycemia was maintained by an exogenous variable infusion of 10% dextrose solution. This group was studied to quantitate morphine's effects on glucose kinetics independent of the counterregulatory response to hypoglycemia.

Processing of blood samples. Blood samples were drawn every 10 min during the basal period and every 15 min thereafter. The collection and immediate processing of blood samples have been described previously (12). Plasma glucose was measured by the glucose oxidase method with a Beckman model II glucose analyzer (Beckman Instruments, Palo Alto, CA). Plasma immunoreactive insulin was assayed by the Sephadex-bound antibody procedure (Pharmacia Fine Chemicals, Piscataway, NJ). Immunoreactive glucagon was measured using Unger's 30,000 antibody obtained from the University of Texas Southwestern Medical School, Dallas, TX. Circulating catecholamines were measured with a radioenzymatic assay (Cat-A-Kit, Upjohn Co., Kalamazoo, MI). Plasma cortisol levels were measured by radioimmunoassay with a kit obtained from Micromedic Systems, Inc. (Horsham, PA). Beta-endorphin was measured by radioimmunoassay using unextracted plasma.

Tracer methods and calculations. Glucose radioactivity in plasma was determined on a Somogyi filtrate (1:10) with 4.5% barium hydroxide plus 4.5% zinc sulfate. Recovery of glucose radioactivity was monitored as follows: an aliquot of the [3-^{3}H]glucose infusate was added to 5 ml of the dog's plasma (drawn immediately before the experiment) and to 5 ml of saturated benzoic acid solution containing 1 mg/ml. Two aliquots of the solution were run with the samples and the counts obtained compared with those expected. Recovery varied from 94–96%. Radioactive water was removed from the glucose samples by overnight evaporation in a vacuum oven at 60°C. Such a treatment did not result in a loss of the [3-^{3}H]glucose. Rates of glucose production (Ra, the rate of appearance of cold glucose in the plasma compartment, milligrams per kilogram per minute) and glucose utilization (Rd, milligrams per kilogram per minute) were calculated according to the method of Wall et al. (13) as simplified by DeBodo et al. (14). This method is based on a single compartment analysis of glucose kinetics in which it is assumed that rapid changes in the specific activity and concentration of glucose do not occur uniformly within the entire glucose pool. To compensate for this nonuniform mixing, the nonsteady state term of the equation is multiplied by a correction factor (pool fraction) of 0.65 as suggested by Cowan and Hetenyi (15). Glucose clearance (Cl, per min) was calculated by dividing Rd by the plasma glucose concentration.

Statistical methods. Statistical analyses were performed using the paired t test, analysis of variance, or the Wilcoxon signed rank test where appropriate. All data are expressed as the mean±standard error of the mean (SEM).

Results

Dose-dependent effects of morphine on glucose homeostasis. Table I shows that morphine infused at 2 mg/h caused no change in plasma glucose concentration. Ra, Rd, and Cl all declined slightly but not significantly. During infusion of the intermediate dose of morphine (8 mg/h), plasma glucose and

1. *Abbreviations used in this paper:* Cl, glucose clearance; Ra, rate of glucose production; Rd, rate of glucose utilization; SRIF, somastatin.

Table I. Effects of Increasing Doses of Morphine Sulfate (2, 8, and 16 mg/h) on Glucose Homeostasis

	Basal	2 mg/h	8 mg/h	16 mg/h
Plasma glucose (*mg/dl*)	95±3	94±3	101±3	139±6*
Ra (*mg/kg/min*)	2.73±0.22	2.43±0.08	3.08±0.19	3.74±0.33*
Rd (*mg/kg/min*)	2.74±0.22	2.56±0.10	2.70±0.15	2.69±0.11
Cl (*ml/kg/min*)	2.90±0.19	2.71±0.14	2.78±0.14	2.06±0.08*
Insulin (*uU/ml*)	16±2	12±2	22±3	31±4*
Glucagon (*pg/ml*)	59±5	53±5	104±15	249±27*
Epinephrine (*pg/ml*)	53±20	30±9*	422±226*	1304±291*

The values represent mean±SEM from measurements obtained throughout each period.
* Significance from basal values with $P < 0.05$.

Ra began to increase but Rd and clearance did not change. At the highest dose of morphine (16 mg/h), plasma glucose and Ra were both significantly elevated while Cl was impaired.

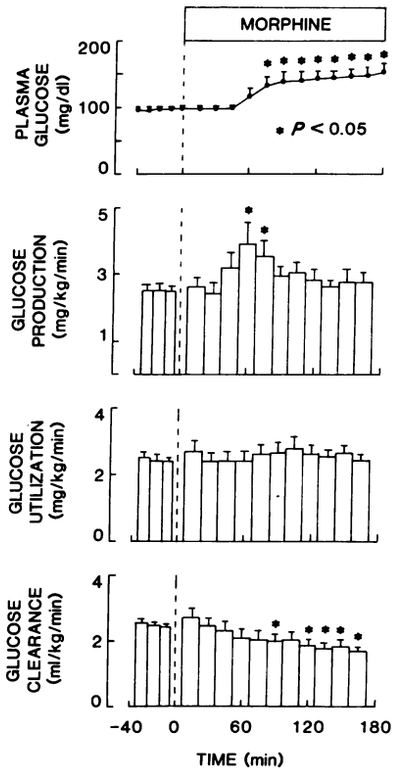

Figure 1. Effects of morphine sulfate (16 mg/h) on plasma glucose, Ra, Rd, and Cl.

During low dose morphine infusion, epinephrine fell 43% ($P < 0.05$), but there were no significant changes in insulin or glucagon. Epinephrine became significantly elevated during the intermediate dose of morphine. Levels of all four hormones were significantly elevated above basal during the high dose morphine infusion.

Hyperglycemic response to morphine. In this protocol, the effect of morphine (16 mg/h) was studied in greater detail. Fig.

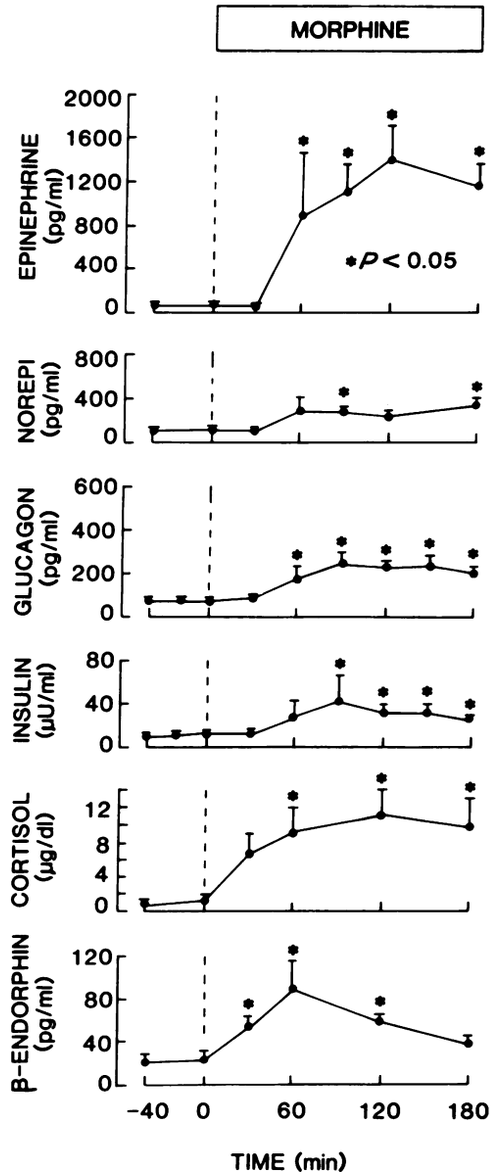

Figure 2. Effects of morphine sulfate (16 mg/h) on plasma epinephrine, norepinephrine (*norepi*), glucagon, insulin, cortisol, and beta-endorphin.

1 shows that morphine caused an increase in plasma glucose from a basal 99±3 to 154±13 mg/dl ($P < 0.05$). This was due to both an increase in Ra (peak 3.9±0.7 vs. 2.5±0.2 basally, $P < 0.05$) and a decrease in Cl (to 1.7±0.2 from 2.5±0.1 basally, $P < 0.05$) with no change in Rd. The hormonal response to morphine in this protocol was complex (Fig. 2). Morphine increased plasma epinephrine (1400±300 vs. 62±8 pg/ml), norepinephrine (335±66 vs. 113±10 pg/ml), glucagon (242±53 vs. 74±14 pg/ml), insulin (30±9 vs. 10±2 μU/ml), cortisol (11.1±3.3 vs. 0.9±0.2 μg/dl), and beta-endorphin (88±27 vs. 23±6 pg/ml), all values $P < 0.05$ compared with basal. All these changes became apparent within the first hour of morphine infusion.

Stability of glucose kinetics during infusion of SRIF with intraportal replacement of basal insulin and glucagon. Glucose kinetics and plasma insulin, glucagon, catecholamines, and cortisol were all stable in the control group as shown in Table II.

Effect of morphine sulfate on glucose kinetics independent of changes in insulin and glucagon. With insulin and glucagon fixed at basal levels, morphine sulfate infused at 2 mg/h caused a substantial fall in plasma glucose (Fig. 3). This hypoglycemic effect became apparent within 15 min of the start of the morphine infusion. Plasma glucose continued to fall such that by 2 h it reached 76±5 mg/dl ($P < 0.05$). This fall was due to an almost immediate inhibition of hepatic Ra by morphine. Ra had decreased to 2.35±0.2 mg/kg per min during the second hour of morphine infusion vs. 3.11±0.2 basally ($P < 0.05$). Glucose utilization was initially unchanged during morphine but it declined gradually as plasma glucose fell and hypoglycemia ensued. As a result of these changes in plasma glucose and Rd, Cl rose by 10% within 2 h of morphine infusion.

In the last hour (120 to 180 min) of morphine infusion, naloxone hydrochloride infused at 2 mg/h did not cause any significant change in either Ra or Rd, and as a result, there was no change in plasma glucose. Thus, in the presence of morphine, naloxone failed to reverse the morphine-induced hypoglycemia.

Fig. 4 demonstrates that the changes in glucose kinetics seen in this protocol are not attributable to changes in either insulin or glucagon which remained stable at basal values of 10±1 μU/ml and 81±16 pg/ml, respectively. Initially, morphine did cause a significant ($P < 0.05$) decrease (45%) in epinephrine. This decrease was similar to that observed in group 1 dogs during low dose morphine infusion. However, as hypoglycemia ensued, circulating levels of both catecholamines rose significantly above basal. During the third hour when plasma glucose had fallen 25%, epinephrine remained significantly elevated above basal at 425±157 pg/ml, while norepinephrine was more modestly elevated. In spite of the persistent elevation of epinephrine, Ra remained below basal. Morphine had no effect on plasma cortisol levels.

Effect of morphine plus euglycemic clamp on glucose kinetics, independent of changes in insulin and glucagon. Fig. 5 shows that in these dogs the infusion of exogenous glucose maintained euglycemia. In this group, Ra fell 43% during morphine infusion (Fig. 5). This was significantly more than the fall seen in group 3 (43% vs. 25%, $P < 0.05$) in which hypoglycemia was allowed to occur. These findings suggest that hypoglycemia blunted morphine's inhibition of Ra in group 3. In addition, with euglycemic clamp, there was no

Table II. Effect of SRIF plus Intraportal Replacement of Basal Insulin and Glucagon on Plasma Glucose, Glucose Kinetics, and Circulating Insulin, Glucagon, Catecholamines, and Cortisol in the Conscious 18-h Overnight Fasted Dog

	Time (*min*)						
	−40–0	30	60	90	120	150	180
Plasma glucose (*mg/dl*)	106±5	106±7	107±8	107±10	107±12	107±13	106±14
Ra (*mg/kg/min*)	3.06±0.28	3.03±0.33	2.86±0.26	3.08±0.30	2.82±0.31	2.81±0.27	2.82±0.29
Rd (*mg/kg/min*)	3.08±0.30	3.02±0.34	2.78±0.27	3.06±0.31	2.81±0.31	2.78±0.26	2.88±0.28
Cl (*ml/kg/min*)	2.96±0.41	3.00±0.51	2.81±0.48	3.08±0.53	2.96±0.61	2.93±0.53	3.00±0.57
Insulin (*uU/ml*)	8±1	8±1	8±1	8±1	8±1	8±1	8±1
Glucagon (*pg/ml*)	97±11	99±14	96±12	101±10	97±9	95±11	94±9
Epinephrine (*pg/ml*)	56±16		69±22		53±22		46±17
Norepinephrine (*pg/ml*)	68±14		65±19		61±19		75±17
Cortisol (*μg/dl*)	2.6±0.7		2.3±0.7		2.6±1.2		2.0±0.7

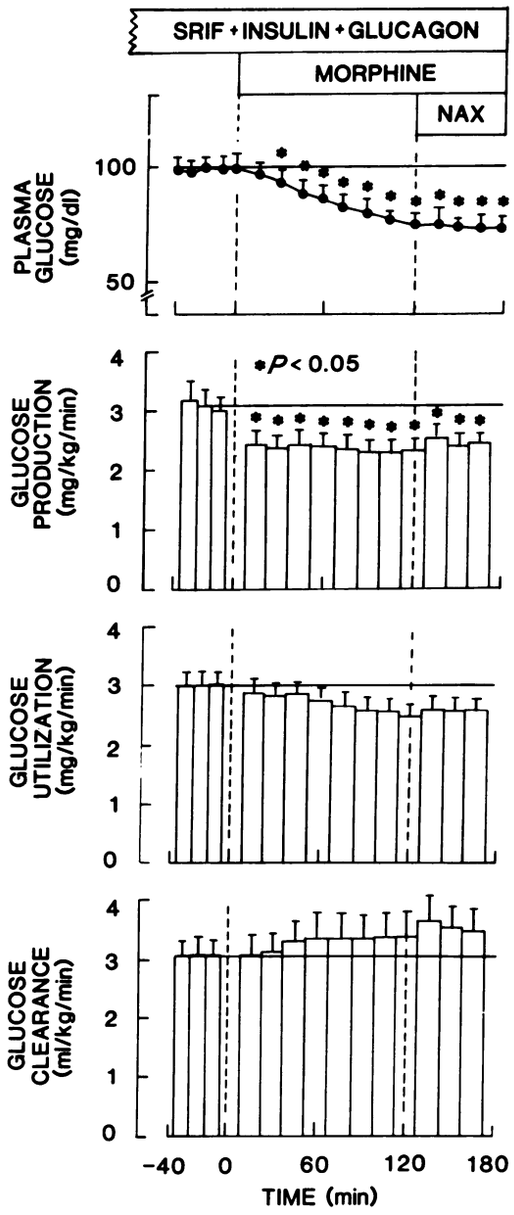

Figure 3. Effects of morphine (2 mg/h) and morphine (2 mg/h) plus naloxone (2 mg/h) on plasma glucose, Ra, Rd, and Cl. *Nax*, naloxone.

change in Rd or clearance during morphine infusion. This is in contrast to the gradual changes in both these parameters seen in group 3.

Fig. 6 shows the effect of morphine on insulin, glucagon, catecholamines, and cortisol in the euglycemic group. Insulin and glucagon did not change but again there was a significant decrease in epinephrine. However, there was no subsequent

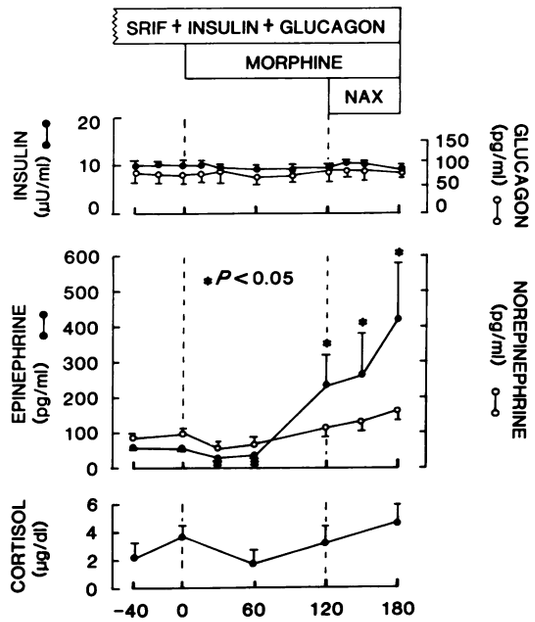

Figure 4. Effects of morphine (2 mg/h) and morphine (2 mg/h) plus naloxone (2 mg/h) on circulating insulin, glucagon, catecholamines, and cortisol.

elevation of epinephrine in this group in contrast to the hypoglycemic protocol. Cortisol was unchanged by morphine.

Discussion

The present study was undertaken to examine the effects of morphine sulfate on glucose homeostasis. Although the hyperglycemic effect of morphine has been well known for decades, the mechanism of opioid-induced hyperglycemia is still controversial. As recently as 1974, Feldberg et al. (5) attributed morphine hyperglycemia to a centrally mediated stimulation of catecholamine release by the opiate (5). Van Loon et al. (7) have explained the hyperglycemic effect of a centrally administered endogenous opioid peptide, β-endorphin, to a similar mechanism.

Also, there have been reports that morphine and other opioid compounds can affect glucose homeostasis by altering secretion by the endocrine pancreas. Based on their studies with the isolated perfused canine pancreas, Ipp et al. (9) hypothesized that the hyperglycemic effect of opioids is due to direct stimulation of the endocrine pancreas. Most recently, Feldman et al. (11) and Reid and Yen (8) have shown that high dose bolus injections of opioids can cause a transient increase in blood glucose which is preceded by an increase in glucagon, and to a lesser extent, insulin. However, in all the studies just mentioned, single high doses of opioids were administered and the possibility that simultaneous changes in the levels of many glucoregulatory hormones occur following

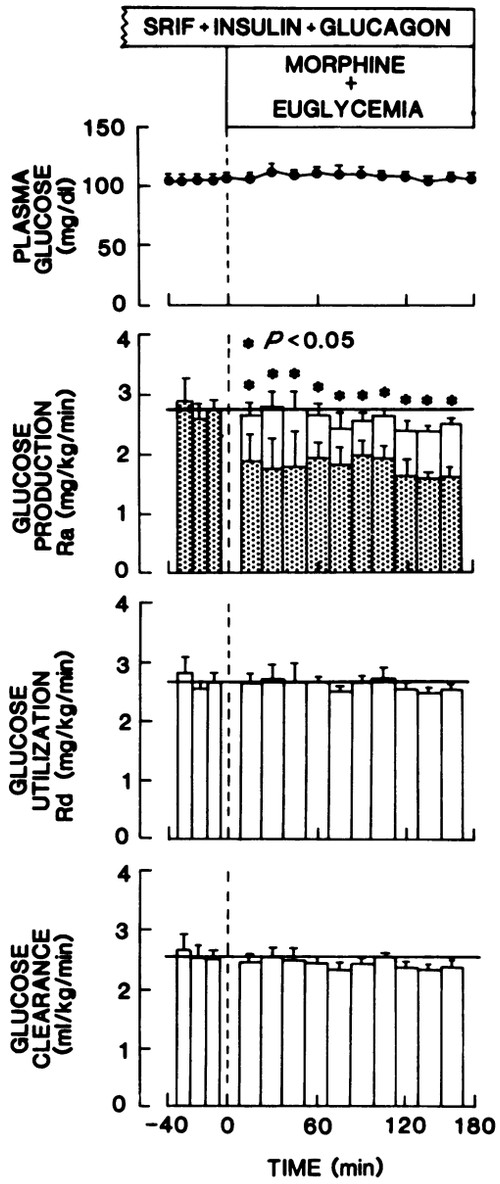

Figure 5. Effects of morphine on plasma glucose and glucose kinetics when dogs are maintained euglycemic with a variable rate exogenous glucose infusion. The stippled portion of the bars represent endogenous glucose production which was calculated by subtracting infused glucose from overall tracer-determined glucose production represented by the sum of stippled and open bars.

opioid administration was not adequately considered. Therefore, the first two protocols in this study were designed to determine the dose response range for morphine hyperglycemia and to define the hormonal and kinetic changes responsible for the hyperglycemic response.

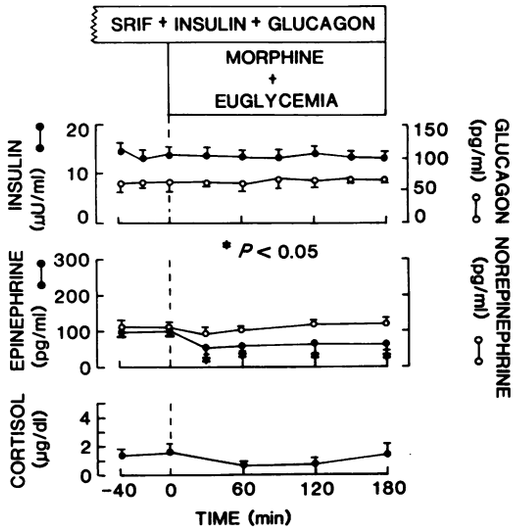

Figure 6. Effects of morphine (2 mg/h) on circulating insulin, glucagon, catecholamines, and cortisol when euglycemia is maintained.

The data from the present study show that, at high doses, morphine has a dual effect on glucose kinetics. Morphine infusion caused an increase in Ra and a decrease in Cl. The increase in Ra can be explained by the combined rise in epinephrine, cortisol, and glucagon. In addition, the decreased clearance can be attributed to the increase in circulating epinephrine. Glucagon has been shown to exert its hyperglycemic effect primarily via the liver (16) without causing any significant changes in peripheral Rd (17). On the other hand, epinephrine stimulates hepatic Ra and has a marked inhibitory effect on Cl. The latter phenomenon has been attributed to an inhibition of insulin's action in the periphery (18). This would explain the marked inhibition in Cl seen in the dogs receiving the highest dose of morphine infusion (16 mg/h), despite a significant rise in circulating insulin levels. Finally, although cortisol by itself may not affect either glucose production or utilization, it has been shown to potentiate the effects of epinephrine and glucagon on Ra (19). It is also possible that morphine itself contributed to the increase in Ra and the decrease in Cl. This, however, seems unlikely in view of the results in the two groups that received morphine plus pancreatic clamp.

Previous studies (1–11, 20) examining the effect of opiate administration on insulin and glucagon in vivo have failed to account for the possibility that simultaneous changes in pancreatic hormones and catecholamines may take place. Ipp et al. (9) claimed that doses of morphine used to cause hyperglycemia in alloxan-diabetic dogs might actually lower epinephrine, and therefore, the hyperglycemia was not mediated by catecholamines. However, that claim was based on a report by another group of investigators on the catechol-lowering effect of morphine in anesthetized dogs undergoing laparotomy (21),

a model clearly different from the conscious dog. Although Ipp et al. (9) did not report levels of catecholamines in their studies, our study demonstrates that morphine, at doses comparable with the ones they used, greatly increases and does not decrease epinephrine. Our results suggest that epinephrine makes a substantial contribution to the hyperglycemia during morphine infusion. Therefore, it is possible that the studies noted above have overestimated the importance of glucagon elevation in the hyperglycemic response to opiates.

In addition, epinephrine can be a potent secretagogue of glucagon both in vitro (22) and in vivo (23–25). It can also inhibit release of insulin (22). This raises the possibility that the rise in epinephrine in our studies may have itself affected pancreatic release of glucagon and insulin. Thus, extension of in vitro evidence that opioids alter secretion of insulin and glucagon from the pancreas (9, 26) to in vivo glucoregulation is complicated. This may be especially important in the case of diabetics in which the ability of epinephrine to stimulate glucagon release is enhanced compared with normal (27). Therefore, interactions among the glucoregulatory hormones that change in response to morphine need to be further evaluated.

In fact, the most important finding from the high dose infusion studies is that morphine does not exert its hyperglycemic effect simply by increasing epinephrine or glucagon alone. Rather, high dose morphine initiates a catabolic response that involves activation of the sympathetic nervous system, the endocrine pancreas, the pituitary-adrenal axis, and at least one endogenous opioid system. The synergistic nature of this response may have important implications for surgical patients, cancer patients, and others who are both treated with morphine and who are prone to stress catabolism.

The effects of low dose morphine infusion on glucose homeostasis stand in contrast to those of the high dose infusion. In the three protocols in which it was infused at 2 mg/h, morphine lowered basal levels of epinephrine. This result is similar to findings of Taborsky et al. (21) in anesthetized dogs. However, its significance is uncertain.

Since low dose morphine did not increase catecholamines or cortisol, we could study morphine's effect on glucose kinetics independent of changes in other hormones by combining a low dose infusion with a pancreatic clamp. This was achieved in protocols 3, 4, and 5 by infusion of SRIF with intraportal replacement of basal insulin and glucagon.

The results for the control group are similar to previously reported values (28) showing that, in 18-h fasted dogs, infusion of somatostatin with intraportal replacement of basal insulin and glucagon results in stable glucose kinetics and hormones. In addition, the levels of plasma glucose, glucose turnover parameters, and hormones are similar to those reported for the 18-h fasted dogs which received only saline (28).

At the low dose used in groups 4 and 5, morphine has a hypoglycemic effect which is primarily due to inhibition of hepatic Ra. The small changes in Rd and Cl observed in group 4 raised the possibility of a small effect of morphine on the peripheral tissues as well. This, however, was not substantiated by the data obtained in group 5 dogs. When euglycemia was maintained during morphine infusion, the fall in Rd and, hence, the rise in Cl were prevented, suggesting that these changes were a function of the declining plasma glucose and not morphine itself.

The hormonal data for both groups 4 and 5 indicate that morphine's inhibition of Ra is not due to changes in either circulating insulin, glucagon, or cortisol. On the other hand, the significant elevation in epinephrine seen by the end of 2 h of morphine infusion in group 4 may account in part for blunting the decrease in Ra in that group. When hypoglycemia was prevented in group 5, epinephrine remained significantly below basal levels throughout morphine infusion and Ra remained maximally suppressed. This would be consistent with the postulated role of epinephrine as a mediator of the counterregulatory response to hypoglycemia (22), although it is interesting that the rise in epinephrine did not increase Ra. It is also of interest to note that the inhibition of Ra was initially greater in the euglycemic group than in the hypoglycemic group. The reason for this difference is not clear but it cannot be explained by epinephrine since the levels were comparable in the two groups during the first hour of morphine infusion.

The mechanism by which morphine inhibits glucose production is not completely clear from this study. It is possible that morphine acts via a central mechanism to cause a change in either autonomic or humoral outflow that ultimately affects the liver. Our data show that there are no good candidates among the major glucoregulatory hormones that could mediate a central mechanism. The decline below basal levels of circulating epinephrine following low dose morphine infusion is not a likely mechanism for this inhibition. The inhibitory effect of morphine was still apparent even when there was a hypoglycemia-induced rise in epinephrine as seen in group 4 after 2 h of morphine infusion. Nevertheless, our data cannot rule out a central effect mediated via autonomic innervation of the liver.

A second possibility is that morphine exerts a direct effect on the liver to decrease glucose production. The nature of such an interaction is not quite clear. It does not seem to involve the mu (μ) opiate receptors which are specific for morphine and inhibited by naloxone (30). This is supported by the fact that Ra was not restored to basal levels with naloxone infusion, even in the presence of high catecholamine response to hypoglycemia. This finding is similar to a previous report of naloxone's failure to reverse opiate effects on glucose homeostasis (11).

In summary, we studied the effect of morphine sulfate on glucose homeostasis under a variety of conditions. Data from dose-response studies indicate that the effects of low and high dose morphine infusion are disparate. In the intact dog, 2 mg/h morphine decreases plasma epinephrine with no change in

plasma glucose. At high doses, morphine causes hyperglycemia secondary to increased hepatic Ra and decreased Cl by the peripheral tissues. These effects can be explained by elevations of circulating epinephrine and glucagon. The hormonal response underlying morphine-induced hyperglycemia is, however, much more widespread than previously reported. Morphine initiates a complex catabolic response involving the sympathetic nervous system, the pancreas, and the pituitary-adrenal axis.

We also report a hypoglycemic effect of a low dose infusion of morphine when the endocrine pancreatic function is fixed at basal levels. This effect is due to inhibition of hepatic Ra. It is independent of detectable changes in insulin, glucagon, cortisol, and epinephrine. Whether this hypoglycemic effect is centrally mediated or results from interaction of opiates directly with the liver remains to be determined.

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