The Effect of Hyperinsulinemia on Glucose Homeostasis During Moderate Exercise in Man

DONALD J. CHISHOLM, ARTHUR B. JENKINS, DAVID E. JAMES, AND EDWARD W. KRAEGEN

SUMMARY

Moderate exercise in man for 1 h results in a two- to threefold increase in glucose disappearance (R_d) and hepatic glucose production (R_a) so that euglycemia is maintained. The mechanism controlling the increase in R_a is not known, although circulating levels of insulin and glucagon have been suggested as important regulatory factors.

To assess the importance of circulating insulin levels on exercise-induced glucose flux, we have examined the response to 60-min exercise on a bicycle ergometer at 60% maximal oxygen uptake (Vo_2 max) in five normal male subjects on two occasions. A constant i.v. infusion of insulin (20 mU/kg/h) or saline was begun 60 min before exercise. R_a and R_d were measured by a non-steady-state constant [3-^{3}H]glucose infusion technique.

During the control (saline) study serum insulin (IRI) fell from 6.4 ± 1.8 (SEM) to 4.4 ± 1.4 mU/L ($P < 0.05$). During the insulin infusion IRI was maintained at 23.0 ± 0.8 mU/L with a modest drop in plasma glucose before exercise, 5.4 ± 0.2 to 4.0 ± 0.4 mmol/L. Hyperinsulinemia during exercise did not affect peak responses of either R_a (control 1.88 ± 0.25 versus 2.00 ± 0.17 mmol/min, NS) or R_d (control 1.89 ± 0.26 versus 1.94 ± 0.18 mmol/min, NS) nor did it result in a significant fall in plasma glucose (control −0.2 ± 0.2 versus −0.2 ± 0.4 mmol/L). Moreover, plasma glucagon (IRG) had not changed significantly after 30-min exercise during insulin infusion when R_a had increased to 195% of the pre-exercise level. Plasma cortisol, norepinephrine, and growth hormone rose during exercise, but the elevation was not significantly greater during insulin infusion than in the control study.

Thus, during moderate hyperinsulinemia in normal man, exercise does not cause a fall in plasma glucose and hepatic glucose output is undiminished. This study demonstrates that a decrease in IRI, elevation of IRG, or a change in IRI/IRG ratio are not important in initiating hepatic glucose output during exercise.
DIABETES 31:603–608, July 1982.

From the Garvan Institute of Medical Research, St. Vincent's Hospital, Sydney 2010, Australia.
Address reprint requests to Dr. D. J. Chisholm at the above address.
Received for publication 25 September 1981 and in revised form 11 March 1982.

Normal man maintains blood glucose within very narrow limits during moderate exercise for short time periods (30–90 min) by increasing hepatic glucose output to closely match muscle glucose utilization.[1] However, the mechanism regulating glucose turnover remains to be clarified. Low levels of insulin are essential for glucose utilization by muscle.[2] A modest fall in IRI has been found during exercise together with a rise in IRG. These changes have been suggested as important regulators of hepatic glucose output during exercise,[3–6] although other studies have questioned their importance.[2,3,7,8]

It has been suggested that hypoglycemia during exercise in diabetics on conventional insulin therapy is due largely to increased absorption from an exercising limb with resultant elevation of IRI.[8,9] However, other studies have demonstrated a fall in blood glucose during exercise without an increase in insulin levels.[10] With the use of insulin infusion devices, peripheral hyperinsulinemia is an obligatory consequence of insulin delivery via routes other than the portal circulation.[11,12] Thus it is important to define the role of insulin levels in the regulation of glucose flux during exercise as a basis for suitable exercise algorithms for insulin infusion systems.

The aim of the study was, first, to determine whether normal subjects exercising at 60% Vo_2 max in the presence of mild hyperinsulinemia could maintain their pre-exercise blood glucose level and, second, to examine the effect of hyperinsulinemia on exercise-induced changes in counterregulatory hormones and glucose flux (R_a and R_d).

METHODS

Subjects. Five healthy male subjects aged 21–40 yr, weight 64–84 kg of 97–122% ideal body weight, exercised on a Monark bicycle ergometer for 60 min at 60% Vo_2 max on 2 days, on one occasion with and on the other without an

i.v. infusion of insulin. Vo_2 max was determined on a previous occasion during a brief (5–10 min) submaximal exercise period at a fixed work load using Åstrand's nomograms.[13] No subjects were athletes in training but all performed some sporting activity. Workloads performed indicated moderate physical fitness. In an additional study four healthy male subjects aged 21–40 yr, weight 66.4–88 kg, 98–108% ideal body weight, received an insulin infusion without being required to exercise (insulin–no exercise study). The nature, purpose, and possible risks involved in the studies were explained and voluntary written consent was obtained.

Methods. Each study began at 8:00–8:30 a.m. after an overnight fast. Intravenous cannulae were inserted in the antecubital vein of both forearms for infusion and sampling. The subjects were seated comfortably in an armchair during the rest period. From the start of the study [3-^{3}H]glucose (specific activity 455GBq/mmol, Amersham Corp., Arlington Heights, Illinois) was infused at the rate of 25 μCi/h (without a priming dose) by a Harvard infusion pump (Harvard Apparatus, South Natick, Massachusetts). After 90 min a further infusion was added (time 0 in the figures); this infusion was either isotonic saline or purified porcine insulin, 20 mU/kg/h (Actrapid, Novo Industries, Copenhagen, Denmark) in degraded gelatin solution (Haemaccel, Hoechst Pharmaceutical Co.) to avoid loss of insulin onto delivery tubing. The infusions of [3-^{3}H]glucose and saline or insulin continued to the termination of the study. Sixty minutes after the start of the saline or insulin infusion, with the exception of the insulin–no exercise study, exercise was begun and continued for 60 min. During the saline–exercise study workload was adjusted according to pulse rate recorded at 5-min intervals; during the insulin–exercise study the workload was identical to that performed during the saline–exercise study (pulse rate was not used to modify the workload as the lower plasma glucose might have exaggerated the tachycardia).

Plasma glucose was determined by an immobilized glucose-oxidase method (Yellow Springs Model 23AM Glucose Analyzer, Yellow Springs, Ohio). Plasma samples for ^{3}H-glucose determination were deproteinized with $ZnSO_4$ and $Ba(OH)_2$; 1 ml of protein-free supernatant was evaporated to dryness at 60°C and redissolved in 1 ml 0.1 M acetic acid and 7 ml Riafluor (New England Nuclear, Boston, Massachusetts) for counting in a liquid scintillation spectrometer. Correction for quenching was calculated using an external (133 Ba) standard.

Plasma and serum samples for hormone assays were stored at −20°C. Blood samples for glucagon assay were immediately mixed with aprotinin (Trasylol), chilled, and separated rapidly. Serum IRI, growth hormone, cortisol, glucagon, and C-peptide were measured by radioimmunoassay. The glucagon assay uses the RCS5 antiserum[14] obtained from Dr. S. R. Bloom and reagents for the C-peptide assay were supplied by Novo Research Institute.[15] Plasma norepinephrine was determined using a modified gas chromatograph/mass spectrometer method[16] and plasma free fatty acids (FFA) by the method of Ho and Meng.[17]

All venous samples for assay were obtained from the arm contralateral to the infusions. R_a (systemic glucose appearance) and R_d (glucose disappearance) were calculated using the non-steady-state method of Radziuk et al.[18]

Statistical comparisons were made using the Student's paired *t* test for comparisons within each study and between the insulin–exercise and saline–exercise studies. A nonpaired *t* test was used to compare the insulin–exercise and insulin–no exercise studies.

RESULTS

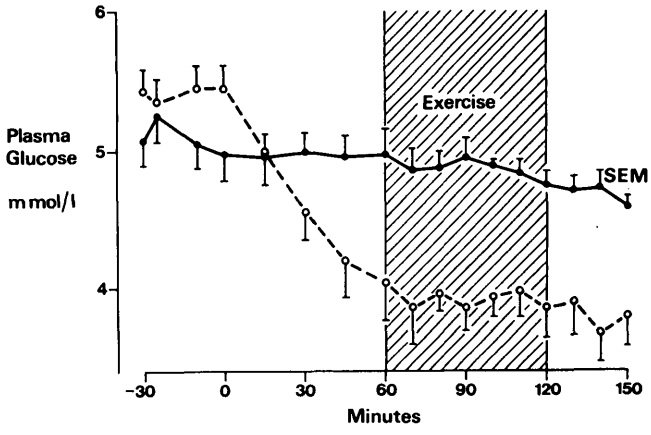
Workload performed in both exercise studies was 34.7 ± 2.0 Kpm × 10^3. During the saline–exercise study heart rate ranged between 125 and 135 and mean blood pressure was 152/77. Mean heart rate was not significantly (4 beats/min) faster with insulin infusion.

In the insulin–exercise study plasma glucose fell from 5.4 ± 0.2 to 4.0 ± 0.4 mmol/L ($P < 0.01$) in the 60 min before exercise and was 1.0 mmol/L lower than in the saline–exercise study at the initiation of exercise. However, there was no significant fall in plasma glucose during exercise in either study (Figure 1). Serum IRI fell during the saline–exercise study from 6.4 ± 1.8 to 4.4 ± 1.4 at 60 min ($P < 0.05$) but was maintained at approximately 23 mU/L during insulin infusion (22.6 ± 2.8 and 23.0 ± 2.5 mU/L at initiation and completion of exercise, Figure 2). Plasma C-peptide (Figure 3) fell during insulin–exercise in a manner consistent with suppression of endogenous insulin release (1.6 ± 0.3 at 0, 0.9 ± 0.3 at start of exercise, 0.3 ± 0.1 μg/L at completion of exercise) but also fell significantly during the saline–exercise study (1.8 ± 0.2 to 1.3 ± 0.2, $P < 0.05$).

During the saline–exercise study the changes in R_a and R_d before exercise were not significant. R_d rose from 0.77 ± 0.10 to a peak level of 1.89 ± 0.26 mmol/min after 40 min exercise. The response of R_a closely matched R_d in timing and magnitude, rising from 0.7 ± 0.14 to 1.88 ± 0.25 mmol/min after 32 min exercise (Figures 4 and 5). During insulin–exercise there was a significant ($P < 0.05$) but transient fall in R_a and rise in R_d ($P < 0.025$ at 60 min) due to the insulin infusion; R_a returned toward basal values before exercise. During exercise the elevation of R_a closely matched R_d and both responses were very similar to the saline–exercise study, R_d rising from 1.13 ± 0.26 to 1.94 ± 0.18 mmol/min and R_a rising from 1.07 ± 0.23 to 2.00 ± 0.17 mmol/min, both peak levels recorded after 32 min exercise.

A small but significant rise in FFA occurred during saline–exercise (0.70 ± 0.1 to 0.79 ± 0.1 mmol/L, $P < 0.05$) whereas FFA fell during insulin–exercise (0.70 ± 0.1 at 0

FIGURE 1. Plasma glucose (mean ± SEM) levels before and during exercise with saline (●——●) or insulin (20 mU/kg/h) (○---○) infusion beginning at time 0.



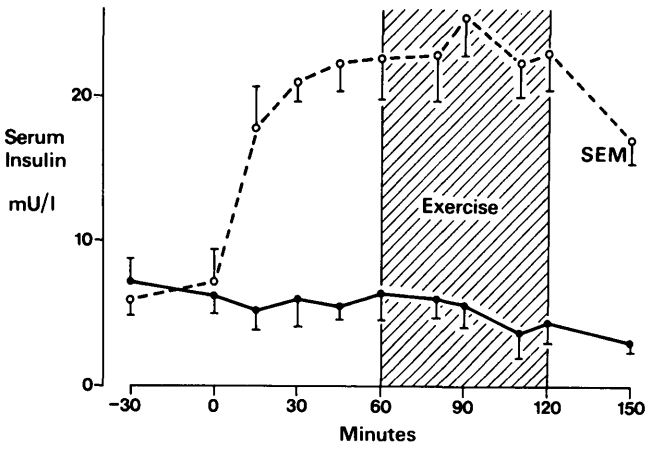


FIGURE 2. Serum insulin (mean ± SEM) levels before and during exercise with saline (●——●) or insulin (20 mU/kg/h) (O----O) infusion beginning at time 0.

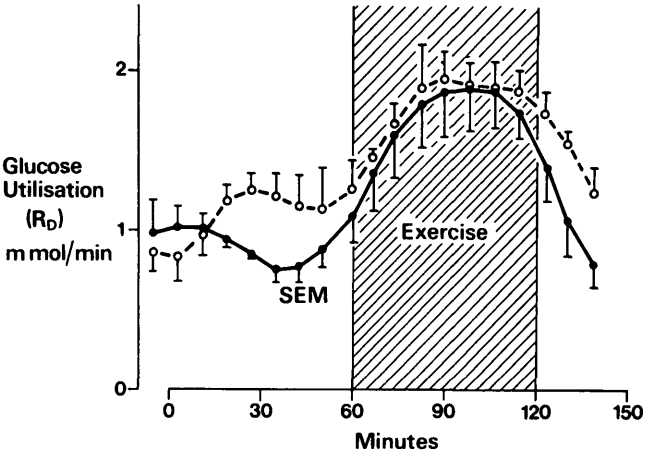


FIGURE 4. Systemic glucose disappearance (R_d) before and during exercise with saline (●——●) or insulin (20 mU/kg/h) (O----O) infusion beginning at time 0. Mean ± SEM.

min to 0.47 ± 0.05 at 120 min, $P < 0.025$) as seen in Table 1. There was a highly significant difference between FFA levels during and after exercise for the two studies (at 120 min control 0.79 ± 0.9, insulin infusion 0.47 ± 0.05, $P < 0.01$).

Responses of counterregulatory hormones are shown in Table 1. Plasma IRG elevation was significantly ($P < 0.05$) greater at completion of exercise with insulin–exercise than saline–exercise. However, after 30 min exercise the difference was not significant and no increase over the pre-exercise level had occurred in three of the five subjects receiving insulin. The responses of cortisol, growth hormone, and norepinephrine were not significantly different between the insulin–exercise and saline–exercise studies.

Subjects were specifically questioned about any subjective difference in exercise tolerance for the two studies. Only one subject noted a difference, finding it subjectively easier to perform the exercise during the insulin infusion. No subject experienced hypoglycemic symptoms.

In the insulin–no exercise study (Table 2) plasma glucose followed a similar pattern to the insulin–exercise study with a fall in plasma glucose from 5.3 ± 0.1 to 4.3 ± 0.2 mmol/L during the first hour of insulin infusion and no significant change in the second hour. R_a and R_d both returned toward basal levels in the second hour of insulin infusion. R_a did not rise significantly above basal in this study and was highly significantly ($P < 0.002$) less than the peak R_a during insulin–exercise. Plateau IRI and both absolute levels and rate of fall of C-peptide were very similar to the insulin–exercise study. Moreover, calculation of insulin production rate from C-peptide data[19] indicated no difference in delivery of endogenous insulin into the portal vein at the start of exercise between the insulin–no exercise and insulin–exercise studies (each 3 mU/min) and an insignificant difference (2.4 versus 2.1 mU/min) 20 min later.

DISCUSSION

Moderate physical exertion in untrained, normal humans is usually associated with a fall in serm insulin and a rise in glucagon.[3] It has been suggested that the reduction in serum insulin has an important role in stimulating hepatic glucose output[4] or at least in sensitizing the liver to the action of hormones or other factors that would stimulate hepatic glucose output.[3,6] A previous study using a three- to fourfold higher rate of insulin infusion (with concurrent glucose administration) demonstrated a major inhibition of hepatic glucose output during exercise.[4] Whatever the mechanism controlling hepatic glucose output, it seems capable

FIGURE 3. Serum C-peptide (mean ± SEM) levels before and during exercise with saline (●——●) or insulin (20 mU/kg/h) (O----O) infusion beginning at time 0.

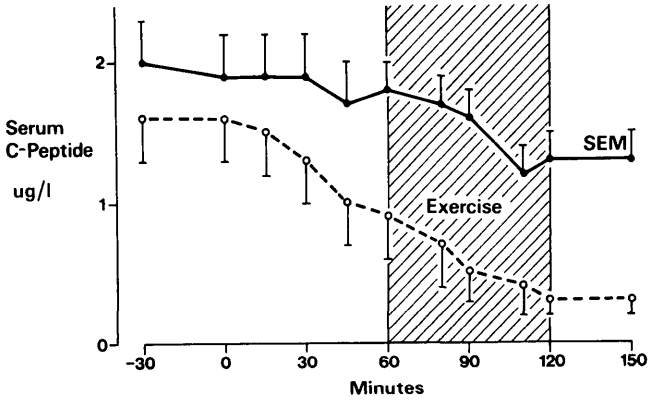


FIGURE 5. Systemic glucose appearance (R_a) before and during exercise with saline (●——●) or insulin (20 mU/kg/h) (O----O) infusion beginning at time 0. Mean ± SEM.

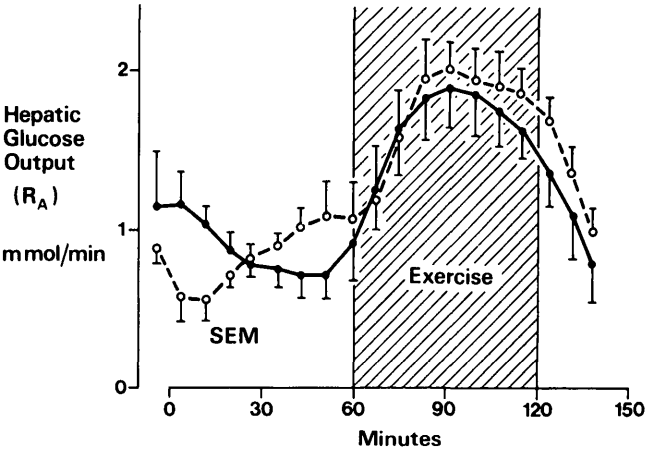


TABLE 1
Response of plasma nonesterified fatty acids (NEFA), plasma glucagon (IRG), serum growth hormone (GH), serum cortisol, and plasma norepinephrine (NE) before and during exercise with saline or insulin infusion (mean ± SEM)

	Time (min)	0	60	90	120
NEFA	Saline	0.70 ± 0.09	0.73 ± 0.08	0.70 ± 0.05	0.79 ± 0.09*
(mmol/L)	Insulin	0.66 ± 0.12	0.56 ± 0.06	0.49 ± 0.05*	0.47 ± 0.05*†
IRG (ng/L)	Saline	26 ± 7	27 ± 5	42 ± 8	43 ± 13
	Insulin	69 ± 19	42 ± 8	62 ± 16	172 ± 23†
GH (mU/L)	Saline	4.3 ± 1.3	2.2 ± 0.5	19.4 ± 4.6*	43.6 ± 2.7‡
	Insulin	3.0 ± 0.51	5.4 ± 1.8	65 ± 29	102 ± 38
Cortisol	Saline	376 ± 51	342 ± 25	380 ± 90	396 ± 97
(nmol/L)	Insulin	283 ± 26	215 ± 20	373 ± 80	515 ± 95
NE	Saline	—	3.4 ± 0.6	4.6 ± 0.9*	—
(nmol/L)	Insulin	—	4.0 ± 1.3	5.1 ± 1.5	—

Saline or insulin was infused from 0 to 150 min.
Subjects were exercised from 60 to 120 min.
* $P < 0.05$, ‡ $P < 0.01$ versus time 0. † $P < 0.05$ during insulin–exercise versus saline–exercise.

of achieving a response that closely matches peripheral glucose utilization[1] thereby allowing only small variations in the blood glucose level during moderate exercise over short (30–90 min) time periods.

This study was designed to assess the effects of mild hyperinsulinemia (of a degree likely to occur during therapy with insulin infusion systems) on glucose flux and counterregulatory hormones in normal subjects during moderate exercise.

During the saline–exercise study the expected modest fall in insulin and C-peptide was observed. During insulin–exercise a substantially greater plateau insulin level was achieved (23 mU/L), approximately quadrupling peripheral insulin levels. Assuming that the portal/peripheral vein ratio of serum insulin concentration is approximately 2–3/1,[12] portal vein insulin would also have been mildly elevated. Despite hyperinsulinemia, these subjects displayed a remarkable ability to match hepatic glucose output to peripheral glucose utilization during exercise and thus maintain the pre-exercise level of plasma glucose. Moreover, peak responses of R_a (and R_d) were no less than in the saline–exercise study.

The mechanisms responsible for the accelerated glucose uptake into muscle during normal exercise are not clear (see review by Vranic and Berger),[3] although it has been suggested that insulin availability is a major controlling influence.[2] It is apparent from our data that peripheral hyperinsulinemia does not affect R_d during exercise. This result is consistent with the proposal that in the presence of a critical (low) level of insulin[3] the increased R_d seen during exercise is regulated mainly by intracellular events contingent on the exercise-induced stimulation of muscle glycolysis.[20]

Because peripheral insulin levels do not always closely reflect portal vein concentrations,[21] one must consider whether a change in portal vein insulin levels during the insulin–exercise study could have contributed to the normal R_a response. First, there is no doubt that portal vein hyperinsulinemia would have been achieved in both the insulin–exercise and insulin–no exercise studies. Moreover, the rate of decline of C-peptide suggests that endogenous insulin release was largely suppressed before exercise. From the C-peptide data we have estimated endogenous insulin release[19] and have calculated that the fall in portal vein insulin delivery during exercise in the insulin–exercise study would have been approximately 1 mU/min. Finally, the close similarity between C-peptide levels during the insulin–exercise and insulin–no exercise studies for the time period corresponding to the first 20 min of exercise suggests that portal vein insulin concentrations were very similar. However, the R_a response in the insulin–exercise study was greatly in excess of the plateau R_a in the study without exercise ($P < 0.002$).

The lower plasma glucose during insulin–exercise compared with saline–exercise might have augmented R_a and helped to counterbalance the effects of hyperinsulinemia. In this regard it is noteworthy that in the insulin–no exercise study R_a (and R_d) returned to values close to basal levels once a (lower) steady-state blood glucose had been achieved. This raises the interesting possibility that in situations of modest hyper- or hypoinsulinemia normal glucose turnover may occur at a new (lower or higher) setpoint of

TABLE 2
Response of plasma glucose (PG), serum insulin (IRI), serum C-peptide (CP), and systemic glucose appearance (R_a) and disappearance (R_d) during insulin infusion without exercise (mean ± SEM)

Time	0	60	80	100	120
PG (mmol/L)	5.3 ± 0.1	4.3 ± 0.2	4.4 ± 0.2	4.4 ± 0.2	4.4 ± 0.2
IRI (mU/L)	7.8 ± 2.0	23.9 ± 3.0	26.6 ± 2.4	27.6 ± 3.0	26.3 ± 1.9
CP (μg/L)	1.57 ± 0.24	0.79 ± 0.12	0.67 ± 0.13	0.60 ± 0.15	0.51 ± 0.12
R_a (mmol/min)	1.14 ± 0.27	1.28 ± 0.15	1.09 ± 0.09	1.13 ± 0.19	1.09 ± 0.28
R_d (mmol/min)	1.23 ± 0.29	1.26 ± 0.16	1.12 ± 0.13	1.11 ± 0.16	1.17 ± 0.15

blood glucose. In this context it is important to compare the results of this study with a recent report regarding the effects of hyperinsulinemia during exercise where basal blood glucose levels were maintained by use of a glucose-controlled glucose infusion system.[22] In that study mild hyperinsulinemia caused a very large increase in glucose requirement, suggesting that both the basal and exercise-induced hepatic glucose output had been suppressed. They concluded that mild hyperinsulinism interferes with the normal metabolic response to exercise and that the normal fall in insulin levels with exercise is an important regulatory process. Comparing their study with this, it would seem that the setpoint of blood glucose is critically important and that a normal metabolic response to exercise will occur during hyperinsulinemia if the blood glucose level is allowed to find a lower setpoint.

Irrespective of the plasma IRI level, both R_a and R_d declined during the last 20 min of exercise. It has been suggested that this phenomenon may be related to increased utilization of fatty acids by muscle.[20] In this study plasma FFA levels (which reflect FFA availability to muscle[23]) were suppressed during insulin infusion but there was no change in the pattern of R_d, nor was any greater subjective difficulty experienced in performing the exercise. Thus it seems unlikely that the decline in R_d is related to availability of FFA from the circulation.

Was the normal exercise-induced increment in R_a during hyperinsulinemia achieved via the counterregulatory hormones? Glucagon, cortisol, growth hormone, and norepinephrine were measured and only glucagon levels demonstrated a significantly greater elevation during insulin–exercise than saline–exercise. However, glucagon levels had not risen significantly after 30-min exercise during insulin infusion while R_a had increased to 195% of the pre-exercise level. More importantly, three of the five subjects had shown no glucagon rise at this point, despite a profound increase in R_a. Failure of glucagon to rise at this time may be related to the suppressive effect of insulin (without hypoglycemia) on glucagon release.[24] It has been recently demonstrated that peripheral vein glucagon levels appropriately reflect changes in portal vein concentrations, though the changes are of lesser magnitude;[21] thus it seems unlikely that there was a major change in portal vein glucagon levels in the first 30 min of the insulin–exercise study. It may therefore be concluded that glucagon is unimportant as an initial stimulus to R_a during exercise. Recently it has been demonstrated that elevated glucagon levels have a prolonged effect on hepatic gluconeogenesis.[25] It is possible that the substantial late rise in glucagon seen during insulin–exercise would contribute importantly to glucose supply during prolonged exercise. Similarly, while no significant augmentation of the response of cortisol, growth hormone, and norepinephrine was seen during insulin infusion, it is possible that a modest increment in levels of these hormones acting synergistically with glucagon[26] contributed significantly to R_a during the later phase of the study. However, these hormonal responses, because of the time course of their action, seem unlikely to provide the initial stimulus to R_a.

What, then, is the mechanism controlling hepatic glucose production during exercise? Direct regulation by subtle changes in plasma glucose has been suggested[20] and there is no doubt that hepatic glucose output may be influenced by the blood glucose level per se.[27] However, measurement of arterial plasma glucose during the early stages of moderate exercise has indicated a small elevation[4] rather than the fall that would be required to stimulate glucose production. In the present study venous plasma glucose from a nonexercising area fell by 1 mmol/L or more during insulin infusion (insulin–exercise and insulin–no exercise studies) without stimulating R_a above basal levels. However, there was a profound increase in R_a during exercise without further depression of the plasma glucose and in the presence of unchanged IRI levels. Thus regulation by blood glucose levels seems unlikely. Release of a factor from exercising muscle that stimulates hepatic glucose production has been suggested and is compatible with the results of this study. However, support for this hypothesis is lacking at present.[2,20] Finally, direct neural stimulation of hepatic glucose output would be consistent with our results and with the recent demonstration of central neural regulation of the cardiorespiratory response to exercise.[28] Further study will be required to clarify the controlling mechanism. However, it is clear that changes in insulin, glucagon, or the insulin:glucagon ratio seen during moderate exercise in normal subjects are not critical to the initiation of normal hepatic glucose output during exercise.

In clinical practice it has been suggested that diabetics treated by insulin infusion systems are less susceptible to exercise-induced hypoglycemia than diabetics on conventional therapy.[29] Moreover, a study of insulin-dependent diabetics receiving an i.v. insulin infusion at substantially lower rates than used in this study[8] showed no fall in blood glucose during exercise. Certainly this study would suggest that mild peripheral hyperinsulinemia (which results from systemic insulin delivery systems) would not, of itself, cause hypoglycemia during moderate exercise.

ACKNOWLEDGMENTS

This study was supported by the National Health and Medical Research Council of Australia. The expert assistance of Sister Margot Hewett, Dr. George Smythe, and Brenda Rice is gratefully acknowledged.

REFERENCES

[1] Wahren, J., Felig, P., Ahlborg, G., and Jorfeldt, L.: Glucose metabolism during leg exercise in man. J. Clin. Invest. *50*:2715–25, 1971.

[2] Vranic, M., Kawamori, R., Pek, S., Kovacevic, N., and Wrenshall, G. A.: The essentiality of insulin and the role of glucagon in regulating glucose utilization and production during strenuous exercise in dogs. J. Clin. Invest. *57*:245–55, 1976.

[3] Vranic, M., and Berger, M.: Exercise and diabetes mellitus. Diabetes *28*:147–63, 1979.

[4] Felig, P., and Wahren, J.: Role of insulin and glucagon in the regulation of hepatic glucose production during exercise. Diabetes *28*(Suppl. 1): 71–75, 1979.

[5] Issekutz, B., Jr.: Energy mobilization in exercising dogs. Diabetes *28*(Suppl. 1):39–44, 1979.

[6] Issekutz, B., Jr.: The role of hypoinsulinemia in exercise metabolism. Diabetes *29*:629–35, 1980.

[7] Gollnick, P. D., Soule, R. G., Taylor, A. W., Williams, C., and Ianuzzo, C. D.: Exercise-induced glycogenolysis and lipolysis in the rat: hormonal influence. Am. J. Physiol. *219*(3):729–33, 1970.

[8] Zinman, B., Murray, F. T., Vranic, M., Albisser, A. M., Liebel, B. S., McClean, P. A., and Marliss, E. B.: Glucoregulation during moderate exercise in insulin treated diabetics. J. Clin. Endocrinol. Metab. *45*(4):641, 1977.

[9] Koivisto, V. A., and Felig, P.: Effects of leg exercise on insulin absorption in diabetic patients. N. Engl. J. Med. *298*(2):79–83, 1978.

[10] Kemmer, F. W., Berchtold, P., Berger, M., Starke, A., Cüppers, H. J.,

Gries, F. A., and Zimmerman, H.: Exercise-induced fall of blood glucose in insulin-treated diabetics unrelated to alteration of insulin mobilization. Diabetes *28*:1131–38, 1979.

[11] Schade, D. S., Eaton, R. P., and Spencer, W.: Normalization of plasma insulin profiles in diabetic subjects with programmed insulin delivery. Diabetes Care *3*:9–14, 1980.

[12] Kraegen, E. W.: The necessity and feasibility of normalising plasma insulin levels in diabetics using insulin delivery systems. *In* New Approaches to Insulin Therapy. Irsigler, K., Kunz, K. N., Owens, D. R., and Regal, H., Eds. Lancaster, U.K., MTP Press Ltd., pp. 249–56, 1981.

[13] Astrand, I.: Aerobic work capacity in men and women with special reference to age. Acta Physiol. Scand. *49*(Suppl):169, 1960.

[14] Alford, F. P., Bloom, S. R., and Nabarro, J. D. N.: Glucagon levels in normal and diabetic subjects: use of a specific immunoabsorbent for glucagon radioimmunoassay. Diabetologia *13*:1–6, 1977.

[15] Heding, L. G.: Radioimmunological determinations of human C-peptide in serum. Diabetologia *11*:541–48, 1975.

[16] Smythe, G. A., Brandstater, J. F., Bradshaw, J. E., and Lazarus, L.: A simple procedure for the assay of brain biogenic amines by selected-ion monitoring: its application to the elucidation of the mechanism of prolactin release induced by 3-iodo-L-tyrosine. Aust. J. Biol. Sci. *32*:335–41, 1979.

[17] Ho, R. J., and Meng, H. C.: A simple and ultrasensitive method for determination of free fatty acid by radiochemical assay. Anal. Biochem. *31*:426–36, 1969.

[18] Radziuk, J., Norwich, K. H., and Vranic, M.: Experimental validation of measurements of glucose turnover in nonsteady state. Am. J. Physiol. *234*(1):E84–93, 1978.

[19] Eaton, R. P., Allen, R. C., Schade, D. S., Erickson, K. M., and Standefer, J.: Prehepatic insulin production in man: kinetic analysis using peripheral connecting peptide behavior. J. Clin. Endocrinol. Metab. *51*:520–25, 1980.

[20] Newsholme, E. A.: The control of fuel utilization by muscle during exercise and starvation. Diabetes *28*(Suppl. 1):1–7, 1979.

[21] Polonsky, K., Jaspan, J., Pugh, W., Dhorajiwala, J., Abraham, M., Blix, P., and Moossa, A. R.: Insulin and glucagon breakthrough of somatostatin suppression. Importance of portal vein hormone measurements. Diabetes *30*:664–69, 1981.

[22] Martin, M. J., Horwitz, D. L., Nattrass, M., Granger, J. F., Rochman, H., and Ash, S.: Effects of mild hyperinsulinemia on the metabolic response to exercise. Metabolism *30*:668–94, 1981.

[23] Wahren, J., and Hagenfeldt, L.: Free fatty acid and ketone body metabolism during exercise in diabetics. Acta Pediatr. Scand. Suppl. *283*:39–44, 1980.

[24] Warne, G. L., Alford, F. P., Chisholm, D. J., and Court, J.: Glucagon and diabetes: complete suppression of glucagon by insulin in human diabetes. Clin. Endocrinol. *6*:277–84, 1977.

[25] Cherrington, A. D., Williams, P. E., Shulman, G. I., and Lacy, W. W.: Differential time course of glucagon's effect on glycogenolysis and gluconeogenesis in the conscious dog. Diabetes *30*:180–87, 1981.

[26] Eigler, N., Sacca, L., and Sherwin, R. S.: Synergistic interactions and physiologic increments of glucagon, epinephrine and cortisol in the dog. A model for stress-induced hyperglycemia. J. Clin. Invest. *63*:114–23, 1979.

[27] Liljenquist, J. E., Mueller, G. L., Cherrington, A. D., Perry, J. M., and Rabinowitz, D.: Hyperglycemia per se (insulin and glucagon withdrawn) can inhibit hepatic glucose production in man. J. Clin. Endocrinol. Metab. *48*: 171–75, 1979.

[28] Eldridge, F. L., Millhorn, D. E., and Waldrop, T. G.: Exercise hyperpnea and locomotion: parallel activation from the hypothalamus. Science *211*:844–86, 1981.

[29] Pickup, J. C., Keen, H., Viberti, G. C., and Bilous, R. W.: Patient reactions to long-term outpatient treatment with continuous subcutaneous insulin infusion. Br. Med. J. *282*:766–68, 1981.