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Lactic Acid, Magnesium, Metformin and Lactic Acidosis

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ABSTRACT

Lactic acidosis is a medical condition characterized by a build-up of excessive amounts of lactate and consequent metabolic acidosis. Lactate production is promoted by catecholamines as well as by the hindrances in pyruvate metabolism to ATP. One crucial factor in mitochondrial function is intracellular magnesium content, which is indirectly observed extracellularly, via its serum contents (less than 1 % of body Mg) or serum (Mg:Ca) ratio because convenient methods for direct Mg evaluations are expensive, missing or need reference values. Nuoranne has found that serum (Mg:Ca) ratio and the time (T, d) following the low-Mg diet explained blood pH by 62 %. (Sterile) fever associated with lactic acidosis is treated in chapter Temperature. Metformin toxicology has been assessed by some experiments separately or associated with other factors. Direct or indirect data associated with magnesium and production of lactate are treated with Delirium tremens and grass tetany.

Conclusions: Increase in lactic acid can be prohibited and treated with Mg by apparently healthy sportsmen and swines. The primary cause of lactic acid overproduction is not deficiency in oxygen supply but difficulties in oxidative phosphorylation and ATP production to keep normal cell function (and recovery), which are Mg [and (Mg:Ca)] dependent. Role of metformin is obviously to be a bystander, in situations, where its help is not sufficient. Even in those situations relative Met content can be associated with decreased mortality risk. Liberation from Mg deficiency needs methodological and statistical solutions.

Keywords: Lactic Acidosis; Magnesium; Metformin, Diabetes; TCA (Tricarboxylic Acid – Krebs) Cycle; ATP Production; Alcoholism; Grass Tetany; Delirium Tremens; Catecholamines; LDH, ROS

Abbreviations: ATP: Adenosine Triphosphate; Ca: Calcium; LDH: Lactate Dehydrogenase; Met: Metformin; Mg: Magnesium; Nadir pH: The Lowest pH; ROS: Reactive Oxygen Species

Introduction

About Lactic Acid Production and Metabolism

Lactic acidosis is a medical condition characterized by a build-up of lactate [La] (especially l-lactate) in the body, with formation of an excessively low pH in the bloodstream. It is a form of metabolic acidosis, in which excessive acid accumulates due to a problem with the body's oxidative metabolism [1]. Wikipedia gave 36 causal agents for lactic acidosis, including metformin, but without magnesium deficiency [1]. PubMed Search [2] ["lactic acid" metformin magnesium] gave only one result, which was not associated with body magnesium status.

It is generally known that the production of lactic acid (often named by its anion "lactate" [3]) increases when the demand for ATP and oxygen exceeds supply, as occurs during intense exercise and ischaemia [4]. Nowadays is known that lactate also serves as a major circulating carbohydrate fuel and enables the uncoupling of carbohydrate-driven mitochondrial energy generation from glycolysis [4]. Lactate and pyruvate together serve as a circulating redox buffer that equilibrates the NADH/NAD ratio across cells and tissues [4]. During fermentation, the NADH is used to reduce pyruvate to lactate, which is then excreted [4]. This process results in a net yield of two ATP and two lactate molecules per glucose, without consuming any oxygen [4]. In respiration, the NADH electrons and pyruvate generated by glycolysis are shuttled into the mitochondria, where they are consumed and subsequently produce copious usable energy (approximately 25 ATP molecules per glucose) [4].

Lactate turnover reflects lactate release primarily from muscle, gut, adipose, and erythrocytes and uptake by the liver and kidney, primarily for the purpose of energy production (Krebs (TCA) cycle) while the remainder is used for gluconeogenesis (Cori cycle) [5]. Healthy mitochondria function well, even at low O2 levels such that

dysoxia is rare and low O2 is likely to be a minor factor in the increasing concentrations of lactate [6]. Catecholamines promote glycogen breakdown to lactate [6]. In the (old) crossroad from pyruvate to a) lactate or b) ATP via TCA cycle the b) route can be hindered e.g. by mitochondrial diseases [6], low mitochondrial density [6] or thiamine deficiency [7], so promoting lactate production.

Observations on magnesium

Magnesium has an important role in ATP synthesis [8]. (ATP: Adenosine triphosphate, a nucleotide that provides energy to drive and support many processes in living cells, such as muscle contraction [9]). Magnesium deficiency (defined by S-Mg & lt; 0.8 mmol/) was detected by 23 % of critically ill patients, this proportion was (1.6 – 2.0-fold) higher by patients with increased S-lactate content, diabetics and alcoholics [10].

Study on Serum Metformin, Lactate, Blood pH and Mortality

In a study on databases of cases by metformin overdose with documented mortality data and values of serum lowest ("nadir") pH, highest ("peak") lactate level, and metformin concentrations, with outlines of their treatments [11]. The databases searched included MEDLINE from 1950 to June 2007, EMBASE from 1974 to June 2007, CINAHL from 1982 to June 2007, and TOXNET from 1965 to June 2007; these ranges encompassed the maximal time range limits of each database.

Number of cases fulfilling inclusion criteria was 22, five of them died. The represented data are from Table 1 in [11], partially analyzed by the author with IBM SPSS Statistics, version 29 and MS Excel. Ranges, (means & SD) of the parameters: metformin (Met): 0.3 – 188 (67.2 & 58.1) μg/ml; peak lactate: 1.4 – 47 (17.0 & 14.1) mmol/L; (nadir) pH: 6.59 – 7.49 (7.1 &0.3). Mortality got values: 1 for death, 0 for survivors. Four of non-survivors had got renal transplantation therapy. None of the intentional overdose patients whose serum nadir pH was over 6.9, maximum lactate concentration less than 25 mmol/L, or maximum metformin concentration less than 50 μg/mL died. Regression of death by [Met, lactate and pH] represents 61 % of the total variation of death ($p < 0.001$). Beta coefficients of this regression equation were: [-0.0035;+0.162;-0.626 - respectively]. Beta coefficient of Met was weak, but negative. According to one pilot study the average plasma Met (prescribed 500 – 3 000 mg Met/d) concentrations was 1846 ng/mL (<LoQ-5560 ng/mL) and independent of the prescribed daily dose [12]. By three cases in [11] plasma Met was below (5.6 μg/ml) 5600 ng/ml.

The same data [11] were selected by the highest values of Met including all (5) non-survivors. The number of cases was 12. The ranges by parameters were: Met 50.9 - 188 μg/ml, lactate 4.2-47, nadir pH 6.59 – 7.49. Regression of death by different factors: Met predicted death by 1 % (p 0.762, i.e, non-significantly), (nadir) pH by 56.4 % ($p = 0.005$) and lactate by 53.6 % ($p = 0.007$). Regression of Death by [Met, lactate and pH] explained deaths by 59.1% ($p = 0.056$, trend like association). Beta coefficients: Met -0.162; Lactate +0.244; Nadir pH -0.571, i.e. association of death was, as expected, negative with pH and positive with lactate and (N.B.) negative with Met. Strength of associations evaluated by single absolute Beta coefficient values divided by their sum was: Met 16.6, Lactate 25.0 and Nadir pH 58.5 %. Strongest detrimental association was with pH and protective association with Met. These results are accordant with that Met therapy improves the altered levels of magnesium and GSH in diabetic rats [13].

Experiments by Magnesium and Metformin on lactate and pH

Lactate increase of sportsmen can be prophylactically inhibited by Mg [14]. Dietary experiment has shown that serum lactic acid content can be increased by low-magnesium diet, without muscle exhaustion, increasingly, after 40-60 days ad 6.3 (vs. control 4.6) mmol/L (and base excess reduced below -4 mmol/l [15]). Even by Escherichia coli Mg-deficiency has increased production of lactate and decreased respiration [16]. In the magnesium experiment of Nuoranne et al. [15] Serum Mg: Ca ratio and duration of low-Mg diet [time (T, d)] explained blood pH by equation, pH: 6.98 – 0.0017*T+ 1.25*(Mg:Ca) ($P_{time} < 0.001$, $P_{(Mg:Ca)} < 0.01$). "The equation represents 62.0% of the total variation of blood pH." A thirteen weeks experiment by rats showed that the no observable adverse effect level (NOAEL) of metformin was 200 mg/kg/day [17], i.e. 14 000 mg for a human weighting 70 kg, which responds 5 x the human maximal daily dose, 3g [18]. Minimal metabolic acidosis and lactate increase was observed with metformin level 600 mg/kg/day.

Temperature

When "energy aimed for ATP formation is disturbed, the excessive energy is changed to warmth " [19]. In the feeding experiment of Nuoranne, et al. [15] regression of body temperature (BT, C^0) by time (T, d, days) and serum lactate (mmol/L) gave equation: BT = 38.49 - 0.00064*T + 0.017 *lactate content (P.time non-sig, *P.lact < 0.05) [15]. Nuoranne wrote that he had become accustomed to regard elevated skin temperature and sweating as signs of Mg deficiency [19]. The temperature of a sow can be increased ad 41-42 centigrade. The only acute treatment by 100 ml 20 % MgSO4 subcutaneously has been sufficient (veterinary surgeons are accustomed with high doses of magnesium). The result was to be seen even within one hour, after that treatment continued by usual oral Mg supplementation (Nuoranne 1977) [19]. Even by grass tetany temperature can increase ad 41-42 centigrade [19]. Symptoms like Delirium tremens (alcohol withdrawal syndrome) can be achieved if S-Mg declines to about 0.5 mmol/L [20]. Delirium tremens [21], (associated with Mg deficiency, e.g. [10]) "include shaking, shivering, irregular heart rate, and sweating. People may also hallucinate. Occasionally, a very high body temperature or seizures may result in death [21]." Metformin, which accumulates and increase lactate production in intestine, anyhow reduces blood lipopolysaccharides and its initiated low-grade inflammation [22].

Mg works like an on-demand antioxidant, but this ability is decreased in Mg-deficiency [23], which can increase ROS (Reactive Oxygen Species), IL-6 and TNF-α production [24] and temperature (fever).

Discussion

The understanding of the role of lactate has been increased remarkably during the last 50 years [4,5,6]. The role of magnesium in lactate formation is known, but because Mg is mainly intracellular cation and its extracellular measurement data (in serum less than 1 %) are unsatisfactory. We have need of easily available method for determination of body or muscle Mg status, [25-27]. Heart muscle damages were detected by all pigs with the lowest dietary Mg level [19], {why Nuoranne considered that Mg can have a role in the etiology of human heart diseases, too [19] as Professor Pentti Halonen taught in the 1970's: "heart infarct is myocardial necrosis, which has two etiological factors: one is the deficiency of oxygen, the other someone (unknown) metabolic factor" [28]. Possibly the metabolic factor is lactic acid as a consequence of the weakness in ATP production [23]. In situations, where lactate concentration is 6 mmol/L at rest, as in [15], the benefits of lactate [29] have been lost. The dietary Mg experiment produced severe lactic acidosis (lactate content was 6 mmol/L) [15], c.f. a given reference for severe lactic acidosis is serum lactate concentrations of > 4 mmol/L [10]. Significance of association between body temperature (BT, C^0) and serum lactate (mmol/L) could have been higher, if time had been removed from the regression [15]. Met can increase intestinal lactate production in epithelial cells and microbiome [22], which is possibly beneficial [30].

Conclusion

Managed lactate seems to be a beneficial power and health product, but unmanaged increased lactate predicts mortality risk. Deficiency of magnesium, associated with reduced ATP production and unmanaging of inflammation, is enriched with the diseases associated with lactic acidosis, as diabetes, which is associated with metformin medication. The role of metformin seems to be a bystander, in situations, where its help is not sufficient. Even in such situations relative Met content can associated with decreased mortality risk. Solution to Mg deficiency needs methodological (and statistical) measures.

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