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Opiates modulate insulin action in vivo in dogs

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Summary. To investigate the influence of opiates on insulin action in vivo, we induced mild physiological hyperinsulinaemia (15–20 mU/l) in five trained conscious dogs in the absence or presence of ongoing infusion with the opiate agonist D-met^2-pro^5-enkephalinamide (DMPE, 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$), or the opiate antagonist naloxone (1.25 mg followed by 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The effects on glucose production and glucose utilization were measured by isotope dilution using 3-^{3}H-glucose. Glucose fell similarly over 30 min in response to insulin in controls (0.021 ± 0.003 mmol $\cdot l^{-1} \cdot min^{-1}$), and both the DMPE and naloxone studies (0.016 ± 0.002 mmol $\cdot l^{-1} \cdot min^{-1}$ and 0.017 ± 0.003 mmol $\cdot l^{-1} \cdot min^{-1}$, respectively). In control dogs, insulin lowered glucose by transiently suppressing production by 0.028 ± 0.006 mmol $\cdot kg^{-1} \cdot min^{-1}$ at 20–30 min without changing utilization. In contrast, in both the DMPE and naloxone studies insulin lowered glucose by markedly raising utilization at 20 min by 0.094 ± 0.017 and 0.139 ± 0.022 mmol $\cdot kg^{-1} \cdot min^{-1}$, respectively. Furthermore, insulin failed to suppress production in both DMPE and naloxone studies and, as plasma glucose fell, production rose in both treatment groups at 20 min by 0.045 ± 0.012 and 0.089 ± 0.022 mmol $\cdot kg^{-1} \cdot min^{-1}$ respectively. The counter-regulatory hormone glucagon was transiently suppressed by insulin at 20 min in controls, but not in the treatment groups; cortisol and adrenaline rose at 30 and 45 min respectively in the naloxone group only. No other changes were noted in counter-regulatory hormones. Thus hormonal changes do not appear to account for the early pronounced rise in glucose utilization leading to the fall in glucose in the DMPE and naloxone studies. We conclude that the morphine-like agent DMPE and high doses of the opiate antagonist naloxone modulate insulin-induced glucose fluxes in vivo, promoting both glucose utilization and production. These effects may be direct or indirect, and may serve a function in the redistribution of glucose during stress responses.

Key words: Opiates; naloxone, insulin action, glucose production, glucose utilization, counter-regulatory hormones.

The endogenous opiates appear to play a role in the regulation of various physiological processes controlled by the central nervous system including stress responses [1–2]. The acute response to opiates may include a transient increase in blood glucose as first demonstrated in cats given intraventricular morphine [3]. Recent studies in man [4–6] and dogs [7] demonstrate that endogenous opiates, when given intravenously, may variably affect insulin and glucagon secretion or blood glucose levels. In addition, the opiate receptor antagonist, naloxone, can increase insulin release in vitro [8] and glucagon secretion in diabetic dogs [9]. In man, naloxone infusion prior to intravenous glucose resulted in an increase in peak blood glucose concentration and glucose area, while insulin and glucagon levels were no different than in controls [10], whereas infusion of an enkephalin analogue prior to oral glucose diminished the insulin response without altering the blood glucose profile compared to controls [11]. These latter findings suggest that, in addition to their effects on insulin or glucagon secretion, opiates may modulate glucose disposal or alter tissue sensitivity to insulin. To investigate more directly the possibility that opiates modulate tissue sensitivity to insulin, we examined the effect of opiates and opiate blockade on glucose fluxes induced by mild physiological hyperinsulinaemia.

Material and methods

Experimental animals

Studies were performed on five conscious female mongrel dogs weighing 7.5–10.5 kg; each dog had been trained to stand quietly in a harness throughout each study.

Experimental design

Glucose kinetics, (i.e. production and utilization) were determined in each dog on three occasions: a control study during normal saline (0.154 mol/l) infusion: during infusion of the morphine-like enkephalin analogue, D-met^2-pro^5-enkephalinamide [12] (DMPE) (Peninsula Laboratories, San Carlos, California, USA); and during infusion of the opiate antagonist, naloxone (Endo Laboratories, Garden City,

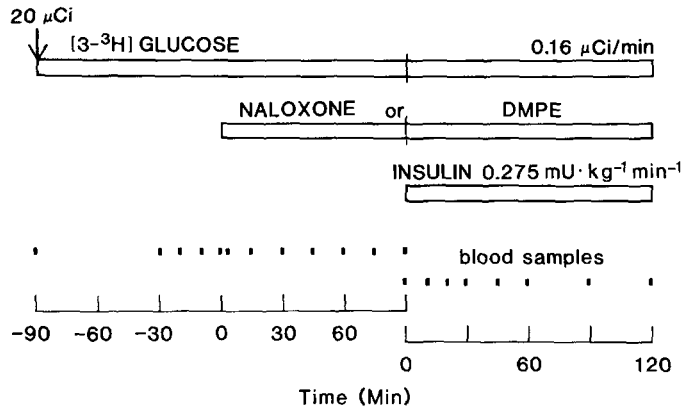

Fig. 1. The study protocol indicating times of commencement and duration of infusion of administered agents and times of blood sampling. DMPE was infused at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$; naloxone was given as 1.25 mg over 1 min followed by 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$

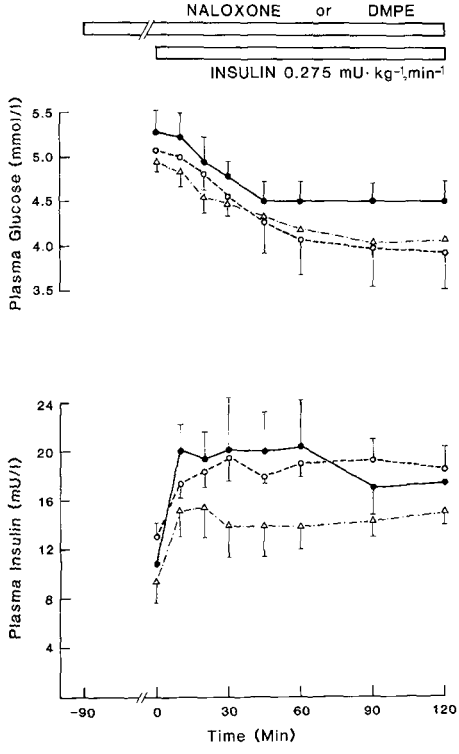

Fig. 2. Changes in plasma glucose and insulin levels following the commencement of insulin infusion. There was a similar fall in glucose and rise in insulin in controls (insulin infusion alone O- - -O), or during ongoing DMPE (△ — · — △) or naloxone (●——●) infusion

New York, USA). Control studies were performed first in each dog but DMPE or naloxone studies were in random order. Each study examined the effects of these agents on glucose kinetics during modest sustained hyperinsulinaemia. The study protocol is outlined in Figure 1.

After an overnight fast (12–16 h), three 20 G cannulae were inserted into anterior limb veins for infusion, and an 18 G cannula was inserted into a hind limb for sampling. A primed-continuous infusion of 3-^{3}H glucose (New England Nuclear, Boston, Massachusetts, USA) was begun (20 μCi bolus followed by 0.16 μCi/min) and when steady-state specific activity was achieved (90 min), one of the following was given: infusion of DMPE 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$; naloxone 1.25 mg in 2 ml saline over 1 min followed by 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the remainder of the study; or saline control infusions. Each test substance was infused continuously for a total of 210 min. After the first 90 min of infusion when steady state was re-established (time 0), regular insulin (Lilly, Indianapolis, Indiana, USA), 0.275 $mU \cdot kg^{-1} \cdot min^{-1}$ was infused. In controls, insulin infusion alone was given for a total of 120 min. All substances infused were prepared in NaCl (0.154 mol/l) mixed with 1% bovine serum albumin. Blood was drawn at timed intervals as indicated in Figure 1. In each sample, we measured plasma glucose, insulin, 3-^{3}H glucose specific activity, glucagon, cortisol, adrenaline and noradrenaline.

Analysis of samples

Each blood sample was collected into chilled tubes containing aprotinin (500 KIU/ml) and EDTA, except for 1 ml of blood which was collected into tubes containing reduced glutathione for catecholamine determination. Samples were kept on ice and centrifuged at 4 °C within 2 h of collection to separate plasma.

Plasma glucose was determined using a glucose analyser (Yellow Springs Instruments, Yellow Springs, Ohio, USA). Insulin, glucagon and cortisol were determined by radioimmunoassay as described previously [13]. Glucagon was assayed using a C-terminal specific antiserum following acetone extraction to remove interfering substances [14]. Sensitivity of the assay was 20 pg/ml and the intra-assay coefficient of variation was 10%. Adrenaline and noradrenaline were determined by radioenzymatic assay [15]. Plasma glucose specific activity was measured by precipitating plasma proteins with $Ba(OH)_2$ and $ZnSO_4$ and evaporating the supernatant. The residue containing 3-^{3}H glucose was dissolved in water and 5 ml of scintillation fluid (New England Nuclear 8a70, Boston, Massachusetts, USA) was added. Samples were counted in a liquid scintillation counter with automatic quench correction (Tracor Analytic, Austin, Texas, USA).

Calculations and statistical analysis

Glucose production and glucose utilization (both in $mmol \cdot kg^{-1} \cdot min^{-1}$) were calculated in steady and non-steady states using Steele's equations and a rapidly mixing pool fraction of 0.65, as validated in dogs by Radziuk et al. [16]. 3-^{3}H glucose has been shown to exhibit < 5% recycling into glucose [17]. It was therefore assumed that the ^{3}H from all labelled glucose metabolized was converted to water.

Because each animal underwent all three studies, comparisons between control and study groups were made at each time point using the paired t-test. Changes from baseline were also analyzed using paired t-test or one-way analysis of variance where appropriate. Data are expressed as mean ± SEM.

Results

Over the first 15 min of DMPE or naloxone infusion (from −90 min) there were transient changes in glucose production, utilization and hormones (data not shown). By time 0 a steady state had been established for glucose, glucose turnover and hormones and was similar to controls.

The commencement of insulin infusion at time 0 increased plasma insulin from basal levels of 9–13 to levels of 15–20 mU/l, with no significant difference between control and treatment groups (Fig. 2). In response to insulin there was a similar fall in plasma glucose in control, DMPE and naloxone groups over 30 min of 0.21 ± 0.003, 0.016 ± 0.002, and 0.017 ± 0.003 $mmol \cdot kg^{-1} \cdot min^{-1}$ respectively (Fig. 2). Glucose production and utilization are shown in Figure 3. Steady-state baseline glucose production and utilization were similar in the control, DMPE, and naloxone groups (0.158 ± 0.017, 0.169 ± 0.022, 0.156 ± 0.017 $mmol \cdot kg^{-1} \cdot min^{-1}$

Table 1. Effect of insulin infusion on plasma adrenaline and noradrenaline concentration during infusion of DMPE, naloxone or saline

	Time (min)					
	Basal 0	10	20	45	90	120
Plasma adrenaline (% of basal)						
DMPE	100±30	102±26	129±32	146±48	139±14	133±14
Naloxone	100±25	125±34	148±43	171±39[a]	165±28[a]	178±38[a]
Control	100±32	88±30	115±36	109±30	142±36	146±36
Plasma noradrenaline (% of basal)						
DMPE	100±20	102±26	94±23	76±13	88± 9	106±22
Naloxone	100±20	74±20	110±20	119±23	110±12	137±24
Control	100±25	85±19	100±21	96±26	105±35	89±16

Results expressed as mean±SEM; [a] $p<0.05$ relative to basal

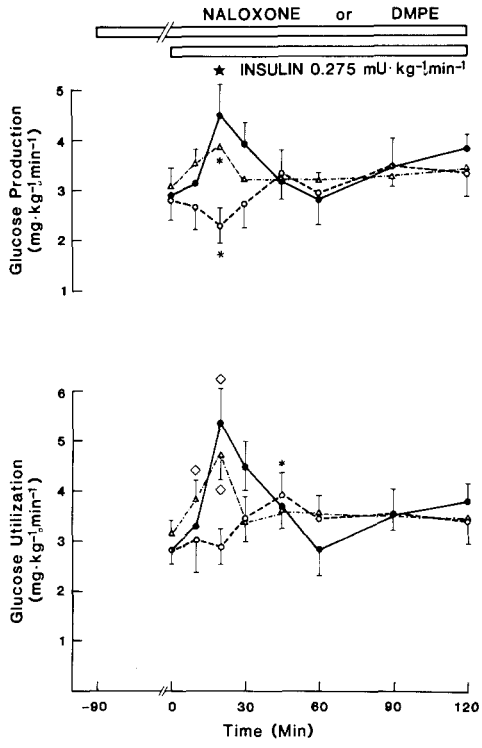

Fig. 3. Glucose production and utilization: insulin + DMPE (△ – · – △), insulin + naloxone (●——●), compared with controls (insulin alone) (○ – – –○). Whereas in controls glucose production fell and glucose utilization was unchanged at 20 min, glucose production and utilization rose by 20 min in both DMPE- and naloxone-groups. *$p<0.05$, ★$p<0.02$, ◇$p<0.01$ compared to baseline

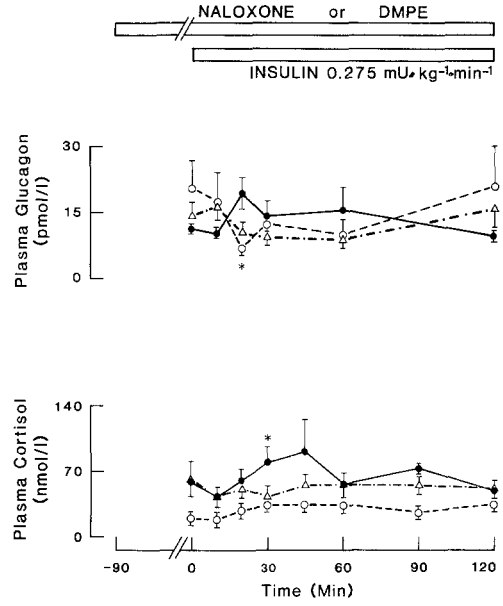

Fig. 4. Plasma glucagon and cortisol during the infusions: insulin + DMPE (△ – · – △), insulin + naloxone (●——●) or saline control (○ – – –○). Glucagon fell transiently during insulin infusion in controls, while glucagon did not change in the experimental groups. Cortisol rose at 30 min in the naloxone group. *$p<0.05$ compared to baseline

respectively). In the control studies, the initial fall in blood glucose after starting insulin (Fig. 2) was due to a transient fall in glucose production at 20 min of 0.28 ± 0.006 mmol·kg^{-1}·min^{-1} without any change in glucose utilization ($p<0.05$; Fig. 3). A transient rise in utilization occurred in controls at 45 min ($p<0.05$; Fig. 3). In contrast, in both the DMPE and naloxone studies, the initial fall in plasma glucose after starting insulin was due to a marked rise in glucose utilization by 20 min, of 0.094 ± 0.017 and 0.139 ± 0.022 mmol·kg^{-1}·min^{-1}, respectively (Fig. 3). Furthermore, insulin failed to suppress glucose production in both treatment studies and, as plasma glucose fell, glucose production rose in both the DMPE and naloxone studies at 20 min by 0.045 ± 0.012 and 0.091 ± 0.019 mmol·kg^{-1}·min^{-1} respectively. Thus, although the fall in blood glucose was similar in all studies, with both DMPE and naloxone treatment this was due to a rise in glucose utilization which exceeded an associated rise in glucose production, rather than suppression of glucose production as occurred during the control saline infusion.

The hormonal changes in plasma are illustrated in Figure 4 and Table 1. There was a transient but significant fall in glucagon ($p<0.05$) in the control study at 20 min of insulin infusion. An apparent rise in glucagon at that time in the naloxone study was not significant,

and no other change in glucagon was noted in the DMPE or naloxone studies (Fig. 4). Cortisol rose in the naloxone study after 30 min of insulin infusion ($p < 0.05$), but there was no change in controls or in the DMPE study (Fig. 4). A small but significant rise in adrenaline occurred in the naloxone study after 45 min of insulin infusion ($p < 0.05$), but there were no other changes in adrenaline or noradrenaline in response to insulin infusion in any of the three studies (Table 1).

Discussion

Our study was designed to consider possible influences of endogenous opiates on insulin action rather than on hormone secretion in vivo. Infusion of DMPE, a potent opiate agonist, with morphine-like activity [12], altered the mechanism by which physiological hyperinsulinaemia lowered blood glucose. Whereas in control studies insulin acted primarily by transiently suppressing glucose production, as previously described [18] during DMPE infusion insulin acted by promoting glucose utilization. Concurrent high dose infusion of the opiate antagonist naloxone with insulin modified the in vivo mechanism of action of insulin in a similar manner to DMPE. These findings may have relevance to the possible role of the opiates in the chlorpropamide-alcohol flush phenomenon [19] and the pathophysiology of non-insulin-dependent diabetes [20].

The predominant effect of the opioid agents used in this study was an early increase in peripheral glucose uptake in response to insulin, such that plasma glucose fell similarly in response to insulin in both treatment and control studies despite the rise in glucose production in the treatment studies. The site and the mechanism of the observed effects remain unclear, but several possibilities can be considered. The enhancement of insulin action on peripheral glucose uptake may have been mediated in part by affecting the release of glucose counter-regulatory hormones. Growth hormone was not measured but reportedly plays only a minor role in glucose counter-regulation [21]. While glucagon was transiently suppressed after 20 min of insulin infusion in controls as previously described [22], glucagon did not change in the two treatment studies. Failure to suppress glucagon could partially explain reduced hepatic sensitivity to insulin, and hence failure to suppress glucose production. Glucose production could then rise in response to the falling blood glucose. Glucagon, however, has no significant effect on peripheral or splanchnic tissues [23], and so could not account for the major increase in glucose utilization which led to the fall in glucose in the treatment studies. No demonstrable effect of the agents used on catecholamine or cortisol levels was evident by 20 min, when the maximal influence on glucose turnover was seen. Since catecholamines and cortisol inhibit glucose utilization [21], suppression of these hormones should have occurred if they were mediating the enhancement of glucose utilization.

In the absence of hormonal changes, it is possible that DMPE and naloxone influenced muscle, fat, or liver to enhance the effect of insulin action at these insulin sensitive sites [23]. Opiates may act on such non-neural tissues either as a result of enkephalins locally released from sympathetic nerve terminals [24], or as a result of circulating β-endorphin, which rises in response to stress [25]. Alternatively, these effects may have been indirect, via actions on the brain, inducing secondary effects on the sympathetic nervous system. Opiates injected into the brain can act on glucose-responsive neurons and elicit marked peripheral effects via the sympathetic nervous system [26, 27]. DMPE has been shown to have especially marked morphine-like effects on the brain when given peripherally [12]. Naloxone, in the dose used, also crosses the blood-brain barrier [10].

Opiate effects may therefore occur via the sympathetic nervous system by acting either centrally or peripherally. Although changes in plasma noradrenaline did not occur, changes in the release of noradrenaline from sympathetic nerve terminals may not be reflected by changes in their circulating blood levels. Opiates generally act as inhibitors of neurotransmission [28]. We have shown elsewhere that, during combined α and β-sympathetic blockade, the effect of hyperinsulinism on glucose turnover is identical to the effects seen in this study [29], suggesting that inhibition of sympathetic action may be a mechanism for the opiate-induced effects observed in this study.

The apparent paradoxical finding that naloxone had similar effects to DMPE is not unique [30]. When given in the absence of exogenous opiates, the effects of naloxone depend on the doses used; conflicting results on pituitary hormone release have been reported with different doses of naloxone [31, 32]. High doses, as used in the present study to ensure passage into the brain, have often induced morphine-like effects on various central nervous system functions [30]. Naloxone is able to mimic morphine or β-endorphin in stimulating insulin release in the isolated dog pancreas [8], and naloxone could not block the effect of β-endorphin on the endocrine pancreas of healthy and diabetic man [6]. Pre-treatment of rats with intraperitoneal naloxone led to a subsequent marked increase in brain opiate binding [33], suggesting a possible mechanism by which naloxone may induce opiate-like effects under some conditions.

We speculate that our findings of increased insulin action in vivo during DMPE infusion may reconcile the apparent paradox of increased glucose uptake during stress. In response to stress such as burns or shock, hepatic glucose production mediated by neural and hormonal mechanisms initially increases but is frequently associated with increased glucose uptake into peripheral tissues [34, 35], a response not consistent with the known effects of increased sympathetic activity and catecholamine release [21]. In addition, insulin levels have generally been low in these studies [35]. Increased sensitivity of muscle to insulin-stimulated glucose up-

take immediately following vigorous exercise in rats and in man has recently been reported [36, 37]. Since opiates are released during stress and exercise, our results suggest the possibility that opiates increase the effect of insulin in peripheral tissues, enhancing glucose entry into muscle or other metabolically active sites, while inhibiting insulin's effect at the liver, thereby allowing increased glucose availability for peripheral metabolism. Further studies are necessary to explore this possibility.

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References

1. Krieger DT, Martin JB (1981) Brain peptides. N Engl J Med 304: 944–951
2. Morley JE (1981) The endocrinology of the opiates and opioid peptides. Metabolism 30: 195–209
3. Felberg W, Gupta KP (1974) Morphine hyperglycaemia. J Physiol (Lond) 238: 487–502
4. Reid RL, Yen SSC (1981) β-endorphin stimulates the secretion of insulin and glucagon in humans. J Clin Endocrinol Metab 52: 592–594
5. Stubbs WA, Jones A, Edwards CRW, Delitalia G, Jeffcoate WJ, SJ, Besser GM, Bloom SR, Alberti KGMM (1978) Hormonal and metabolic responses to an enkephalin analogue in normal man. Lancet 2: 1225–1227
6. Feldman M, Kiser RS, Unger RH, Li CH (1983) Beta endorphin and the endocrine pancreas: studies in healthy and diabetic human beings. N Engl J Med 308: 349–353
7. Ipp E, Dhorajiwala JM, Moossa AR, Rubenstein AH (1980) Enkephalin stimulates insulin and glucagon release in vivo and accentuates hyperglycaemia in diabetic dogs. Clin Res 28: 396A (Abstract)
8. Ipp E, Dobbs R, Unger RH (1978) Morphine and β-endorphin influence the secretion of the endocrine pancreas. Nature 276: 190–191
9. Robinson RP, Williams PE, Gooch BR, Abumrad NN (1982) The effect of morphine and naloxone on plasma glucagon and glucose production in the diabetic dog. Diabetes 31 (Suppl 2): 161A (Abstract)
10. Morley JE, Baranetsky NG, Wingert TD, Carlson HE, Hershman JM, Melmed S, Levin SR, Jamison KR, Weitzman R, Chang RJ, Varner AA (1980) Endocrine effects of naloxone-induced opiate receptor blockade. J Clin Endocrinol Metab 50: 251–257
11. Jeanrenaud X, Maeder E, Del Pozo E, Felber JP (1981) Enkephalin-induced glucose-insulin dissociation in man. Diabetologia 21: 287 (Abstract)
12. Szekely JI, Ronai AZ, Dunai-Kovacs Z, Miglecz E, Berzetri I, Bajusz S, Graf L (1977) (D-met^2,pro^5)-Enkephalinamide: a potent morphine-like analgesic. Eur J Pharmacol 43: 293–294
13. Sperling MA, DeLamater PV, Phelps D, Fiser RH, Oh W, Fisher DA (1974) Spontaneous and amino acid-stimulated glucagon secretion in the immediate postnatal period. Relation to glucose and insulin. J Clin Invest 53: 1159–1166
14. Walter RM, Dudl RJ, Palmer JP, Ensinck JW (1974) The effect of adrenergic blockade on the glucagon responses to starvation and hypoglycemia in man. J Clin Invest 54: 1214–1220
15. Peuler DJ, Johnson GA (1977) Simultaneous single isotope radioenzymatic assay of plasma norepinephrine, epinephrine and dopamine. Life Sci 21: 625–636
16. Steele R, Wall JS, De Bodo RC, Altszuler N (1956) Measurement of size and turnover rate of body glucose pool by the isotope dilution method. Am J Physiol 187: 15–24
17. Altszuler N, Barkai A, Bjerknes C, Gottlieb B, Steele R(1975) Glucose turnover values in the dog obtained with various species of labeled glucose. Am J Physiol 229: 1662–1667
18. Sacca L, Sherwin R, Hendler R, Felig P (1979) Influence of continuous physiologic hyperinsulinemia on glucose kinetics and counterregulatory hormones in normal and diabetic humans. J Clin Invest 63: 849–857
19. Pyke DA (1979) Diabetes: the genetic connections. Diabetologia 17: 333–343
20. Mason JS, Heber D (1982) Endogenous opiates modulate insulin secretion in flushing non-insulin-dependent diabetics. J Clin Endocrinol Metab 54: 693–697
21. Gerich J, Cryer P, Rizza R (1980) Hormonal mechanisms in acute glucose counterregulation: the relative roles of glucagon, epinephrine, norepinephrine, growth hormone, and cortisol. Metabolism 29: 1164–1175
22. Chiasson JL, Liljenquist JE, Finger FE, Lacy WW (1976) Differential sensitivity of glycogenolysis and gluconeogenesis to insulin infusions in dogs. Diabetes 25: 283–291
23. Liljenquist JE, Keller U, Chiasson JL, Cherrington AD (1979) Insulin and glucagon actions and consequences of derangements in secretion. In: De Groot LJ (ed) Endocrinology. Grune and Stratton, New York, pp 981–996
24. Wilson SP, Klein RL, Chang KJ, Gasparis MS, Viveros OH, Yang WH (1980) Are opioid peptides co-transmitters in noradrenergic vesicles of sympathetic nerves? Nature 288: 707–709
25. Amir S, Brown ZW, Amit Z (1979) The role of endorphins in stress: evidence and speculations. Neurosci Biobehav Rev 4: 77–86
26. Ono T, Oomura Y, Nishino H, Sasaki K, Muramoto K, Yano I (1980) Morphine and enkephalin effects on hypothalamic glucoresponsive neurons. Brain Res 185: 208–212
27. Van Loon GR, Appel NM (1981) β-endorphin-induced hyperglycemia is mediated by increased central sympathetic outflow to adrenal medulla. Brain Res 204: 236–241
28. North RA, Egan TM (1982) Electrophysiology of peptides in the peripheral nervous system. Br Med Bull 38: 291–296
29. Werther GA, Joffe S, Artal R, Banach W, Sperling M (1981) Is the autonomic nervous system involved in the recovery of glucose output during physiologic hyperinsulinemia. Diabetes 30 (Suppl): 108A (Abstract)
30. Sawynok J, Pinsky C, LaBella FS (1979) On the specificity of naloxone as an opiate antagonist. Life Sci 25: 1621–1632
31. Wakabayashi I, Demura R, Miki N, Ohmura E, Miyoshi H, Shizume K (1980) Failure of naloxone to influence plasma growth hormone, prolactin, and cortisol secretion induced by insulin hypoglycaemia. J Clin Endocrinol Metab 50: 597–599
32. Serri O, Rasio E, Somma M (1981) Effects of naloxone on insulin-induced release of pituitary hormones. J Clin Endocrinol Metab 53: 206–208
33. Pert BC, Pasternak G, Snyder SH (1973) Opiate agonists and antagonists discriminated by receptor binding in brain. Science 182: 1359–1361
34. Wolfe RR, Miller HI, Spitzer JJ (1977) Glucose and lactate kinetics in burn shock. Am J Physiol 232: E415–E418
35. Wilmore DW, Mason AD, Jr, Pruitt BA, Jr (1976) Insulin response to glucose in hypermetabolic burn patients. Ann Surg 183: 314–320
36. Richter EA, Garetto LP, Goodman MN, Ruderman NB (1982) Muscle glucose metabolism following exercise in the rat. Increased sensitivity to insulin. J Clin Invest 69: 785–793
37. Ahlborg G, Felig P (1982) Lactate and glucose exchange across the forearm, legs and splanchnic bed during and after prolonged leg exercise. J Clin Invest 69: 45–54

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