ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 2001 May; 22 (5): 385-392
http://www.chinaphar.com

Review

Advantages of pyruvate over lactate in peritoneal dialysis solutions

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KEY WORDS lactates; pyruvates; dialysis solutions; acidosis; superoxides; neutrophils; apoptosis; glucose; oxidation-reduction; NF-kappa B

ABSTRACT

This review discusses effects of both lactate and pyruvate, and high glucose in peritoneal dialysis solutions (PDS) on leukocytes, mainly on intracellular pH ($[pH]_i$), glucose metabolic pathways, and apoptosis. Lactate-based PDS (L-PDS) are bioincompatible primarily due to the low pH, high lactate, and glucose excess in both individual and combination. High lactate in an *acidi milieu* would induce severe intracellular acidosis of leukocytes, and high glucose may disturb glucose metabolic pathways and activate protein kinase C (PKC) and nuclear factor-kappa B (NF-κ B) of the cells, leading to apoptosis. Pyruvate-based PDS (P-PDS) are novel experimental PDS. Evidence shows that P-PDS are superior in biocompatibility. Pyruvate protection of cells has been confirmed in many fields besides the PDS area. Although the underlying mechanism whereby P-PDS preserve cell function is not fully understood, it may be associated with the maintenance of $[pH]_i$ close to physiological, due to its low buffering capacity, improvement of cellular glucose metabolic pathways and redox state, and sustainment of intracellular calcium ($[Ca^{2+}]_i$) homeostasis in high glucose concentrations. It may also inhibit PKC and NF-κ B activation in high glucose. In addition, pyruvate is a strong antioxidant, a scavenger of hydrogen peroxide (H_2O_2). However, exogenous pyruvate in PDS could not be an energy source for cells and also the Crabtree effect might not occur in neutrophils. Pyruvate is a hopeful candidate of buffers in PDS in the near future. Further observation of P-PDS is strongly needed with peritoneal cells to verify the cell protection both *in vitro* and *in vivo* before clinic trials.

INTRODUCTION

Conventional lactate-based peritoneal dialysis solutions (L-PDS) are unphysiologic fluids, which have been employed in continuous ambulatory peritoneal dialysis (CAPD) for over two decades. Novel experimental pyruvate-based peritoneal dialysis solutions (P-PDS) were recently found to be superior in biocompatibility. It is possible that P-PDS would be a potent alternative in the near future. The present review discusses effects of both lactate and pyruvate, and high glucose on human leukocytes, mainly on intracellular pH ($[pH]_i$), glucose metabolism, and apoptosis, to elucidate advantages of pyruvate in peritoneal dialysis solutions (PDS) and its probable mechanisms of the cell protection.

LACTATE-BASED PERITONEAL DIALYSIS SOLUTIONS

Abbreviations AGEs: advanced glucosylation end-products; AR: aldose reductase; B-PDS: bicarbonate-based peritoneal dialysis solutions; $[Ca^{2+}]_i$: intracellular calcium; CAPD: continuous ambulatory peritoneal dialysis; DAG: diacylglycerol; FMLP: formyl-methionyl-leucyl-phenylalanine; GDP: glucose degradation products; GLUT: glucose transporter; HBSS: Hanks' balanced salt solution; HMPS: hexose monophosphate shunt; HPMC: human peritoneal mesothelial cells; L-PDS: lactate-based peritoneal dialysis solutions; MCT: monocarboxylate transporter; NAD: oxidized nicotinamide adenine dinucleotide; NADH: reduced nicotinamide adenine dinucleotide; NADP: oxidized nicotinamide adenine dinucleotide phosphate; NADPH: reduced nicotinamide adenine dinucleotide phosphate; NF-κ B: nuclear factor-kappa B; NO: nitric oxide; O_2^-: superoxide; PDC: pyruvate dehydrogenase complex; PDS: peritoneal dialysis solutions; PFK: phosphofructokinase; $[pH]_e$: extracellular pH; $[pH]_i$: intracellular pH; PKC: protein kinase C; P-PDS: pyruvate-based peritoneal dialysis solutions; TAC: tricarboxylic acid cycle; TNF: tumor necrosis factor.

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Received 2000-12-06 Accepted 2001-02-27

ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 2001 May; 22 (5)
E-mail aps@mail.shcnc.ac.cn Phn/Fax 86-21-6474-2629

A pH of PDS plays an essential role in biocompatibility In 1981, it was first demonstrated that L-PDS were bioincompatible. The detrimental effects are mainly due to the low pH (5.0 – 5.5), high *dl*-lactate (35 – 40 mmol·L^{-1}), and glucotoxicity including high concentrations of *D*-glucose (76 – 215 mmol·L^{-1}), glucose degradation products (GDP), and advanced glucosylation end-products (AGE).

It was discovered in 1991 that acidic L-PDS could create prompt and substantial intracellular acidosis in human neutrophils *in vitro*[1]. The $[pH]_i$ of resting value could fall precipitously within 3 min, usually from 7.1 down to 6.0, while the extracellular pH ($[pH]_e$) was remained at 5.2. By comparison, euhydric L-PDS preserved a greatly higher $[pH]_i$ of 6.8. However, the severe reduction of $[pH]_i$ and the inhibition of partial cell function, ie, superoxide (O_2^-) production, oxygen consumption, and intracellular glutathione, merely developed in an acidic medium containing a high level of lactate[2].

In a five-month clinic dialysis with neutralized L-PDS revealed that total leukocyte counts in the efferent decreased and the leukocyte viability increased, compared with acidic L-PDS. The phenomenon above may be explained by the hypothesis that a specialized H^+/$lactate^-$ cotransport system exists in the plasma membraoe of human neutrophils[3,4]. This monocarboxylate transporter (MCT) family (MCT2) with a high affinity for lactate and pyruvate, is strongly pH-dependent. Acidic $[pH]_e$ enhances lactate influx along with H^+ in symport across the membrane following the H^+ gradient, resulting in an accumulation of intracellular protons and a suppression of respiratory burst activation and oxidative metabolism of cells. In peritoneal macrophages, lactate uptake is exclusively mediated via a specific MCT in a high pH-dependent manner as well. The lactate influx rate of neutrophils is a function of extracellular lactate levels. It is roughly twofold greater when lactate is over 20 mmol·L^{-1} than below 10 mmol·L^{-1}. Thus, it was postulated that cell dysfunction responsible for peritoneal infection by L-PDS is primarily due to the $[pH]_i$ reduction of exposed cells *in vivo*. The equilibration of pH value and lactate content in L-PDS close to plasma levels takes 30 – 60 min dwell time in patient's peritoneal cavity. During the very first 5 min of each instillation, the pH of afferent/residual mixtures in the cavity may be still below 6.0 and the concentration of lactate over 20 mmol·L^{-1}, particularly on the catheter surface where the acidic pH is most pronounced and peritonitis is more susceptible. Evidence has established *in vitro* that by exposing human neutrophils to $[pH]_e$ 5.2 L-PDS for as little as 5 min, O_2^- generation and oxygen consumption were completely suppressed, accompanied with rapid and severe intracellular acidification. Following the transient acidosis, cell dysfunction, at least in part including O_2^- generation system[5], might be irreversible although intracellular acidosis in this rather early phase could be instantaneously and entirely restored[6].

Findings above provide a therapeutical basis to neutralize PDS before instillation and utilize bicarbonate-based PDS (B-PDS, equimolar bicarbonate substitute for lactate or at their various ratios) and a two-chamber system for raising the pH of solutions in recent clinical trials. The $[pH]_i$ monitoring showed that both euhyric L-PDS and euhydric B-PDS did not cause marked changes in $[pH]_i$[7]. A variety of cell functions remained subsequently. Although bicarbonate/lactate based PDS, with a physiologic pH and highly reduced GDP, in double-chambered bags showed superior in biocompatibility, they might be still not perfect to entirely replace conventional L-PDS, due to unknown long-term risks and the manufacture complexity.

Lactate excess is harmful for cellular metabolism The addition of lactate 20 mmol·L^{-1} to Hanks' Balanced Salt Solution (HBSS) at pH 7.0 caused a slight $[pH]_i$ decline in macrophages. By raising lactate up to 40 mmol·L^{-1}, the $[pH]_i$ of cells fell further. Acidic L-PDS could completely inhibit O_2^- production and mobilization of intracellular calcium ($[Ca^{2+}]_i$) by Zymosan or *N*-formyl-methionyl-leucyl-phenylalanine (FMLP)-stimulated neutrophils. The high lactate containing HBSS at pH 7.4 also induced an evident suppression of $[Ca^{2+}]_i$ mobilization. Meanwhile, the pH adjustment of L-PDS could improve $[Ca^{2+}]_i$ activation, but not entirely restore the $[Ca^{2+}]_i$ response as well as O_2^- production. In addition, in contrast to euhydric L-PDS, B-PDS (pH 7.4) allowed a significantly better increase of $[Ca^{2+}]_i$ release in the cells[8], superior IL-6 release and mitochondrial dehydrogenase activity in monocytes. B-PDS even containing high glucose also revealed higher cellular ATP contents of neutrophils and human peritoneal mesothelial cells (HPMC).

There are little data available showing the effect of L-PDS on cytosolic redox state, but the presence of such a high lactate in PDS, which is a 20- to 40-fold of the blood level, could markedly reduce the cytosolic oxidation potential of leukocytes. High lactate functions prin-

cipally as a cytosolic reductant[9], which reduces oxidized nicotinamide adenine dinucleotide (NAD) to reduced nicotinamide adenine dinucleotide (NADH) by lactate dehydrogenase (LDH). The decline of NAD/NADH ratio would inhibit the glycolytic activity, leading to suppressing hexose monophosphate shunt (HMPS) for O_2^- generation, as results showed that a euhydric L-PDS facilitated less O_2^- formation by neutrophils than its B-PDS counterpart[10].

All above indicate that high lactate *per se* in PDS would have direct deleterious impacts on cells. High lactate in an *acidi milieu* will deteriorate harmful effects on cellular metabolism. Despite the lack of direct evidence of glucose metabolic inhibitions by L-PDS in leukocytes, it was demonstrated that human red cells (RBC) exposed to L-PDS (pH 5.5) with lactate17 mmol $\cdot L^{-1}$ resulted in an evident depression of activities of key glycolytic enzymes and a great inhibition in glucose consumption and ATP production, accompanied simultaneously with an acute $[pH]_i$ decrement[11]. Due to their similar high glycolysis rates, it would be conceivable that results from RBC are in consonance with those of leukocytes under identical conditions.

High glucose is cytotoxic In addition to its hyperosmotic effect, formation of AGE and impacts of GDP in PDS[12], high glucose-induced glucotoxicity may be mainly the stimulation of sorbitol pathway and activation of PKC in leukocytes. Human leukocytes, particularly neutrophils, belong in the category of "unusual tissues" in glucose metabolism. Although it has been well known that high glucose induces an acute depression of O_2^- generation by leukocytes, the mechanism of which is not fully understood[13].

Up to date yet little investigation regarding carbohydrate metabolism on leukocytes exists in peritoneal dialysis, but extensive studies in physiology, diabetes, and ischemia-reperfusion injury have revealed metabolic properties of cells. Human leukocytes are characterized with high anaerobic and aerobic glycolysis and active sorbitol pathway. The cells are specified with aldose reductase (AR) that is highly localized to certain cell types, such as len epithelium, neuron, mesangial cells, HPMC, and RBC. In neutrophils, glucose uptake across the cell membrane is a passive process through facilitative glucose transporter molecules (GLUT family, predominantly GLUT2 and GLUT9)[14,15].

Normally, glucose is metabolized by glycolysis to produce ATP and by HMPS to create reduced nicotinamide adenine dinucleotide phosphate (NADPH) for O_2^- generation in neutrophils, of which the tricarboxylic acid cycle (TAC) is inactive, due to a paucity of mitochondria. Hexokinase in glycolysis has a much high affinity with K_m – 5 mmol $\cdot L^{-1}$ for glucose. The enzyme would be saturated when cells are incubated with high glucose, particularly in combination with low pH media. Whereas, AR has a low affinity with K_m 100 – 250 mmol/L. In general, glucose 5 mmol $\cdot L^{-1}$ is a poor substrate for it. However, as the concentration increases, the high cytosolic glucose is reduced to sorbitol in the first step of sorbitol pathway by the concomitantly enhanced activity of AR with NADPH as a co-factor[16]. NADPH-oxidase and AR compete for NADPH, due to similar K_m values. Thus, in the presence of high glucose, NADPH is diverted through the pathway and away from the O_2^- generation and regeneration of glutathione, leading to an acute inhibition of O_2^- formation and other impairments of leukocytes. In addition, cytosolic accumulation of sorbitol would be oxidated to fructose in the second step of the pathway by sorbitol dehydrogenase coupled with reduction of NAD to NADH, presumably further reducing NAD/NADH ratio for glycolysis in L-PDS. But, in this regard, evidence is not available in neutrophils.

Recently, it was reported that following a transient suppressive effect, high glucose-enriched L-PDS increased O_2^- generation in a dose-dependent manner by human peripheral and peritoneal phagocytes with a peak at 6 h incubation. It was presumed that HMPS would be enhanced with glucose concentrations, leading to the increment of O_2^- generation[17]. High glucose-enhanced O_2^- production was observed in many cell types including endothelial cells, mesangial cells, HPMC, and leukocytes. However, endothelial cells cultured in glucose 33 mmol $\cdot L^{-1}$ showed an impairment of HMPS activity with an insufficient NADPH supply. The impairment was *D*-glucose-specific and concentration-dependent and the glucose effect was apparent as early as 1 h after cell exposure. A recent study on human neutrophils revealed that although O_2^- production increased with *D*-glucose levels at 0 – 5 mmol $\cdot L^{-1}$, a plateau of 2.5-fold at 5 – 10 mmol $\cdot L^{-1}$ was reached within 20 min[18]. Therefore, glucose over physiologic levels would promote intracellular content of glucose, probably due to overexpression of the low-affinity, high K_m GLUT2 (GLUT9)[14], but not enhance HMPS activity. Rather, NADPH supply for creating O_2^- might be depressed in leukocytes. In a long-term incu-

ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 2001 May; 22 (5)
E-mail aps@mail.sbcnc.ac.cn Phn/Fax 86-21-6474-2629

bation with high glucose, as mentioned above in human phagocytes with L-PDS, elevated glucose levels can cause an elevation of the membranous PKC activity, which is also sorbitol pathway-dependent and crucially involved in the stimulation of O_2^- generation. PKC is activated with glucose, because high glucose enhances *de novo* synthesis of diacylglycerol (DAG), a potent physiologic activator of PKC[12,19], and induces a rise of $[Ca^{2+}]_i$ in leukocytes. In addition, an increased O_2^- production may also occur via auto-oxidation of glucose and/or nonenzymatic protein glucation. However, abnormal carbohydrate metabolisms need to be verified with PDS in peritoneal phagocytes.

PYRUVATE-BASED PERITONEAL DIALYSIS SOLUTIONS

P-PDS improve cell function In 1994, it was first reported that experimental P-PDS, equimorlar pyruvate replacement of lactate, greatly improved acute cytotoxic effects on human leukocytes, peritoneal macrophages, and HMPC *in vitro*. It is noteworthy that in sharp contrast to L-PDS counterparts, acidic P-PDS (pH 5.2 – 5.6) with 1.5 % glucose revealed a normal viability, proliferation, and cytokine release of HPMC, even 4.25 % glucose-enriched P-PDS still maintained the integrity, rate of proliferation and IL-1 ra release of cells. O_2^- generation by human leukocytes (peritoneal macrophages, peripheral mononuclear cells, and neutrophils) and chemotaxis of granulocytes in pH 5.4 P-PDS were comparably as controls. Mononuclear cells preincubated in acidic P-PDS and control media exhibited comparable tumor-necrosis factor (TNF)-alpha mRNA signals, and showed by far less inhibitory effects on the production of cytokines. In conclusion, pyruvate in PDS maintained cell function even at low pH or in the presence of high glucose[20,21].

Although L-PDS could induce apoptosis of peritoneal phagocytes and HPMC, recent results demonstrated that high glucose *per se* in L-PDS could induce a dose-dependent apoptosis of leukocytes[22]. A pilot study further indicated that pyruvate in PDS could protect cells against apoptosis in a dose- and time-dependent manner *in vitro*, even with 4.25 % PDS. Also, a preliminary experiment *in vivo* showed that O_2^- generation and TNF-alpha secretion of macrophages from uremic rats following a five-week dialysis were higher in P-PDS group than in L-PDS one. Interestingly, metabolic acidosis was more effectively corrected in the former than in the latter, and the nutritional state was better after dialysis with P-PDS than with L-PDS as well (abstracts: XXXVI Congress of ERA-EDTA; 1999 Sep 5 – 8; Madrid, Spain. p 304, 1999; J Am Soc Nephrol 1998; 9: 236A). More recently, direct evidence indicated that pyruvate in culture media protected rat peritoneal mesothelial cells against oxidant injury by H_2O_2, adding one more support of pyruvate as a potentially useful buffer for PDS[23].

Pyruvate preserves physiologic $[pH]_i$ and may sustain activities of enzymes It was discovered in 1995 that acidic P-PDS mixed *in vitro* with residual peritoneal effluent in the ratio of 10:1 created a markedly higher pH of 7.1 in contrast to a pH of 6.2 of L-PDS counterpart[24]. The neutrophilic $[pH]_i$ monitoring *in vitro* indicated that P-PDS at pH 5.2 preserved a near physiological $[pH]_i$ value, due to the presence of pH 7.4 phosphate-buffered saline solution in cell suspension, whereas identical acidic L-PDS induced a severe $[pH]_i$ reduction[25]. Alternatively, P-PDS at $[pH]_e$ 5.2 also showed a drastic depression of O_2^- prodution and oxygen consumption by Zymosan or FMLP-stimulated neutrophils, accompanied with a severe $[pH]_i$ reduction. Findings above were verified by the investigation in Europe.

Because of its lower buffering capacity of buffer pair in P-PDS, the $[pH]_e$ of exposed cells with pH 7.4 suspensions would be higher in P-PDS than in L-PDS. The higher $[pH]_e$, via $[pH]_i$, would engender the favorable cell function. On the other hand, the ratio between the concentrations of lactate and lactic acid in L-PDS at pH 5.5 will be 50:1. If the buffer is 40 mmol·L^{-1}, only 0.78 mmol·L^{-1} of lactate is undissociated. Correspondingly, the ratio between pyruvate and pyruvic acid in P-PDS will reach 1000:1, and merely as little as 0.039 mmol·L^{-1} of pyruvate are undissociated. It suggests that a comparably extreme majority of the buffers was dissociated in an *acidi milieu*. The particular MCT (MCT2) of human neutrophils, which accounts for all of lactate anions uptake, has a similar affinity for both lactate and pyruvate[3,4]. None of both permeates via nonionic diffusion to any significant degree in human neutrophils[26]. Thus, acidic P-PDS could also bring about equally rapid and profound intracellular acidosis, the same as L-PDS if acidic $[pH]_e$ of both PDS is comparable.

Pyruvate-mediated $[pH]_i$ preservation is crucially of importance for cellular carbohydrate metabolism. It is well known that the rate-limiting enzymes of glycolysis

are extraordinarily pH-sensitive, particularly phosphofructokinase (PFK) and pyruvate dehydrogenase complex (PDC). It just took as little as 5 min that the PFK activity was markedly decreased when the pH of cell-free system was dropped from 7.6 to 7.2. An inhibition of PFK could induce severe interference with cellular energy metabolism in human neutrophils: depletion of ATP and NADPH-oxidase activity, and multifunctional inhibition including the suppression of phagocytosis, O_2^- generation, and cytokine production[27]. Pyruvate as an end product of glycolysis, coupled with PDC, is the sole functional link between glycolysis and TAC in human neutrophils. Normally, the activity of PDC is much low, even could not be detected in the cells[28]. Thus, it seems to be impossible that there would be a functional TAC activity, even glycolysis, in neutrophils with intracellular acidosis.

Therefore, exogenous pyruvate could not be as an energy source to enter TAC, being metabolized in neutrophilic mitochondria even with normal $[pH]_i$. The above conclusion was supported by preliminary experimental evidence with P-PDS in Europe.

The presumption might be impossible that the Crabtree effect occurred in human neutrophils exposed to high glucose-enriched P-PDS[20, 21], as results also indicated that both L-PDS and B-PDS at pH 7.4 did not inhibit cellular ATP contents with glucose concentrations in the cells[8], but acidic L-PDS did. Unfortunately, the $[pH]_e$ of P-PDS/cell mixtures in the original articles was not concerned.

In addition, NADPH-oxidase that serves to transport electrons from cytosolic NADPH to molecular oxygen, producing O_2^- is also highly pH-dependent and ATP-required with an optimal pH 7.0 – 7.5. Enzymes in glutathione redox cycle are largely pH-sensitive as well. Thus, intracellular acidification would critically depress the main cytosolic reducing power. Conversely, one of major causes of neutrophilic apoptosis is the activation of the specific acid endonuclease. The activation is dependent on acidic $[pH]_i$, triggering apoptosis.

Further, the motivation of $[Ca^{2+}]_i$ is also critically influenced with $[pH]_i$. A preliminary measurement showed that compared with euhydric L-PDS, there was an evident transient increase of FMLP-stimulated neutrophilic $[Ca^{2+}]_i$ motivation by P-PDS counterpart (unpublished data). In this regard, the pyruvate-mediated $[Ca^{2+}]_i$ activation also occurred in rat myocytes[9]. Although no data so far are available of pyruvate effects on cytosolic activities of enzymes, acidic P-PDS would probably sustain activities of key cytosolic enzymes and $[Ca^{2+}]_i$ homeostasis, primarily via a near physiologic $[pH]_i$ maintained.

Pyruvate may improve glucose metabolism pathways and protect cells against apoptosis

Pyruvate and lactate at high concentrations have greatly opposite effects on the cytosolic redox state. An earlier experiment showed that in 5-min preincubation at pH 7.2 pyruvate 5 mmol·L^{-1} stimulated both glucose consumption and CO_2 production of human RBC by 20 % and 40 %, respectively, whereas lactate 5 mmol·L^{-1} had no effect on glucose consumption and reduced CO_2 production. It was recently suggested in len epithelium and endothelial cells that high pyruvate could markedly stimulate the conversion of pyruvate to lactate by LDH with NADH and/or NADPH as co-factors, competitively inhibiting NADPH-dependent reduction of aldehyde sugars to polyols in the first step of sorbitol pathway since the enzyme, LDH, might also use NADPH for the reductive reaction[29,30].

More importantly, pyruvate may increase the oxidation of NADH to NAD as rapidly as NAD is reduced to NADH in the second step of pathway[31]. Thus, high cytosolic pyruvate acts actually as a strong oxidant[9], raising NAD/NADH and oxidized nicotinamide adenine dinucleotide phosphate (NADP)/NADPH ratios. With an inactive TAC in leukocytes, therefore, it could be presumed that in the presence of such a supra physiologic pyruvate in P-PDS, the anaerobic utilization of exogenous pyruvate would competitively inhibit the sorbitol pathway in high glucose media and improve NAD-dependent glycolytic pathway and preserve NADP-dependent diversion of high glucose to HMPS and glutathione redox cycle[30].

Additionally, pyruvate may also inhibit PKC activity in leukocytes. In a rat skin chamber granulation model, a glucose (30 mmol·L^{-1})-induced increase in DAG and vascular functional changes could be completely prevented by the addition of pyruvate 3 mmol·L^{-1}. The effects of exogenous pyruvate on DAG synthesis may be twofold: it reduces substrate level, dihydroxyacetone phosphate, and reduces the availability of the co-factor, NADH, needed for the reduction of substrate, resulting in an attenuation of PKC activity[19].

It was reported in 1985 that exogenous pyruvate could protect mammalian cells from H_2O_2, although it has been recognized for almost one century that H_2O_2 causes a rapid nonenzymatic and stoichiometric decarboxylation of pyruvate and related alpha-keto acids.

ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 2001 May; 22 (5)
E-mail aps@mail.shcnc.ac.cn Phn/Fax 86-21-6474-2629

Subsequent studies indicated the protective role of pyruvate in H_2O_2-induced renal, neuronal, and ischemic-reperfusive injuries, and injury in transplant reject reaction *in vitro* or *in vivo*. Recently, it was also demonstrated in mouse thymocytes and human lymphoid cell lines that pyruvate protected cells from H_2O_2-mediated cell death[32,33]. Intracellularly produced reactive oxygen species by human neutrophils would accelerate neutrophilic apoptosis[34]. Therefore, it is likely that pyrvate as a scavenger of both exogenous and endogenous H_2O_2 would protect neutrophils against oxidative stress-induced apoptosis. In this regard, pyruvate also acts as an antioxidant. As to macrophages and HPMC, the potent effect of pyruvate may additionally be relevant to the protection against oxidative injury to DNA posed by H_2O_2. Regularly, mitochondrial DNA does not undergo fragmentation during apoptosis. The relative preservation of mitochondrial function might be associated with the copious amount of mitochondrial pyruvate. A recent study with U937 cells revealed that pyruvate 5 mmol·L^{-1} in glucose 30 mmol·L^{-1} could prevent cells exposed to H_2O_2 from apoptosis due to promoting the formation of intramitochondrial NADH[35]. Moreover, it might be also possible that pyruvate suppresses AGEs formation and accumulation from high glucose in patient's peritoneal cavity.

Nitric oxide (NO) that phagocytes produced with NADPH as a co-factor also plays an essential role in cell defense and apoptosis. Although NO is bifunctional regulator of apoptosis, evidence indicated that the simultaneous enhancement of intracellular O_2^- and NO specifically by high *D*-glucose in endothelial cells rapidly activated the transcription factor, nuclear factor-kappa B (NF-κ B), by the formation of peroxynitrite, leading to the induction of apoptosis[36]. The NF-κ B activation may be a critical regulator of human granulocyte apoptosis. Significantly, the NF-κ B activation by high glucose could be prevented by antioxidants, including pyruvate, vitamin E, and inhibitors of NO synthase.

According to findings above, it is reasonable to speculate that pyruvate in P-PDS would be able to protect peritoneal phagocytes in high glucose against apoptosis both *in vitro* and *in vivo*. The superior biocompatibility of P-PDS and pyruvate protection of cells are certain, but the correction of abnormal metabolisms and transdution signalings by pyruvate has to be verified with P-PDS in peritoneal cells. Pyruvate is a normal intermittent of glucose metabolism, and able to freely diffuse among intercellular, intracellular, and mitochondrial compartments. An intravenous pyruvate loading test in human subjects demonstrated its safety in the clinical applicability.

CONCLUSION

Intracellular acidification of leukocytes induced by the high acidity of L-PDS is a primary detrimental effect in the bioincompatibility of PDS. High lactate and glucose excess including GDP and AGE play individually a pivotal role as well. Various combinations among them would contribute to more cytotoxic effects on host defense cells.

Pyruvate replacement of lactate in PDS preserves efficiently multiple cellular functions, almost completely overcoming harmful effects offered by lactate. Although the underlying mechanisms whereby pyruvate protects cells are not fully elucidated, the fundamental effect of pyruvate protection in P-PDS may be associated with the maintenance of a near physiologic $[pH]_i$ due to its lower buffering capacity, the activities of key glycolytic enzymes remaining subsequently. In addition, studies in areas other than PDS have shown that pyruvate may improve glucose metabolic pathways and preserve cellular redox state in high glucose conditions, sustain $[Ca^{2+}]_i$ homeostasis and protect cells against apoptosis as a potent non-enzymatic scavenger of H_2O_2. Before clinic trials, further extensive investigations are strongly needed with P-PDS both *in vitro* and *in vivo*, particularly on the interaction with cytosolic redox state among pyruvate, O_2^-, and NO in peritoneal phagocytes and HPMC. Pyruvate is a potent and attractive candidate as a dialysate buffer. The future of PDS will lie in combinations and additives, but P-PDS could be an entire substitute for conventional L-PDS. The observation on the cell protection of pyruvate in PDS may benefit not only in CAPD, but also in the treatment of diabetes, cardiovascular diseases, and transplantation and their complications.

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ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 2001 May; 22 (5)
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丙酮酸盐在腹膜透析液中优于乳酸盐

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主题词 乳酸盐类; 丙酮酸盐类; 透析液; 酸中毒; 超氧化物; 中性白细胞; 细胞凋亡; 葡萄糖; 氧化还原; NF-κ B

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