REVIEW ARTICLE

Sports Med 2005; 35 (7): 575-583
0112-1642/05/0007-0575/$34.95/0

Glucoregulation During Exercise
The Role of the Neuroendocrine System

Robert H. Coker[1] and *Michael Kjaer*[2,3]

1 Nutrition, Metabolism, and Exercise Laboratory, Department of Geriatrics, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA
2 Sport Medicine Research Unit, Bispebjerg Hospital, Copenhagen, Denmark
3 Copenhagen Muscle Research Centre, University of Copenhagen, Copenhagen, Denmark

Contents

Abstract

Under normal healthy conditions, exercise initiates simultaneous elevations in hepatic glucose production (glucose R_a) and glucose utilisation. As a result, circulating glucose levels are maintained at a relatively constant level. This relatively simple and effective relationship between the liver and the skeletal muscle is maintained by a complex interplay of circulating and locally released neuroendocrine controllers. In large part, exercise-induced changes in the pancreatic secretion of glucagon and insulin are primarily responsible for the stimulation of glucose R_a during moderate exercise. However, exercise imposed on an additional metabolic stress (heavy exercise and poorly controlled diabetes mellitus) can increase sympathetic drive and has been suggested for decades to play a significant role in glucoregulation. In addition, blood-borne feedback and afferent reflex mechanisms may further modulate the glucose R_a response to exercise. This article discusses new findings from novel animal and human experiments specifically designed to examine the regulatory components of the neuroendocrine system and their influence on glucoregulation during exercise.

1. Glucoregulation During Moderate Exercise

The neuroendocrine regulation of exercise-induced changes in hepatic glucose production (glucose R_a) is a complex system (figure 1). Studies utilising the pancreatic clamp technique in dogs have demonstrated that glucagon and insulin are responsible for ~60% and ~55% of the exercise-induced increment in glucose R_a, respectively.[1,2]

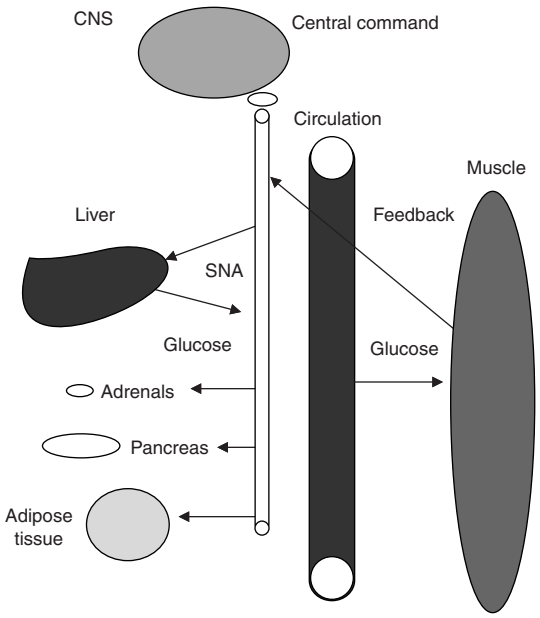

Fig. 1. An overview of factors in involved in the regulation of hepatic glucose production. **SNA** = sympathetic nerve activation.

The importance of glucagon and insulin in the stimulation of glucose R_a during exercise has also been demonstrated in humans using similar pancreatic clamp techniques.[3] The advantage of the pancreatic clamp technique in dogs is that glucagon and insulin are introduced into the portal circulation that preserves their physiological entry site. Using this methodological approach, the regulatory roles of glucagon and insulin sum to control >100% of glucose R_a during moderate exercise due to the overlap in the mechanism of action by both hormones.[4]

The catecholamines have also been proposed to stimulate glucose R_a under conditions of particularly high metabolic stress (heavy exercise, diabetes).[5,6] Sympathetic activity is known to increase dramatically in conjunction with glucose R_a at the onset of exercise and these responses can be exaggerated under the aforementioned conditions.[7-9] For example, catecholamines may increase as much as 10- to 15-fold during heavy exercise with little to no change in arterial glucagon and/or insulin in the first few minutes of heavy exercise.[9] This supports the notion that the catecholamines may be involved in the stimulation of glucose R_a during heavy exercise.

2. Adrenergic Mechanisms and Heavy Exercise: Animal Models

It is important to mention that the ability of the catecholamines to directly stimulate glucose R_a is dependent on their delivery to the liver. Catecholamines are delivered by the circulation (adrenaline [epinephrine] and noradrenaline [norepinephrine]) and by sympathetic nerve activity (noradrenaline). The gut extracts 50% of the plasma catecholamines delivered to it (figure 2).[7] Extraction of this magnitude leads to portal adrenaline concentrations that are ~50% of the arterial adrenaline concentrations.

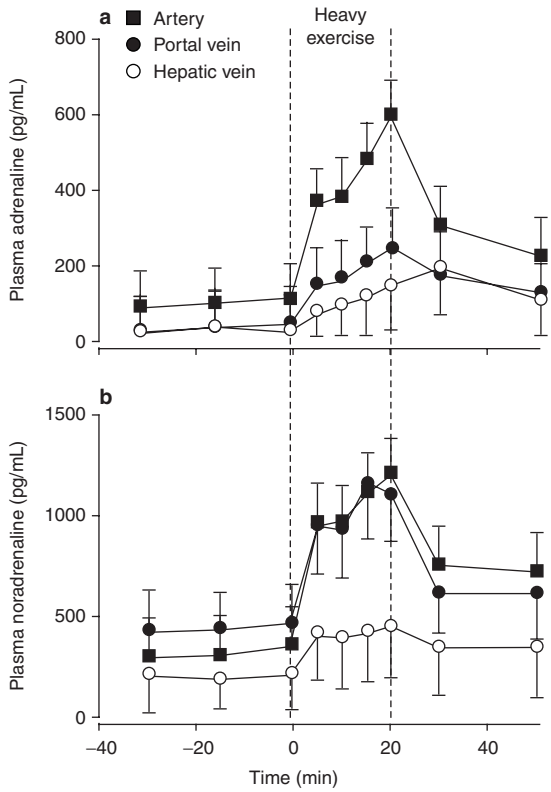

Fig. 2. Arterial, portal vein, and hepatic vein plasma (**a**) adrenaline (epinephrine) and (**b**) noradrenaline (norepinephrine) concentrations in the basal state and during heavy exercise. Values are significantly increased for both hormones from basal levels at t = 5, 10, 15 and 20 minutes for arterial, portal vein and hepatic vein ($p < 0.05$). Data are means ± standard error of the mean; n = 7.

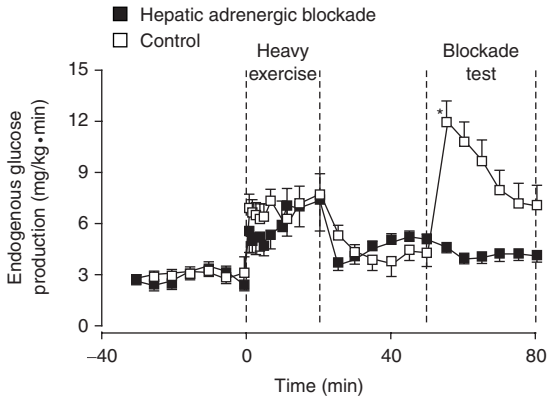

Fig. 3. Endogenous glucose production during basal, heavy exercise, recovery and blockade test periods. Data are means ± standard error of the mean; n = 7 for control and n = 6 dogs for hepatic adrenergic blockade. * $p < 0.05$ difference between the two groups.

Because of the sympathetic innervation of the gut, portal vein noradrenaline concentrations are largely similar to arterial noradrenaline concentrations. Despite the similarity between arterial and portal vein noradrenaline levels, noradrenaline is 30-fold less effective in the stimulation of R_a compared with adrenaline.[10] Thus, it seems clear that arterial adrenaline levels overestimate those at the liver, and noradrenaline is less effective compared with adrenaline in stimulating glucose R_a.

Despite splanchnic kinetics that weaken the impact of catecholamines in the stimulation of glucose R_a, previous studies have still postulated that they are the primary mediators of glucose R_a during heavy exercise.[5] These authors concluded that the catecholamines were the principal stimulus of the increase in glucose R_a based upon a correlation analysis. In contrast, studies that utilised the intraportal infusion of phentolamine and propranolol to block α- and β-adrenoceptors at the liver had no effect on glucose R_a or net hepatic glucose output (NHGO) during heavy exercise in dogs[11] (figure 3). These studies utilised rapid arterial sampling, arteriovenous difference techniques (NHGO), advanced glucose tracer methodology and a novel method of adrenergic blockade to accurately assess the role of the catecholamines acting directly at the liver in the stimulation of glucose R_a.[11] Intraportal delivery of phentolamine and propranolol resulted in minimal extrahepatic effects (similar insulin, glucagon, glycerol, free fatty acids [FFA] and heart rate responses in both groups) in these studies due to the efficient hepatic extraction and the reduced delivery of the blockers. Therefore, experimental strategies designed to specifically address the role of hepatic adrenergic mechanisms do not support their role in the stimulation of glucose R_a during heavy exercise.

3. Adrenergic Mechanisms: Human Models

A variety of novel experimental methodologies have been employed to study the role of neuroendocrine regulation in the stimulation of glucose R_a in humans.[12-17] In accordance with findings from animal studies, exercise-induced increases in glucose R_a were identical in liver-transplant recipients (presumably free of hepatic innervation) compared with healthy control subjects. The exercise-induced increases in glucose R_a were also similar in liver-transplant recipients as well as kidney-transplant recipients who received a similar hormonal and immunosuppressive drug treatment.[13] Liver-transplant recipients were investigated approximately 8 months after surgery and showed no sign of reinnervation in any of the patients as judged from the content of noradrenaline in liver biopsies.[18] These findings indicate that sympathetic liver nerves do not play an important role for the exercise-induced rise in glucose R_a.

The role of hepatic nerves has also been investigated in healthy humans by anaesthetising the coeliac ganglion that provides sympathetic innervation of the liver, the pancreas and the adrenal medulla. During these studies, infusion of somatostatin suppressed pancreatic hormone secretion and exercise-induced changes in glucagon and insulin were mimicked via peripheral infusion.[12] During coeliac ganglion blockade, glucose R_a increased similar to findings in control experiments. This was true whether or not exercise-induced increases in adrenaline were mimicked via exogenous infusion. However, when adrenaline was infused at supraphysiological doses, adrenaline was able to enhance glucose R_a during exercise.[12] Furthermore, exogenous adrenaline in-

fusion that produced normal physiological levels in adrenalectomised individuals augmented glucose R_a only during the early stages of exercise, and the maximal response was not altered, not even during intense exercise[17] (figure 4). Taken together, sympathetic liver nerves or circulating noradrenaline does not appear to be important in the stimulation of glucose R_a during heavy exercise, and circulating adrenaline plays only a minor role during intense exercise, and late during prolonged exercise.

4. Blood-Borne Feedback versus Neural Mechanisms

In order to understand the relative role of blood-borne feedback versus neural mechanisms in the regulation of glucose R_a, studies were completed in spinal-cord injured individuals utilising electrical stimulation of paralysed muscle to induce cycling.[14] During cycling exercise in spinal-cord injured individuals, glucose uptake increased by 50%, whereas blood glucose declined, and glucose R_a did not increase from resting levels.[14] However, the fact that sympathetic impairment in these individuals did not allow for an exercise-induced decrease in pancreatic insulin release, made it possible that lack of a rise in R_a was because of the inhibitory effect of high insulin levels.

In a similar experiment, functional electrical stimulation (FES) was utilised in healthy individuals who had their lower limbs paralysed with epidural anaesthesia. Cycle exercise was performed using FES in these subjects at an oxygen uptake of almost 2 L/min and plasma glucose dropped indicating that the rise in glucose R_a during involuntary electrical exercise was falling behind the rise in peripheral glucose uptake.[16] However, the exercise-induced reduction in plasma insulin was less pronounced during FES versus voluntary control exercise without blockade. The importance of unidentified blood factors regulating glucose R_a is yet to be determined. Interestingly, in a perfusion model with rat muscle and liver in series, it has been shown that substances released from contracting muscle can cause a release of glucose from the liver.[19] It is also important to mention that recent studies from our

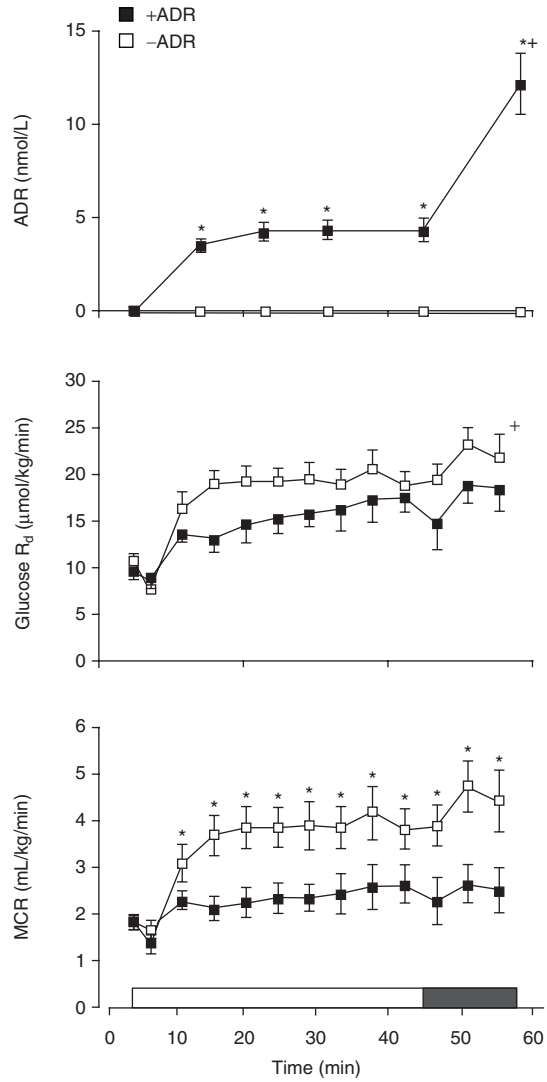

Fig. 4. Plasma adrenaline (epinephrine) [ADR], rates of glucose disappearance (R_d) and metabolic clearance rates (MCR) during cycling exercise at 68% of maximum oxygen consumption ($\dot{V}O_{2max}$) for 45 minutes, followed by 84% of $\dot{V}O_{2max}$ in adrenalectomised subjects with saline (−ADR) or adrenaline (+ADR) infusion commencing at the onset of exercise and increased at 45 minutes. Data are means ± standard error of the mean (n = 6). * indicates significantly different ($p < 0.05$) from +ADR; + indicates significantly different ($p < 0.05$) main effect from +ADR. Horizontal bar represents the complete absence of ADR.

laboratory have demonstrated a decrement in glucose or a signal elicited by a moderate decrement in glucose stimulates glucose release from the liver,

independent of catecholamine and/or hormone-induced action on the liver during moderate exercise.[20] These data support the contention that small decrements in portal plasma glucose may have a stimulatory influence on glucose R_a.

Neural reflexes from working muscles have been demonstrated to be important in the stimulation of glucose R_a. Although electrical stimulation of the central end of cut muscle nerves (n. femoralis) in animals resulted in both an increase in plasma glucose and in glucose R_a,[21] reduction of afferent neural feedback by partial lumbar epidural sensory blockade in humans did not influence glucose R_a during exercise.[15] Therefore, afferent neural reflex mechanisms can cause increased glucose mobilisation during exercise, but it is probably not essential in healthy individuals. However, in patients with metabolic disorders in their skeletal muscle, neural feedback mechanisms may be of more importance. In myophosphorylase deficiency (McArdle's disease, no intramuscular glycogenolysis), exercise mobilisation of extramuscular fuel (e.g. glucose) was more pronounced compared with healthy controls, and compensated for the impairment in glycogenolysis.[22] This larger response in glucose R_a is most likely because of neural feedback directly from metabolism in working muscle (table I). This occurs, because substances likely to act as blood-borne feedback signals, such as glucose or FFA, did not decline and showed similar plasma levels as in healthy control subjects. When glucose was infused to mimic the increment in glucose release from the liver, glucose R_a was abolished, indicating that the blood-borne mediated inhibition of glucose R_a was intact in these individuals.[22] It is attractive to accept these findings as an attempt to supply the muscle with an alternative carbohydrate fuel under conditions in which glycogenolysis is impaired. However, it is more difficult to explain the exaggerated mobilisation of glucose also found during exercise in patients with phosphofructokinase deficiency as well as with mitochondrial myopathy.[23,24] The responses during exercise in the two latter groups contributes to increased substrate mobilisation and thereby potentially encourages an augmented synthesis of adenosine triphosphate (ATP), but at the same time it results in an accumulation of nonoxidised substrates in contracting muscle. As in patients with McArdle's disease, the endocrine and glucose mobilising responses are most likely due to neural feedback and may be linked to the oxidative demands of the muscle rather than to the oxidative capacity of the muscle.

Table I. Hepatic glucose production during exercise in patients with metabolic disorders. Exercise-induced increase in hepatic glucose production measured by isotope dilution technique ([3-^{3}H]glucose) during 20 minutes of cycling in patients with metabolic disorders and control subjects[22-24]

Metabolic disorder	Glucose R_a (μmol/kg/min)
McArdle's disease (n = 3)	31 ± 7[a]
Controls	
same absolute	19 ± 5
same relative	26 ± 4
Mitochondrial myopathy (n = 4)	28 ± 5[a]
Controls	
same absolute	12 ± 1
same relative	18 ± 2
Phosphofructokinase deficiency	30 ± 4[a]
Controls	
same absolute	18 ± 2
same relative	20 ± 1

a Difference between patients with metabolic disorders and control subjects ($p > 0.05$).

R_a = hepatic glucose production.

5. Peripheral Glucose Uptake

The role of adrenaline in regulating glucose uptake during exercise has been examined in adrenaline-deficient, bilaterally adrenalectomised humans[17] (figure 5). Glucose uptake always increased in response to exercise, but was lower and metabolic clearance was reduced with the infusion of adrenaline. This demonstrates that adrenaline plays an inhibitory role in muscular glucose uptake during exercise, and is in line with findings in humans who receive adrenaline infusion in the resting state. Furthermore, these results are also corroborated by studies in rodents where glucose transport was reduced with adrenaline infusion despite increased glucose transporter (GLUT 4) translocation.[25] Taken together with the findings on glucose R_a, adrena-

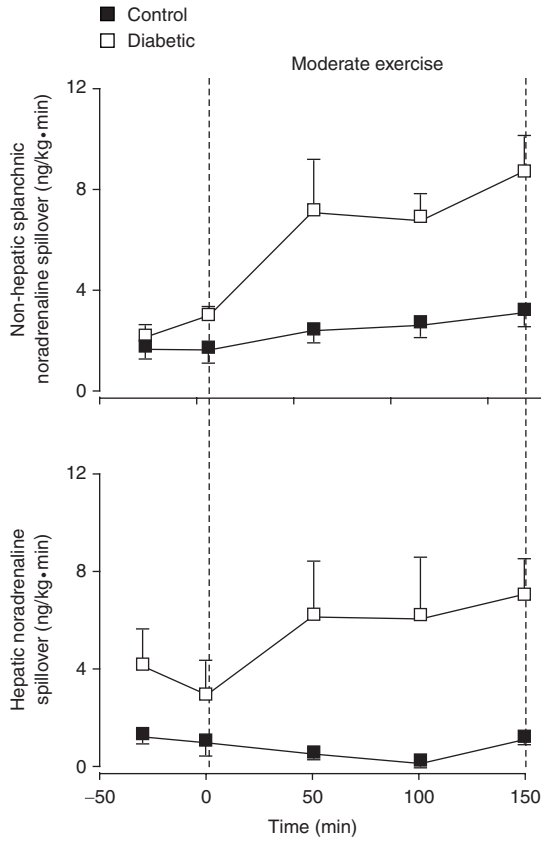

Fig. 5. Non-hepatic splanchnic and hepatic noradrenaline (norepinephrine) spillover during the basal and moderate exercise periods in normal control (n = 6) and diabetic (n = 5) dogs. Non-hepatic splanchnic noradrenaline spillover was significantly greater in the diabetic group at t = 50, 100 and 150 minutes of exercise versus the normal control group ($p < 0.05$). Hepatic noradrenaline spillover was significantly greater in the diabetic group throughout the experiment versus the normal control group ($p < 0.05$). Data are means ± standard error of the mean.

line infusion in adrenalectomised humans seems to result in a mismatch by simultaneously enhancing glucose R_a and inhibiting glucose clearance, causing an increase in plasma glucose levels during exercise.

6. Adrenergic Mechanisms and Exercise in Diabetes Mellitus

It has been proposed that exercise-induced changes in glucose fluxes may be more sensitive to adrenergic stimulation in poorly controlled diabetes.[26,27] Studies have also demonstrated increased non-hepatic splanchnic and hepatic noradrenaline spillover (index of sympathetic drive) during exercise in alloxan-diabetic dogs compared with normal healthy dogs (figure 6).[8] The efficacy of the direct stimulation of glucose R_a by the catecholamines is also supported by studies that demonstrate a reduction in glucose R_a as a result of peripheral propranolol administration during exercise in depancreatised dogs.[6] However, it is important to understand that the regulatory elements by which adrenergic mechanisms can mediate glucoregulation during exercise in the poorly controlled diabetic state are multifactorial. This is largely because of the possibility of adrenergic stimulation influencing the

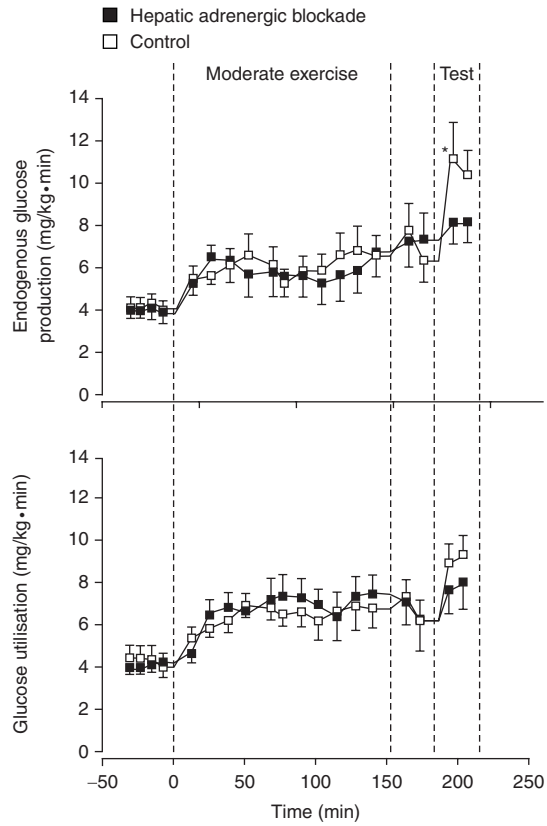

Fig. 6. Endogenous glucose production and glucose utilisation during the basal, exercise, recovery and blockade test periods in poorly controlled diabetes mellitus. Data are means ± standard error of the mean, n = 6 dogs for controls and n = 6 dogs for hepatic adrenergic blockade. * $p < 0.05$ difference between the two groups.

rate of hepatic glycogenolysis and/or gluconeogenic parameters (peripheral or hepatic mechanisms).

The effect of hepatic adrenergic stimulation on glucose R_a during exercise in diabetes has been studied using intraportal infusions of phentolamine and propranolol in exercising alloxan-diabetic dogs. The results of these studies demonstrated that the hepatic adrenergic blockade had no effect on the stimulation of glucose R_a during exercise in diabetes (figure 6).[28] Exercise-induced FFA and glycerol responses were not affected by the hepatic adrenergic blockade in these studies. Thus, the stimulatory effects of the catecholamines on the peripheral mobilisation of gluconeogenic substrate were preserved. The use of the intraportal adrenergic blocker delivery in this study allowed the direct effects of the catecholamines on the liver to be distinguished from their indirect effects (peripheral mobilisation of gluconeogenic substrate) and demonstrated that direct adrenergic stimulation does not play a role in the stimulation of glucose R_a during exercise in poorly controlled diabetes.

Support for glucagon as a critical element in the stimulation of glucose R_a during exercise in health and diabetes has been provided.[2,4] In addition, recent investigations have shown a 4-fold greater exercise-induced increment in portal vein glucagon in alloxan-diabetic dogs compared with normal healthy dogs (figure 7).[29] This excessive increment may be partially responsible for the needless increase in glucose R_a during exercise in the poorly controlled diabetic state because of glucagon's stimulatory effects on glycogenolysis and gluconeogenesis.[2,4] Although the catecholamines may not be involved in the direct stimulation of glucose R_a via hepatic adrenergic mechanisms, increased sympathetic drive during exercise in diabetes[8] may influence the mobilisation of gluconeogenic precursors and could influence hormone secretion adrenergic stimulation of the pancreas.[30,31]

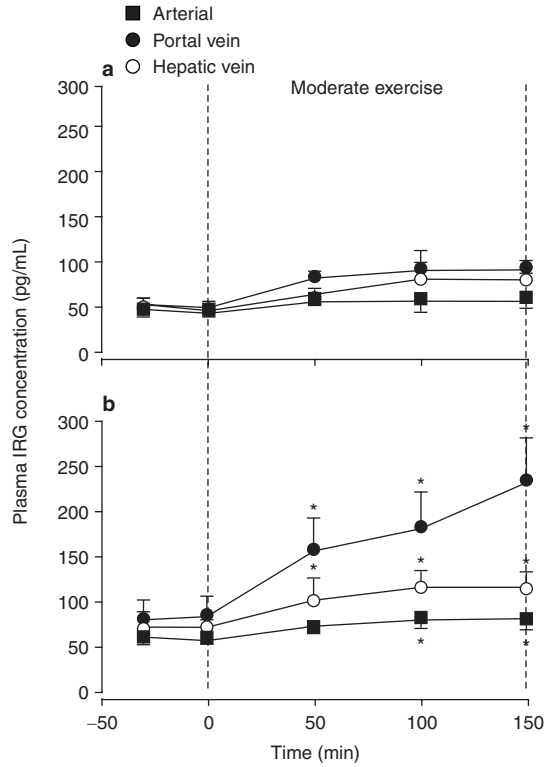

Fig. 7. Arterial, portal vein, and hepatic vein plasma immunoreactive glucagon (IRG) concentrations during basal (–30 to 0 minutes) and exercise (0 to 150 minutes) in (**a**) non-diabetic (n = 6) and (**b**) alloxan-diabetic (n = 5) dogs. Data are means ± standard error of the mean. * $p < 0.05$ difference between non-diabetic and alloxan-diabetic dogs.

7. Adrenergic Mechanisms and Pancreatic Hormones

It seems evident that exercise-induced changes in glucagon and insulin play the most important role in glucoregulation under a variety of conditions (moderate exercise, heavy exercise, and exercise in diabetes). However, the mechanisms that control glucagon and insulin secretion during exercise are not well understood. It is known that vagal and splanchnic nerves can modulate glucagon and insulin secretion.[32] More specifically, α- and β-adrenergic stimulation results in increased pancreatic secretion of glucagon.[30,31] While the stimulation of α-adrenergic mechanisms inhibits insulin secretion, β-adrenergic stimulation increases insulin release.[30,31] Thus, the potential for adrenergic stimulation of changes in pancreatic hormone secretion during exercise does exist.

Studies have shown that the partial denervation of the canine pancreas reduces the increase in glu-

cagon but not the fall in insulin.[33] Unfortunately, glucose kinetics was not assessed in these studies. Furthermore, even though glucagon did not increase as much in the denervated dogs, arterial glucose was not affected. In more recent studies, NHGO and glucose R_a was measured during rest and exercise in dogs whose pancreas was surgically denervated. The completeness of the denervation was verified by a >98% reduction in pancreas tissue noradrenaline. Insulin and glucagon responses to exercise as well as arterial glucose, NHGO and glucose R_a were similar in controls and denervated dogs.[34] Although pancreatic innervation was not essential for the normal exercise-induced increment in glucose R_a, preservation of normal exercise-induced changes in both groups may support a plausible role for circulating catecholamines or some other regulatory factor that serves to ensure glucose homeostasis during exercise

8. Conclusions

Glucagon and insulin are primarily responsible for effective glucoregulation during moderate exercise. Although sympathetic activity is dramatically increased during exercise under conditions of exaggerated metabolic stress such as heavy exercise and poorly controlled diabetes, recent studies have demonstrated that non-hepatic splanchnic extraction reduces adrenaline levels by ~50%. Thus, arterial adrenaline levels overestimate the efficacy of the direct stimulatory effects of adrenaline on glucose R_a. Furthermore, studies utilising a hepatic adrenergic blockade have demonstrated that adrenergic mechanisms acting at the liver are not necessary for the stimulation of glucose R_a during heavy exercise or exercise in poorly controlled diabetes. An excessive increment in glucagon has been demonstrated during exercise in poorly controlled diabetes and may be responsible for the stimulation of glucose R_a despite the prevailing hyperglycaemia. It is also interesting to note that compensatory increases in glucose R_a do occur under conditions of deficient muscle glycogenolysis during exercise, thereby supporting the role of neural and/or blood-borne feedback in the modulation of exercise-induced increments in glucose R_a. Lastly, removal of pancreatic innervation had no effect on exercise-induced changes in glucagon, insulin, or glucose R_a during moderate exercise.

The network of neuroendocrine control illustrates the degree of complexity relative to glucose metabolism during exercise. Nonetheless, exercise-induced changes in glucagon and insulin seem to exert a primary influence of the regulation of glucose R_a, even during intense exercise or under the conditions of poorly controlled diabetes. Future investigations should be designed to elucidate the role of circulating metabolites and/or neural feedback on the modulation of hormone secretion and/or the stimulation of glucose R_a during exercise under various levels of metabolic control.

Acknowledgements

The authors were supported by Juvenile Diabetes Foundation International (JDFI) grant 397104 and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grant ROI-DK-50277.

References

1. Wasserman DH, Lacy DB, Goldstein RE, et al. Exercise-induced fall in insulin and hepatic carbohydrate metabolism during exercise. Am J Physiol 1989; 256: E500-8
2. Wasserman DH, Spalding JS, Lacy DB, et al. Glucagon is a primary controller of the increments in hepatic glycogenolysis and gluconeogenesis during exercise. Am J Physiol 1989; 257: E108-17
3. Wolfe RR, Nadel ER, Shaw JHF, et al. Role of changes in insulin and glucagon in glucose homeostasis in exercise. J Clin Invest 1986; 77: 900-7
4. Wasserman DH, Cherrington AD. Regulation of extrahepatic fuel sources during exercise. In: Rowell LB, Shepherd JT, editors. Handbook of physiology. Columbia (MD): Bermedica Production Ltd, 1996
5. Sigal RJ, Fisher S, Marliss EB. The role of the catecholamines in glucoregulation in intense exercise as defined by the islet cell clamp technique. Diabetes 1996; 45: 148-56
6. Wasserman DH, Lickley HLA, Vranic M. The role of beta-adrenergic mechanisms during exercise in poorly-controlled diabetes. J Appl Physiol 1985; 59: 1282-9
7. Coker RH, Krishna MG, Lacy DB, et al. Sympathetic drive to liver and nonhepatic splanchnic tissue during heavy exercise. J Appl Physiol 1997; 82: 1244-9
8. Coker RH, Krishna MG, Lacy DB, et al. Sympathetic drive to liver and nonhepatic splanchnic tissue during prolonged exercise is increased in diabetes. Metabolism 1997; 46 (11): 1327-32
9. Galbo H. Hormonal adaptations to exercise. New York (NY): Thieme-Stratton Inc., 1983

10. Connolly CC, Steiner KK, Stevenson RW, et al. Regulation of glucose metabolism by norepinephrine in conscious dogs. Am J Physiol 1991; 261: E764-72
11. Coker RH, Krishna MG, Lacy DB, et al. Role of hepatic alpha- and beta-adrenergic receptor stimulation on hepatic glucose production during heavy exercise. Am J Physiol 1997; 273: E831-8
12. Kjaer M, Engfred K, Fernandez A, et al. Regulation of hepatic glucose production during exercise in humans: role of sympathoadrenergic activity. Am J Physiol 1993; 265: E275-83
13. Kjaer M, Keiding S, Engfred K, et al. Glucose homeostasis during exercise in humans with a liver or kidney transplant. Am J Physiol 1995; 268: E636-44
14. Kjaer M, Pollack SF, Weiss H, et al. Regulation of glucose turnover and hormonal responses during exercise: electrically-induced cycling in tetraplegic individuals. Am J Physiol 1996; 271: R191-9
15. Kjaer M, Secher N, Bach FW, et al. Hormonal and metabolic responses to exercise in humans: effect of sensory nervous blockade. Am J Physiol 1989; 257: E95-E101
16. Kjaer M, Secher N, Bangsbo J, et al. Hormonal and metabolic responses to electrically-induced cycling during epidural anesthesia in humans. J Appl Physiol 1996; 80: 2156-62
17. Howlett K, Galbo H, Loretsen J, et al. Effect of adrenaline on glucose kinetics during exercise in adrenalectomized subjects. J Physiol 1999; 519: 911-21
18. Kjaer M, Jurlander J, Galbo H, et al. No reinnervation of sympathetic nerves after liver transplantation in humans. J Hepatol 1994; 20: 97-100
19. Hua X. Studies on the regulation of exercise-induced muscular uptake and hepatic production of glucose. In: Faculty of natural sciences. Copenhagen: University of Copenhagen, 1993
20. Coker RH, Koyama Y, Denny JC, et al. Prevention of overt hypoglycemia during exercise: stimulation of endogenous glucose production independent of hepatic catecholamine action and changes in pancreatic hormone concentration. Diabetes 2002; 51: 1310-8
21. Vissing J, Iwamoto GA, Fuchs IE, et al. Reflex control of glucoregulatory responses by group III and IV muscle afferents. Am J Physiol 1994; 266: R824-30
22. Vissing J, Lewis SF, Galbo H, et al. Effect of deficient muscular glycogenolysis on extramuscular fuel metabolism in exercise. J Appl Physiol 1992; 72: 1773-9
23. Vissing J, Galbo H, Haller RG. Paradoxically enhanced glucose production during exercise in humans with blocked glycolysis due to muscle phosphofructokinase deficiency. Neurology 1996; 47: 766-71
24. Vissing J, Galbo H, Haller RG. Exercise fuel metabolism in mitochondrial myopathy. Ann Neurol 1996; 40: 655-62
25. Bonen A, Megeney LA, McCarthy SC, et al. Epinephrine administration stimulates GLUT 4 translocation but reduces glucose transport in muscle. Biochem Biophys Res Commun 1992; 187: 685-91
26. Shamoon H, Sherwin RS. Beta-adrenergic blockade is more effective in suppressing adrenaline-induced glucose production in type 1 (insulin-dependent) diabetes. Diabetologia 1984; 26: 183-9
27. Sherwin RS, Shamoon H, Hendler R, et al. Epinephrine and the regulation of glucose metabolism: effect of diabetes and hormonal interactions. Metabolism 1980; 29: 1146-54
28. Coker RH, Krishna MG, Lacy DB, et al. Hepatic adrenergic receptors are not essential for the increase in R_a during moderate exercise in diabetes. Am J Physiol 2000; 278: E444-51
29. Coker RH, Lacy DB, Krishna MG, et al. Splanchnic glucagon kinetics in exercising alloxan-diabetic dogs. J Appl Physiol 1999; 86: 1626-31
30. Luyckx AS, Lefebvre PJ. Mechanisms involved in the exercise-induced increase in glucagon secretion in rats. Diabetes 1974; 23: 81-93
31. Samols E, Weir GC. Adrenergic modulation of pancreatic A, B, and D cells. J Clin Invest 1979; 63: 230-8
32. Niijima A. Neural control of the blood glucose level. Jpn J Physiol 1986; 36 (5): 827-41
33. Girardier L, Seydoux J, Berger M, et al. Selective pancreatic nerve section: an investigation of neural control of glucagon release in the conscious unrestrained dog. J Physiol (Paris) 1978; 74: 731-5
34. Coker RH, Lacy DB, Williams PE, et al. Pancreatic innervation is not essential for exercise-induced changes in glucagon, insulin or glucose homeostasis. Am J Physiol 1999; 277: E1122-9

Correspondence and offprints: Dr *Robert H. Coker*, Nutrition, Metabolism, and Exercise Laboratory, DWR Center on Aging, University of Arkansas for Medical Sciences, 4301 W. Markham, Slot 806, Little Rock, AR 72205, USA.
E-mail: CokerRobert@uams.edu