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Pyruvate Research and Clinical Application Outlooks A Revolutionary Medical Advance

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Abstract

Pyruvate holds superior biomedical properties in increase of hypoxia tolerance, correction of severe acidosis, exertion of anti-oxidative stress and protection of mitochondria against apoptosis, so that it improves multi-organ function in various pathogenic insults. Particularly, pyruvate preserves key enzyme: pyruvate dehydrogenase (PDH) activity through direct inhibition of pyruvate dehydrogenase kinas (PDK), as a PDH activator, in hypoxia. Therefore, pyruvate is robustly beneficial for cell/organ function over citrate, acetate, lactate, bicarbonate and chloride as anions in current medical fluids. Pyruvate-enriched oral rehydration salt/solution (Pyr-ORS) and pyruvate-based intravenous (IV) fluids would be more beneficial than WHO-ORS and current IV fluids in both crystalloids and colloids, respectively. Pyruvate-containing fluids as the new generation would be not only a volume expander, but also a therapeutic agent simultaneously in fluid resuscitation in critical care patients. Pyruvate may be also beneficial in prevent and treatment of diabetes, aging and even cancer. Pyruvate clinical applications indicates a new revolutionary medical advance, following the WHO-ORS prevalence, this century.

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Pyruvate in Oral Rehydration Salt

On the 50th anniversary of clinical application with the World Health Organization (WHO)-guided oral rehydration salt/solution (ORS) and oral rehydration therapy (ORT), prestigious journals, Lancet and JAMA, published articles for the memory in 2018 [1,2]. In 1978, the Lancet hailed the ORS for oral treatment of diarrhea and cholera worldwide as a most medical advance in the past century because of the survival of a couple of million lives by the ORT per year [3].

The findings in intestinal physiology, in 1950s, that Sodium-Glucose linked transporters (SGLT1) exist in intestinal epithelium in mammalian are the base of ORS theory, by which sodium easily with glucose is actively and rapidly absorbed and water is passively and massively passed through the intestinal barrier. WHO-ORS consists of powders of sodium bicarbonate or citrate, sodium chloride, potassium chloride and glucose, which is called WHO-ORS I or II. Citrate-based reduced osmolarity one with less sodium chloride and glucose is known as WHO-ORS III, which may be more effective for non-cholera patients with diarrhea [4]. In last decades, due to its superiority of sodium and water absorption, the ORS has been promoted to rescue young patients with burns for vast rehydration with or without intravenous (IV) infusion. Currently, the ORT has been one of guidelines in burn shock resuscitation and it is also effective in resuscitation of burns in adults [5,6].

Since 2012, pyruvate-enriched ORS (Pyr-ORS) has been innovated by equimolar pyruvate of sodium salt to replace bicarbonate or citrate in WHO-ORS (I or II) and so do in reduced osmolarity WHO-ORS (III) also [7-10]. Intriguing findings are that Pyr-ORS reveals marked superiority in resuscitation of hemorrhagic and burn shock in animal models, particularly in severe acidosis correction, visceral blood flow preservation, organ and intestinal barrier protection and survival improvement, compared with WHO-ORSs. Opposite to bicarbonate or citrate, pyruvate of sodium salt holds specific biological and pharmacological properties that benefit critically ill patients: increase of anoxia/hypoxia tolerance, reversal of hypoxic lactic acidosis, anti-oxidative stress and inflammation, protection of mitochondria and anti-apoptosis and so on [11-16]. Of all beneficial advantages above, it may be critical that exogenous pyruvate acts as a stimulator like dichloroacetate (DCA) of the key rate-limited glucose metabolic enzyme, pyruvate dehydrogenase (PDH) activity through the direct inhibition of pyruvate dehydrogenase kinase (PDK), probably via the phosphoinositide 3-kinase (PI3K) pathway, so that exogenous pyruvate increases the active form of non-phosphorylated PDH (PDHa/PDHt: active/total), as substantiated with many research reports in last decades (Fig 1) [17-21]. Therefore, pyruvate is a modulator of glucometabolic disorders, such as Warburg effect, and a protector of multi-organ (particularly brain, heart, liver, kidney and intestine) function in numerous pathogenic insults like hypoxia, trauma/burn and sepsis in critical illnesses, diabetes and aging (see below).

As illustrated with IV or peritoneal pyruvate in severe injured animals [20,21], it was recently first demonstrated with diabetic kidney tissues that oral pyruvate in Pyr-ORS can mostly reactivate the depressed PDH, stimulating glucose oxidative phosphorylation; it also can enhance nicotinamide adenine dinucleotide oxidized/reduced form (NAD^+/NADH) ratio simultaneously induced in the pyruvate reductive reaction, free of energy, by lactate dehydrogenase (LDH) coupled with the NADH oxidative reaction, promoting the regular glycolysis pathway, as indicated in retinal tissues [22]. Thereby, oral pyruvate with its stimulation of hypoxia-inducible factor-1α-erythropoietin (HIF-1α-EPO) signal pathway in both hypoxia and normoxia enables to improve glycolytic and glucose oxidative metabolisms to preserve cell function in various injuries [7-10,14].

Notably, a recent finding displayed that oral Pyr-ORS improved diabetic status: significantly reduced body weight and fasting blood sugar level and robustly raised blood insulin level in diabetic *db/db* mice in the setting of diabetes-established disease. Surprisingly, oral pyruvate in Pyr-ORS reversed the high glucose (HG)-declined pyruvate kinase (PK) and PDH activities, concomitantly with inhibition of the HG-promoted pyruvate dehydrogenase kinase (PDK), in diabetic mice. The restoration of enzyme activities, *in vivo*, was confirmed in the investigation with HK-2 cell line (human proximal tubule epithelial cell line) in HG by pyruvate addition, *in vitro*. Also, the stimulated aldose reductase

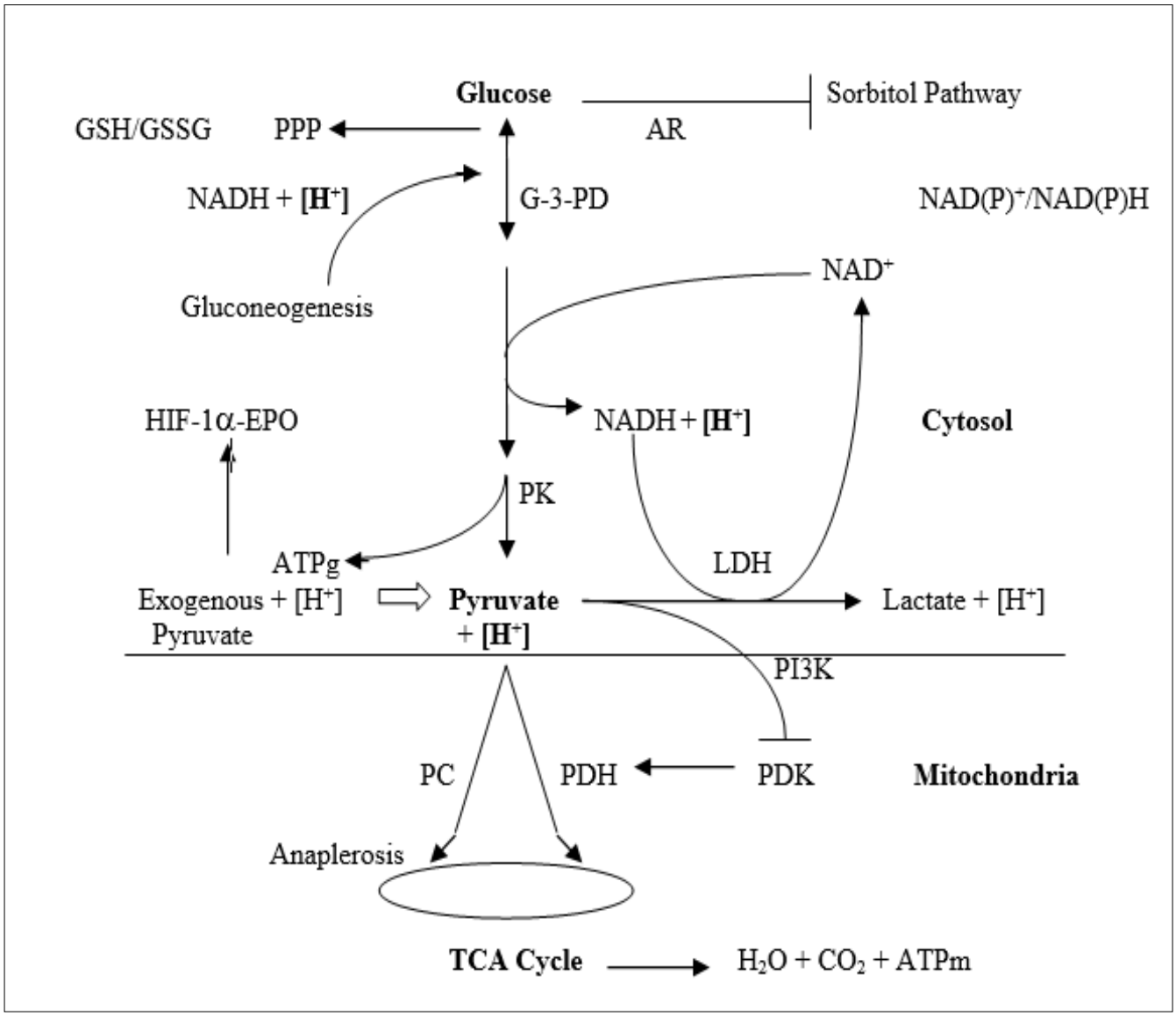

Figure 1. Exogenous and glycolytic pyruvate metabolic pathways and intracellular hydrogen (**[H$^+$]**) consumption in various injuries

Exogenous pyruvate enters cytosol via the MCT system with an extracellular [H$^+$] flux in symport. Pyruvate reductive reaction with LDH produces lactate from pyruvae and consumes **[H$^+$]**, coupled the NADH oxidation to NAD$^+$ with increase of NAD$^+$/NADH ratio. In addition, pyruvate stimulates PK and inhibits AR activities all restores the inhibited glycolytic pathway by various insults, including HG. In mitochondria, exogenous pyruvate also reactivates the declined PDH by various injuries with direct inhibition of PDK probably via the PI3K pathway (Cerniglia GJ, et al. Mol Cancer Ther, 2015), increasing PDHa/PDHt ratio. By stimulation of PC also, exogenous pyruvate promotes anaplerosis and the TCA cycle metabolism, concomitantly consuming **[H$^+$]** during oxidative phosphorylation. Exogenous pyruvate competitive inhibition of AR recovers the HG-promoted sorbitol pathway, increasing NAD(P)$^+$/NAD(P)H ratios. As a result, it restores declined PPP, leading to enhance GSH/GSSG ratio. In pyruvate-based gluconeogenesis, pyruvate consumes additional **[H$^+$]**. Through various metabolic pathways with **[H$^+$]** consumption, pyruvate enables to specifically correct hypoxic lactic acidosis. Further, exogenous pyruvate stimulates HIF-1α-EPO signal pathway in intracellular compartments, favoring most metabolic pathways above.

⟶ increase ⟞ decrease

(AR) levels by HG were fallen in both, *in vivo* and *in vitro*, tests, leading to recover the promoted sorbitol pathway (Fig 1). As a result, the typical glycolysis inhibition and glucometabolic Warburg effect-like disorder in diabetic *db/db* mice was mostly corrected with exogenous pyruvate [23]. Another discovery in the same diabetic model was that oral Pyr-ORS significantly decreased the advanced glycation end products (AGEs) in renal tissues, as demonstrated previously [24,25], and protected kidney function: declines of 24-hour urine protein, urine neutrophil gelatinase associated lipocalin and plasma cystatin C levels (data submitted for publication).

Prior studies discover that oral pyruvate in large doses (about 0.3-1.0g/kg/d) can improve diabetic status, even resulting in hypoglycemia in patients with type 1 diabetes, pancreatic insulin secretion and mitochondrial disorders in adults and children [26-29]. However, single pyruvate is malabsorption and a large dose of pyruvate is gastrointestinal irritative, but a regular dose less than 25 g as a single ingestion is not functional well and no blood pyruvate is raised if only 7.0g/d is orally taken for 7 days [30,31]. The Pyr-ORS is, thus, created by replacement of alkalizers in ORS with equimolar pyruvate; consequently, a regular amount of pyruvate can be sufficiently absorbed from intestine with enough glucose in Pyr-ORS via SGLT1 located in intestinal mucosa to compellingly increase pyruvate levels in blood and tissues to function as anticipated [9,32]. Therefore, oral pyruvate in Pyr-ORS would prevent from multi-organ dysfunction and reverse disorders of glucometabolic pathways and acid-base balance in critical care patients subjected to various injuries [8-10].

Pyruvate in Intravenous Fluid Resuscitation

Generally, sodium pyruvate powders in aqueous solutions are not stable at pH over 5.0 at room temperature [33]. However, pyruvate fluids for clinical uses (from 28 mM in pyruvate Ringer's solution to 154 mM in pyruvate saline, etc.) are long-term stable, if the pH of solutions is adjusted to lower than pH 5.0, at room temperature [34]. Pyruvate systemic protection of cells/ tissues in either anaerobic or aerobic condition includes glucose metabolic pathways and function in red blood cells (RBCs) that may play a critical role in improvement from hypoxia in tissues of critically ill patients [11]. Particularly, pyruvate, as a PDH activator, preserves PDH activity and corrects hypoxic lactic acidosis [12,18-21,35], so that it would be more superior than citrate, acetate, lactate, bicarbonate and chloride as current anions in medical fluids in protection of cell function against various injures in clinical settings [7-14,36]. Although malate might be suitable to correct lactic acidosis in critical care patients [37], it has no protection of RBCs because of its inability to be metabolized as pyruvate under anaerobic condition.

In addition to pyruvate specific benefits in IV resuscitation, experimental pyruvate-based peritoneal dialysis solutions also showed the merits in peritoneal dialysis and peritoneal resuscitation from shock in animal studies [38-40], the similarity as demonstrated with pyruvate-enriched priming solution in experimental bypass surgery [11]. The advantages of pyruvate resuscitation mainly are rapid correction of hypoxic lactic acidosis, distinct multi-organ protection, specific preservation of visceral blood flow and intestinal barrier and profound increment of survival. In addition, as a carrier solution of colloids, pyruvate may eliminate cytotoxicity of hydroxyethyl starch (HES) 130/0.4 on kidney in fluid resuscitation [41]. Accordingly, IV (crystalloids and colloids) or oral pyruvate is not only a volume expander, but also a therapeutic agent to protect against multi-organ dysfunction and metabolic disturbances simultaneously in fluid resuscitation. Due to its stability, superiority and safety without clinical toxicity (LD_{50} > 10g/kg oral pyruvate in rats [42]) [26,29,34,42,43], it is highly possible to manufacture pyruvate-enriched fluids, IV or oral solutions (Pyr-ORS), for dealing with critical care patients from perioperative fluid management to prehospital rescue to win a golden-window time in a large scale, particularly in resource-poor settings like earthquake, in the near future [12,14,44,45].

Pyruvate in Anti-Aging and Beyond

NAD^+, a star molecule for anti-aging, is well recognized in health and diseases [46]. However, pyruvate may be theoretically more beneficial than NAD^+ in protection against aging: 1) exogenous pyruvate anaerobically generates NAD^+ spontaneously by the LDH reduction on the 1:1 basis in all tissues, thus, one pyruvate molecule administered basically equals to one NAD^+ intake; 2) pyruvate has additional beneficial properties over NAD^+, among which the following

pyruvate actions play significantly critical roles in protection of cell function: reactivation of the PDH activity, correction of lactic acidosis, stimulation of HIF-1α-EPO pathway, exertion of anti-oxidative/ nitrosative stress and inhibition of AGEs formation; cellular PDH inhibition, oxidative stress, acidosis and AGEs deposition are involved in pathogenesis of degenerative nervous diseases, including Alzheimer's Disease. Therefore, pyruvate shows robust neuroprotection in many animal studies [32,47]. A recent report supported that pyruvate was equimolarly more beneficial than NAD^+ in cell function, *in vitro* [48]. Besides, it is worthwhile to note that pyruvate may inhibit cancer and improve the effectiveness of chemotherapeutic agents in certain conditions, as several studies substantiated [49-52]. Further, oral pyruvate may protect normal tissues aside from cancer/ tumor, including the protection of skin against radiation injury [53]. However, further studies and clinical trials are warranted to verify these hypotheses.

Although ethyl pyruvate (EP) has been extensively investigated with even better benefits than sodium pyruvate (SP) in cell protection with animal models of various diseases, which further strengthened clinical values with SP. EP has distinct differences from SP. It is required for EP with carboyxlesterase to be hydrolyzed into pyruvate in the plasma and intracellular environment, however, the enzyme is abundant in animals, but absent in humans. EP activation with carboxylesterase in intracellular spaces produces pyruvate, which may, however, rapidly be metabolized, resulting in little impact on peroxides, like H_2O_2 [54,55]. The EP phase II multicenter clinical trial failed ten years ago may support the hypothesis above, in comparison with effective clinical trials with SP [26-29,42,43], basically making the EP, *per se*, clinical prospect hopelessly [56].

Given iatrogenic drawbacks of normal saline and lactate Ringer's solution in fluid resuscitation from critical care patients, the novel pyruvate solutions, such as pyruvate/chloride saline ([Na^+] 154 mmol/L, [Pyr^-] 50 mmol/L, [Cl^-] 104 mmol/L) and pyruvate Ringer's solution ([Pyr^-] 28 mmol/L) in crystalloids and colloids [11,12,34,36,41], may be the new generation of resuscitation fluids. Pyr-ORS as an alternative to IV-fluid can be used as the first-line medicine for fluid therapy, not only in emergency departments, but also in whole hospitals [57]. With this respect, Pyr-ORS would further prompt ORT prevalence in critical care and pre-hospital rescue; of note, it may also prevent and improve diabetes and aging as a function drink in a large population. Pyruvate as the metabolic core of three major substances: glucose, lipid and protein would improve overall treatment outcomes of various diseases and social health care quality amongst acute critical illnesses and chronic diabetes, aging and cancer [58,59]. The prospect of pyruvate applications may be another most important medical advance this century.

Abbreviations

AR: aldose reductase; ATPg: glycolytic ATP; ATPm: mitochondrial ATP; G-3-DP: glyceraldehyde-3-phosphate dehydrogenase; GSH/GSSG: glutathione (reduced/ oxidized); [H^+]: metabolic hydrogen; **[H^+]**: consumed hydrogen; HG: high glucose; HIF-1α-EPO: hypoxia inducible factor-1α-erythropoietin; LDH: lactate dehydrogenase; MCT: monocarboxylate transporter; $NAD(P)^+$/NADH(P): nicotinamide adenine dinucleotide (phosphate): (oxidized/reduced form); PDHa/PDHt: pyruvate dehydrogenase (active/total part); PDK: pyruvate dehydrogenase kinase); PI3K: phosphoinositide 3-kinase; PK: pyruvate kinase; PPP: pentose phosphate pathway; PC: pyruvate carboxylase; TCA cycle: tricarboxylic acid cycle

Conflicts of Interest

No conflicts are declared.

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