**Critical Review**

**d-Lactate in Human and Ruminant Metabolism**

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**ABSTRACT**

d-Lactate is normally present in the blood of mammals at nanomolar concentrations due to methylglyoxal metabolism; millimolar d-lactate concentrations can arise due to excess gastrointestinal microbial production. Grain overload in ruminants, short-bowel syndrome in humans, and diarrhea in calves can all result in profound d-lactic acidemia, with remarkably similar neurological manifestations. In the past, d-lactate was thought to be excreted mainly in the urine, and metabolized slowly by the enzyme d-α-hydroxy acid dehydrogenase. More recent studies reported that mammals have a relatively high capacity for d-lactate metabolism and identified a putative mammalian d-lactate dehydrogenase. A growing body of literature is also emerging describing subclinical elevation of d-lactate as an indicator of sepsis and trauma. This article describes advances in the understanding of d-lactate metabolism, d-lactic acidosis in ruminants and humans, and subclinical elevation of d-lactate. J. Nutr. 135: 1619–1625, 2005.

**KEY WORDS:** • d-lactate • metabolism • acidosis • ruminants • humans • diarrhea

New developments in the understanding of mammalian d-lactate metabolism and d-lactic acidosis, along with several recent articles suggesting the use of plasma d-lactate concentration as a clinical diagnostic tool, indicate the need for a comprehensive review of d-lactate biochemistry.

Lactate, or 2-hydroxypropanoate, was discovered in 1780 by a Swedish chemist, Scheele, who isolated it from sour milk (1). Lactate is the simplest hydroxycarboxylic acid and exists as 2 stereoisomers, or enantiomers, due to its asymmetric C2 atom (Fig. 1). Typically, an enantiomer that rotates light in the clockwise direction is called D, for dextrorotary, and the enantiomer that rotates light counterclockwise is called L, for levorotary. An alternative classification uses + and – based on the similarity of the molecule to the 2 chiral forms of glyceraldehyde. Usually the (+) and D categorizations are the same for a chiral molecule; however, lactate is an exception to these rules, with a levorotary D-isomer and a dextrorotary L-isomer. Both enantiomers have similar physical and chemical properties (2). Lactate has a pK of 3.86 and dissociates freely at physiological pH, yielding a lactate ion:lactic acid ratio of 3000:1.

Normal serum lactate concentration is ~1–2 mmol/L and is considered entirely L-lactate because lactate produced by mammalian cells is nearly all of this form, with the exception of d-lactate formed in nanomolar concentrations via the methylglyoxal pathway. Exogenous sources of D- and L-lactate include fermented foods such as sauerkraut, yogurt, and pickles, and microbial fermentation in the colon, which typically do not pose an acid-base threat (3–5).

L-Lactic acidosis is relatively common, occurring primarily as a result of tissue hypoxia, but also due to drugs and toxins, inborn errors of metabolism, and underlying disease states (6). D-Lactic acidosis is a less common occurrence; however, there are several circumstances in which D-lactate can become elevated in the blood in both ruminants and humans. This review discusses these scenarios and describes the recent studies of subclinical D-lactate elevation in diabetes and as a marker of sepsis, ischemia, and trauma.

**Biochemistry and metabolism of d-lactate**

**Metabolism and excretion.** Serum d-lactate concentration in healthy adults ranges from 11 to 70 nmol/L (5,7–9). Urine excretion is ~0.1 µmol/h (10). D-Lactate is rapidly metabolized to pyruvate by L-lactate dehydrogenase in the liver, but mammals were reported to lack d-lactate dehydrogenase (10,12,13). D-Lactate is thought to be metabolized to pyruvate instead by the enzyme d-α-hydroxy acid dehydrogenase (EC 1.1.99.6), which metabolizes d-lactate at about one-fifth the rate that L-lactate dehydrogenase metabolizes L-lactate (14). Until recently, d-lactate dehydrogenases had been isolated only in lower organisms (15,16), but new studies identified putative human and murine mitochondrial d-lactate dehydrogenases (EC 1.1.1.28) (17,18). Bovine and rat tissues possess considerable d-lactate utilization in vitro (19,20). In humans, parenteral infusion of d-lactate (3.0 mmol/kg) causes increases in pyruvate, alanine, 3-hydroxybutyrate, and acetacetate (10).

D-Lactate is anaplerotic because its transport into the mitochondrial membrane results in the shuttling of oxaloacetate and malate to the cytosol (17). The transport of d-lactate from the cytosol to the mitochondrial matrix allows d-lactate to be oxidized by the putative D-lactate dehydrogenase, which is
located on the inner face of the inner mitochondrial membrane (17). Three novel transporters have been identified that shuttle D-lactate across the mitochondrial membrane: the D-lactate/H+ symporter, the D-lactate/oxoacid antiporter, and the D-lactate/malate antiporter (17).

Controversy regarding the metabolism and excretion of D-lactate in mammals exists in the literature. Conventional opinion is that D-lactate is not well metabolized by mammals and is excreted mainly in the urine (11,13,21–25). This is based largely on Cori’s experiments in the late 1920s (26), confirmed 40 y later (27), demonstrating that D-lactate is poorly metabolized and 30–40% of ingested D-lactate is excreted in the urine, compared with none of the L-isomer. Experiments in the 1980s and 1990s, using either D-lactate or 14C-labeled D-lactate, refuted the earlier results and established that D-lactate is indeed readily metabolized (12,28–30), although the former results continue to be quoted frequently and pervade the current literature.

In humans (n = 10) infused with 1.0–1.3 mmol sodium D-lactate/(kg h), ~90% of D-lactate was metabolized, and 10% excreted in the urine (12). At higher infusion rates of 3.0–4.6 mmol/(kg h), metabolism decreased to ~75% of overall clearance (12). de Vrese et al. (28) determined a half-life of 21 min for D-lactate in the blood of healthy humans given an oral load of 6.4 mmol/kg.Doubling this dosage increased the half-life of D-lactate to 40 min, most likely reflecting the saturation of D-lactate metabolism. Contrary to earlier studies, only 2% of administered D-lactate in that experiment was excreted in the urine in the 24 h after ingestion (28). In rats administered 14C-labeled D-lactate, 3.7% of the total dose was excreted renally, with exhalation of 14CO2 accounting for 85% of excretion (29). The dosage in that study (300 μmol sodium D-lactate/rat) was lower than in Cori’s experiment (19 mmol/kg body weight), and was administered both orally and i.p., rather than by gavage, making comparison difficult. Nevertheless, when the dosage (13.4 mmol/kg) and method of administration (i.g.) were accounted for in an ensuing experiment, still only 0.9% of the total dose was excreted renally and 2.4% excreted as metabolites, with exhalation of 14CO2 accounting for 30–45% of excretion (30); 54–68% of administered 14C was not recovered, likely representing D-lactate metabolized to pyruvate or acetyl CoA and unabsorbed D-lactate, which was excreted in the feces or metabolized by microbes (30). The method of administration accounted for considerable differences in metabolism and excretion, with parenteral infusion resulting in much less unrecovered 14C (8%) than enteral administration (54–68%) (30).

One explanation for the disparities between the very early experiments and the more recent ones is advances in methodologies available for D-lactate analysis, from early nonstereoselective colorimetric assays with low sensitivity (31,32), to more current stereospecific HPLC and capillary electrophoretic methods (33–36). Furthermore, species differences in D-lactate metabolism have been observed. Renal reabsorption of D-lactate in humans is not as efficient as it is in dogs (12,37). D-Lactate is considered a physiological isomer in coprophagous animals because high rates of gastric D-lactate production were reported in rats and rabbits (29). Even between these 2 species, differences were observed in oxidation rate and renal excretion of D-lactate (29). Rats were used in numerous studies defining D-lactate metabolism (17,20,26,29,30,38), and perhaps have less relevance to other species than expected. Stable isotopic investigations could clarify human metabolism of D-lactate.

D- and L-Lactate mutually interfere in renal absorption (12). Even at high doses, L-lactate reabsorption always exceeds 70%, and D-lactate reabsorption never exceeds 50%, even at very low doses (12). At D-lactate plasma concentrations higher than 3.0 mmol/L, renal tubular reabsorption of D-lactate decreases by as much as 30% (12). Reabsorption of lactate occurs against an electrochemical gradient, which indicates active reabsorption (9). Both L- and D-lactate appear to use the same sodium cotransport system, which may contribute to the mutual interference between L- and D-lactate reabsorption (12). Renal tubular reabsorption of lactate is reduced by increased urine volume (39). Oh et al. (12) proposed that D-lactic acidosis may be more prevalent in volume depletion.

D-Lactate is transported into and out of various tissues via the proton-dependent monocarboxylate transporters (MCT-1 to MCT-8) (40). MCTs are expressed in most tissues, were identified in retina, muscle, kidney, brain capillary endothelial cells, cardiac myocytes, enterocytes, hepatocytes, erythrocytes, thymocytes, placenta, and nervous tissue, and have been reviewed extensively (40,41). D-Lactate is absorbed by the small intestinal and colonic epithelial cells (42,43) by MCT-1, which exhibits an uptake coefficient for L-lactate twice that for D-lactate and mutual inhibitory effects (44). Both saturable and nonsaturable absorptive processes are present in rat jejunum (45). The saturable process has a higher affinity for L-lactate than D-lactate, whereas no difference is present between the isomers for the nonsaturable process (45).

D-Lactate may be implicated in the development of metabolic bone disease in patients administered long-term parenteral nutrition for malabsorption. In a study of patients administered total parenteral nutrition for a mean of 74 mo, 2 of 27 subjects had elevated blood D-lactate (1.1 and 2.8 mmol/L). Only those 2 subjects had evidence of osteomalacia; vitamin D, phosphate, aluminum and calcium concentrations were normal (46). Further studies are required to confirm this association and identify the mechanism involved.

**Methylglyoxal pathway.** Methylglyoxal is produced in small amounts from carbohydrate, fat, and protein metabolism (Fig. 2). Due to its reactive and toxic nature, methylglyoxal must be eliminated from the body (47). The glyoxalase pathway is a biochemical process that catalyzes the conversion of methylglyoxal to D-lactate and glutathione via the intermediate S-D-lactoylglutathione by 2 enzymes: glyoxalase I and glyoxalase II (48,49) (Fig. 2). It is a ubiquitous reaction in biological life, taking place in the cytosol of cells and organelles, especially the mitochondria (49). D-Lactate can be used as an indicator of methylglyoxal and is much easier to measure than the unstable methylglyoxal (50).

Serum D-lactate values reported in studies of the methylglyoxal pathway are typically micro- or nanomolar, and generally do not contribute to acidemia. However, after high-dose

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**FIGURE 1** Lactate enantiomers.

<table>
<thead>
<tr>
<th>COOH</th>
<th>COOH</th>
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<tr>
<td>HO - C - H</td>
<td>H - C - OH</td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₃</td>
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L (+) Lactate  D (-) Lactate

**TABLE 1** Lactate enantiomers.


D-Lactic acidosis is a rare metabolic occurrence in humans, but is occasionally observed as a consequence of short-bowel syndrome (SBS). It also occurs in ruminants after overfeeding, inappropriate ruminal fermentation of milk, and as a sequel to diarrhea in neonatal calves. Recently we identified severe D-lactic acidosis in a cat with pancreatic insufficiency, a finding which is particularly interesting because cats are true carnivores (52). D-Lactic acidosis has been defined as metabolic acidosis accompanied by an increase in serum D-lactate concentrations > 2.5–3 mmol/L (53). Patients with D-lactic acidosis have neurological dysfunction characterized by ataxia, slurred speech, and confusion, in association with a high anion gap metabolic acidosis (54,56). Patients may also have episodes of somnolence, hallucinations, clumsiness, nystagmus, blurred vision, ophthalmoplegia, disorientation, dizziness, lethargy, excessive irritability, and abusive behavior, which may last from a few hours to several days (53). In one study, 16 of 33 patients who had jejunoleal by-pass reported symptoms consistent with D-lactate encephalopathy after surgery (57). Jejunoleal by-pass is no longer widely practiced as a bariatric surgery, due to severe metabolic and nutritional consequences (58).

The pathogenesis of D-lactic acidosis in SBS is well elucidated (59). A short or bypassed small intestine causes poor digestion of carbohydrate, which leads to the delivery of sugars to the colon. Initially, increased organic acid production results, reducing pH in the colonic lumen. This acidic environment permits acid-resistant lactobacilli to grow preferentially, with the fermentative production of both D- and L-lactate. D-Lactate accumulates systemically, following the absorption of both enantiomers (59). When the rate of D-lactate production exceeds the body’s capacity for metabolism and excretion, D-lactic acid accumulates in the blood and acidemia and metabolic acidosis result. Some lactobacilli also produce the enzyme DL-lactate racemase, which further contributes to excess D-lactate by converting L-lactate to D-lactate (23,59).

Treatment of D-lactic acidosis in SBS involves bicarbonate and fluid infusion, avoidance of carbohydrates, and administration of oral nonabsorbable antibiotics. Although widely used, antibiotics can induce D-lactic acidosis in SBS patients by promoting overgrowth of resistant D-lactate-producing microbes (60). Rapid resolution is possible with abrupt cessation of oral intake (22,61). Long-term parenteral nutrition is often administered, until adaptation of the residual small intestine allows enteral nutrition (22). Avoiding consumption of Lac-

![Figure 2](https://academic.oup.com/jn/article-abstract/135/7/1619/4663874)

**Figure 2** Methylglyoxal pathway.

![Figure 3](https://academic.oup.com/jn/article-abstract/135/7/1619/4663874)

**Figure 3** Propylene glycol metabolism. ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; GSH, reduced glutathione; PDH, pyruvate dehydrogenase, L-LDH, L-lactate dehydrogenase; o-LDH, putative D-lactate dehydrogenase.
**D-lactic acidosis in diarrheic calves.** Historically, acidosis in diarrheic calves was reported to be caused by the loss of bicarbonate in the feces and the accumulation of L-lactate in the blood (84). It was theorized that diarrhea-induced dehydration resulted in tissue hypoxia and consequently, anaerobic respiration. Until recently, L-lactate was assumed to be the major organic acid present in the blood of diarrheic calves (85). The documented occurrence of acidemia in well-hydrated calves led to investigation of other potential organic acid production (84,86). It is now known that D-lactate accounts for ∼64% of the total increase in organic acids, as measured by anion gap (87,88). Calves can have extremely high D-lactate concentrations, up to 25 mmol/L (87,88). Furthermore, D-lactate production occurs mainly in the large intestine of diarrheic calves, with some calves also producing excess D-lactate in the rumen (88). The mechanism is likely similar to that documented for D-lactic acidosis in SBS in humans except the etiology of the malabsorption is viral infection–induced villous atrophy rather than surgical removal of the small intestine. Failure of the esophageal groove may occur in those calves with excess rumen fermentation; further study is required to clarify this possibility. The absorption of D-lactate from the intestinal lumen, via proton-dependent MCT-1, may be enhanced due to the high concentration of protons produced from excess bacterial fermentation. This, along with decreased barrier function from pathogen invasion and inflammatory processes, may lead to enhanced absorption of D-lactate and the extremely high blood D-lactate present in some diarrheic calves. Dehydration is also common in diarrheic calves and may impair renal removal of hydrogen ions from the blood, exacerbating acidemia.

There is a possibility, although it has not been described, that a similar scenario could occur in diarrheic monogastrics, including humans. Villous atrophy and malabsorption certainly occur in humans suffering from viral diarrhea, but whether there is sufficient fermentation to cause excess D-lactate to accumulate is not known. Metabolic acidosis was identified in human rotaviral diarrhea, and was attributed to carbohydrate malabsorption; however, the identity of the acids was not determined (89).

**Subclinical elevation of D-lactate**

**Diabetes.** In rats, the rate of D-lactate production in tissues with insulin-independent glucose uptake increases under hyperglycemic conditions (38). In that study, diabetic and starved rats had significantly higher concentrations of D-lactate in plasma, liver, and skeletal muscle compared with healthy rats (38). Methylglyoxal concentration was significantly elevated in plasma, but depressed in liver and muscle of starved and diabetic rats, compared with healthy rats. Christopher et al. (48) reported that increased serum D-lactate is associated with ketoacidosis rather than hyperglycemia, suggesting that ketone metabolism by hepatic cytochromes may be a major source of methylglyoxal in diabetic patients. Diabetic patients have roughly twice the blood D-lactate (28 μmol/L) concentrations of normal subjects (13 μmol/L) (50). Enzymes involved in the metabolism of methylglyoxal are elevated in diabetic patients, including aldose reductase, glyoxalase I, and glyoxalase II (90). Complications of diabetes, including retinopathy (91), nephropathy (92), and neuropathy (93) have been attributed to advanced glycation products.
including methylglyoxal. Clinically, \( \textit{D} \)-lactate is unlikely to play an important role in diabetic patients because plasma concentrations appear to be subclinical in terms of neurotoxicity or acid-base imbalance.

\textbf{Infection, ischemia, and traumatic shock.} Infection, ischemia, and trauma all result in significantly elevated blood \( \textit{D} \)-lactate concentrations. Most of these circumstances yield a \( \textit{D} \)-lactate concentration that does not result in acidosis or neurological symptoms; typically, a concentration \(< 1 \text{ mmol/L} \) is observed.

Various pathogenic bacteria produce \( \textit{D} \)-lactate, including \textit{Bacteroides fragilis}, \textit{Escherichia coli}, \textit{Klebsiella pneumonia}, and \textit{Staphylococcus aureus} (94). The use of \( \textit{D} \)-lactate as a marker for infection was proposed in 1986 (94). Indeed, venous blood \( \textit{D} \)-lactate concentration as a predictor in the diagnosis of appendicitis has a lower false negative rate than C-reactive protein or leukocyte count (95). Plasma \( \textit{D} \)-lactate is a sensitive marker for gut failure and endotoxemia in cirrhosis patients, likely due to impaired intestinal barrier function (96). Rats with experimentally induced \( \textit{K. pneumonia} \) peritonitis develop a transient, but severe, \( \textit{D} \)-lactic acidemia (25.6 mmol/L 6 h postinfection) (94). In bacterial meningitis, however, cerebrospinal fluid \( \textit{D} \)-lactate was shown to be a poor indicator of infection, although slight elevations do occur (97).

In critically ill patients with septic shock, intestinal ischemia results in related increases in serum \( \textit{D} \)-lactate concentrations and gastric intramucosal \( \text{CO}_2 \) partial pressure (\( \text{P}_\text{CO2} \)) (98). No relation between \( \text{P}_\text{CO2} \) and \( \text{i} \)-lactate was evident in this population, although in a previous study in pigs, hemorrhagic shock and systemic \( \text{i} \)-lactate were related (99). Profound mucosal necrosis occurred early after resuscitation, implicating failure of the mucosal barrier as the likely cause of \( \textit{D} \)-lactate absorption (100). Patients with mesenteric ischemia at laparotomy had significantly elevated \( \textit{D} \)-lactate concentrations compared with patients operated on for an acute abdomen without intestinal ischemia (e.g., pancreatitis, diverticulitis, adhesions, gangrenous gallbladder); in these patients, \( \textit{D} \)-lactate is a more reliable marker of ischemia than a physical exam (101).

Trauma can also result in elevated serum \( \textit{D} \)-lactate. In pigs, nonvisceral gunshot injuries result in high plasma endotoxin and \( \textit{D} \)-lactate concentrations and necrosis at the ileal villus, even in the absence of hemorrhagic shock (102). In rats, gut ischemia, severe burn injury (30% total body surface area), and acute necrotizing pancreatitis all result in elevated \( \textit{D} \)-lactate (up to 0.65 mmol/L) (103).

The use of \( \textit{D} \)-lactate as a diagnostic aid in clinical practice will require the availability of a \( \textit{D} \)-lactate assay. Generally, this is not the case, and when available, techniques are often based on the \( \textit{D} \)-lactate dehydrogenase enzymatic assay, which has numerous sources of error and is not adequately sensitive for the micromolar changes observed in infection or sepsis (35).

In conclusion, \( \textit{D} \)-lactate, although generally considered the “nonphysiological” isomer of lactate, has an important role in numerous aspects of ruminant and monogastric metabolism, is clinically important in a variety of malabsorptive or gastrointestinal nutrient overload conditions, and may be important in some types of sepsis. Further elucidation of \( \textit{D} \)-lactate metabolism is required, particularly to identify species differences. Probiotics may hold promise for use in prevention or treatment of \( \textit{D} \)-lactic acidosis in SBS, and overfed or diarrheic ruminants. Clinical use of \( \textit{D} \)-lactate as a diagnostic aid for ischemia or infection will depend on access to reliable \( \textit{D} \)-lactate assays, currently not widely available in clinics and hospitals.


