Veech and Valeri. Trauma Cases Rev 2016, 2:025
Volume 2 | Issue 1
ISSN: 2469-5777

Trauma Cases and Reviews

Review Article: Open Access

Using D-β-Hydroxybutyrate Containing Solutions to Treat Hyperglycemia Induced by Shock or Injury Instead of Insulin may Circumvent Insulin Resistance and Provide Cells with the Energy Required to Maintain Vital Processes through Preserving Normal Mitochondrial Function without Causing Hypoglycemia

Veech RL[1] and Valeri CR[2]*

[1]*Laboratory of Metabolic Control, NIAAA, NIH, USA*

[2]*Naval Blood Research Laboratory, USA*

***Corresponding author:** *C. Robert Valeri, MD, NBRL, Inc., 372 Ocean Avenue, Marblehead, MA 01945, USA, Email: navblood@yahoo.com*

Abstract

Severe injury, infection and hemorrhage all cause insulin resistance and hyperglycemia. Insulin resistance blocks glucose entry into cells and the conversion of pyruvate to acetyl CoA impairing cellular energy production. During insulin resistance, glucose cannot enter muscle and fat cells nor can the cell metabolize the lactate given in lactated Ringer's solution with the occurrence of hyperglycemia. More importantly in all cells the mitochondrial pyruvate dehydrogenase (PDH) activity is decreased during insulin resistance leaving the cell deficient in substrates needed to power the Krebs cycle and make ATP. The normal ketone body metabolite D-β-hydroxybutyrate enters the cells via the monocarboxylate transporter mimicking the action of insulin and bypassing the enzymatic block at PDH. Even more importantly, the metabolism of ketone bodies increases the efficiency of mitochondrial energy production.

Insulin resistance prevents the injured cell from metabolizing the lactate produced by glycolysis as well as the lactate administered in Ringer's lactate fluids. This metabolic defect of insulin resistance in the cells of injured patients can be overcome by the administration of Na-D-β-hydroxybutyrate containing solutions which bypass the metabolic block at PDH.

Keywords

Hyperglycemia of trauma, Acute insulin resistance, Inhibition of pyruvate dehydrogenase, D-ß hydroxybutyrate, Reactive oxygen species (ROS), Histone deacetylase

Introduction

Since the time of Claude Bernard, it has been recognized that hyperglycemia accompanies trauma, hemorrhage and severe illness. Hyperglycemia can result from increases in catecholamines, steroid hormones, and glucagon. Recent work now shows that the central actor in the hyperglycemia of trauma results from acute insulin resistance and the inhibition of pyruvate dehydrogenase, PDH, leading to an inability to metabolize the products of glycolysis and a cellular deficiency of redox and phosphorylation energy. The inability to metabolize the glycolytic products leads to a deficiency of substrate for the Krebs TCA cycle with a consequent decrease in the energy of ATP to support vital processes of cells. The substitution of D-β-hydroxybutyrate for the glycolytic product lactate in resuscitation fluids would overcome a number of deficiencies in current fluid therapy and reduce both morbidity and mortality.

Insulin Resistance of Severe Injury

Injury, infection and shock lead to elevation of blood sugar in wounded individuals was observed in Vietnam [1]. Hyperglycemia increased mortality 10 fold in wounded patients with blood sugar > 200 mg/dL and 7 fold in the group with blood sugar greater the 135 mg/dL [2]. Acute insulin resistance follows traumatic injury, infections and burns [3]. It was further shown that in adipose tissue associated with trauma and hemorrhages a rapid loss of the phosphorylation of the insulin receptor and phosphorylation of glycogen synthase, the enzyme responsible for glycogen synthesis [4]. Insulin resistance decreases the transport of glucose [4], into muscle and fat cells, while increasing the glucose output from liver [5]. The major effect of insulin resistance is the inhibition of the pyruvate dehydrogenase, PDH [6-8] which decreases acetyl CoA production, decreases citric acid production, and decreases mitochondrial NADH production required to produce ATP [9]. The result of insulin resistance is to decrease both the redox energy and phosphorylation energy rendering the tissues energy deficient [9].

Overcoming Insulin Resistance

The occurrence of hyperglycemia following brain trauma and hemorrhage led to suggestions that glycemic control using insulin

ClinMed International Library

Citation: Veech RL, Valeri CR (2016) Using D-β-Hydroxybutyrate Containing Solutions to Treat Hyperglycemia Induced by Shock or Injury Instead of Insulin may Circumvent Insulin Resistance and Provide Cells with the Energy Required to Maintain Vital Processes through Preserving Normal Mitochondrial Function without Causing Hypoglycemia. Trauma Cases Rev 2:025

Received: December 21, 2015: **Accepted:** January 11, 2016: **Published:** January 13, 2016

would be of therapeutic benefit [10]. However meta-analysis of studies of glycemic control after trauma showed no decrease in mortality but a significant increase in hypoglycemia after insulin treatment in trauma induced hyperglycemia [11]. It has been shown in a large study of over 3000 subjects that administration of insulin to lower blood glucose to normoglycemic levels resulted in increased mortality [12] the majority of these untoward effects with insulin administration resulted from hypoglycemia.

Ketosis Overcomes Insulin Resistance

The metabolism of ketone bodies mimics the effects of insulin administration and overcomes the inhibition of PDH [9]. The administration of insulin to treat the inhibition of PDH increased the heart content of acetyl CoA by 12 fold whereas the administration of ketone bodies increase heart acetyl CoA by 15 fold [9]. The administration of either insulin or ketone bodies provide acetyl CoA for the Krebs TCA cycle and leads to an increased production of mitochondrial NADH, the substrate for the electron transport system. Co-incident with the reduction of the free mitochondrial [NAD^+]/[NADH] ratio, ketones or insulin oxidized the mitochondrial CoQ/$CoQH_2$ increasing the redox span between site I and site II of the electron transport system and hence the energy of ATP hydrolysis [9].

Elevation of blood ketones in the mouse caused a 6 fold decrease in blood insulin, a 2 fold increase in estimated insulin sensitivity and a decrease in blood glucose [13]. In addition to overcoming insulin resistance, ketosis eliminates the physiological consequences of hypoglycemia, cerebral dysfunction and seizures. In studies of Harvard students by Cahill and his associates during prolonged fasting where blood ketones reached about 7mM, administration of insulin lowered blood glucose to below 1 mM with no seizures and no impairment of cognitive function [14]. This study demonstrated that elevation of blood ketones can replace glucose as a supplier of brain energetic needs even when blood glucose drops below 2 mM, the levels usually associated with seizures in the absence of ketosis.

As discussed earlier, insulin acts by increasing the activity of PDH, thus providing acetyl CoA, the initial substrate of the Krebs cycle. During insulin resistance, PDH is inhibited and the Krebs cycle is deficient in acetyl CoA [9]. Ketone bodies are transported across both cell and mitochondrial membranes by the monocarboxylate transporter, where they are activated by the succinyl CoA transferase and then degraded by thiolase to mitochondrial acetyl CoA, thus supplying the Krebs cycle with energy producing substrate.

The Metabolism of Ketone Bodies Reduces the NADP System the Terminal Destroyer of Reactive Oxygen Species (ROS) while the Ketone Body D-β-Hydroxybutyrate is the Natural Endogenous Inhibitor of Histone Deacetylase

The metabolism of ketone bodies, which reduces mitochondrial NAD^+, lowers the free cytoplasmic [$NADP^+$]/NADPH] ratio [15]. The cytosolic NADP system is the most negative reducing potential in the body of -0.42 V [16]. In near equilibrium with this NADP system is the redox potential of glutathione, which at 4 mM, is the final and most prevalent inactivator of reactive O_2 species. In the same pathway, over expression of the antioxidant enzyme, superoxide dismutase protected animals from acute insulin resistance following trauma [17]. In addition to reducing the NADP system, D-β-hydroxybutyrate is the endogenous specific inhibitor of histone deacetylase class I, III and IV leading to increases of the transcription factors FOXO3A and MT2 increasing the transcription of enzymes of the antioxidant pathway superoxide dismutase (SOD), and catalase which reduce the effects of oxidative stress [18]. Hyperglycemic and hypoxic stress induced cell damage is brought about in large part, through the production of ROS [19]. It had previously been shown that anoxia induced neuronal apoptosis could be ameliorated by administration of the histone deacetylase inhibitor valproic acid [20]. Consistent with the thesis that D-β-hydroxybutyrate mimics the metabolic effects of insulin, D-β-hydroxybutyrate directly inhibits histone deacetylase increasing the activity of the transcription factor FOXO3A [18]. It was earlier shown [21] that insulin itself acts on FOXO3A directly to decrease the transcription of glucose-6-phosphatase and also alters the activity of free radical detoxifying enzymes through alteration of histone deacetylase [18].

Composition of Resuscitation Fluids in Light of Insulin Resistance Induced by Trauma

Little attention has been directed toward the composition of resuscitation fluids. However, there is increasing awareness of the toxic potential of not only the composition of parenteral fluids but their administration based solely on volumetric and caloric needs without consideration of the metabolic and physical chemical properties of the cell [22]. Hartmann developed Ringers lactate in 1934 to prevent the death from hyperchloremic acidosis during the treatment of infantile diarrhea with normal saline [23]. In 1934, racemic lactate was the only metabolizable anion available for use in parenteral fluids. It is now recognized that free radical damage induced by the infusion of racemic D, L lactate containing Ringer's lactate fluids was responsible for the respiratory distress syndrome and pulmonary apoptosis seen during the treatment of wounded soldiers in the Vietnam war [24]. In the same study it was observed that fluids containing D-β-hydroxybutyrate, instead of D, L lactate, avoided this type of toxicity. Without performing clinical studies, but only changing the definition of lactate in the US Pharmacopeia, fluid containing only the physiological form of L- lactate has become available. However, it must be recognized in the light of the evidence of insulin resistance being present in patients with injury of any sort, administration of L-lactate cannot improve the cellular energy and the metabolic blockade of PDH present in hemorrhage and traumatic injury. Administration of fluids containing D-β-hydroxybutyrate can bypass the inhibition of PDH, diminish free radical damage [24] and provide the cell with both redox and phosphorylation energy.

Trauma patients experiencing hemorrhage can develop a syndrome of coagulopathy, hypothermia and acidosis [25,26]. This often fatal syndrome can be treated by restricting the volume of resuscitation fluid given. Addition of D-β-hydroxybutyrate to the resuscitation fluid instead of L-lactate would combat the hypothermia by increasing the mitochondrial O_2 consumption by providing metabolic substrate which can enter the Krebs cycle without the action of PDH, thus increasing heat production. The acidosis can be combated by the production of HCO_3^- resulting from the metabolism of D-β-hydroxybutyrate. Elevation of blood ketone bodies to 7 mM during prolonged starvation, does not alter blood pH, but only lowers blood pCO_2 [27]. Addition of D-β-hydroxybutyrate to parenteral fluids is therefore unlikely to produce significant acidosis, but will diminish the excessive lactate burden often associated with shock and severe illness or injury.

Recently, reviews by Myburgh and Mythen of large scale clinical trials of the outcomes of parenteral fluids, including those containing osmotically active substances has given no reassurance of the effectiveness of current fluid practices [28]. This call for a re-examination of parenteral fluid therapy aimed at preventing iatrogenic injury [22,28] is long overdue and should clearly include tests of fluids containing D-β-hydroxybutyrate.

Disclosures

Richard Veech wrote patents for ketones which are owned by NIH. C. Robert Valeri has no conflicts to report.

References

1. Carey LC, Lowery BD, Cloutier CT (1970) Blood sugar and insulin response of humans in shock. Ann Surg 172: 342-350.
2. Yendamuri S, Fulda GJ, Tinkoff GH (2003) Admission hyperglycemia as a prognostic indicator in trauma. J Trauma 55: 33-38.

3. Li L, Messina JL (2009) Acute insulin resistance following injury. Trends Endocrinol Metab 20: 429-435.

4. Wardzala LJ, Jeanrenaud B (1981) Potential mechanism of insulin action on glucose transport in the isolated rat diaphragm. Apparent translocation of intracellular transport units to the plasma membrane. J Biol Chem 256: 7090-7093.

5. Cherrington AD (2005) The role of hepatic insulin receptors in the regulation of glucose production. J Clin Invest 115: 1136-1139.

6. Mukherjee C, Jungas RL (1975) Activation of pyruvate dehydrogenase in adipose tissue by insulin. Evidence for an effect of insulin on pyruvate dehydrogenase phosphate phosphatase. Biochem J 148:229-235.

7. Taylor SI, Mukherjee C, Jungas RL (1975) Regulation of pyruvate dehydrogenase in isolated rat liver mitochondria. Effects of octanoate, oxidation-reduction state, and adenosine triphosphate to adenosine diphosphate ratio. J Biol Chem 250: 2028-2035.

8. Denton RM, Randle PJ, Bridges BJ, Cooper RH, Kerbey AL, et al. (1975) Regulation of mammalian pyruvate dehydrogenase. Mol Cell Biochem 9: 27-53.

9. Sato K, Kashiwaya Y, Keon CA, Tsuchiya N, King MT, et al. (1995) Insulin, ketone bodies, and mitochondrial energy transduction. FASEB J 9: 651-658.

10. Eakins J (2009) Blood glucose control in the trauma patient. J Diabetes Sci Technol 3: 1373-1376.

11. Wiener RS, Wiener DC, Larson RJ (2008) Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA 300: 933-944.

12. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, et al. (2009) Intensive versus conventional glucose control in critically ill patients. N Engl J Med 360: 1283-1297.

13. Srivastava S, Kashiwaya Y, King MT, Baxa U, Tam J, et al. (2012) Mitochondrial biogenesis and increased uncoupling protein 1 in brown adipose tissue of mice fed a ketone ester diet. FASEB J 26: 2351-2362.

14. Cahill GF, Jr., Aoki TT (1980) Alternate Fuel Utilization in Brain. In: Passonneau JV, Hawkins RA, Lust WD, Welsh FA, Cerebral metabolism and neural function. Williams & Wilkins, Baltimore.234-242.

15. Kashiwaya Y, King MT, Veech RL (1997) Substrate signaling by insulin: a ketone bodies ratio mimics insulin action in heart. Am J Cardiol 80: 50A-64A.

16. Krebs HA, Veech RL (1969) Pyridine nucleotide interrelations. In: Papa S, Tager JM, Quagliariello E, Slater EC, The Energy Level and Metabolic Control in Mitochondria. Bari, Adriatica Editrice.

17. Zhai L, Ballinger SW, Messina JL (2011) Role of reactive oxygen species in injury-induced insulin resistance. Mol Endocrinol 25: 492-502.

18. Shimazu T, Hirschey MD, Newman J, He W, Shirakawa K, et al. (2013) Suppression of oxidative stress by β-hydroxybutyrate, an endogenous histone deacetylase inhibitor. Science 339: 211-214.

19. Kitamura T (2013) The role of FOXO1 in β-cell failure and type 2 diabetes mellitus. Nat Rev Endocrinol 9: 615-623.

20. Li Y, Yuan Z, Liu B, Sailhamer EA, Shults C, et al. (2008) Prevention of hypoxia-induced neuronal apoptosis through histone deacetylase inhibition. J Trauma 64: 863-870.

21. Onuma H, Vander Kooi BT, Boustead JN, Oeser JK, O'Brien RM (2006) Correlation between FOXO1a (FKHR) and FOXO3a (FKHRL1) binding and the inhibition of basal glucose-6-phosphatase catalytic subunit gene transcription by insulin. Mol Endocrinol 20: 2831-2847.

22. Veech RL (1986) The toxic impact of parenteral solutions on the metabolism of cells: a hypothesis for physiological parenteral therapy. Am J Clin Nutr 44: 519-551.

23. Hartmann AF (1934) Theory and practice of parenteral fluid administration. JAMA 103: 1349-1354.

24. Alam HB, Austin B, Koustova E, Rhee P (2001) Resuscitation-induced pulmonary apoptosis and intracellular adhesion molecule-1 expression in rats are attenuated by the use of Ketone Ringer's solution. J Am Coll Surg 193: 255-263.

25. Eddy VA, Morris JA Jr, Cullinane DC (2000) Hypothermia, coagulopathy, and acidosis. Surg Clin North Am 80: 845-854.

26. Mikhail J (1999) The trauma triad of death: hypothermia, acidosis, and coagulopathy. AACN Clin Issues 10: 85-94.

27. Cahill GF Jr, Herrera MG, Morgan AP, Soeldner JS, Steinke J, et al. (1966) Hormone-fuel interrelationships during fasting. J Clin Invest 45: 1751-1769.

28. Myburgh JA, Mythen MG (2013) Resuscitation fluids. N Engl J Med 369: 1243-1251.