## Introduction

This paper discusses certain aspects of the metabolic acidosis which accompanies heavy exercise, concentrating on the factors influencing hydrogen ion production and the associated effects on carbon dioxide output and ventilation. Classical concepts of lactic acidosis in exercise were established many years ago (Hill, 1932; Margaria, Edwards & Dill, 1933) and continue to be widely accepted. In situations where oxygen delivery to muscles does not match the demands for oxidative phosphorylation of ADP through aerobic metabolism, the deficit in energy needs (the 'oxygen deficit') is met by anaerobic glycolysis with the production of lactic acid. Thus lactic acid production may occur at the onset of exercise, in the transition between one work load and one of higher power or when very heavy exercise is undertaken. The consequent rise in blood lactate concentration is accompanied by an equivalent fall in blood bicarbonate concentration, by an increase in carbon dioxide output ($V_{\text{CO}_2}$) which is relatively greater than the increase in oxygen uptake ($V_{\text{O}_2}$) and by a high respiratory exchange ratio ($R = V_{\text{CO}_2}/V_{\text{O}_2}$). The concept of an 'anaerobic threshold' has been introduced (Wasserman, Whipp, Koyal & Beaver, 1973); this may be defined practically during an exercise test, in which power is progressively increasing, by observing the point at which there is an abrupt increase in ventilation ($V_e$) for a given $V_{\text{O}_2}$; i.e. the point at which the ventilatory equivalent for oxygen ($V_e/V_{\text{O}_2}$) increases.

Although the acidosis of exercise is ascribed to imbalance between muscle oxygen demand and supply, it is difficult to establish a causal relationship between oxygen debt and changes in blood lactate concentration (Harris, 1969). Furthermore there is evidence that acidosis per se may impair muscle performance in spite of an adequate oxygen supply (Jones, Sutton, Taylor & Toews, 1977). For these reasons the point of departure for the present review will be the removal of $H^+$ from muscles rather than the delivery of oxygen to them. In the last decade increasing attention has been paid to mechanisms of muscle $H^+$ release, buffering and transfer; muscle lactate production and its subsequent metabolism; carbon dioxide evolution and excretion. This recent research allows us to look at the acidosis of exercise and the associated changes in carbon dioxide output and ventilation from an alternative standpoint to the classical oxygen-centred concept.

Energy for muscle contraction is released from the splitting of ATP:

$$\text{ATP} \rightarrow \text{ADP} + P_1 \quad (1)$$

As stores of ATP are limited there is a need for rapid resynthesis, if exercise is to continue. An immediately available source is the phosphocreatine (PCr) stored in muscle:

$$\text{PCr} + \text{ADP} \rightarrow \text{creatinine} + \text{ATP} \quad (2)$$

Ignoring for the time being fats and amino acids, the other fuels are glycogen in muscle and glucose made available by the liver. Although both may be hydrolysed aerobically or anaerobically, evidence obtained from muscle enzyme activities suggests that glycogen is the preferred source when anaerobic processes are required (Newsholme & Start, 1973). For glucose the aerobic process may be simply represented by eqn. (3) (Lehninger, 1975).

$$\text{Glucose} + 6\text{O}_2 + 36\text{P}_1 + 36\text{ADP} \rightarrow 6\text{CO}_2 + 36\text{ATP} + 6\text{H}_2\text{O} \quad (3)$$

As ATP is used in the conversion of glucose into
glucose 6-phosphate, one more ATP molecule is synthesized when the reaction begins with glycogen. The anaerobic process starting with glycogen, is shown by eqn. (4).

\[
\text{(Glycogen-glucose) + 3P}_1 + 3\text{ADP} \rightarrow 2 \text{ lactic acid} + 3\text{ATP}
\] (4)

At physiological pH almost all of the lactic acid is in the dissociated form, so that two H\(^+\) are formed in the reaction expressed in this way.

**Source of protons during exercise**

The simple biochemical relationships above yield only a shortsighted view of proton release because the ionic state of the reactants is ignored. As they may exist in either acidic or basic forms, the net charges need to be taken into account. Reference to a biochemistry text (Lehninger, 1975) will show that the equations may be written more accurately and the source of protons is not what it seemed at first. The reaction represented in eqn. (1) leads to the production of protons and may be described as shown by eqn. (5).

\[
\text{ATP}^{4-} + \text{H}_2\text{O} \rightarrow \text{ADP}^{3-} + \text{P}_i^{2-} + \text{H}^+ \quad \text{ (5)}
\]

(or \(\text{MgATP}^{2-} + \text{H}_2\text{O} \rightarrow \text{MgADP}^{1-} + \text{P}_i^{2-} + \text{H}^+)\)

Similarly for eqn. (2), the creatine kinase reaction leads to absorption of protons:

\[
\text{PCr}^{2+} + \text{ADP}^{3-} + \text{H}^+ \rightarrow \text{Cr}^+ + \text{ATP}^{4-} \quad \text{(6)}
\]

The aerobic hydrolysis of glucose to carbon dioxide and water, linked to oxidative phosphorylation of ADP, absorbs protons. The more accurate form of eqn. (3) is written as shown by eqn. (7) (Lehninger, 1975).

\[
\text{Glucose} + 36\text{ADP}^{3-} + 36\text{P}_i^{2-} + 36\text{H}^+ + 6\text{O}_2 - 6\text{CO}_2 + 36\text{ATP}^{4-} + 42\text{H}_2\text{O}
\]

(7)

If this reaction maintains the content of ATP, there is no net change in protons because the protons liberated (eqn. 5) are absorbed and oxidized through electron transport to oxygen (eqn. 7).

The early part of glycolysis leading to the formation of pyruvate is associated with the production of reduced nicotine adenine dinucleotide (NADH) and a proton and the subsequent re-formation of NAD\(^+\) from NADH requires the removal of two protons. In contrast to aerobic glycolysis (eqn. 7), in which protons enter the electron carrier chain, in anaerobic glycolysis the two protons are passed to lactate:

\[
\text{pyruvate}^- + \text{NADH} + \text{H}^+ \rightarrow \text{lactate}^- + \text{NAD}^+
\]

It should be noted that both pyruvic acid (\(pK_a = 2.5\)) and lactic acid (\(pK_a = 3.9\)) are both highly dissociated at physiological pH and lactic acid as such is not formed. Eqn. (4) is then rewritten as eqn. (8).

\[
\text{(Glycogen-glucose) + 3P}_1^{2-} + 3\text{ADP}^{3-} + \text{H}^+ \rightarrow 2 \text{lactate}^- + 3\text{H}_2\text{O} + 3\text{ATP}^{4-}
\]

(8)

If this reaction maintains ATP content, it is balanced by eqn. (5):

\[
3\text{ATP}^{4-} + 3\text{H}_2\text{O} \rightarrow 3\text{ADP}^{3-} + 3\text{P}_i^{2-} + 3\text{H}^+
\]

(9)

Addition of eqns. (8) and (9) gives

\[
\text{(Glycogen-glucose) → 2 lactate}^- + 2\text{H}^+ \quad \text{(10)}
\]

The end result is that in addition to absorbing two protons through the formation of lactate\(^-\), anaerobic glycolysis with phosphorylation of ADP results in the removal of two protons in muscle as lactate\(^-\) plus an additional proton for each lactate\(^-\); it is as if lactic acid had been produced.

To maintain the function of muscle the lactate\(^-\) then has to be excreted and the H\(^+\) formed either excreted or buffered. The maximum rates of flux in each of these processes are not easily determined. Estimates of ATP turnover are obtained from measurements of power; for glycolysis changes in muscle glycogen and lactate content and changes in plasma lactate\(^-\) concentration are used. Theoretical maximal flux through metabolic pathways may also be estimated from measurements of rate-limiting or flux-generating enzyme activities in muscle samples. The reader is referred to the review of McGilvery (1975) for a discussion of the rates in different biochemical pathways during exercise.

**Effect of pH on the ionic changes**

We should pause and question the accuracy of the 'ionic' equations (5–8) at physiological pH in the light of the dissociation constants of the reactants. Knowledge of the \(pK\) of a reaction enables us to apply the Henderson–Hasselbalch equation and calculate the proportion of undissociated to dissociated radicals which will exist at any given pH. At a pH of 7.2, eqn. (5) may be written as follows:

\[
0.36\text{ATP}^{4-} + 0.64\text{ATP}^{3-} \rightarrow 0.32\text{ADP}^{3-} + 0.68\text{ADP}^{2-} + 0.72\text{HPO}_4^{2-} + 0.28\text{H}_2\text{PO}_4^- + 0.72\text{H}^+
\]

and, at a pH of 6.2, as

\[
0.85\text{ATP}^{3-} + 0.15\text{ATP}^{2-} \rightarrow 0.83\text{ADP}^{2-} + 0.17\text{ADP}^{1-} + 0.21\text{HPO}_4^{2-} + 0.79\text{H}_2\text{PO}_4^- + 0.23\text{H}^+
\]
Thus at the lower pH the proton release from this reaction is less (0.23 compared with 0.72) than that described by eqn. (6).

For the phosphocreatine reaction the following situation applies at pH 7.2 (for simplicity, ATP and ADP are ignored):

$$\text{PCr}^{2-} + \text{H}_2\text{O} \rightarrow \text{Cr}^+ + 0.72\text{HPO}_4^{2-} + 0.28\text{H}_2\text{PO}_4^- - 0.28\text{H}^+$$

and the following situation applies at pH 6.2:

$$\text{PCr}^{2-} + \text{H}_2\text{O} \rightarrow \text{Cr}^+ + 0.21\text{HPO}_4^{2-} + 0.79\text{H}_2\text{PO}_4^- - 0.79\text{H}^+$$

Thus at the lower pH phosphocreatine is able to bind more protons and ATP splitting yields fewer protons. The effectiveness of this last reaction in absorbing protons in exercising muscle is highest when the phosphocreatine concentration is high and the pH relatively low. As the change in muscle phosphocreatine concentration with exercise is often great, this reaction plays a larger part in proton release or absorption than changes in ATP, ADP or phosphates. Conversely, it can play only a small part in heavy exercise once the phosphocreatine concentration has fallen.

It is clear that changes in pH and organic phosphate concentration are factors that may lead to a dissociation between lactate$^-$ and H$^+$ formation in exercise.

**Control of muscle pH**

We now consider the controversial area of muscle pH. Controversial, first because of the difficulties in measuring intracellular pH and, second, because pH in the cytosol of the muscle cell may differ from that in the mitochondria due to the compartmentation of key reactions and thus of H$^+$. Poole-Wilson (1978), in a review, concluded that several methods may yield qualitative estimates of changes in the intracellular pH but none is yet able to measure pH quantitatively in situations such as ischaemia, where the intracellular pH is changing rapidly. Also we know more about the changes in muscle pH which follow extracellular acidosis or alkalosis (Adler, Roy & Relman, 1965; Heisler, 1975) than those that result from intracellular processes (Piiper, 1972; Sahlin, 1978).

In addition to the buffering effect of the high-energy phosphate compounds and inorganic phosphate already mentioned, amino acids and proteins are effective buffers, contributing as much as 60% to the buffering capacity of muscle (Sahlin, 1978). Rahn, Reeves & Howell (1975) have pointed out the importance of the imidazole group of histidine, which has a pK close to the pH of resting muscle. Muscle [HCO$_3^-$] amounts to 10 mmol/l in resting muscle, which means that it contributes 20–30% to the total buffering capacity of muscle.

Carbon dioxide takes part in many reactions in intermediary metabolism, either as CO$_2$ or HCO$_3^-$; production of carbon dioxide is usually the result of decarboxylation: the cleavage of a carboxyl (–COO$^-$) group from its parent molecule. When carbon dioxide dissolves in water it is present almost entirely as CO$_2$; its hydration is controlled by carbonic anhydrase: CO$_2$ + H$_2$O $\rightleftharpoons$ H$_2$CO$_3$. At physiological pH, H$_2$CO$_3$ is almost completely dissociated: H$_2$CO$_3$ = H$^+$ + HCO$_3^-$.

This series of reactions may begin at either end; a rise in Pco$_2$ will tend to increase [HCO$_3^-$] because H$^+$ are largely buffered by the non-bicarbonate systems. Entry of H$^+$ will force the reaction in the opposite direction and if carbon dioxide leaves the system by diffusion, [HCO$_3^-$] falls. The bicarbonate concentration may also fall if the concentration of other anions, such as lactate$^-$, increases.

During exercise, the high rates of metabolic production of carbon dioxide impose a stress on the rate at which the reactions occur. As the activity of carbonic anhydrase is probably low in muscle fibres (Maren, 1967), diffusion is the main mechanism by which carbon dioxide leaves muscles. Although plasma also has low carbonic anhydrase activity, other work suggests that it is present in capillary walls (Effros & Weissman, 1979), tending to facilitate diffusion by lowering the boundary Pco$_2$ and increasing [HCO$_3^-$]. The carriage of carbon dioxide in venous blood is dominated by the buffering effect of deoxygenated haemoglobin. Changes within erythrocytes occur very rapidly, due to their high carbonic anhydrase activity, but the velocity with which full equilibration occurs between erythrocytes and plasma, in terms of H$^+$ and HCO$_3^-$, is a matter of some argument; equilibration may not be complete by the time venous blood arrives in the lungs.

Although increases in [H$^+$] are reduced by buffering, the metabolic flux is so great in heavy exercise that even the large buffering capacity of muscle (Piiper, 1972) may be unable to control pH within tolerable limits. Processes tending to remove H$^+$ from muscle then assume great importance.

**H$^+$ efflux from muscle**

Many studies have shown that increases in plasma [lactate$^-$] during exercise are equal to falls
in \([\text{HCO}_3^-]\) (Keul, Doll & Keppeler, 1967), which has led to the proposition that lactate\(^-\) and \(\text{H}^+\) leave muscle together. However, it may be expected that in some situations lactate\(^-\) will leave muscle in greater amounts than \(\text{H}^+\), due to the buffering of \(\text{H}^+\) by various intracellular mechanisms. There is controversy regarding the mechanisms of lactate\(^-\) and \(\text{H}^+\) efflux from muscle. In isolated muscle preparations the efflux of lactate is closely dependent on \([\text{HCO}_3^-]\) of the perfusate (Mainwood, Worsley-Brown & Paterson, 1972). If \([\text{HCO}_3^-]\) is lowered in normal subjects, plasma [lactate\(^-\)] is less for a given level of exercise and muscle [lactate\(^-\)] is relatively higher (Sutton, Jones & Toews, 1980), suggesting that lactate\(^-\) efflux is reduced. Mainwood & Lucier (1972) and Roos (1975) have argued that lactic acid leaves muscle in the undisassociated form, only dissociating when it reaches the higher pH environment of the perfusing blood. This theory has the attraction of not requiring energy or ionic exchanges and places the control of lactate distribution, between the muscle cell and the extracellular space, on the transmembrane pH gradient (Roos, 1975).

In addition to the efflux of \(\text{H}^+\) associated with lactate\(^-\), \(\text{H}^+\) move out of muscles in exchange for \(\text{Na}^+\) and \(\text{HCO}_3^-\) may move in, in exchange for \(\text{Cl}^-\) (Aickin & Thomas, 1977). The link between lactate\(^-\) and \(\text{H}^+\) efflux from muscle and their dependence on blood \([\text{HCO}_3^-]\), sets the scene for a vicious cycle in heavy exercise when intracellular \([\text{H}^+]\) and [lactate\(^-\)] are increasing rapidly and plasma \([\text{HCO}_3^-]\) is falling to low levels, tending to reduce the removal of both ions from muscle.

A further mechanism for proton removal from muscle may be afforded by the excretion of amino acids. It has been known for several years that the rates of muscle efflux of alanine and glutamine are much higher than those of other amino acids, in spite of the fact that their concentration in muscle is low. The origin and metabolism of muscle amino acids has been reviewed by Goldberg & Chang (1978). Because of the high muscle efflux and hepatic uptake of alanine, Mallette, Exton & Park (1969) and Felig & Wahren (1971) proposed the glucose–alanine cycle, in which production of alanine by muscle is followed by hepatic gluconeogenesis with subsequent utilization of glucose by muscle. Seen in this context the cycle is a potential provider of energy substrate. However, it may also play an important role in the regulation of muscle pH. As alanine \(pK_a = 6.1\) is formed by the transfer of an amino group (from branched-chain amino acids via glutamate) to pyruvate, a proton is donated

\[
\text{Glutamate}^- + \text{pyruvate}^- \rightarrow \text{alanine}^+ + (\alpha\text{-oxoglutarate})^2^-.
\]

Subsequent efflux of alanine from muscle thus leads to a loss of \(\text{H}^+\) from the cell.

Glutamine formation is associated with the incorporation of ammonia, which is produced through the purine nucleotide cycle (Lowenstein, 1972). A series of reactions thus leads to excretion of ammonia, with net loss of \(\text{H}^+\). The final reaction in muscle is probably the glutamine synthetase reaction.

\[
\text{Glutamate}^- + \text{NH}_3 + \text{ATP}^4^- \rightarrow \text{glutamine}^+ + \text{ADP}^3^- + \text{P}_i^-.
\]

If \(\text{ATP}^4^-\) is then resynthesized from \(\text{ADP}^3^- + \text{P}_i^-\), the net effect leads to incorporation of \(\text{H}^+\) into glutamine, which then leaves muscle to be taken up by kidney, liver and gut and metabolized. The rates of muscle efflux of alanine and glutamine (Wahren, Hagenfeldt & Felig, 1975) are an order of magnitude less than the rate of lactate efflux, so their contribution to muscle \([\text{H}^+]\) control is probably minor.

The movement of lactate\(^-\) into blood effectively removes protons from muscle, but this process would be self-limiting if lactate\(^-\) were not then removed from blood. Uptake and metabolism of lactate\(^-\) by other tissues shifts the proton load from muscle fibres unable to handle protons metabolically and enables more lactate\(^-\) to leave them, without a progressive rise in plasma [lactate\(^-\)].

**Fate of lactate**

It used to be thought that lactate was formed only when oxygen delivery was inadequate but it is now clear that it may be produced at all levels of work, except perhaps very light exercise continued for a long time. In addition to an inadequate oxygen supply to muscle, insufficient activity of enzymes at critical points in muscle biochemical pathways may lead to the maximum flux capacity being reached; the anaerobic, pyruvate-to-lactate, reaction may then assume increasing importance. For example, there is evidence that pyruvate dehydrogenase (Toews, Ward, Leveille, Sutton & Jones, 1979) may become rate limiting if muscle undergoes disuse atrophy and rate limitation at other points, including the electron-transport chain, occurs in a number of mitochondrial myopathies (Land & Clark, 1979).
In steady-state exercise a constant plasma [lactate−] indicates a balance between its production in muscle and its uptake from blood by various tissues which are able to metabolize it, of which muscle, heart and liver are the most important. The type 2, fast-twitch glycolytic muscle fibres are recruited particularly in heavy exercise and will produce lactate at high rates. Type 1 fibres, on the other hand, have a high oxidative capacity, will have a lower [lactate−], a lower NADH/NAD ratio and will take up lactate− and convert it into pyruvate for oxidative phosphorylation:

\[
\text{Lactate}^- + 3\text{O}_2 \rightarrow \text{CO}_2 + \text{HCO}_3^- + 3\text{H}_2\text{O}
\]

For every mol of lactate−, a mol of HCO₃⁻ will be produced. As the RQ of the reaction is 0.66, this reaction will reduce the effect that H⁺ entry into blood has on total carbon dioxide output. This pathway for lactate uptake is important during exercise as it allows muscle to use lactate as fuel.

The second major site of lactate removal is the liver, where lactate is converted into glucose, thus providing fuel for muscle (the Cori cycle). Although this process was also thought to regenerate HCO₃⁻, this may not be extensive during exercise as energy is used and there is a net production of protons according to the following stoichiometry (McGilvery, 1970):

\[
2 \text{lactate}^- + 4\text{ATP}^- + 2\text{GTP}^- + 6\text{H}_2\text{O} \rightarrow \text{glucose} + 4\text{ADP}^- + 2\text{GDP}^- + 6\text{P}^- + 4\text{H}^+
\]

Thus glucose production tends both to reduce energy stores and to increase [H⁺] in liver. During rest and in light exercise, hepatic oxygen delivery is able to meet this demand; however, in heavy exercise the liver redox potential may shift to a more reduced state and ATP concentration may also fall (Houghton, Hawkins, Williamson & Krebs, 1971). In this way the liver pays for the removal of protons from exercising muscles. This view is supported by studies in which sodium L(+)lactate was infused at a constant rate in healthy subjects for long enough to achieve a steady state of gas exchange, [lactate−] and [HCO₃⁻] (Ryan, Sutton, Toews & Jones, 1979). At rest the lactate infusion was associated with an increase in oxygen intake, no change in R, a large increase in [lactate−] and a small increase in [HCO₃⁻]; these changes were interpreted as being mainly related to gluconeogenesis. During exercise, on the other hand, the same rate of lactate infusion had no effect on oxygen intake, reduced R and led to a smaller increase in [lactate−] and a larger increase in [HCO₃⁻] than at rest; this was interpreted to indicate greater oxidation of lactate− during exercise. Rowell, Kraning, Evans, Kennedy, Blackmon & Kusumi (1966) measured hepatic–splanchnic removal of lactate at rest and during treadmill exercise. They concluded that hepatic uptake might account for up to half the total lactate production in exercise; at rest hepatic uptake was sufficient to account for all the lactate produced. Studies in rat liver suggest that glucose production from lactate may reach a maximum rate at [lactate−] 5 mmol/l in the perfusate (Exton & Park, 1967); if this applies to human liver it may contribute to the rapid rise in [lactate−] in heavy exercise, when values well in excess of 5 mmol/l are found.

**Plasma lactate, plasma bicarbonate and carbon dioxide output**

During most forms of exercise, any increase in plasma [lactate−] is accompanied by an equivalent fall in [HCO₃⁻]. Although the roughly equal fall in [HCO₃⁻] with the increase in [lactate−] may be considered to be an indication of equal efflux of H⁺ and lactate− from muscle, it is also to be expected through the common ion effect, with a fall in [HCO₃⁻] occurring to maintain ionic balance in plasma. Moreover, owing to the buffering effect of plasma buffers, entry of lactate− and H⁺ in equimolar amounts would be expected to lead to a smaller fall in [HCO₃⁻], owing to the formation of carbonic acid, than any accompanying change in [lactate−].

At this point we may summarize with three general conclusions: first, the relationship between muscle production of lactate− and H⁺ need not be stoichiometric, particularly if changes occur in buffering systems; secondly, H⁺ and lactate− may leave muscle independently; thirdly, in any relatively steady state, changes in [HCO₃⁻] may follow mainly from changes in [lactate−], itself representing a balance between lactate− production and lactate− uptake and metabolism.

We now turn to the effect of these interactions on carbon dioxide balance during exercise. The competing effects of metabolic carbon dioxide production and the circulatory and ventilatory changes in exercise lead to an increase in mixed venous carbon dioxide content and pressure and in muscle tissue PCO₂. An amount of carbon dioxide is thus stored in rapidly exchanging carbon dioxide stores (Cherniack & Longobardo, 1970), determined by the tissue PCO₂ and the tissue carbon dioxide dissociation curve. As with blood, the curve tends to flatten with increasing mixed venous PCO₂ (Jones & Jurkowski, 1979).
Thus during exercise where power output is progressively increased, a large volume of carbon dioxide may be stored during light work, but an increasing proportion of the metabolic carbon dioxide production has to be excreted as the exercise and the tissue \( \text{PCO}_2 \) increase. The capacity to store carbon dioxide is further reduced by falling \([\text{HCO}_3^-]\) in plasma and extracellular water.

As already pointed out, entry of \( \text{H}^+ \) into venous blood or a fall in \([\text{HCO}_3^-]\) due to an increase in \([\text{lactate}^-]\) are associated with a rise in \( \text{PCO}_2 \) due to a shift in the carbonic acid reactions. If carbon dioxide output is measured during the change from one steady state to another and the contributions from aerobic metabolism and stored carbon dioxide are subtracted, the derived excess carbon dioxide is closely correlated with the lactate accumulation calculated from the associated change in plasma \([\text{lactate}^-] \) (Clode, Clark & Campbell, 1967). The closeness of fit between excess carbon dioxide expired and the change in plasma \([\text{lactate}^-] \) from one work load to another is to be expected from the equivalent fall in \([\text{HCO}_3^-] \); the excess carbon dioxide derives directly from bicarbonate. Less easily explained are the reports of excess carbon dioxide during steady-state exercise at high work rates (N. L. Jones, G. J. F. Heigenhauser, A. Kuksis, G. Matsos, J. S. Sutton & C. J. Toews, unpublished work) or under hypoxic conditions (Jones, Robertson, Kane & Hart, 1972). In these studies constant values of increased \([\text{lactate}^-] \) were associated with an increase in carbon dioxide output, which appeared to be linearly related to plasma \([\text{lactate}^-] \) (Taylor & Jones, 1979). The explanation may lie in the two mechanisms for lactate metabolism in exercise: gluconeogenesis or oxidation, occurring in situations where \( \text{H}^+ \) are leaving muscle. The entry of \( \text{H}^+ \) leads to excretion of carbon dioxide in the lungs and a potential fall in \( \text{HCO}_3^- \), which may be rapidly made up from many sources of carbon dioxide.

**Effects of changes in muscle pH and plasma \([\text{HCO}_3^-]\)**

Studies with a variety of methods suggest that the intracellular muscle pH may fall as low as 6.2 in heavy exercise, and plasma pH as low as 6.8 (Hermansen & Osnes, 1972), and it seems likely that these changes contribute to fatigue (Jones et al., 1977). Falls in muscle pH may influence the activity of rate-limiting enzymes, although not in a uniform or simple way (Laidler & Bunting, 1973). The enzyme most extensively studied is phosphofructokinase, which catalyses the conversion of fructose 6-phosphate into fructose diphosphate. The activity of phosphofructokinase is inhibited by a fall in pH, but the resulting increase in the concentration of fructose 6-phosphate restores its activity (Trived & Danforth, 1966). As fructose 6-phosphate is in equilibrium with glucose 6-phosphate, the concentration of glucose 6-phosphate also rises. Glucose 6-phosphate is a powerful inhibitor of hexokinase and phosphofructokinase (Newsholme & Start, 1973), so that inhibition of glycolysis may occur at sites remote from the initial inhibition of phosphofructokinase. The effects of pH on other enzyme systems are less well known but are likely to be as important.

In addition to the effect on lactate efflux from muscle, mentioned above, high plasma \([\text{lactate}^-] \) and low plasma \([\text{HCO}_3^-] \) are associated with an inhibition of lipolysis in adipose tissue, resulting in a reduction in plasma free fatty acid concentration and turnover rate (Issekutz, Miller, Paul & Rodahl, 1965; N. L. Jones, G. J. F. Heigenhauser, A. Kuksis, G. Matsos, J. R. Sutton & C. J. Toews, unpublished work). As muscle uptake of free fatty acids is a function of their plasma concentration, muscles are deprived of a major source of energy, tending to make further demands on glycogenolysis. However, there is evidence that when free fatty acids are not available from adipose tissue stores triglyceride hydrolysis occurs within muscle (Essén, 1978), suggesting that different lipolytic control mechanisms exist in muscle compared with adipose tissue.

**Conclusion**

My aim in this brief review has been to stimulate a re-examination of the processes which result in accumulation of lactate and fall in bicarbonate in blood during heavy exercise. The production of lactate by muscle is not necessarily accompanied by an equivalent amount of \( \text{H}^+ \) and the two probably enter blood from muscle at different rates. Of the two main pathways for removal of lactate from blood, one requires energy and one generates energy; the relative importance of these two processes in helping to control blood lactate concentration deserve further study. Finally the relationship between increases in blood lactate and increases in expired carbon dioxide and ventilation may be in part coincidental and due to the interplay of several factors. More may be involved in the causation of an ‘anaerobic threshold’ in the ventilatory response to increasing oxygen demands than lactate production.
alone. Moreover, in the near future we may have to question whether the capacity for heavy exercise depends as much on oxygen delivery to muscles as on the removal from them of protons and carbon dioxide.

References


