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The Impact of Insulin Resistance and Signalling in Systemic and Local Acidosis

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Abstract

The majority of pathological ailments, such as diabetes mellitus, cancer, and inflammation, are associated with glucose metabolic abnormalities and can result in local or systemic acidosis by overriding the body's natural buffering capacity. This uncomplicated finding implies that acidity and insulin metabolism or insulin receptor signalling are closely related. In this review, we compiled the most recent research on the effects of extracellular and intracellular pH fluctuations on insulin resistance, as well as the role that insulin plays in causing acidosis. Insulin stimulates glycolysis, which has an impact on acidity. The reduction of pH in turn lowers insulin sensitivity or action, albeit the exact process is unknown. Apart from the common association of ketoacidosis with diabetes, there are additional significant and intricate variables

Keywords:
insulin receptor, ion/proton transporters, glucose metabolism, acidosis, and acid-sensing ion channels

Introduction

Strong regulation is in place to maintain acid-base balance and pH, which are crucial for proper physiology and cell function. Since changes in the extracellular space have an immediate effect on the intracellular cytosolic pH and since the cell machinery is very sensitive to changes in intracellular H+ concentration, precise pH maintenance is required both at the extracellular level and in the cytosol. Extracellular pH frequently remains within restricted ranges and around neutral values to maintain the acid-base balance. The pH of arterial blood, which is kept between 7.36 and 7.44, and the pH of venous blood, which is approximately 7.6, are the two most significant examples. Several intracellular and extracellular buffers are accessible at various body areas as an immediate response against pH changes.

In this situation, the pH value varies substantially based on the kind of tissue, the metabolic activity of every cell, and the gap between the specific cell and the nearest capillary vessel. Technical issues have prevented this area from being more thoroughly researched. However, using imaging instruments and biochemical assays, next-generation addresses enable the real-time monitoring of intracellular pH, proton pumping, and live-cell metabolism, possibly leading to greater comprehension of the phenomenon in the future.

There are various clinical circumstances that can lead to the body fluids' buffering actions being overcome. There are numerous possible reasons for both localised and systemic acidosis. Growth factors or cytokines that increase cell metabolism, vascular illness, ischaemia, infection, tumours or inflammation may all contribute to local acidification [1, 2, 3, 4]. A lack of oxygen and low pH are features common to fracture haematoma in the early stages of healing [5]. likewise as shown by Marunaka et al., interstitial fluids surrounding a variety of tissues, including the brain, have a substantially lower pH even in pre-disease phases [6]. On a systemic level, anaemias, acquired immunodeficiency syndrome, anaerobic exercise, gastroenteritis, excessive protein or other acidifying substance ingestion, and respiratory and kidney problems are sources of excessive H+ accumulation.
The greatest physiological anabolic agent known to biology is insulin, which restricts the breakdown and release of fats, proteins, and carbs into circulation while promoting their synthesis and storage [7]. Additionally to being very active in the liver and muscle cells, insulin is frequently linked to the uptake of fatty acids, particularly in adipose cells [8]. Nonetheless, practically every mammalian cell has insulin receptors (IR), which allows it to react to insulin. Macrophages, endothelial cells, and insulin-producing cells in the pancreas are other noteworthy insulin target cells having a metabolic role [9].
We reviewed how insulin activity affects pH control in this paper, and how pH variations affect signals from insulin and glucose metabolism at both the extracellular and intracellular levels.
Increased Glycolysis and Local Acidosis Mediated by Insulin
Insulin's capability to stimulate glycolysis in response to a rise in blood glucose levels is one of its main roles. Glycolysis then leads to the formation of lactic acid. This is a cause-and-effect connection between acidosis and hyperlactatemia, a recurrent clinical characteristic of diabetes patients [10]. It is unclear, therefore, how diabetes's high blood lactate concentration and acidity are related. In a clinical setting, lactic acidosis can arise from either defective lactate metabolism or excessive tissue-level lactate generation. surprisingly, a mixed acid-base disturbance accompanied by simultaneous respiratory or metabolic alkalosis can also cause hyperlactatemia in situations where serum pH is normal or when there is alkalosis.
For more details on the excessive manufacture of lactate, it's crucial to remember that it's frequently believed that acidosis connected to lactic acid production results from lactic acid dissociation and H+ generation [11]. This idea was rejected by Robergs in 2004 when he established that the reaction catalysed by lactic dehydrogenase (LDH) creates lactate rather than lactic acid and that lactate creation actually uses H+ [12]. More recently, Corbet et al. proposed that lactate and H+ ions are distinct entities based on the same idea [13]. Specifically, in deep hypoxia, only small fractions of each combine to create lactic acid, and lactate and

H+ are formed independently, with the pKa (~3.9) for carboxyl hydrogen dissociation remaining

Furthermore, as some glucose molecules are diverted into other metabolic pathways, the entire transformation of glucose into two lactate molecules and two H+ ions in hypoxic cancer cells is only theoretical when most of glucose-derived pyruvate turns into lactate [13]. However, since lactate is carried across the cell membrane by monocarboxylic acid transporters (MCT), mainly by the MCT4, through a symport of H+ across the cell membrane, the lactate gradient across the membrane impacts H+ efflux [14]. Lastly, once lactate enters the extracellular space, a number of interacting variables affect the lactate-based acid-base balance. These variables include the conservation of mass and electrical charge balance, as well as the equilibria within the formation of carbonate and bicarbonate (Figure 1).

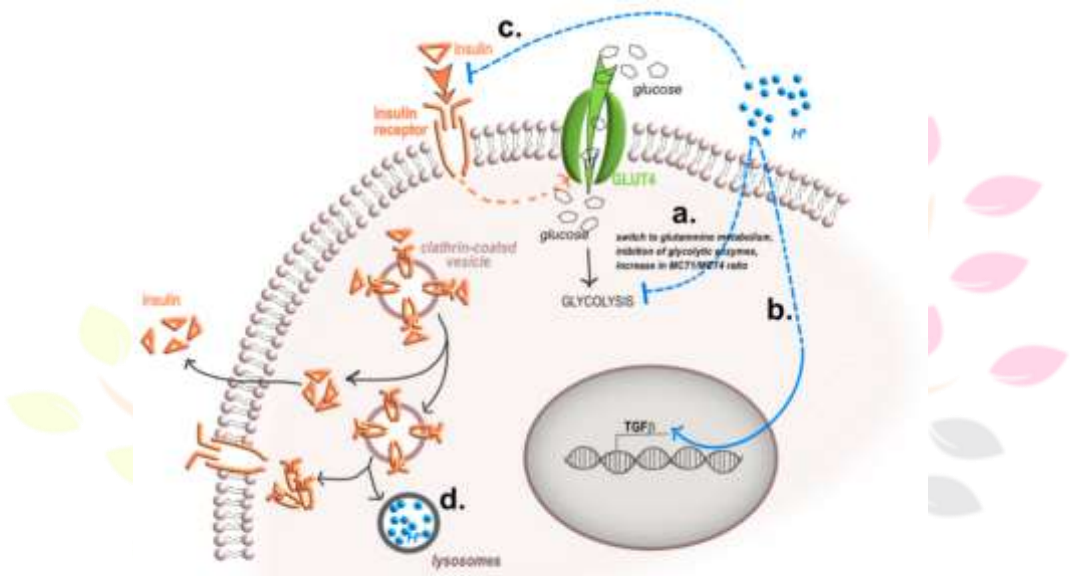

Figure 1. Extracellular acidification occurs due to insulin stimulation. Insulin stimulated glycolysis and the uptake of glucose by the glucose transporters (GLUT). Proton and lactate concentrations rise over time as a result of glycolysis's accumulation of lactate. Then, protons are transported across the cell membrane by a variety of transporters, especially monocarboxylate transporters (MCT), which also move lactate to the extracellular space (the orange arrow shows the route of insulin; the green arrow shows the route of lactate, protons, and products of glycolysis; the blue arrow shows the route of protons).

Conclusions

Acidosis impacts insulin resistance and sensitivity in a variety of complicated methods. Notably, as acute and chronic acidosis effects can have completely distinct effects, time of acidosis exposure is an important consideration in this situation. Several strategies, including the administration of bicarbonate, have been suggested in mice models to treat acid-related diseases [4,88]. subsequently applied to clinical settings, the findings of these studies may have unexpected and negative effects for human health.

Limiting dietary acid load can be a feasible choice and a relevant path to long-term enhancement of glucose equilibrium and prevention for disorders linked to insulin

resistance, such as type 2 diabetes. The existing findings are, however, severely flawed by constraints pertaining to patient acid load evaluation, dietary factors, and metabolic situation; additionally, the results are doubtful due to the paucity of reliable data regarding the underlying pathophysiology. Moreover, there is a dearth of evidence from interventional studies, and the trials that have been conducted thus far have not shown any beneficial effects from alkali supplementation [89]. However, the relationship between pH regulation and insulin metabolism is a fascinating field of research for the development of new treatment strategies. In addition, in therapeutic practice, data that has been gathered

1.Mogi, C.; Nakakura, T.; Okajima, F. Role of extracellular proton-sensing OGR1 in regulation of insulin secretion and pancreatic beta-cell functions. *Endocr. J.* **2014**, *61*, 101–110. [**Google Scholar**] [**CrossRef**]
2.Punnia-Moorthy, A. Evaluation of pH changes in inflammation of the subcutaneous air pouch lining in the rat, induced by carrageenan, dextran and Staphylococcus aureus. *J. Oral. Pathol.* **1987**, *16*, 36–44. [**Google Scholar**] [**CrossRef**]
3.Di Pompo, G.; Lemma, S.; Canti, L.; Rucci, N.; Ponzetti, M.; Errani, C.; Donati, D.M.; Russell, S.; Gillies, R.; Chano, T.; et al. Intratumoral acidosis fosters cancer-induced bone pain through the activation of the mesenchymal tumor-associated stroma in bone metastasis from breast carcinoma. *Oncotarget* **2017**, *8*, 54478–54496. [**Google Scholar**] [**CrossRef**] [**PubMed**]
4.Arnett, T. Regulation of bone cell function by acid-base balance. *Proc. Nutr. Soc.* **2003**, *62*, 511–520. [**Google Scholar**] [**CrossRef**] [**PubMed**]
5.Ratel, S.; Duche, P.; Hennegrave, A.; Van Praagh, E.; Bedu, M. Acid-base balance during repeated cycling sprints in boys and men. *J. Appl. Physiol. (1985)* **2002**, *92*, 479–485. [**Google Scholar**] [**CrossRef**] [**PubMed**] [**Green Version**]
6.Frassetto, L.A.; Morris, R.C., Jr.; Sebastian, A. Effect of age on blood acid-base composition in adult humans: Role of age-related renal functional decline. *Am. J. Physiol.* **1996**, *271*, F1114–F1122. [**Google Scholar**] [**CrossRef**] [**PubMed**]
7.Kolosenko, I.; Avnet, S.; Baldini, N.; Viklund, J.; De Milito, A. Therapeutic implications of tumor interstitial acidification. *Semin. Cancer Biol.* **2017**, *43*, 119–133. [**Google Scholar**] [**CrossRef**] [**PubMed**]
8.Massa, A.; Perut, F.; Chano, T.; Woloszyk, A.; Mitsiadis, T.A.; Avnet, S.; Baldini, N. The effect of extracellular acidosis on the behaviour of mesenchymal stem cells in vitro. *Eur. Cell. Mater.* **2017**, *33*, 252–267. [**Google Scholar**] [**CrossRef**] [**PubMed**]
9.Marunaka, Y.; Yoshimoto, K.; Aoi, W.; Hosogi, S.; Ikegaya, H. Low pH of interstitial fluid around hippocampus of the brain in diabetic OLETF rats. *Mol. Cell. Ther.* **2014**, *2*, 6. [**Google Scholar**] [**CrossRef**] [**PubMed**] [**Green Version**]
10.Chang, L.; Chiang, S.H.; Saltiel, A.R. Insulin signaling and the regulation of glucose transport. *Mol. Med.* **2004**, *10*, 65–71. [**Google Scholar**] [**PubMed**]
11.Goguen, J.M.; Halperin, M.L. Can insulin administration cause an acute metabolic acidosis in vivo? An experimental study in dogs. *Diabetologia* **1993**, *36*, 813–816. [**Google Scholar**] [**CrossRef**]
12.Haeusler, R.A.; McGraw, T.E.; Accili, D. Biochemical and cellular properties of insulin receptor signalling. *Nat. Rev. Mol. Cell Biol.* **2018**, *19*, 31–44. [**Google Scholar**] [**CrossRef**]

13.Adeva-Andany, M.; Lopez-Ojen, M.; Funcasta-Calderon, R.; Ameneiros-Rodriguez, E.; Donapetry-Garcia, C.; Vila-Altesor, M.; Rodriguez-Seijas, J. Comprehensive review on lactate metabolism in human health. *Mitochondrion* **2014**, *17*, 76–100. [**Google Scholar**] [**CrossRef**]
14.Seheult, J.; Fitzpatrick, G.; Boran, G. Lactic acidosis: An update. *Clin. Chem. Lab. Med.* **2017**, *55*, 322–333. [**Google Scholar**] [**CrossRef**]
15.Robergs, R.A.; Ghiasvand, F.; Parker, D. Biochemistry of exercise-induced metabolic acidosis. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2004**, *287*, R502–R516. [**Google Scholar**] [**CrossRef**] [**PubMed**] [**Green Version**]
16.Corbet, C.; Feron, O. Tumour acidosis: From the passenger to the driver's seat. *Nat. Rev. Cancer* **2017**, *17*, 577–593. [**Google Scholar**] [**CrossRef**]
17.Halestrap, A.P.; Price, N.T. The proton-linked monocarboxylate transporter (MCT) family: Structure, function and regulation. *Biochem. J.* **1999**, *343*, 281–299. [**Google Scholar**] [**CrossRef**] [**PubMed**]
18.Spugnini, E.P.; Sonveaux, P.; Stock, C.; Perez-Sayans, M.; De Milito, A.; Avnet, S.; Garcia, A.G.; Harguindey, S.; Fais, S. Proton channels and exchangers in cancer. *Biochim. Biophys. Acta* **2015**, *1848*, 2715–2726. [**Google Scholar**] [**CrossRef**] [**PubMed**]
19.Naylor, J.M.; Kronfeld, D.S.; Freeman, D.E.; Richardson, D. Hepatic and extrahepatic lactate metabolism in sheep: Effects of lactate loading and pH. *Am. J. Physiol.* **1984**, *247*, E747–E755. [**Google Scholar**] [**CrossRef**] [**PubMed**]
20.Warburg, O. On the origin of cancer cells. *Science* **1956**, *123*, 309–314. [**Google Scholar**] [**CrossRef**]
21.Goldenberg, J.M.; Cardenas-Rodriguez, J.; Pagel, M.D. Preliminary Results that Assess Metformin Treatment in a Preclinical Model of Pancreatic Cancer Using Simultaneous [(18)F]FDG PET and acidoCEST MRI. *Mol. Imaging Biol.* **2018**, *20*, 575–583. [**Google Scholar**] [**CrossRef**] [**PubMed**]
22.Longo, D.L.; Bartoli, A.; Consolino, L.; Bardini, P.; Arena, F.; Schwaiger, M.; Aime, S. In Vivo Imaging of Tumor Metabolism and Acidosis by Combining PET and MRI-CEST pH Imaging. *Cancer Res.* **2016**, *76*, 6463–6470. [**Google Scholar**] [**CrossRef**] [**PubMed**]
23.Yajima, M.; Ui, M. Carbohydrate metabolism and its response to catecholamines as modified in alkalotic rat. *Am. J. Physiol.* **1975**, *228*, 1046–1052. [**Google Scholar**] [**CrossRef**] [**PubMed**] [**Green Version**]
24.Uajima, M.; Ui, M. Hydrocortisone restoration of the pH-dependent metabolic responses to catecholamines. *Am. J. Physiol.* **1975**, *228*, 1053–1059. [**Google Scholar**] [**CrossRef**] [**PubMed**] [**Green Version**]
25.Igarashi, M.; Yamatani, K.; Fukase, N.; Daimon, M.; Ohnuma, H.; Ogawa, A.; Tominaga, M.; Sasaki, H. Effect of acidosis on insulin binding and glucose uptake in isolated rat adipocytes. *Tohoku J. Exp. Med.* **1993**, *169*, 205–213. [**Google Scholar**] [**CrossRef**]
26.Cuthbert, C.; Alberti, K.G. Acidemia and insulin resistance in the diabetic ketoacidotic rat. *Metabolism* **1978**, *27*, 1903–1916. [**Google Scholar**] [**CrossRef**]
27.Mak, R.H. Effect of metabolic acidosis on insulin action and secret27.ion in uremia. *Kidney Int.* **1998**, *54*, 603–607. [**Google Scholar**] [**CrossRef**]
28Reaich, D.; Graham, K.A.; Channon, S.M.; Hetherington, C.; Scrimgeour, C.M.; Wilkinson, R.; Goodship, T.H. Insulin-mediated changes in PD and glucose uptake after correction of acidosis in humans with CRF. *Am. J. Physiol.* **1995**, *268*, E121–E126. [**Google Scholar**] [**CrossRef**]

29.Sauter, N.S.; Schulthess, F.T.; Galasso, R.; Castellani, L.W.; Maedler, K. The antiinflammatory cytokine interleukin-1 receptor antagonist protects from high-fat diet-induced hyperglycemia. *Endocrinology* **2008**, *149*, 2208–2218. [**Google Scholar**] [**CrossRef**] [**PubMed**]
30.Feve, B.; Bastard, J.P. The role of interleukins in insulin resistance and type 2 diabetes mellitus. *Nat. Rev. Endocrinol.* **2009**, *5*, 305–311. [**Google Scholar**] [**CrossRef**]
31.Robey, I.F.; Baggett, B.K.; Kirkpatrick, N.D.; Roe, D.J.; Dosescu, J.; Sloane, B.F.; Hashim, A.I.; Morse, D.L.; Raghunand, N.; Gatenby, R.A.; et al. Bicarbonate increases tumor pH and inhibits spontaneous metastases. *Cancer Res.* **2009**, *69*, 2260–2268. [**Google Scholar**] [**CrossRef**]
32.ella Guardia, L.; Thomas, M.A.; Cena, H. Insulin Sensitivity and Glucose Homeostasis Can Be Influenced by Metabolic Acid Load. *Nutrients* **2018**, *10*, 618. [**Google Scholar**] [**CrossRef**]