# Blood Glucose Regulation during Prolonged, Submaximal, Continuous Exercise: A Guide for Clinicians

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### Abstract

Management of many chronic diseases now includes regular exercise as part of a viable treatment plan. Exercise in the form of prolonged, submaximal, continuous exercise (SUBEX; i.e., ~30 min to 1 h, ~40-70% of maximal oxygen uptake) is often prescribed due to its relatively low risk, the willingness of patients to undertake, its efficacy, its affordability, and its ease of prescription. Specifically, patients who are insulin resistant or that have type 2 diabetes mellitus may benefit from regular exercise of this type. During this type of exercise, muscles dramatically increase glucose uptake as the liver increases both glycogenolysis and gluco-neogenesis. While a redundancy of mechanisms is at work to maintain blood glucose concentration ([glucose]) during this type of exercise, the major regulator of blood glucose is the insulin/glucagon response. At exercise onset, blood [glucose] transiently rises before beginning to decline after ~30 min, causing a subsequent decline in blood [insulin] and rise in blood glucagon. This leads to many downstream effects, including an increase in glucose output from the liver to maintain adequate glucose in the blood to fuel both the muscles and the brain. Finally, when analyzing blood [glucose], consideration should be given to nutritional status (postabsorptive versus postprandial) as well as both what the analyzer measures and the type of sample used (plasma versus whole blood). In view of both prescribing exercise to patients as well as designing studies that perturb glucose homeostasis, it is imperative that clinicians and researchers alike understand the controls of blood glucose homeostasis during SUBEX.

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## Introduction

In addition to type 2 diabetes mellitus (T2DM),<sup>1,2</sup> management of many chronic diseases now includes regular exercise as part of a viable treatment plan.<sup>3</sup> Specifically, prolonged, submaximal (~40–70% of maximal oxygen uptake [VO<sub>2max</sub>]), continuous exercise

(SUBEX) is often recommended for patients with chronic diseases. This is due perhaps to (1) low risk of injury (particularly for already-compromised patients), (2) comfort of exercise and willingness of patient to engage in it, (3) significant metabolic improvements, (4) ease of under-

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**Abbreviations:** (ACSM) American College of Sports Medicine, (ADP) adenosine diphosphate, (AMPK) adenosine monophosphate kinase, (ATP) adenosine triphosphate, (cAMP) cyclic adenosine monophosphate, (CB) capillary blood, (E) epinephrine, (F26BP) fructose-2,6-bisphosphate, (FFA) free fatty acid, (GLUT) glucose transporter, (HSL) hormone-sensitive lipase, (IRS-1) insulin-receptor substrate-1, (NE) norepinephrine, (OGTT) oral glucose tolerance test, (PI3-K) phosphatidylinositol 3-kinase, (SUBEX) prolonged, submaximal, continuous exercise, (T2DM) type 2 diabetes mellitus, (VB) venous blood, (VO<sub>2max</sub>) maximal oxygen uptake, (VP) venous plasma

standing exercise prescription by patient, (5) affordability (e.g., walking and running), and (6) ease of prescription by clinician (i.e., it is a broad prescription that can induce positive changes with many patients with differing pathologies without a need for overly specific instructions). (The interested reader is directed to Reference 4 for a discussion on exercise prescription concerns.)

As scientists continue to work to elucidate the mechanisms involved in T2DM, clinicians continue to translate benchwork into practical methods for treating the millions of patients afflicted with the disease. In addition to its many benefits to healthy populations, exercise is now well supported as an effective prescription for patients with T2DM, acting therapeutically both acutely and chronically.<sup>1-3</sup> Specifically, it has been shown that an acute bout of submaximal exercise can lower blood glucose concentration ([glucose]) for 2 to 48 h postexercise<sup>1,5</sup> and improve insulin sensitivity for up to 72 h after cessation of any given exercise bout. In addition, chronically engaging in moderate physical activity (e.g., ~150 min/week) and reducing weight by 5-7% though diet modification greatly reduces the risk of progressing from impaired glucose tolerance to T2DM.<sup>2</sup>

In their 2000 position stand, the American College of Sports Medicine (ACSM) recommends that patients with T2DM engage in a total of 1000 kcal/week of energy expenditure (3-5 days of exercise/week), mostly in the form of low to moderate (40-70% of VO<sub>2max</sub>) exercise.<sup>1</sup> The American Diabetes Association currently recommends 150 min/week of exercise at an intensity of 40-60% VO2max no less than three days a week and never with more than two consecutive days without physical activity.<sup>2</sup> Because improved insulin sensitivity from an exercise bout lasts no more than 72  $h_r^{2,6}$  it is critical that these patients maintain a regular exercise schedule. In 1998, Rogers and colleagues<sup>7</sup> demonstrated that improvements in glucose tolerance and reductions in insulin resistance can be obtained in patients with T2DM after only one week of daily exercise at 70% of VO<sub>2max</sub>. Kang and associates<sup>8</sup> published work in which improvements in insulin sensitivity of patients with T2DM were achieved after one week of exercise at 70%  $VO_{2max}$  but not 50%  $VO_{2max}$ (calorically matched). These studies suggested that the short-term effect of exercise on insulin sensitivity might be mediated through glycogen depletion. However, other studies have shown that muscle triglyceride content is inversely related to insulin sensitivity,9-11 suggesting that lower-intensity exercises are effective for increasing insulin sensitivity.

Evidence<sup>12</sup> has indicated that both "moderate" (40-55% of  $VO_{2max}$ ) and "vigorous" (55–80% of  $VO_{2max}$ ) exercise improve β-cell function. Slentz and coworkers<sup>12</sup> demonstrated that a "vigorous" exercise group reduced visceral fat by 7% over eight months, while the "moderate" intensity group did not alter visceral fat. While this study has been referenced as showing the importance of "vigorous" exercise in reducing cardiovascular risk,13 it should be noted that the delineations of "moderate" and "vigorous" in this study are both similar to the ACSM's category for "moderate" exercise (40-70% of VO<sub>2max</sub>). Thus it appears that exercise in the "upper" moderate zone (closer to 70% or 80% of  $VO_{2max}$ ) might have the greater influence over visceral fat loss, while exercise in the "lower" moderate zone (40% or 50% VO<sub>2max</sub>) might have the greater influence over improving  $\beta$ -cell function. Although the exact mechanisms are unclear, it appears that SUBEX leads to both acute and chronic positive adaptations.

Because clinicians are now relying more on exercise prescription to manage major metabolic disorders like T2DM, it is imperative that physicians and other primary health care providers understand the normal blood glucose changes during SUBEX. Many of the responses described in this paper differ markedly from the response of blood glucose to maximal exercise. In seminal work exploring this response, Hermansen and colleagues<sup>14</sup> showed that blood [glucose] increased from a resting value of 82.6 mg/dl (~4.6 mM) to 170.7 mg/dl (~9.5 mM) after five bouts of running "all-out" for 60 s with a 4 min rest between. Although exploring the response to maximal exercise is beyond the scope of this review, it is helpful to note that, during maximal exercise (>100% of VO<sub>2max</sub>), no "steady state" is obtained and blood [glucose] increases, reaching a peak ~7 min postexercise.<sup>14</sup> The purpose of this review is to provide physicians and other clinicians with a concise yet thorough review of normal blood glucose regulation during SUBEX.

## Response to Prolonged, Submaximal, Continuous Exercise

Both at rest and during muscular exertion, glucose is the major fuel for the mammalian central nervous system. Thus evolution has spawned blood glucose homeostasis that is controlled by a redundancy of mechanisms. The normal plasma [glucose] (~5.5 mM, ~100 mg/dl) provides the brain with more than adequate substrate, as cerebral metabolism is not impaired until plasma [glucose] has declined to less than ~3.6 mM (~65 mg/dl).<sup>15</sup>

While the sympathetic nervous system and the endocrine system work together to maintain blood [glucose], our main focus will be on the endocrinologic mechanisms that maintain blood [glucose] in typical (~30 min to 1 h), submaximal (~40–70% of VO<sub>2max</sub>, i.e., below the lactate threshold), continuous exercise.

Certain "glycemic threshold" plasma glucose concentrations have been analyzed utilizing the hypoglycemic clamp technique and arterialized venous blood (VB) to examine the physiological response to glucose perturbations. As plasma [glucose] declines to ~4.5 mM (~81 mg/dl; with normal physiological day-to-day activities), insulin secretion is suppressed. When plasma [glucose] declines further to ~3.7 mM (~67 mg/dl), glucagon, growth hormone, and epinephrine (E) release is increased.<sup>16,17</sup> As plasma [glucose] declines further to ~3.6 mM (~65 mg/dl) and below, brain metabolism begins to be impaired and cortisol secretion increases dramatically.<sup>16</sup> Severe hunger is stimulated at levels around 3.0 mM (~54 mg/dl), and cognitive dysfunction with an eventual result in coma and death begins to occur around 2.6 mM (~47 mg/dl).<sup>16,17</sup>

It is apparent that any physical stress imposed on the body that requires an increase in muscle metabolism and at least some subsequent utilization of blood glucose obligatorily requires strict glucose regulatory mechanisms. When the metabolism of skeletal muscles is greatly increased over a period of time, they begin to deplete their own glycogen stores and compete against the brain for the glucose available in the blood (e.g., glucose released from the liver). Furthermore, when hepatic metabolism is significantly increased during prolonged exercise and/or chronically in other highly gluconeogenic circumstances (starvation), ketone bodies are formed, which, in many cases, provide usable fuel for the brain in the face of declining blood glucose.<sup>18</sup> However, a prolonged reliance on this mechanism for homeostasis can lead to acidosis, coma, and death,<sup>19</sup> underscoring the importance of blood glucose regulation in the face of perturbations.

Although there has been some research suggesting that a  $\beta$  isoform of glucose-6-phosphatase exists in skeletal muscle and may contribute to blood glucose homeostasis during rest,<sup>20</sup> during extended times of high metabolic demand of skeletal muscle (prolonged exercise), the primary sources of energy for any given muscle comes from intracellular glycogen stores, blood glucose released into circulation from the liver, free fatty aids (FFAs) released into circulation from adipocytes, and lactate released from other muscles.<sup>19,21</sup>

The typical human blood [glucose] response to SUBEX is best shown in **Figure 1**.<sup>22</sup> As exercise begins, the increased energy demand of skeletal muscle causes an increase in glucose uptake via glucose transporters (GLUTs), the most important being GLUT4. However, blood [glucose] transiently rises due to an immediate release of glucose from the liver. While originally thought to be due to sympathetic innervations of the liver, liver-transplant patients show the same glucose rise at the onset of exercise as control patients.<sup>23</sup> Regardless of the origin of this transient increase, it is short lived, and blood [glucose] soon begins to decline.



**Figure 1.** The typical blood glucose response during SUBEX. Error bars were omitted for clarity. Reproduced with permission from Zinker *et al.*<sup>22</sup>

Blood [glucose] typically does not fall more than 10–15% during this normal response (Figure 1), despite the fact that the liver has more than doubled its output of glucose; skeletal muscle is taking up great quantities of glucose.<sup>19,22</sup> In contrast to the relative maintenance of [glucose] in normal subjects, numerous studies demonstrate that the acute response of patients with T2DM to SUBEX is a decline of 1-2 mM (~20-40 mg/dl) in plasma [glucose] (see Reference 24). Finally, O'Brien and associates<sup>25</sup> analyzed expired gases collected during a marathon to calculate an average respiratory exchange ratio (RER; VCO<sub>2</sub>/VO<sub>2</sub>) of 0.93, exemplifying the high reliance on glucosyl units during prolonged exercise, even in the face of glycogen depletion. As exercise continues, the rate of decrease in blood [glucose] slows as hormonal responses work to maintain the appropriate concentration. The sympathetic nervous system contributes to these changes during

exercise via  $\alpha$ -adrenergic (on  $\beta$  cells) and  $\beta$ -adrenergic (on  $\alpha$  cells) receptors on the pancreas to decrease insulin or increase glucagon, respectively.<sup>26</sup>

## The Insulin/Glucagon Response

The insulin/glucagon response to SUBEX in humans is the most important regulator of plasma glucose.<sup>27</sup> While neural factors seem to contribute to an immediate increase in gluconeogenic activity and glycogenolytic release from the liver, the circulating [glucagon]/[insulin] ratio plays the dominant role in hormonal control during SUBEX.<sup>27–30</sup>

## Insulin

#### Structure and Secretion

Expression of the insulin gene, INS (chromosome 11), is highly regulated by plasma [glucose], as well as by circulating fatty acids.<sup>31</sup> Dyslipidemia causes downregulation of transcription, while elevated plasma [glucose] causes increases in transcription rate.<sup>31</sup> Additionally, glucose has been implicated in exerting gene expression control over insulin during transcription, preRNA splicing, and by increasing or decreasing mRNA stability.32 After the preprohormone is formed, the signal sequence is cleaved in the endoplasmic reticulum and the prohormone is secreted into vesicles for release as insulin and C-peptide upon proper stimulation. A high "energy charge" [adenosine triphosphate (ATP)/adenosine diphosphate (ADP)] of the cell initiates release of insulin, as detailed here.<sup>32</sup> The final circulating form of insulin is a monomer consisting of an  $\alpha$  and  $\beta$  chain connected by two disulfide bonds.  $^{33}$ 

The secretion of insulin is primarily regulated by the blood [glucose]. This is highlighted in a review by Soria *et al.*<sup>34</sup> Briefly, GLUT2 proteins exist on the membrane of pancreatic  $\beta$  cells. These GLUT2 proteins have a relatively high Km for glucose (~20 mM) and thus respond markedly to changes in blood [glucose]. Furthermore, hexokinase IV (glucokinase) has a relatively high activity, and this phosphorylation of glucose once inside the cell is classically considered the rate-limiting step in glucose flux.<sup>35</sup> This influx of glucose and subsequent phosphorylation and metabolism in  $\beta$  cells of the pancreas cause an increase in the ATP/ADP ratio of the cell, which initiates closure of the ATP-dependent K<sup>+</sup> channels.<sup>34</sup> This depolarization causes voltage-gated Ca<sup>++</sup> channels to open, initiating docking and secretion of insulin from secretory vesicles.<sup>34</sup>

### Binding and Signaling

After binding (e.g., at a skeletal myocyte), insulin then exerts its action of increasing glucose uptake into the cell

via a well-characterized signaling cascade (see **Figure 2**). The insulin receptor binds insulin, dimerizes, and subsequently autophosphorylizes. This causes activation of the receptor tyrosine kinase on one of the  $\beta$  subunits on the cytoplasmic leaflet, which, in turn, phosphorylates intracellular proteins, most notably insulin-receptor substrate-1 (IRS-1).<sup>36,37</sup> This IRS-1 activation has been implicated in many events, including signaling that leads to long-term changes in gene expression, which is beyond the scope of this review.

Insulin-receptor substrate-1 also leads to the translocation in adipocytes and myocytes of GLUT4s from intracellular pools to the cytosolic membrane (including t-tubules) to increase glucose uptake via a phosphatidylinositol 3-kinase (PI3-K)-mediated mechanism that activates a serine/threonine kinase cascade.<sup>38,39</sup> Furthermore, it appears that both exercise and hypoxia also induce translocation of GLUT4s from intracellular sites to the membrane.<sup>15,28,39–41</sup> In 2002, Khayat *et al.*<sup>41</sup> described the differences between exercise-induced and insulin-induced GLUT4 translocation. In brief, it appears from numerous studies that, while insulin utilizes the PI3-K-mediated mechanism, exercise and hypoxia do not utilize this pathway. Furthermore, it has been suggested that these mechanisms even recruit different intracellular GLUT4



**Figure 2.** Simplified schematic of insulin binding at a skeletal muscle cell membrane and subsequent GLUT4 translocation. The dimerized insulin receptor is shown as four filled-in rectangles. Insulin binds, leading to dimerization and phosphorylation of the intracellular subunits of the insulin receptor. This leads to phosphorylation of many proteins, including IRS-1. This then leads to activation of PI3-K, leading to translocation of GLUT4s to the cell membrane, allowing an increase in glucose uptake. Note that exercise also induces translocation of GLUT4s, but independently of PI3-K and possibly from a separate intracellular pool.

pools, such that their effects are additive.<sup>41,42</sup> *In vitro* studies inhibiting the PI3-K mechanism in rat muscles support this as contractions, but not insulin, still stimulated GLUT4 translocation.<sup>43,44</sup> This contractions-induced translocation is still being investigated. Various signals have been implicated in this activity, including Ca<sup>++</sup>, adenosine monophosphate kinase (AMPK), and nitric oxide.<sup>42,45,46</sup> Work in rodents and other models has suggested that there are two contraction-induced GLUT4 translocation pathways: a Ca<sup>++</sup>-mediated pathway predominant in both fast and slow twitch fiber types and a separate AMPKmediated pathway that seems to be present only in fast twitch fibers (see Reference 47).

Insulin binding at the liver also begins signaling that induces phosphorylation of intracellular signals, but these lead to increases in both glycogen synthase and phosphofructokinase-2 activity (which increases fructose-2,6-bisphosphate [F26BP], leading to an increase in glycolysis).<sup>37</sup> This relates little to prolonged exercise, in which insulin levels decrease. However, the removal of this insulin "signal" at the liver and subsequent binding of glucagon allows active gluconeogenesis to proceed, as explained later.

Adipocytes are also affected by insulin binding. Insulin promotes anabolism at adipocytes via a similar GLUT4 translocation as seen in skeletal muscle cells.<sup>39</sup> Further, an increase on the order of micromolar concentrations in plasma insulin in humans has been shown to inhibit lipolytic actions by more than 50% of basal activity.<sup>48</sup> The mechanism of lipolytic inhibition with increasing levels of plasma [insulin] has been attributed to degradation of cyclic adenosine monophosphate (cAMP) by activating phosphodiesterase-3, which is activated by PI3-K (see earlier insulin signaling explanation). The end result is that hormone-sensitive lipase (HSL) is activated less with the removal of the cAMP stimulus.<sup>49</sup>

Further discussion of lipolytic mechanisms of exercise will be discussed within the context of catecholamines, as one function of E is to inhibit insulin release. Keeping insulin levels low allows FFAs to circulate in higher quantities, available for use by tissues, sparing glucose.<sup>48,50</sup>

Finally, Brooks and Mercier<sup>51,52</sup> proposed and have received experimental support for the "crossover" concept (**Figure 3**) to characterize the reliance on a larger and larger percentage of lipid metabolism as exercise intensity is decreased. As shown in **Figure 3**, the crossover concept describes lipid metabolism as providing ~60% of metabolic needs for nonactive skeletal muscle and the body at rest.

At submaximal exercise intensities ( $\sim$ 40–70% of VO<sub>2max</sub>), we can expect lipid metabolism to provide  $\sim$ 25–45% of metabolic demand of skeletal muscles.

## Glucagon

#### Structure and Secretion

The preprohormones that are encoded by the glucagon gene, GCG (chromosome 2), in the  $\alpha$  cells of the pancreas are much larger than glucagon and encompass the coding for many other proteins as well. Secretion of glucagon is inhibited by the  $\alpha$ -cell glucose concentration. Also, high concentrations of amino acids seem to increase glucagon secretion, while high circulating FFAs seem to inhibit release.<sup>32</sup>

### **Binding and Signaling**

While glucagon exerts no direct action at muscle cells, it does increase the output of glucose by the liver. The primary regulator of plasma [glucagon] is the circulating [glucose].<sup>53</sup> As mentioned in the introduction, a drop to ~3.7 mM (~67 mg/dl) in plasma glucose is a potent stimulus for glucagon secretion from the  $\alpha$  cell of the pancreas.<sup>16,17</sup>

Glucagon binds its G-protein-coupled receptor at the liver. This initiates a stimulatory cascade via increasing adenyl cyclase activity and increased cAMP.<sup>54</sup> Cyclic adenosine monophosphate phosphorylates several intracellular proteins, which leads to phosphorylation of glycogen phosphorylase to its more active "a" form. This active form induces rapid glycogenolysis.



**Figure 3.** The "crossover" concept originally proposed by Brooks and Mercier.<sup>52</sup> As intensity of exercise increases, there is greater and greater reliance on carbohydrate as a fuel source. Reproduced with permission from Brooks and Mercier. CHO, carbohydrate.

Simultaneously, glucagon binding at the liver (Figure 4) also stimulates gluconeogenic activity by phosphorylating the fructose-2,6-bisphosphatase/phosphofructokinase-2 enzyme, activating its phosphatase activity to decrease the F26BP in the cell. Fructose-2,6-bisphosphate is a potent stimulator of glycolysis, and in this situation, gluconeogenesis, not glycolysis, is preferred.<sup>37</sup> Furthermore, increases in plasma amino acid stimulate glucagon production; the presence of high amino acid levels can then be utilized in gluconeogenesis at the liver.53 With increasing exercise duration, the amount of cortisol secreted increases in order to preserve plasma [glucose] with a resultant increase in glucagon to promote gluconeogenesis. A complete review of inhibitors and stimulators of glucagon secretion is found in a review by Dunning and associates.53 It must be emphasized that these signals interact in a coordinated fashion<sup>53</sup> to control glucagon secretion from  $\alpha$  cells of the pancreas. In the perfused rat pancreas, it was demonstrated that glucagon also promotes lipolysis (making FFAs available for utilization at myocytes and glycerol available for



**Figure 4.** Simplified schematic of glucagon binding at a hepatocyte cell membrane and subsequent signaling that ultimately leads to glucose release into the blood. Glucagon binds its G-protein-coupled receptor, which causes the intracellular G $\alpha$  subunit to activate adenylate cyclase, which catalyzes cAMP formation, which then activates protein kinase A, which phosphorylates both phosphorylase kinase and the fructose-2,6-bisphosphatase/phosphofructokinase-2 enzyme; the latter leads to a decrease in F26BP, causing a decrease in glycolysis and allowing an increase phosphorylates glycogen phosphorylate to the more active "a" form, causing a rapid breakdown of glycogen and ultimately leading to release of glucose from the cell to the blood. Note that this figure has been simplified for clarity; not shown are numerous other signaling and metabolic steps involved. AC, adenylate cyclase; PKA, protein kinase A.

gluconeogenesis at hepatocytes), with FFAs and ketones exerting some negative feedback control over glucagon secretion.  $^{55}$ 

During prolonged exercise, the main stimulus that promotes an increase in glucagon secretion from the pancreas  $\alpha$  cells is a drop in plasma [glucose] and concomitant drop in plasma [insulin]. It has been further noted that a fall in [insulin] in exercising dogs increases the sensitivity of the liver to glucagon outside of any [glucagon] changes,<sup>56</sup> perhaps due to increases in receptor number, as Légaré and coworkers57 exhibited with endurance-trained rats. Also, studies in humans have suggested that E fluctuations may attenuate plasma glucose changes in the face of clamped glucagon or insulin levels,<sup>27,30</sup> again exemplifying the redundancy of controls that exist for such a critical system.58 Furthermore, the pancreas is replete with adrenergic nerve innervation to  $\alpha$  cells and  $\beta$  cells, yet total denervation in dogs showed no deleterious effects in glucagon or insulin regulation with exercise.59

# Exercise Training and the Catecholamine Response

In response to prolonged exercise, plasma [insulin] gradually declines as plasma [glucose] declines. However, **Figures 5** and **6** show that, with training, this decrease in [insulin] and increase in [glucagon] that is normally seen with submaximal exercise is attenuated.<sup>60</sup>

The seemingly inexplicable ability of a trained athlete to exhibit nonsignificant changes in plasma [glucagon] and plasma [insulin] during such a large glucose flux has been explained in part by a reduction in sympathetic outflow for the same absolute intensity after training, such that lower levels of E and norepinephrine (NE) are circulating.<sup>60</sup> Because these catecholamines stimulate both a decrease of plasma [insulin] and an increase of plasma [glucose] can still be maintained adequately.<sup>60</sup> Curiously, the plasma glucagon response is attenuated even at the same relative intensity after training, presumably with more catecholamine release (see **Figure 6**).

As shown in **Figure 7**, the same relative intensity does elicit a greater catecholamine response in trained people. These trained athletes require a greater increase in [catecholamine] because of their increase in metabolic demands at that relative intensity; the gluconeogenic, glycogenolytic, and lipolytic responses are potentiated.<sup>61</sup> Epinephrine and NE both bind at the liver to increase glycogenolysis and gluconeogenesis while promoting glycogenolysis at the muscle and lipolysis at adipocytes.<sup>62-64</sup> Postganglionic sympathetic nerve endings release ~95% NE and ~5% E during sympathetic stimulation of an organ (e.g., the liver and other visceral organs),<sup>35</sup> while sympathetic innervation of the adrenal medulla releases



**Figure 5.** Plasma insulin concentrations during exercise at 60% of  $VO_{2max}$ , both before (filled circles/solid curve) and after (filled squares/ dotted curve) training. Error bars have been omitted for clarity. Reproduced with permission from Gyntelberg *et al.*.<sup>60</sup> WR, work rate.



**Figure 6.** Plasma glucagon concentrations during exercise at 60% of VO<sub>2max</sub> both before (filled circles/solid curve) and after (filled squares/dotted curve/same absolute work rate; empty squares/solid line/ same relative work rate) training. Error bars have been omitted for clarity. Reproduced with permission from Gyntelberg *et al.*<sup>60</sup> WR, work rate.

~80% E and ~20% NE.<sup>35</sup> During exercise in humans, the response in circulating concentration changes of NE greatly exceeds that of  $E^{61,65}$  due in large part to "spillover" from sympathetic nerve endings. However, in exercises such as those around 50–60% of VO<sub>2max</sub> (i.e., SUBEX), the catecholamine response is considered to be minimal; the aforementioned [glucagon]/[insulin] ratio is the main regulator of blood [glucose] during these situations.<sup>61</sup>

Interestingly, men and women display markedly different plasma NE and E responses during SUBEX,<sup>66</sup> despite plasma glucose responses that do not differ. In an elegant



**Figure 7.** Plasma **(A)** NE and **(B)** E responses at different work rates between trained (filled bars) and untrained (empty bars) subjects. Error bars omitted for clarity. Asterisks denote significant differences between the groups at any given work rate. Note that the differences seen between trained and untrained are in the NE response but not the E response. Reproduced with permission from Greiwe *et al.*.<sup>61</sup>

study of humans designed specifically to investigate the differences between the sexes in response to SUBEX, Davis *et al.*<sup>66</sup> determined plasma NE, E, pancreatic polypeptide (a marker of vagal input on pancreas), insulin, glucose, and glucagon, among other variables. Men showed a greater response in plasma NE, E, pancreatic polypeptide, insulin suppression, systolic blood pressure, and carbohydrate oxidation; women showed a greater response in lipolysis. Plasma [glucagon] was not different between the two sexes. (The interested reader is directed to Reference 66 for a full discussion of the differences between the sexes during SUBEX.)

## Lipolysis

It would be incomplete to not at the very least mention lipolysis and the catecholamine-induced lipolysis with exercise. As exercise duration increases and insulin levels decline, lipolysis of adipose tissue is increased. This is because even very small increases in plasma [insulin] inhibit lipolysis (via inhibition of HSL) to a great deal, and removal of this inhibition allows for greater lipolytic activity.<sup>48,50</sup>

Adipocytes express both  $\alpha$ -adrenergic and  $\beta$ -adrenergic receptors.<sup>62</sup> The  $\beta$ -adrenergic receptors mediate lipolysis during exercise (by activation of HSL via a G-protein), while the  $\alpha$ -adrenergic receptors appear to modulate lipolysis at rest (by inhibition of HSL via a different G-protein).<sup>67,68</sup> During the transition from 25% to 65% of VO<sub>2max</sub>, catecholamine levels begin to rise slightly and have been implicated in the increase in lipolysis, despite the observation that further increases in intensity and catecholamine concentration attenuate lipolytic activity in exercising humans.<sup>69</sup>

To examine this phenomenon in vivo, Mora-Rodriguez and Coyle<sup>64</sup> infused cyclists with E during four occasions, all at 25% of  $VO_{2max}$ . The result was an increase in FFA appearance in the plasma, as well as an increase in plasma insulin, yet with less oxidation of lipids. The investigators also had the subjects cycle at 45% of VO<sub>2max</sub> as a second control and saw less lipolysis overall when compared to the control trial at  $25\%\ VO_{2max}\!.^{64}$ It has been proposed from previous studies in humans and rodents that the decrease in lipolysis with increasing exercise intensity is due to blood shunting and a redistribution of blood flow away from low metabolic activity tissues to high metabolic activity tissues.70,71 Further support for this comes from the presence of  $\alpha$ -1 adrenergic receptors on the arterioles that mediate vasoconstriction.49 While proposed mechanisms are still

being explored, it has been shown that, beyond exercise intensities of ~65% of  $VO_{2max}$ , lipolysis in humans seems to plateau, despite increases in plasma catecholamines.<sup>69</sup>

## What Is Being Measured

Although an in-depth analysis of glucose measurements in blood compartments is beyond the scope of this review, it should be noted that glucose is unequally distributed between red blood cells and plasma.72-74 Further, measured values are dependent on nutritional status (postabsorptive versus postprandial) and sampling site (arterial versus venous). Similar to the case for lactate,<sup>75</sup> confusion may result when clinicians interpret a whole blood result on the basis of normal plasma values, or vice versa. Currently, many recommendations are based on studies of venous plasma (VP) concentrations converted to whole blood,<sup>74</sup> capillary blood (CB) is often used for both diagnoses and home monitoring.74,76 Because the difference between whole blood values and plasma values can vary markedly, converting whole blood values to plasma equivalents or vice versa is not ideal.

In 2002, Haeckel et al.74 measured glucose concentrations specifically in VP, VB, and CB in 147 patients who had varying glucose responsiveness (results are rounded and summarized in Table 1; reader should see Reference 74 for complete results). Briefly, the fasting VP-to-VB ratio was 1.14, was not different between diabetic subjects and control subjects (p = .37), and was stable throughout an oral glucose tolerance test (OGTT).74 The VP-to-CB ratio varied from 1.08 in the fasted state to 0.97 in the postprandial state in healthy individuals (p < .001), while diabetic subjects were 1.11 in both the fasted and the 2 h postprandial state (p = .92) (mean of 1.05 among all patients from fasted through 2 h OGTT). The CB-to-VB ratio varied from 1.04 in the fasted state to 1.23 in the fed state in healthy individuals (p < .001), while diabetic subjects ranged from 1.03 in the fasted state to 1.04 in the postprandial state (mean of 1.12 among all patients from fasted through 2 h OGTT). Although few major errors are likely to result from these differences, clinicians should be aware of the differences, especially as they may apply to specific situations.

## Conclusion

Mammalian blood [glucose] is maintained by a redundancy of mechanisms<sup>58</sup> that ensure adequate substrate to both the brain and other organs for continued survival (**Figure 8**). While other types of exertion may enlist different homeostatic mechanisms for maintenance of blood

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Relationship Glucose <sup>a</sup>	between	Plasma	and	Whole	Blood	1

Patient Group	Nondiabetic patients	Diabetic patients	All patients					
VP to VB								
Fasting VP:VB	1.12	1.16	1.14					
Postprandial VP:VB	1.15	1.16	1.16					
Mean 2 h OGTT VP:VB	1.14	1.15	1.15					
VP to CB								
Fasting VP:CB	1.08 <sup>b</sup>	1.11	1.11					
Postprandial VP:CB	0.97 <sup>b</sup>	1.11	1.04					
Mean 2 h OGTT VP:CB	1.00	1.09	1.05					
CB to VB								
Fasting CB:VB	1.04 <sup>c</sup>	1.03	1.03					
Postprandial CB:VB	1.23	1.04	1.14					
Mean 2 h OGTT CB:VB	1.17 <sup>c,d</sup>	1.06 <sup>d</sup>	1.12					

 <sup>a</sup> Adapted with permission from Haeckel and colleagues.<sup>74</sup>
<sup>b,c,d</sup> These figures denote significance between two variables. Note that this is not an exhaustive statistical analysis, but statistical differences are merely reproduced from the original study, where the interested reader is directed for further analyses.

glucose, maintenance of blood glucose during SUBEX is regulated mainly by the insulin/glucagon response. Furthermore, it should be noted that a redundancy of mechanisms for regulation of blood [glucose] exists. Experiments manipulating these variables must be examined carefully, as many times changes in other homeostatic mechanisms (catecholamine response, lipolytic activity, sensitivity of the liver, receptor number) result from manipulation of the insulin or glucagon response in order to ensure proper maintenance of blood [glucose] and adequate delivery of substrate to the brain.

Accordingly, care should be taken in administering clinical trials in which one or more of these variables are altered. Evidence continues to accrue in favor of lactate as a viable substrate for many tissues that otherwise utilize glucose,<sup>77</sup> and cancer research has provided evidence that the well-known Cell-to-Cell Lactate Shuttle Theory in muscle physiology<sup>78</sup> is also at work in tumors,<sup>79,80</sup> raising questions of potential treatment options by perturbing glucose/lactate concentrations.<sup>81</sup> Because glucose is so tightly regulated with such a redundancy of mechanisms, understanding and appreciating blood glucose regulation is critical.



**Figure 8.** The major systems involved in blood glucose homeostasis during SUBEX. Depicted in the center is a cylinder representing blood [glucose] during exercise. As shown in the figure, during exercise, blood glucose maintenance is a balance between glucose appearance (e.g., from the liver) and glucose disposal (e.g., into the muscles). The central nervous system has direct influence on several organs during exercise via neuronal innervations (dotted line arrows). This figure does not distinguish between autonomic (liver, blood vessels, pancreas) or somatic (skeletal muscle) innervations. Large black arrows pointing in both directions between blood glucose and an organ represent humoral communication. Below each organ's name, the major changes seen during SUBEX are listed. Note that this figure has been simplified for clarity; not shown are other changes/communications, including the brain receiving neuronal feedback from various organs. CNS, central nervous system.

With the now well-known therapeutic effects of both acute and chronic bouts of submaximal exercise for patients with chronic diseases, it is of paramount importance that clinicians understand the normal hormonal homeostatic mechanisms that function during these exercises on both an acute and chronic level. As we move into an age of unparalleled molecular technological advancement, it is imperative that we continue to explore homeostatic mechanisms from a whole animal level down to a subcellular level, lest we overlook potential therapeutic treatments that target both molecular and systemic effectors.

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