Intensive Care Med (2003) 29:511–514
DOI 10.1007/s00134-002-1629-3

EDITORIAL

Xavier Leverve

Hyperglycemia and oxidative stress: complex relationships with attractive prospects

Received: 26 October 2002
Accepted: 29 November 2002
Published online: 27 February 2003

X. Leverve (✉)
Bioénergétique Fondamentale et Appliquée, INSERM E0221,
Université Joseph Fourier,
2280 rue de la Piscine BP 53 X, 38041 Grenoble Cedex, France
e-mail: Xavier.Leverve@ujf-grenoble.fr
Tel.: +33-4-76514386
Fax: +33-4-76514218

X. Leverve
Département de Médecine Aiguë Sépcialisée,
Hôpital A. Michallon,
Centre Hospitalier Universitaire de Grenoble,
38043 Grenoble Cedex 9, France

The major impact of stress, inflammation, or infection on glucose homeostasis has long been recognized as a central metabolic adaptation to severe illnesses [1, 2, 3]. If insulin resistance can be considered as a major change in the hormonal environment [4, 5], in association with some other changes [6], the resulting effects on glucose concentration and/or metabolism (overall turnover, oxidative and nonoxidative routes) and their consequences appear to be more ambiguous. A relationship between hyperglycemia and increased susceptibility to infection has long been postulated, but after the pioneering work of Cuthbertson [7] glucose infusion was also recognized to be a major way to limit the extent and the morbid consequences of lean body mass wastage following surgery and other diseases [8, 9]. Similarly, insulin resistance was regarded either as an adaptive event, permitting to reroute the glucose toward high metabolic priorities (wounded or immune tissues) at the expense of the insulin-dependent territories (muscle and adipocytes) or, conversely, as a deleterious event, indicating the incapacity of β-cells to secrete sufficient amounts of insulin [4, 9, 10, 11].

Several additional data obtained in type I or II diabetes, in brain-compromised patients, and more generally in severe diseases have accumulated that indicate a possible deleterious effect of insulin resistance and high glucose per se. The paradox regarding glucose, however, either bad or good, still persists since in cardiac surgery or after an acute myocardial infarction, the use of a glucose-insulin-potassium (GIK) mixture shows beneficial effects despite the resulting increase in blood glucose [12, 13, 14, 15]. The splendid work of van den Berghe and her group [16] showing an impressive improvement in both morbidity and mortality in ICU patients undergoing a tight control of blood glucose by insulin might be regarded as a cornerstone in our appreciation and understanding of metabolic disorders in the ICU and their consequences, regardless of the interesting debate concerning patient population, best level of glycemia, actual underlying mechanism, etc. In *Intensive Care Medicine* the work presented by Perner et al. [17] contains additional data, indicating that high glucose may impair neutrophil cells by affecting oxidative metabolism, a crucial pathway for the antimicrobial effect.

Nevertheless, despite these new data indicating a deleterious effect of high glucose, the question remains as to understand why glucose is sometimes beneficial but sometimes clearly detrimental. Three parameters must probably be considered separately, although physiologically very tightly connected: (a) blood (cellular?) level of glucose, (b) rate of glucose metabolism (both oxidative and nonoxidative), and (c) insulin level (among several other circulating factors) required to obtain a given steady state. As oxygen, and probably many other metabolites, glucose is not only a unique substrate, it is also a powerful signaling molecule and any change in blood glucose must be considered as a very complex event with a variety of consequences. It is highly probable that in the absence of any exogenous (medical) intervention the state of insulin resistance is clearly beneficial, permitting to redirect the molecules of glucose

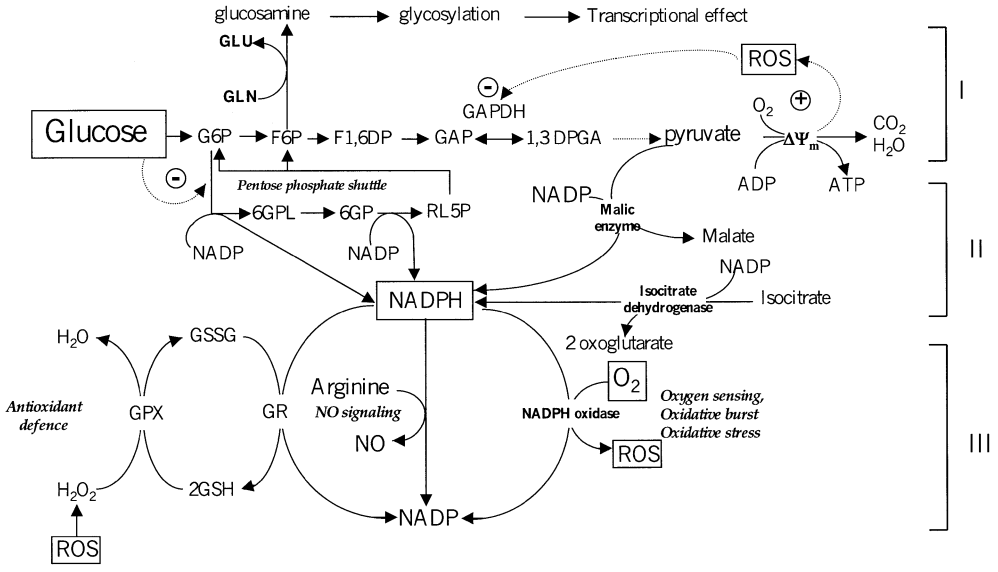

Fig. 1 Glucose, oxidative signaling, and oxidative stress. Glucose metabolism is central in mitochondrial and cytoplasm redox metabolism. *I* High glucose concentration enhances glycolysis leading to a higher mitochondrial membrane potential resulting in an increased mitochondrial ROS production, which in turn inhibits GAPDH. Hence the flux is redirected toward glucosamine pathway, responsible for the transcriptional effects of hyperglycemia. *II* In addition to pyruvate (malic enzyme) and isocitrate (cytosolic NADPH-dependent isocitrate dehydrogenase), glucose is a major metabolite for the generation of NADPH in the cytosol at the level of the pentose phosphate pathway. High glucose inhibits G6PDH leading to decrease NADPH formation. *III* NADPH is crucial in the redox homeostasis since its metabolism can lead to NO formation (*NOS*) or superoxide anion (NADPH oxidase, reactive oxygen species, *ROS*) on the pro-oxidant side and to the reduction in glutathione (glutathione reductase, *GSH*) a key intermediate in the defense against excess of oxidative pressure. *GAPDH* Glyceraldehydephosphate dehydrogenase; *1,3-DPGA* 1, 3-diphosphoglyceraldehyde; *6PGL* 6-phosphogluconolactone; *6PG* 6-phosphogluconate; *GLU* glutamic acid; *GLN* glutamine; *GPX* glutathione peroxidase; *GR* glutathione reductase; *GSSG* oxidized glutathione; *GSH* reduced glutathione

(very valuable when obtained by gluconeogenesis from muscle protein breakdown) towards compulsory pathways [4, 18]. Nowadays, thanks to modern medicine, glucose is certainly no longer a very valuable substrate since it is routinely infused to patients, and the consequences of insulin resistance on blood glucose concentration are probably largely magnified by the routine use of intravenous glucose infusion compared to the pure pathophysiological response. The use of exogenous insulin permits blood glucose to be maintained in a near-physiological range or its increase to be limited. However, it has also some drawbacks such as hypoglycemia, which can be minored by attentive bedside care, and activation of lipogenesis, with the possible harmful fatty liver [19].

It seems reasonable to propose that glucose, as an energetic substrate, is a beneficial metabolite, and this is probably the explanation for the positive effect of its infusion as reported in several studies, including Cuthbertson's postoperative state and GIK infusion, among many other clinical conditions. The harmful effect of glucose is then most probably related to its role as signaling molecule, and the main question is to understand how and why. This was a pressing question in the world of diabetologists, and therefore not surprisingly the major recent advances came from researchers working in this field. It appears that cellular glucose sensing is related to reactive oxygen species (ROS) metabolism [20, 21, 22]. Briefly (see Fig. 1), high extracellular glucose induces an activation of the glycolytic pathway, resulting in an enhanced pyruvate oxidation, which is associated with a higher mitochondrial membrane potential ($\Delta\Psi_m$). This high $\Delta\Psi_m$ is responsible for an increased ROS production, which in turn inhibits glycolysis by a negative feedback located on the glyceraldehyde phosphate dehydrogenase (GAPDH), the flux of carbon being then oriented towards glucosamine pathway, responsible for the transcriptional consequence of high extracellular glucose. Hence, according to these data, high glucose is associated with an enhanced ROS production, this effect being responsible for the harmful consequences of hyperglycemia [22, 23]. This proposal represents a major advance in our understanding of the deleterious effects of hyperglycemia. This fact is well established, meaningful and may lead to fruitful therapeutic prospects.

It is noteworthy, however, how nothing is simple in metabolism, and how the truth is often shaded by complexity. Indeed, in the work presented by Perner et al. [17] high glucose impairs superoxide production! These results are actually found in isolated blood neutrophils, while the data presented by Du et al. have been obtained

in endothelial cells [22]. Nevertheless, it seems that high glucose is able to induce either an increase and a decrease in ROS production, the deleterious effect being possibly related to both effects!

The metabolism of ROS involves a mitochondrial production of superoxide (O_2^-) at the level of complexes 1 and 3 of the respiratory chain, associated with powerful matricial antioxidant mechanisms. In addition to such ROS metabolism located in mitochondria, however, cytoplasm is also a very important compartment regarding ROS metabolism, glucose being potentially involved in both pathways. As noted above, stimulation of glycolysis is responsible for a mitochondrial production of ROS (see Fig. 1), and in addition glucose is also involved in a pathway of major importance regarding cytosolic redox homeostasis: the pentose phosphate pathway (PPP), a pathway shunting the first part of glycolysis. The main function of this pathway is to produce the reducing equivalent NADPH, an indispensable cofactor for the production of ROS by neutrophils at the level of the plasma membrane linked NADPH oxidase (see Fig. 1). Hence activation of PPP by glucose is expected to increase the production of ROS in neutrophils, reinforcing thus the main function for the killing of bacteria. Recently, however, it has been shown that high glucose is a powerful inhibitor of the first step of PPP, the glucose-6-phosphate dehydrogenase (G6PDH) [24]. Therefore, as shown in the work of Perner et al., high glucose actually results in a decrease in ROS production from neutrophils, thus impairing its bactericide function [17]. This finding is in very good agreement with data reporting an impaired antimicrobial function related to a G6PDH deficiency in humans [25, 26, 27].

Again, nothing is simple. Indeed, although NAPDH is a main factor for the production of ROS by the NADPH oxidase, it is also the mandatory cofactor for the glutathione reductase, the key enzyme in the cytosolic pathway of ROS scavenging [28, 29]. Hence by providing NADPH (see Fig. 1), glucose metabolism by PPP is necessary for the cytosolic struggle against ROS, while in the presence of excessive glucose concentration, the impairment of the first step of PPP is responsible for a decrease in NADPH availability, leading to a decreased antioxidant defense. In addition, it must be noted that two other pathways are of importance regarding the cytosolic generation of NADPH, namely pyruvate via malic enzyme flux [30] and isocitrate via cytosolic NADPH-dependent isocitrate dehydrogenase [31], two key steps in the regulation of redox homeostasis.

From these considerations it appears that glucose obviously plays a very subtle role in oxidant cellular signaling. It can either increase or decrease ROS production and can either increase or decrease the antioxidant defense according to (a) the level of extracellular glucose concentration, (b) the cell type, and most probably (c) the endocrine and paracrine environment. Therefore it is not surprising that any change in blood glucose must be considered as a complex event and taking care of glycemia and redox homeostasis will be probably central in the management of ICU patients in the next years.

Acknowledgements Dr. Christiane Keriel is gratefully acknowledged for the critical review of the manuscript.

References

1. Ross H, Johnston IDA, Wellborn TA, Wright AD (1966) Effect of abdominal operation on glucose tolerance and serum levels of insulin, growth hormone and hydrocortison. Lancet II:563–566
2. Beisel WR (1975) Metabolic response to Infection. Annu Rev Med 26:9–23
3. Goldstein SA, Elwyn DH (1989) The effects of injury and sepsis on fuel utilization. Annu Rev Nutr 9:445–473
4. Fernandez-Real JM, Ricart W (1999) Insulin resistance and inflammation in an evolutionary perspective: the contribution of cytokine genotype/phenotype to thriftiness. Diabetologia 42:1367–1374
5. Ruderman NB, Saha AK, Vavvas D, Witters LA (1999) Malonyl-CoA, fuel sensing, and insulin resistance. Am J Physiol 276:E1–E18
6. Alberti KGMM, Batstone GF, Foster KJ, Johnston DG (1980) Relative role of various hormones in mediating the metabolic response to injury. J Parenter Enteral Nutr 4:141–145
7. Cuthbertson D (1932) Observations on the disturbances of metabolism by injury to the limbs. Q J Med 1:233–246
8. Allison SP, Hinton P, Chamberlain MJ (1968) Intravenous glucose-tolerance, insulin, and free-fatty-acid levels in burned patients. Lancet II:1113–1116
9. Hinton P, Allison SP, Littlejohn S, Lloyd J (1971) Insulin and glucose to reduce catabolic response to injury in burned patients. Lancet 1:767–769
10. Wolfe RR (1997) Substrate utilization/ insulin resistance in sepsis/trauma. Baillieres Clin Endocrinol Metab 11:645–657
11. Kelley DE, Mandarino LJ (2000) Fuel selection in human skeletal muscle in insulin resistance: a reexamination. Diabetes 49:677–683
12. Kones RJ (1975) Glucose, insulin, and potassium therapy for heart disease. History of GIK therapy. N Y State J Med 75:1463–1492
13. Sievers J, Lindh J, Johansson BW, Karnell J (1966) Acute myocardial infarction treated by glucose-insulin-potassium (GIK) infusion. Cardiology 49:239–247
14. Fath-Ordoubadi F, Beatt KJ (1997) Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials. Circulation 96:1152–1156
15. Zhu P, Lu L, Xu Y, Greyson C, Schwartz GG (2000) Glucose-insulin-potassium preserves systolic and diastolic function in ischemia and reperfusion in pigs. Am J Physiol Heart Circ Physiol 278:H595–H603

16. Berghe G van den, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R (2001) Intensive insulin therapy in the critically ill patients. N Engl J Med 345:1359–1367
17. Perner A, Nielsen SE, Rask-Madsen J (2002) High glucose impairs superoxide production from isolated blood neutrophils. Intensive Care Med (http://dx.doi.org/10.1007/s00134-002-1628-4)
18. Wilmore DW, Aulick LH, Mason AD, Pruitt BA (1977) Influence of the burn wound on local and systemic response to injury. Ann Surg 186:444–458
19. Jolliet P, Leverve X, Pichard C (2001) Acute hepatic steatosis complicating massive insulin overdose and excessive glucose administration. Intensive Care Med 27:313–316
20. Brownlee M (2001) Biochemistry and molecular cell biology of diabetic complications. Nature 414:813–820
21. Nishikawa T, Edelstein D, Brownlee M (2000) The missing link: a single unifying mechanism for diabetic complications. Kidney Int Suppl 77:S26–S30
22. Du XL, Edelstein D, Rossetti L, Fantus IG, Goldberg H, Ziyadeh F, Wu J, Brownlee M (2000) Hyperglycemia-induced mitochondrial superoxide overproduction activates the hexosamine pathway and induces plasminogen activator inhibitor-1 expression by increasing Sp1 glycosylation. Proc Natl Acad Sci USA 97:12222–12226
23. Asahina T, Kashiwagi A, Nishio Y, Ikebuchi M, Harada N, Tanaka Y, Takagi Y, Saeki Y, Kikkawa R, Shigeta Y (1995) Impaired activation of glucose oxidation and NADPH supply in human endothelial cells exposed to H2O2 in high-glucose medium. Diabetes 44:520–526
24. Zhang Z, Apse K, Pang J, Stanton RC (2000) High glucose inhibits glucose-6-phosphate dehydrogenase via cAMP in aortic endothelial cells. J Biol Chem 275:40042–40047
25. Tsai KJ, Hung IJ, Chow CK, Stern A, Chao SS, Chiu DT (1998) Impaired production of nitric oxide, superoxide, and hydrogen peroxide in glucose 6-phosphate-dehydrogenase-deficient granulocytes. FEBS Lett 436:411–414
26. Spolarics Z, Siddiqi M, Siegel JH, Garcia ZC, Stein DS, Ong H, Livingston DH, Denny T, Deitch EA (2001) Increased incidence of sepsis and altered monocyte functions in severely injured type A-glucose-6-phosphate dehydrogenase-deficient African American trauma patients. Crit Care Med 29:728–736
27. Leopold JA, Cap A, Scribner AW, Stanton RC, Loscalzo J (2001) Glucose-6-phosphate dehydrogenase deficiency promotes endothelial oxidant stress and decreases endothelial nitric oxide bioavailability. FASEB J 15:1771–1773
28. Hashida K, Sakakura Y, Makino N (2002) Kinetic studies on the hydrogen peroxide elimination by cultured PC12 cells: rate limitation by glucose-6-phosphate dehydrogenase. Biochim Biophys Acta 1572:85–90
29. Kashiwagi A, Asahina T, Nishio Y, Ikebuchi M, Tanaka Y, Kikkawa R, Shigeta Y (1996) Glycation, oxidative stress, and scavenger activity: glucose metabolism and radical scavenger dysfunction in endothelial cells. Diabetes 45 [Suppl 3]:S84–S86
30. Kashiwagi A, Nishio Y, Asahina T, Ikebuchi M, Harada N, Tanaka Y, Takahara N, Taki H, Obata T, Hidaka H, Saeki Y, Kikkawa R (1997) Pyruvate improves deleterious effects of high glucose on activation of pentose phosphate pathway and glutathione redox cycle in endothelial cells. Diabetes 46:2088–2095
31. Lee SM, Koh HJ, Park DC, Song BJ, Huh TL, Park JW (2002) Cytosolic NADP (+)-dependent isocitrate dehydrogenase status modulates oxidative damage to cells. Free Radic Biol Med 32:1185–1196