

PATTERNS OF METABOLIC RECOVERY FROM EXERCISE IN AMPHIBIANS AND REPTILES

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Summary

The physiological responses of amphibians and reptiles undergoing vigorous exercise are qualitatively similar to those of other vertebrates. Oxygen consumption increases rapidly to rates that are three- to 10-fold the rates at rest. The aerobic response to graded exercise in locomoting reptiles and amphibians is for the most part linear. Oxygen transport by the cardiovascular system during exercise is accomplished by factorial increases in heart rate and oxygen extraction from arterial blood in a fashion similar to that in mammals. Increments in stroke volume during exercise are small or in some cases negative. The influence of temperature or of intracardiac shunting on the cardiovascular function of active amphibians and reptiles is poorly understood. These aerobic responses to exercise are accompanied by robust anaerobic contributions to energy metabolism, resulting in significant lactate accumulation and glycogen depletion. The rate of lactate accumulation during exercise is generally greater in reptiles than in amphibians, but in all cases is so rapid that the only significant substrate source to support anaerobic energy production is muscle glycogen. Vigorous behavior in these animals is therefore limited to some degree by the maintenance and replenishment of muscle glycogen stores. Whereas data from rats and dogs suggest that most lactate is oxidized to CO₂ following exercise, amphibians and reptiles appear to use lactate as a substrate for immediate muscle glycogen replenishment. Data from a variety of amphibians and lizards demonstrate that lactate removal following activity and glycogen replenishment are stoichiometrically and temporally related. Studies employing isotopically labelled compounds in intact frogs and lizards indicate that most lactate is resynthesized to glycogen during recovery. *In vivo* studies suggest skeletal muscle as the site for gluconeogenesis from lactate, and *in vitro* studies from many laboratories demonstrate a gluconeogenic capacity in skeletal muscle of lizards, frogs and salamanders. The liver appears to play no significant role in recovery metabolism in any of these classes. Data from lizard muscle suggest that oxidative fiber types have the most significant gluconeogenic capacity, and that the process may be stimulated by the hormonal milieu that exists following exercise. Whereas the recovery metabolism of many mammals seems to facilitate the rapid return of acid–base balance *via* lactate oxidation, the strategy of lactate removal employed by amphibians and reptiles provides for a

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mechanism of immediate muscle glycogen replenishment and consequently a re-established capacity for subsequent activity.

Introduction

The concept of exercise in a lizard or salamander is incomprehensible to some. Indeed, the mental picture of a small lizard basking beneath a saguaro cactus or a salamander residing beneath a fallen tree trunk does not exactly conjure up a situation where $\dot{V}_{O_{2max}}$ or lactate accumulation has much relevance. Perhaps in recognition of this problem of perception, physiologists interested in the exercise physiology and metabolism of amphibians and reptiles have taken to referring to their work as the study of activity physiology, although the rest of the terminology and many of the experimental designs are identical to those used by exercise physiologists. Studies of active reptiles and amphibians have made fundamental contributions to our understanding of the biology and natural history of these animals. They have also provided a different perspective on exercise physiology that has begun to influence mammalian exercise physiology as well (Gaesser and Brooks, 1984).

The physiological study of active amphibians and reptiles has continued to progress and evolve since its beginnings nearly a quarter of a century ago when physiological ecologists began to consider changes in heart rate of lizards in context with the changes in standard metabolic rates caused by variations in body temperature (Bartholomew and Tucker, 1963; Dawson, 1967). These studies were soon expanded to include consideration of anaerobic energy production during forced exercise (Moberly, 1968). By the mid 1970s, measurement of the aerobic and anaerobic contributions to energy production during forced exercise in amphibians and reptiles was routine (reviewed by Bennett, 1978, 1982). These techniques have since been employed to estimate the energetic costs of locomotion, foraging costs and the energetic costs of a variety of natural behaviors (Taigen and Pough, 1985). Comprehensive studies of the respiratory and cardiovascular responses to exercise in amphibians (Withers *et al.* 1988) and reptiles (reviewed by Gleeson and Bennett, 1985) have been fewer in number, although sufficient to describe a general pattern of response in anuran amphibians and in lizards.

Exercise physiology to some is interpreted as the study of physiological adaptation to exercise training. Such studies in amphibians and reptiles have been very few in number. Selected anuran amphibians have been shown to undergo some modest adaptation to sprint and endurance exercise. The clawed frog *Xenopus laevis* increased its sprint and long-distance swimming speed by 30–40 % in response to task-specific long-term training (Miller and Camilliere, 1981). *Rana pipiens* trained to hop to exhaustion on a treadmill for 6.5 weeks not only showed 35 % increases in endurance but also showed increased activities of oxidative enzymes in hindlimb muscles and a greater rate of lactate removal from muscle following exhaustion (Cummings, 1979). In contrast, lizards have not been shown

be responsive to laboratory training regimens. Neither sprint training (Gleeson, 1979) nor submaximal treadmill exercise (Garland *et al.* 1987) resulted in significant performance, metabolic or enzymatic adaptation consistent with a pattern known to occur following analogous training in mammals. This has led to speculation that lizards may be metabolically inflexible relative to other animals (Gleeson, 1979; Garland *et al.* 1987). This idea has not been thoroughly tested, although lizard muscle does respond to chronic electrical stimulation in a manner similar to endurance-trained mammalian muscle (T. T. Gleeson and S. L. Lindstedt, unpublished data), indicating that saurian muscle does possess some degree of metabolic plasticity that can be expressed under extreme conditions. The fact that reptilian muscle does not readily adapt to vigorous exercise training regimens or captivity in and of itself is probably not a research question of the first priority. This metabolic rigidity may have interesting consequences, however, for animals that undergo seasonal fluctuations in activity in the field.

There are currently two areas of research within the discipline of comparative activity physiology that are making interesting contributions to our understanding of vertebrate exercise physiology. The first of these is focused upon the question of how vertebrates recover metabolically from exhaustive exercise. These studies focus upon mechanisms of lactate removal and glycogen resynthesis, and are distributed across the fish, amphibian and reptilian literature. The second focus of activity is on interspecific variation in physiological and morphological traits. This research is directed at identifying characters that are predictive of interspecific variation in locomotor performance. These studies have not yet produced results of general application, but they are potentially able to identify characters that limit locomotor behavior and, thus, are very important in the context of understanding the physiological consequences of exercise in non-mammalian vertebrates. These studies have recently been reviewed by Garland and Losos (1992), and so are not discussed in detail here.

The body of this article focuses upon the physiological responses of amphibians and reptiles during and following vigorous activity. As will be apparent, most of the available data are limited to frogs and lizards. There are relatively few data from urodele amphibians, and even fewer on apodan amphibians (caecilians, gymnophiones). Our conception of reptilian responses to exercise is dominated by data from iguanid lizards. Snakes, turtles, rhynchocephalians and crocodylians are poorly represented in the data base. These are significant limitations, for the limited data prohibit us from making general statements about either vertebrate group in most cases. This issue of limited data will be returned to at the close of this paper as suggestions for additional work are offered.

In the section that follows immediately, I summarize the general response of amphibians and reptiles to vigorous activity. I have not tried to provide an exhaustive bibliography, but rather only an introduction to the literature. I will then use this general introduction as an entry into a discussion of the literature available on the strategies of metabolic recovery employed by amphibians and reptiles. Throughout this review I have tried to emphasize similarity where it exists

rather than force a contrast between amphibians and reptiles, for it appears that the two groups are physiologically more similar than once was believed.

Physiological responses to exercise

The metabolic responses of amphibians and reptiles to forced exercise are fundamentally similar. Rates of oxygen consumption (\dot{V}_{O_2}) increase by 3–10 times resting levels when exercise is vigorous (Bennett, 1978; Taigen and Pough, 1982). There is considerable interspecific variation in the aerobic capacities within both groups, with some species capable of much greater mass-corrected rates of \dot{V}_{O_2} than others. The factorial aerobic scope ($\dot{V}_{O_{2max}}/\dot{V}_{O_{2rest}}$) increases with increased body mass in anurans (Taigen and Pough, 1982), although the implications of that to the exercise capacity of large anurans are unclear. Factorial aerobic scopes do not appear to be strongly influenced by mass in lizards (Bennett, 1982). The greatest reported factorial aerobic scope (27.7) in lizards is that of the small, 27 g varanid *Varanus gilleni* (Bickler and Anderson, 1986), which, unlike its widely foraging congeners, is a secretive, arboreal animal. In general, however, species of lizards and snakes active in the field possess higher aerobic capacities than do more sedentary species. This generality is not nearly as prominent in anuran amphibians (Taigen and Pough, 1982).

The aerobic response to graded exercise in locomoting reptiles and amphibians is for the most part linear. Lizards increase their \dot{V}_{O_2} in proportion to increased treadmill speed until $\dot{V}_{O_{2max}}$ is attained. The net energetic cost of locomotion (C_n , ml O_2 g⁻¹ km⁻¹) decreases with increased body mass and is not significantly different from that for quadrupedal mammals (reviewed by John-Alder *et al.* 1986). Snakes and turtles show qualitatively similar responses to exercise (Jackson and Prange, 1979; Walton *et al.* 1990). Salamanders walking on treadmills demonstrate a metabolic response to increments in speed qualitatively similar to that of lizards, although C_n appears to be reduced to about 60–80 % of that of comparably sized lizards. Lunglessness does not seem to influence net cost of transport, although $\dot{V}_{O_{2max}}$ is lower in lungless salamanders than in comparably sized salamanders with lungs (Full *et al.* 1988). Hopping toads increase their rate of oxygen consumption in response to increasing locomotor speeds at a greater rate than predicted for similar-sized quadrupeds. As a result, net costs of locomotion are nearly 2.5 times as expensive for hopping toads than for lizards and mammals of the same size (Walton and Anderson, 1988). With the exception of the data for hopping toads, all the data indicate that the aerobic response of reptiles and amphibians to graded exercise is qualitatively similar to that of mammals.

Cardiovascular responses to exercise

Increased rates of oxygen consumption during exercise are accompanied by

Expanded cardiovascular function in reptiles and amphibians. Few data are available that describe the cardiovascular responses to exercise beyond reporting changes in heart rate or blood pressure. Data from lizards indicate that they increase both cardiac output and oxygen extraction during treadmill exercise (Gleeson *et al.* 1980). Ventilation is apparently sufficient to maintain arterial P_{O_2} and oxygen content up to work loads that elicit maximal oxygen consumption (Mitchell *et al.* 1981). Data from toads describe a similar response, where an eightfold increase in \dot{V}_{O_2} is accompanied by corresponding increases in heart rate and in oxygen extraction (Withers *et al.* 1988). Cardiovascular responses to exercise are illustrated in a three-dimensional format in Fig. 1. Each volume represents the rate of oxygen delivery as the product of the three cardiovascular variables on the right-hand side of the equation:

$$O_2 \text{ delivery} = f_H \times V_S \times (Ca_{O_2} - C\bar{v}_{O_2}),$$

where O_2 delivery is expressed as $\text{ml } O_2 \text{ kg}^{-1} \text{ min}^{-1}$, heart rate (f_H) in beats min^{-1} , stroke volume (V_S) in ml beat^{-1} , and arterial–mixed venous ($Ca_{O_2} - C\bar{v}_{O_2}$) O_2 difference in $\text{ml } O_2 \text{ ml blood}^{-1}$.

Fig. 1 illustrates for rat and dog a pattern of cardiovascular response that is typical of most mammals. Cardiovascular adjustments to exercise principally involve increases in both f_H and in oxygen extraction. Stroke volume increases during exercise are proportionally much less important. Varanid lizards appear to respond in a way similar to that of mammals. Iguanid lizards and the marine toad, in contrast, demonstrate slight reductions in V_S during exercise relative to rest. Additionally, marine toads appear to increase O_2 delivery mainly by increasing oxygen extraction from the blood more than by increasing cardiac output ($f_H \times V_S$) *per se*. The responses of these animals to exercise are discussed in more detail elsewhere (Gleeson *et al.* 1980; Gleeson and Bennett, 1985; Withers *et al.* 1988). The limited data present many questions that are as yet unanswered. The influence of body mass on reptilian and amphibian cardiovascular function is unknown because of the limited data available. There is an allometric pattern to the mammalian data that is only hinted at in Fig. 1, but is clearly evident when a larger selection of mammals is included in the data set. As body mass decreases, the maximal oxygen delivery volumes illustrated in Fig. 1 become broader as $f_{H_{\max}}$ increases and thinner as $V_{S_{\max}}$ decreases. Whether the same pattern exists in lower vertebrates is unknown. Variable body temperature is also expected to have a considerable effect on the cardiovascular response to exercise in ectothermic vertebrates, as body temperature is likely to affect not only heart rate but also cardiac contractility and oxygen-binding characteristics of blood. A hint of the influence of temperature on cardiovascular function is provided by comparison of the toad and lizard responses in Fig. 1. Data from toads were collected at body temperatures roughly 10°C cooler than those for the other animals represented and may account for the apparent emphasis in the toad on O_2 extraction rather than a more balanced increment in both cardiac output and extraction during exercise, as seen in the other animals. Thermal effects on ectothermic cardiovascu-

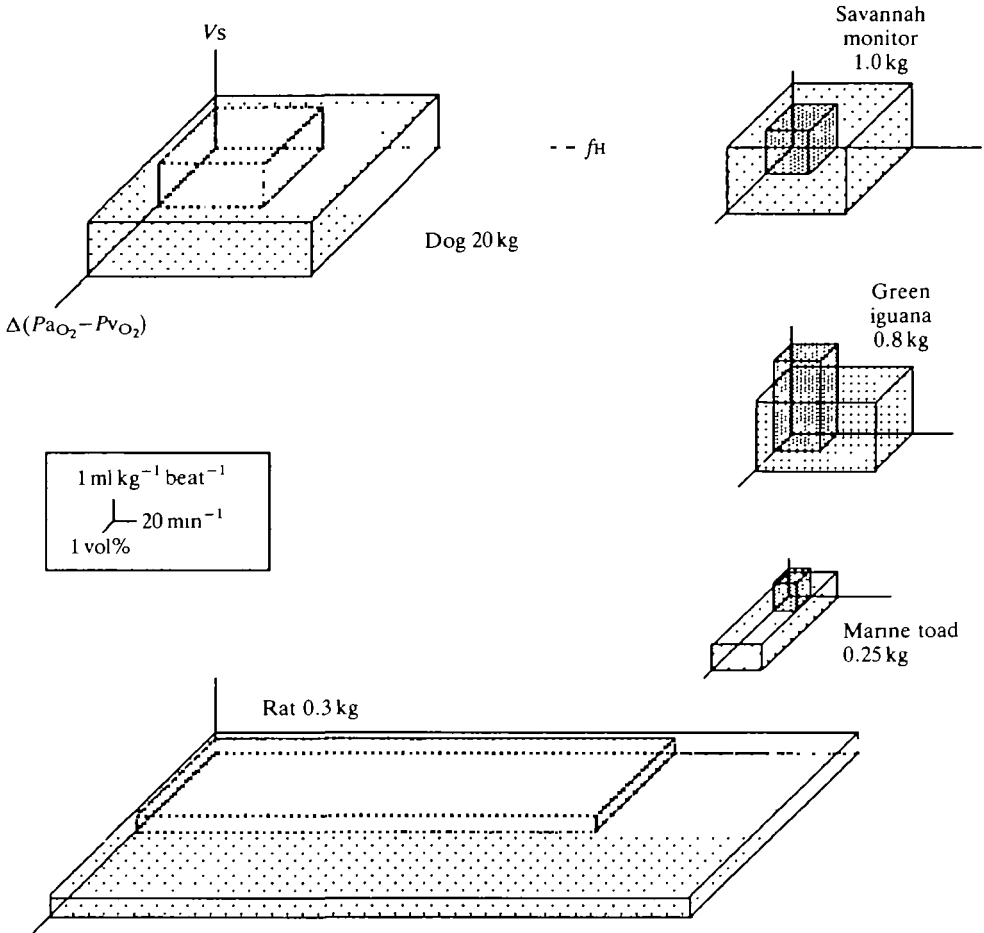


Fig. 1. Three-dimensional representation of cardiovascular adjustments to exercise in selected vertebrates. Each enclosed volume represents oxygen delivery under rest or maximal exercise conditions as the product of heart rate, stroke volume and arterial-mixed venous oxygen extraction. Resting conditions are shaded, exercise volumes are stippled. See key for units. Illustrations were prepared from data found in Gleeson and Baldwin (1981, rat), Withers *et al.* (1988, toad) and Gleeson *et al.* (1980, all others).

lar function are discussed in more depth in Gleeson and Bennett (1985). The variability and degree of regulation of cardiac separation of oxygenated and deoxygenated blood as a function of exercise are also features of cardiovascular function that have not yet been adequately addressed in lower vertebrates. The Withers and Hillman (1988) model for anuran cardiovascular function predicts that variance in the degree of separation may have considerable effects on oxygen transport during exercise. A good model system in which to study these questions has yet to be developed.

Lactate production during exercise

Lactate accumulation is a nearly universal response to exercise in lower vertebrates, accompanying the respiratory and cardiovascular responses summarized above. Lactate production is very rapid. Whole-body lactate accumulation in a variety of small lizards averages 8.5 mmol kg^{-1} during the first 30 s of exercise (Fig. 2). Rates of accumulation in anuran amphibians are generally half to one-third of reptilian rates, but still quite significant from an energetic perspective (Bennett, 1982). These rates result in maximum whole-body lactate concentrations at exhaustion of approximately 18 mmol l^{-1} in lizards and snakes and 10 mmol l^{-1} in amphibians. Peak blood lactate concentrations of $16\text{--}20 \text{ mmol l}^{-1}$ are common in lizards (Gleeson and Bennett, 1985). Putnam (1979) reported peak blood lactate concentration of $25\text{--}39 \text{ mmol l}^{-1}$ in two species of anurans.

The resulting ATP generation *via* glycolysis that accompanies lactate accumulation in lizards and frogs is responsible for 60–80 % of the total ATP generated during exercise of only a few minutes duration. This is in contrast to the 5–20 % contribution that lactate accumulation makes to the energetic support of similar activity in small rodents (Ruben and Battalia, 1979) and presumably other mammals as well. This greater emphasis on anaerobic glycolysis for the support of vigorous exercise has several consequences for the biology of amphibians and reptiles. Muscle contractile function and whole-animal locomotor performance are both negatively impacted by prior activity (Putnam, 1979; Gleeson, 1980). This response could be due to pH depression, glycogen depletion or other factors associated with exercise. Vigorous exercise will almost always result in an

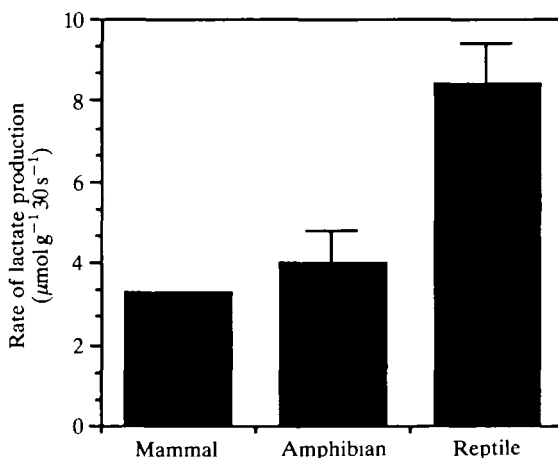


Fig. 2. Initial rates of lactate production during the first 30 s of vigorous exercise in reptiles, amphibians and small rodents. Data are means and 1 s.e.m. of six reptile species and 10 amphibian species calculated from Bennett (1982). Data from two rodent species are estimated from Ruben and Battalia (1979). The data illustrate a similar rate for lactate production during the initial phase of exercise in all three groups.

acid–base imbalance associated with the lactic acid production. Lactate and hydrogen ion accumulations are two of several factors associated with the onset of fatigue in animals (Roberts and Smith, 1989), and perhaps limit the duration or intensity of activity under some circumstances. It is also reasonable to assume that the state of muscle glycogen depletion following exercise also constrains subsequent behavior in these animals, just as glycogen stores appear to influence endurance exercise in mammals (Roberts and Smith, 1989).

Post-exercise depressions in blood pH of 0.5–1.0 unit are common and mean that recovery from exhaustion starts with blood pH in the range 6.6–7.0 (Putnam, 1979; Gleeson and Bennett, 1985). The effect of this acidosis on physiological function is uncertain. Muscle contractile function has been shown to recover from a fatigued state more slowly in an acidic extracellular environment (Renaud and Mainwood, 1985; Roberts and Smith, 1989), which suggests a pH effect on recovery. Carrier-mediated lactate transport across the sarcolemmal membrane is known to involve cotransport of protons and hence the rate of lactate transport is influenced by both intracellular and extracellular pH (Mason and Thomas, 1988; Roth and Brooks, 1990). pH-sensitive lactate transport into and out of muscle fibers predicts that, at the organismal level, recovery metabolism will also be pH-sensitive. Glycogen synthesis from lactate has recently been shown to be stimulated by acidic extracellular conditions (pH=6.5) in rat muscle (Bonen *et al.* 1990), supporting the above prediction.

In addition to well-documented respiratory adjustments (Gleeson and Bennett, 1985), lactate metabolism is an important process for re-establishing acid–base balance following exercise. Both lactate oxidation and the gluconeogenic conversion of lactate to glucose remove protons stoichiometrically with lactate anions. The alkalizing effect of lactate removal has been demonstrated in varanid lizards, where animals infused with sodium lactate become alkalotic (Mitchell and Gleeson, 1985) as lactate anions and protons are consumed during the recovery process.

It is also true, however, that vigorous activity in amphibians and reptiles is accompanied by partial depletion of muscle glycogen stores (Putnam, 1979; Gleeson, 1982; Fig. 3) which could also be a factor significant in depressing muscle function and locomotor performance following exercise. In the section that follows, the pattern of recovery from exhaustive exercise is considered in more detail, with an emphasis on how amphibians and reptiles remove lactate and re-establish resting glycogen concentrations in muscle. The data indicate that both amphibians and reptiles utilize a significant fraction of the post-exercise lactate as a substrate for direct glycogen resynthesis.

Patterns of metabolic recovery

There is no consistent relationship between post-exercise oxygen consumption and lactate removal in amphibians and reptiles. The most striking disjunction between lactate removal and elevated oxygen consumption after exercise is in

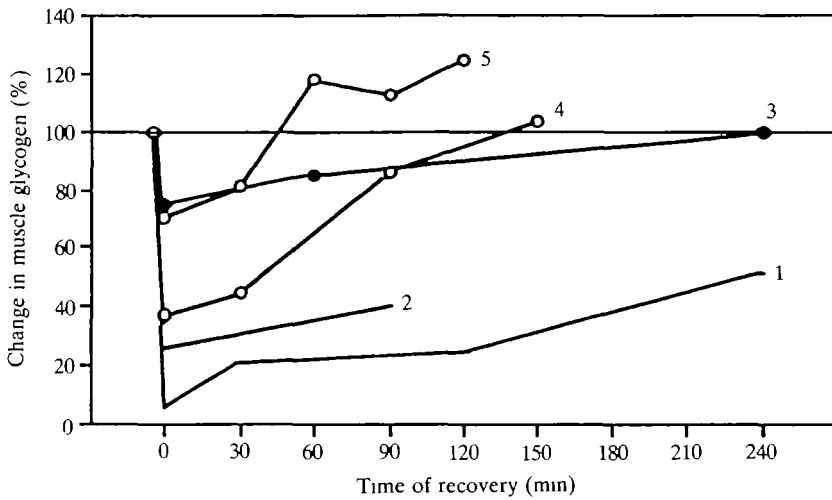


Fig. 3. Change in muscle glycogen level as a function of time following exercise. Data are from mammals (solid lines), amphibians (line and filled circles) and lizards (line and open circles). Line 1: rat, resting glycogen ($[\text{glycogen}]_{\text{rest}} = 31 \mu\text{mol glucosyl units g}^{-1}$ muscle (Gaesser and Brooks, 1984); line 2: man, $[\text{glycogen}]_{\text{rest}} = 150 \mu\text{mol g}^{-1}$; line 3: frog, $[\text{glycogen}]_{\text{rest}} = 100 \mu\text{mol g}^{-1}$ (P. Fournier and H. Guderley, in preparation); line 4: lizard, $[\text{glycogen}]_{\text{rest}} = 16 \mu\text{mol g}^{-1}$ (Gleeson, 1982); line 5: lizard, $[\text{glycogen}]_{\text{rest}} = 47 \mu\text{mol g}^{-1}$ (Gleeson and Dalessio, 1989).

anuran amphibians, where lactate accumulation persists for hours after \dot{V}_{O_2} has returned to pre-exercise rates (Bennett and Licht, 1973; Withers *et al.* 1988). The same pattern is often (Gleeson, 1980; Gleeson and Bennett, 1985), but not always (Gleeson and Dalessio, 1989), observed in lizards. In rats, post-exercise \dot{V}_{O_2} remains elevated long after blood lactate concentrations have returned to normal, while the opposite appears to occur in man. These observations have contributed to the recent re-evaluation of the original theory of oxygen debt, which suggested that a significant fraction of the post-exercise \dot{V}_{O_2} was attributed to the energetic cost of lactate removal (see Gaesser and Brooks, 1984). It now appears that post-exercise \dot{V}_{O_2} has a complex cause or causes, of which lactate metabolism may only be a part.

Lactate removal

Lactate removal following exercise is a process that proceeds much more slowly in reptiles and amphibians than in mammals (Fig. 4), even when the difference in body temperature is taken into account. Rats and man require no more than 30–60 min to return blood lactate to resting levels after exhaustive exercise (see Gaesser and Brooks, 1984). In contrast, many reptiles and amphibians require hours for lactate levels to return to normal (Moberly, 1968; Cushman *et al.* 1976; Gleeson, 1980; Gleeson and Bennett, 1985; Withers *et al.* 1988). The rate of lactate removal is temperature-sensitive in lizards. Laboratory measurements of

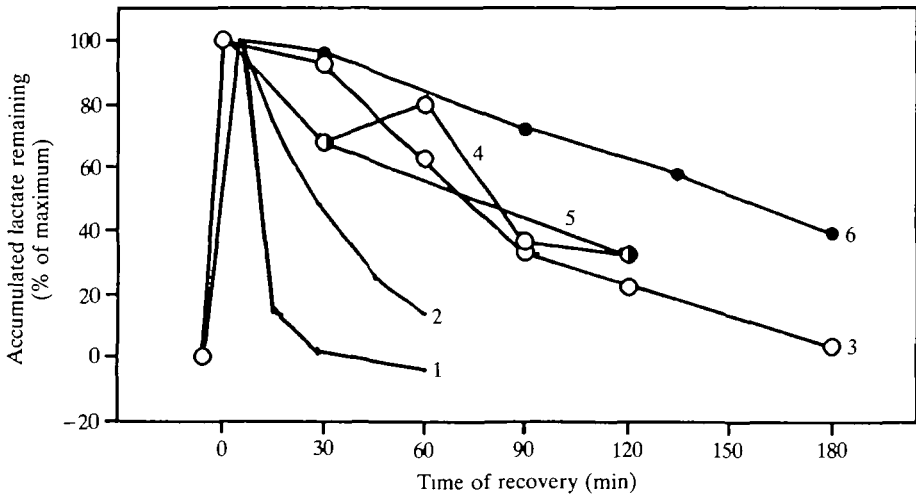


Fig. 4. Change in blood lactate concentration as a function of time following brief exercise. Data are normalized to the percentage of maximum lactate accumulation remaining at any given time, and illustrate the longer times required for lactate removal by amphibians and reptiles relative to mammals. Symbols as in Fig. 3. Line 1: rat, $[\text{lactate}]_{\text{max}}=6 \text{ mmol l}^{-1}$ (Brooks *et al.* 1973); line 2: man, $[\text{lactate}]_{\text{max}}=15 \text{ mmol l}^{-1}$ (Åstrand *et al.* 1986); line 3: marine iguana, $[\text{lactate}]_{\text{max}}=17 \text{ mmol l}^{-1}$ (Gleeson, 1980); line 4: desert iguana, $[\text{lactate}]_{\text{max}}=21 \text{ mmol l}^{-1}$ (Gleeson and Dalessio, 1989); line 5: frog, $[\text{lactate}]_{\text{max}}=10 \text{ mmol l}^{-1}$ (Bennett and Licht, 1973); line 6: salamander, $[\text{lactate}]_{\text{max}}=15 \text{ mmol l}^{-1}$ (Bennett and Licht, 1973).

Q_{10} values of 1.5–2.5 (Moberly, 1968; Bennett and Licht, 1972; Gleeson, 1980) suggest that animals selecting cooler temperatures at which to recover will slow their rate of lactate removal considerably. The temperature sensitivity of lactate removal may have important consequences for the fate of lactate, as the gluconeogenic and oxidative pathways that are employed in lactate removal may be differentially affected by temperature. This aspect of lactate metabolism has not yet been addressed in either group of vertebrates.

Coulsen (1987) has suggested that the rate of lactate removal is mass-dependent in all vertebrates. Basing his argument on the known relationship between body mass and resting or standard metabolic rates, Coulsen suggested that recovery rates might range from 2.9 h for 5 g *Anolis* lizards to 1.8 days for 700 kg alligators. Actual data on this point are incomplete. Recovery times in *Anolis* at preferred body temperatures are approximately 90 min (Bennett and Licht, 1972), while those for crocodiles ranging from 0.4 to 180 kg average approximately 180 min, with no size effect intraspecifically (Seymour *et al.* 1985). In between are data from a number of lizards ranging between 0.1 and 1 kg, which also exhibit recovery times in the 120–180 min range (Gleeson, 1980, 1982; Gleeson and Dalessio, 1989). Amphibian data are also unclear on this point. Interpretation of the data presently available suggests that no strong relationship exists between body mass and recovery time for these animals.

Fate of post-exercise lactate

Glycogen replenishment is temporally and stoichiometrically matched to lactate removal in most amphibians and reptiles studied (Figs 3 and 4). This has been shown to be true in snakes (Gratz and Hutchison, 1977), lizards (Gleeson, 1982; Gleeson and Dalessio, 1989), salamanders (Hutchison *et al.* 1977) and frogs (P. Fournier and H. Guderley, in preparation). This linkage has suggested to the above authors a substrate-product relationship where lactate provides the carbon skeleton for glycogen resynthesis. The same relationship has been inferred from the data for rainbow trout (Milligan and Wood, 1986). This is a significantly different pattern from that seen in rats (Gaesser and Brooks, 1984). Numerous studies in rats support the original observation of Brooks *et al.* (1973) that glycogen depletion remains long after lactate levels have returned to normal. The principal pathway for lactate removal has been shown to be oxidation to CO₂ and H₂O in rats (Brooks *et al.* 1973; Gaesser and Brooks, 1984), and the different patterns of lactate and glycogen metabolism seen in ectothermic vertebrates compared with mammals suggest that there is a different fate for lactate following exercise. This has led to a number of studies to determine the metabolic fate of lactate in reptiles and amphibians.

In vivo experimentation to determine the mechanism of lactate removal supports the conclusion of a non-oxidative fate for lactate. In the anuran amphibian *Bufo americanus*, only about 7% of the ¹⁴C-labelled lactate injected into exhausted animals appeared as ¹⁴CO₂ after 4 h of recovery at 20°C (Withers *et al.* 1988), although nearly all the post-exercise lactate accumulation had been eliminated. Label was found to be deposited in most tissues of the toad, with levels in skeletal muscle and skin being the most significant. This study indicated that 22–39% of the label found in each tissue was in glycogen, with a similar fraction in protein. In an analogous study of the lizard *Dipsosaurus dorsalis*, 2 h of recovery from exhaustive treadmill running at preferred temperatures of 40°C resulted in metabolic removal of nearly 80% of the accumulated lactate (Gleeson and Dalessio, 1989). Approximately 16% of the removed lactate was oxidized under these conditions, accounting for 40% of the total oxygen consumption following exercise. Distribution of the ¹⁴C at the end of 2 h suggested that approximately 50% of the metabolized lactate was gluconeogenically converted to glucose or glycogen while another 7% was incorporated into protein. These studies of intact animals provide persuasive evidence that the recovery strategy of frogs and lizards does not emphasize the oxidative removal of lactate (Fig. 5). These data are supported by a much larger and older literature on *in vitro* experimentation which collectively documents the ability of amphibian and reptilian muscle to convert lactate to glycogen. These data are discussed below.

Locus of post-exercise lactate metabolism

One logical site for the gluconeogenic removal of lactate in vertebrates would be the liver, a tissue noted for its gluconeogenic capacity (Kraus-Friedmann, 1984).

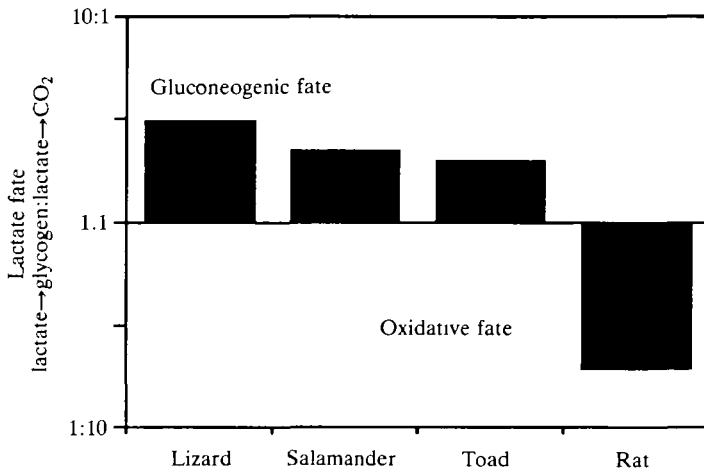


Fig. 5. Relative fate of post-exercise lactate in selected vertebrates. Ratios are based upon moles of lactate oxidized to CO_2 and H_2O versus moles converted to glucose or glycogen. Data from Gleeson and Dalessio (1989, lizard); S. J. Wickler and T. T. Gleeson (unpublished results, salamander); Withers *et al.* (1988, toad); Brooks and Gaesser (1980, rat).

Such a role for the liver would require the export of lactate from muscle coupled to hepatic glucose production; glucose would then be taken up by the muscle and used to synthesize glycogen. There are several lines of evidence that suggest that the liver is not of central importance during recovery from exhaustive exercise in reptiles and amphibians. The most striking data come from the dissertation research of Paul Fournier (P. Fournier and H. Guderley, in preparation), who found that the pattern and magnitude of lactate removal and muscle glycogen synthesis were no different in hepatectomized and in normal *Rana pipiens*. This demonstrates quite clearly that liver is not an important participant in recovery metabolism in frogs. They went on to show that perfused livers of *Rana* are largely incapable of converting lactate to glucose, despite possessing the enzymatic machinery to do so. The failure of frog liver to metabolize lactate is consistent with the data of Phillips and Hird (1977), who demonstrated the lack of a gluconeogenic capacity in liver slices of the axolotl (*Siredon mexicanum*) and the lack of key gluconeogenic enzymes in the liver of the toad *Bufo marinus*.

Another line of evidence against hepatic involvement in recovery comes from the lizard *Dipsosaurus dorsalis*. The skeletal muscle of this lizard has been shown to utilize little glucose *in vivo* during recovery (Gleeson and Dalessio, 1990). Only 9% of the post-exercise glycogen synthesis could be attributed to uptake of blood glucose during 2 h of recovery, a situation incompatible with a mechanism employing hepatic glucose as a source for glycogen synthesis. In addition, only a small amount of [^{14}C]glucose was formed by *Dipsosaurus* following [^{14}C]lactate injection *in vivo* (Gleeson and Dalessio, 1989), despite the capacity of reptilian

er for lactate utilization *in vitro* (Phillips and Hird, 1977; S. J. Wickler and T. T. Gleeson, unpublished data).

The literature supports the conclusion that the locus for lactate metabolism is skeletal muscle. Amphibian skeletal muscle was shown to possess the capacity for direct conversion of lactate to glycogen in the early portion of this century by Meyerhof, Hill and others (references in Gaesser and Brooks, 1984). More recently, glycogen synthesis from lactate has been shown to occur in *Rana* muscle using a variety of techniques and protocols (Gourley and Suh, 1969; Bendall and Taylor, 1970; Connett, 1979). The study of Gourley and Suh suggests that when amphibian muscle is exposed to resting glucose and moderate lactate concentrations, lactate will be preferentially oxidized while glucose is used as a substrate for glycogen synthesis. The other studies show that, when lactate is provided as the sole substrate, or with acetate, approximately 5–6 times as much lactate is converted to glycogen as is oxidized, consistent with the early observations of Meyerhof. Recent work has shown that salamander muscle from neotenic *Ambystoma tigrinum* also utilizes lactate as a gluconeogenic rather than oxidative substrate (S. J. Wickler and T. T. Gleeson, unpublished data). These *in vitro* results with amphibian muscle are all consistent with the pattern of lactate metabolism observed *in vivo* described earlier.

Lizard muscle also demonstrates a gluconeogenic capacity. Iliofibularis muscle from the hindlimb of the desert iguana is capable of synthesizing glycogen directly from lactate *in vitro* when lactate is the only available substrate, or when it is in combination with glucose (see Fig. 7). There appears to be a seasonal component to this capacity, as animals tested in winter lacked the capacity evident in summer animals (Gleeson, 1985). This capacity appears to be utilized *in vivo* after vigorous activity and results in hindlimb muscle glycogen concentrations 24% above pre-exercise values (Gleeson and Dalessio, 1990). Current research indicates a similar capacity in the lizard *Anolis carolinensis* (S. J. Wickler and T. T. Gleeson, unpublished data).

Muscle fiber type specificity for gluconeogenesis

The segregation of oxidative and glycolytic fibers in the iliofibularis muscle of *Dipsosaurus dorsalis* has allowed evaluation of the gluconeogenic capacity of lizard fiber types. The iliofibularis (IF) muscle of *Dipsosaurus* is composed of two oxidative and one glycolytic fiber type which have been well characterized physiologically (Fig. 6). The red portion of the IF is composed of a slow, oxidative fiber type (SLO) and a fast-twitch, oxidative, glycolytic (FOG) fiber type in the ratio of approximately 1:3. The larger white region of the IF contains 100% fast-twitch, glycolytic (FG) fibers. The red IF is characterized as having greater capillary and mitochondrial densities than does the white region of the muscle. When red and white bundles of the IF are incubated with lactate, only the red IF demonstrates an increase in glycogen concentration (Gleeson, 1985). When incubated with ¹⁴C-labelled lactate or glucose, all three fiber types demonstrate label incorporation into glycogen, although FG fibers do so at a reduced rate equal

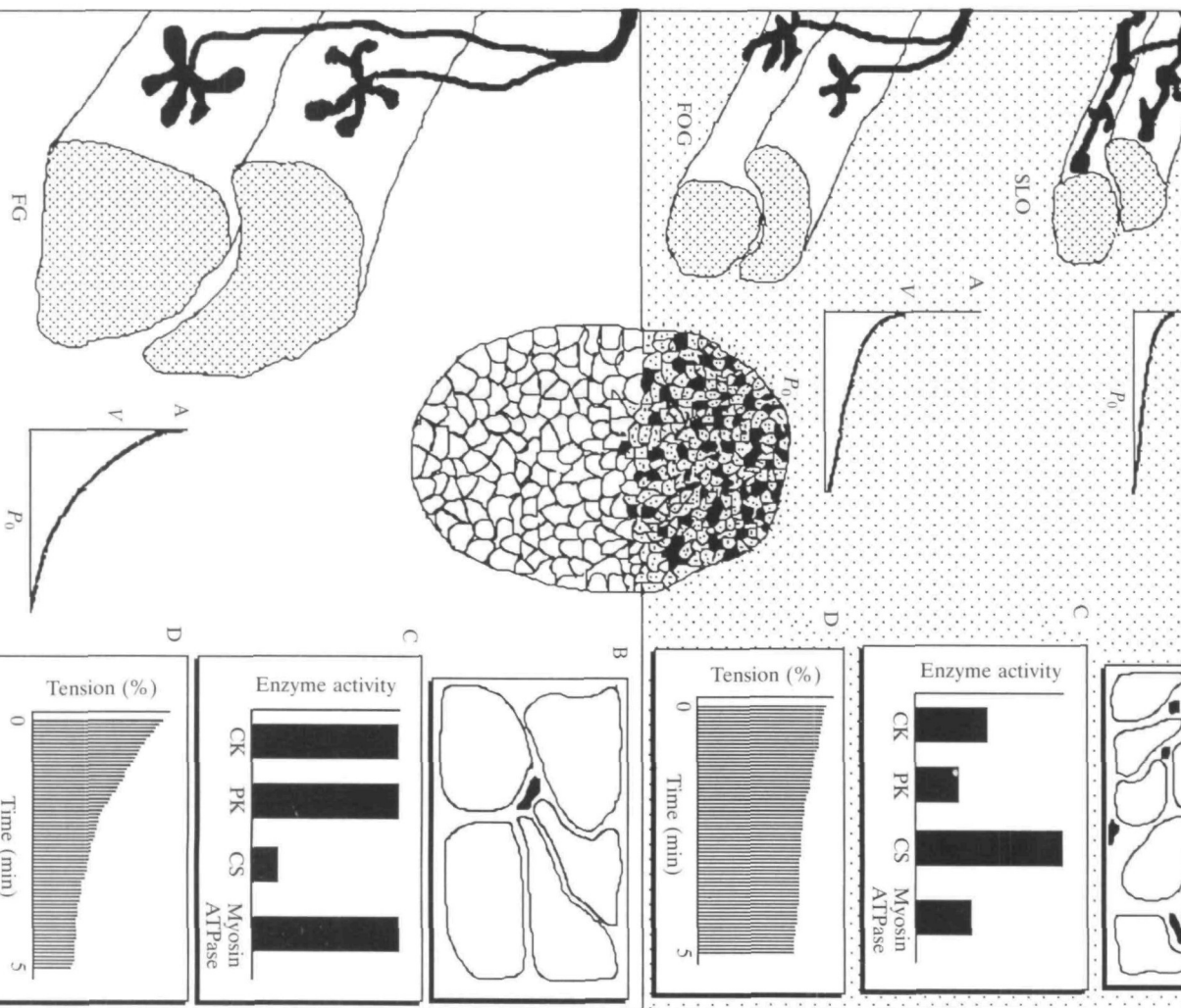


Fig. 6. A summary of the fiber type composition and physiological characteristics of the iliofibularis (IF) muscle of the iguanid lizard *Dipsosaurus dorsalis* used in studies of lactate metabolism. The red region of the IF (shaded portion) is composed of slow oxidative (SLO) fibers, which are multi-terminally innervated, and focally innervated fast oxidative glycolytic (FOG) fibers. The white portion of the IF is composed entirely of focally innervated fast glycolytic (FG) fibers. Force-velocity curves (A) illustrate the relative shortening velocity of the three types. B illustrates the relative fiber dimensions and capillary densities. C illustrates the relative activities of creatine kinase (CK), pyruvate kinase (PK), citrate synthase (CS) and myosin ATPase of the red and white regions of the IF. D illustrates the fatigue resistance of the two regions when stimulated to twitch (1 Hz) for 5 min. Data for A and B are from Gleeson *et al.* (1984) and Johnston and Gleeson (1987); data for C and D are from Gleeson *et al.* (1980) and Gleeson and Harrison (1988).

to one-fifth of the rate of FOG and SLO fibers (Fig. 7). Fibers incubated *in vitro* also demonstrate a rate of glycogen synthesis from lactate that is approximately 10 times the rate of synthesis from glucose, consistent with the *in vivo* substrate preferences of intact muscle (Gleeson and Dalessio, 1990).

Fiber types behave similarly *in vivo*. Vigorous treadmill activity depletes fiber glycogen by 25 % in the red IF and 42 % in the white FG fibers, while fiber lactate concentrations increase to 35 and 48 mmol l⁻¹, respectively (Fig. 7). During recovery, SLO and FOG glycogen increases to 139 % of resting concentrations. The glycogen concentration of FG fibers of the iliofibularis remains depressed, although lactate concentrations return to normal. The data appear to suggest that FG-derived lactate is used to support glycogen synthesis in SLO and FOG fibers. Brooks (1985, 1986) described a phenomenon in mammalian muscle where glycolytic fiber types produce lactate during exercise while oxidative fiber type utilize the lactate as an oxidative substrate. He coined the term 'lactate shuttle' to describe the process. In reptiles, the lactate shuttle appears to operate, but with a different end result. In *Dipsosaurus*, SLO and FOG fibers appear to be net utilizers of the lactate produced by FG fibers, but the fate of the lactate is gluconeogenesis rather than oxidation. To the extent that more glycogen is synthesized in SLO and FOG fibers during recovery than was utilized during exercise, oxidative fiber types are essentially sinks for lactate produced by FG fibers – a gluconeogenic version of the mammalian lactate shuttle.

There are no data on the specificity for lactate metabolism in amphibian muscle fiber types. Comparative data are presently available from rats, rabbits and man. Perfused hindlimb and incubated muscle experiments with rat muscles have shown that fast-twitch fiber types have a greater capacity to synthesize glycogen directly from lactate than do slow-twitch fibers (FG=FOG ≫ SO), although lactate incorporation into glycogen is diminished when physiological glucose concentrations are also available to the muscle (McLane and Holloszy, 1979; Bonen *et al.* 1990). This is a very different pattern from that found in lizards, both in terms of the ranking of fiber type capacity and in the competitive effect of glucose as a

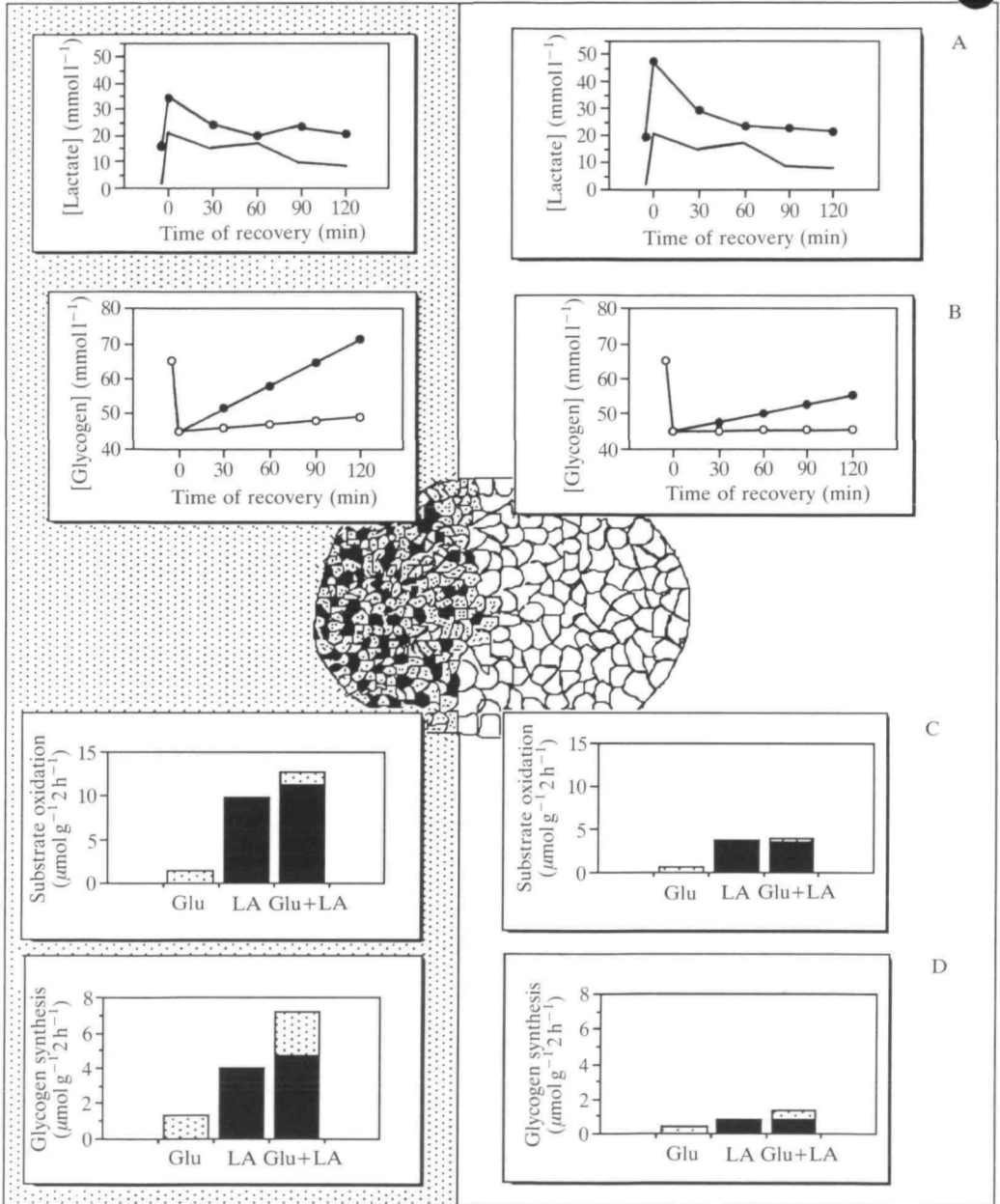


Fig. 7

glycogenic substrate. In the intact rat, post-exercise rates of glycogen synthesis are greater in FOG and SO fibers than in FG fibers (Terjung *et al.* 1974; Hutber and Bonen, 1989), which is in contrast to expectations if lactate was an important glycogen precursor. Rabbit fiber types *in vitro* behave similarly (Pagliassotti and Donovan, 1990). In man, the situation is confused by conflicting reports

Fig. 7. A summary of lactate and glycogen metabolism in the red (left) and white (right) regions of the iliofibularis of the lizard *Dipsosaurus dorsalis*. (A) *In vivo* muscle lactate concentration before and following 5 min of exhausting exercise (lines and circles). The reference line is for blood lactate concentration under the same conditions. (B) *In vivo* rates of glycogen synthesis from lactate (filled circles) and glucose (open circles) following injection of ^{14}C -labelled substrate at the point of exhaustion. (C) *In vitro* rates of substrate oxidation when fiber bundles are incubated for 2 h in 8.5 mmol l^{-1} glucose (Glu) and 15 mmol l^{-1} lactate (LA) alone and combined. Substrate oxidation is expressed in μmoles of glucose equivalents. (D) *In vitro* rates of glucose and lactate incorporation into muscle glycogen under the same conditions as in C. Units are as in C. Data in A and B are from Gleeson and Dalessio (1990), and in C and D from Gleeson and Kolok (1990).

Calculations based upon substrate concentration changes and metabolite exchange across splanchnic and muscle beds indicate that roughly 50% of post-exercise lactate is gluconeogenically removed by muscle (Hermansen and Vaage, 1977; Åstrand *et al.* 1986). Others, using similar techniques or isotopic tracers, have concluded that 20% or less of the accumulated lactate is gluconeogenically removed following exercise (Gaesser and Brooks, 1984; Brooks, 1986; Peters Futre *et al.* 1987). Human fiber type specialization for lactate metabolism has yet to be determined.

Fiber type specificity in lactate metabolism is of significance both intra- and interspecifically. Putnam *et al.* (1980) have shown that different muscles within a single species vary considerably in their fiber type composition. Such variation would predict that different muscles function differently during recovery; muscles enriched with FOG or SLO fibers would be expected to function as lactate sinks relative to muscles poor in these fiber types. Considerable variation in fiber type composition of a single muscle also exists among individuals. The oxidative (and gluconeogenic) fibers of the iliofibularis of male *Dipsosaurus* vary between 8 and 48% of muscle cross-sectional area, while the oxidative regions of two other muscles vary between 5 and 30% (Gleeson and Harrison, 1988). Individuals with high proportions of oxidative fiber types would be predicted to have roughly twice the capacity for lactate-supported gluconeogenesis than would individuals with impoverished fiber populations. Such fiber type variation might well be responsible for variable rates of lactate accumulation during exercise as well. Data that test these hypotheses would be most interesting.

Differences in fiber type composition among related species might also suggest different patterns of lactate metabolism in those animals. Fiber type variation in homologous muscles of different species of amphibians (Putnam and Bennett, 1983; Morgan and Proske, 1984) and reptiles (Guthe, 1981; Gleeson, 1983) is considerable. These differences have usually been discussed in terms of the activity capacity or locomotor behavior of the animals compared. It is likely, however, that these differences also translate into differences in lactate metabolism that have yet to be investigated.

Concluding remarks

Lactate metabolism is centrally important to the biology of active amphibians and reptiles. We have a reasonable understanding of the conditions for and magnitude of lactate production during activity. The consequences of the acidosis and the glycogen depletion resulting from anaerobic energy production are less well understood. Based upon limited studies of anuran amphibians and lizards, a pattern has emerged for lactate removal that is different from that in most mammals studied. The skeletal muscle of amphibians and reptiles is an important gluconeogenic organ following activity. It is not clear that the liver plays any significant role in recovery metabolism. The regulation of muscle gluconeogenesis is probably influenced by pH, body temperature, seasonality, hormone titers following exercise and by other variables. These factors have yet to be investigated in depth. How the behavior of a fatigued animal might alter the pattern of recovery metabolism is also unknown.

The biochemical pathways employed by amphibians and reptiles in metabolizing lactate are also worthy of study, as several studies have shown gluconeogenesis to occur in muscles, despite the uncertain presence of enzymes required for hepatic gluconeogenesis (see references in Bendall and Taylor, 1970; McLane and Holloszy, 1979; Pagliassotti and Donovan, 1990). The specialization of amphibian fiber types for lactate metabolism and the implications of variable fiber type composition for individual or species capacities for muscle-based metabolic recovery are also presently unknown.

It is apparent that the pattern of lactate metabolism in frogs and lizards is different from that in rats, rabbits and probably most other mammals. The significance of such a strategy of recovery metabolism for these animals is not yet clear. Two non-exclusive suggestions have been offered. Withers *et al.* (1988) have suggested that gluconeogenic removal of lactate in ectothermic vertebrates is much faster than would be a strategy of lactate oxidation, and therefore acid-base balance is re-established more quickly. This argument is based upon the known, low rate of oxidative metabolism of ectothermic vertebrates relative to comparable-sized endotherms. Gleeson and Dalessio (1989, 1990) have speculated that a gluconeogenic fate for lactate serves to replace muscle glycogen stores rapidly, a feature beneficial for animals dependent upon glycogen-supported glycolysis for the energetic support of vigorous activity. Such a pattern of lactate removal would, therefore, better defend the behavioral repertoire of the animal than would a strategy where muscle glycogen is not quickly replaced. A significant handicap to efforts made to answer these and related questions is the lack of a broader perspective of lactate metabolism in amphibians and reptiles. Our current focus on anuran amphibians and on lizards probably blinds us to the real metabolic variability that exists among vertebrates. A broader phylogenetic approach to our study of lactate metabolism would allow us to consider the physiology of recovery within the context of diverse behaviors and locomotor capacities, and it would allow us to employ an evolutionary approach to some of the questions above that is not possible at present.

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