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Lactate and the GPR81 receptor in metabolic regulation: implications for adipose tissue function and fatty acid utilisation by muscle during exercise

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Abstract
Lactate is increasingly recognised to be more than a simple end product of anaerobic glycolysis. Skeletal muscle and white adipose tissue are considered to be the main sites of lactate production and release. Recent studies have demonstrated that there is a specific G-protein coupled receptor for lactate, GPR81, which is expressed primarily in adipose tissue, and also in muscle. Lactate inhibits lipolysis in adipose tissue by mediating, through GPR81, the anti-lipolytic action of insulin. A high proportion (50% or more) of the glucose utilised by white adipose tissue is converted to lactate and lactate production by the tissue increases markedly in obesity; this is likely to reflect a switch towards anaerobic metabolism with the development of hypoxia in the tissue. During exercise, there is a shift in fuel utilisation by muscle from lipid to carbohydrate, but this does not appear to be a result of the inhibition of lipolysis in the main adipose tissue depots by muscle-derived lactate. It is suggested instead that a putative autocrine lactate loop in myocytes may regulate fuel utilisation by muscle during exercise, operating via a muscle GPR81 receptor. In addition to being an important substrate, lactate is a key signal in metabolic regulation.

Key words: Adipose tissue: GPR81 lactate receptor: Lactate: Lipolysis: Muscle

Lactate is a major end product of the metabolism of glucose by cells through the glycolytic pathway. Skeletal muscle is considered to be the main organ of lactate production, but adipose tissue is also quantitatively important. Typically, the production of lactate is increased as oxidative metabolism falls when oxygen levels are low, being maximal under conditions of anoxia. During exercise, however, the production and release of lactate from skeletal muscle are greatly elevated as a result of an increased glycolytic rate subsequent to the stimulation of glycogenolysis and of glucose uptake as oxidative phosphorylation approaches maximal rates. Although lactate is utilised for the synthesis of glucose in the liver by gluconeogenesis and as a fuel in oxidative tissues, until recently it has been widely considered as a metabolic end product and the cause of acidosis-induced peripheral fatigue. However, perspectives on the physiological role of lactate have changed radically and it is now evident that it functions as a distinct metabolic signal, with its reported actions including the induction of insulin resistance in skeletal muscle(1) and the stimulation of inflammation in L6 cells and macrophages(2).

Recent studies(3) have demonstrated that there is a specific lactate receptor through which the metabolite has a marked anti-lipolytic action. Importantly, lactate has now been shown to mediate the well-recognised anti-lipolytic effect of insulin(4). The new perspectives on lactate as a key metabolic regulator are considered here, together with the potential implications for both the sparing of fat oxidation in muscle during high-intensity exercise and adipose tissue function in obesity.

Abbreviations: cAMP, cyclic AMP; PKA, protein kinase A.

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GPR81 – the lactate receptor

Several G-protein coupled receptors are expressed in adipose tissue, some of which are regarded as orphan receptors. These include the G-protein coupled receptor subfamily of hydroxy-carboxylic acid receptors, the ligands of which are intermediates in energy metabolism. One particular member of this subfamily, GPR81, has been found to be a selective receptor for lactate(3,4). The related protein, GPR109A, is a receptor for the ketone body 3-hydroxybutyrate, while GPR109B is a receptor for 3-hydroxy-octanate and other 3-hydroxylated β-oxidation products(5). Lactate is not, however, an agonist for GPR109A or GPR109B.

GPR81 appears to be expressed principally in adipose tissue(3), although limited expression is also evident for liver and kidney as well as in skeletal muscle. Expression is high in each of the major white adipose tissue depots and also occurs in brown, as well as white, fat(3). Cell culture studies with 3T3-L1 adipocytes indicate that GPR81 is expressed, and receptor protein found, only in differentiated adipocytes; minimal or no GPR81 gene expression or protein is evident before the induction of differentiation in 3T3-L1 cells(3). Although little is known on the regulation of GPR81 expression in adipocytes, in microarray studies we have noted a strong down-regulation of GPR81 gene expression in human adipocytes exposed to macrophage-conditioned medium over 24 h(6). This suggests that macrophage-derived inflammatory factors, such as TNF-α and IL-1β, may play an important regulatory role in GPR81 expression.

Lactate and lipolysis

The binding of t-lactate to the GPR81 receptor leads to a G_{i}-dependent inhibition of adenyl cyclase and thus of cyclic AMP (cAMP) accumulation. It also inhibits the forskolin-induced increase in cAMP level(3) and the increase stimulated by isoprenaline(4). These observations are consistent with the physiological evidence that lactate can have a direct anti-lipolytic action, given that cAMP is a key mediator in the control of lipolysis. Indeed, the increased circulating lactate levels associated with severe exercise were proposed in the 1970s as leading to the inhibition of lipolysis(7), and an anti-lipolytic action of the metabolite was first indicated at that time(8). No effect of lactate is evident, however, in humans infused with concentrations of lactate up to 2-4 mM(9), and lactate has been reported to inhibit stimulated, though not basal, lipolysis(10).

Lactate, at concentrations of 5 mM and above, has now been shown to inhibit both glycerol and NEFA release from adipocytes in cell culture(3). This direct anti-lipolytic action of lactate has been documented in white adipocytes from rodents and from humans(3). Studies on transgenic GPR81-deficient mice have demonstrated that the effect is mediated through the GPR81 receptor since in these animals, in contrast to the wild-type, the anti-lipolytic effect of lactate is essentially abolished(4). Although the published data relate to white adipocytes, presumably lactate has a similar anti-lipolytic action in brown fat, given the presence of the GPR81 receptor in brown adipocytes, in addition to white.

Lactate mediates the anti-lipolytic effect of insulin

The concept that lactate binds to the adipocyte GPR81 receptor reducing cAMP levels and thereby suppressing lipolysis has recently been subject to a further major development. It has, of course, long been recognised that a number of hormones and other factors have lipolytic or anti-lipolytic actions, with noradrenaline released from sympathetic nerve endings being considered as the main physiological stimulator of lipolysis(11). Of the several known anti-lipolytic factors, insulin plays a particularly prominent role; indeed, the inhibition of lipolysis is an important action of insulin. In a key study published recently, the anti-lipolytic action of insulin was reported to be mediated by lactate through the GPR81 receptor(4).

Several strands of evidence point to lactate mediating the insulin-dependent inhibition of lipolysis via GPR81. At the cellular level, while isoprenaline stimulates lipolysis in both wild-type and GPR81-deficient mice, the anti-lipolytic effect of insulin in the presence of high levels of glucose is greatly attenuated in white adipocytes from the deficient mice(3). Lactate is, of course, released from adipocytes following insulin-dependent glucose uptake. Similarly, administration of glucose to wild-type mice resulted in a marked decrease in cAMP levels in white adipose tissue, but in GPR81-deficient mice the effect was reduced(4). Further, in vivo studies with mice, the intraperitoneal injection of glucose resulted in increased release of lactate and a fall in NEFA release from subcutaneous white adipose tissue in wild-type animals. In GPR81-deficient mice, however, although lactate release was unaltered relative to the wild-type, the release of NEFAs was not inhibited despite similar plasma insulin levels in the two groups(4). Parallel results were obtained in terms of plasma levels; lactate, glucose and insulin were the same, but a rapid and marked fall in NEFA concentration was only evident in the wild-type animals.

From these results, it is proposed that within white adipose tissue an autocrine/paracrine loop operates in which lactate derived from glucose, especially postprandially following the insulin-stimulated increase in glucose uptake, mediates the anti-lipolytic effect of insulin(4). As a consequence, in the presence of carbohydrate, lipid is retained by adipocytes. In the following sections, we consider the implications of this perspective in relation to adipose tissue function in obesity and to substrate utilisation by muscle during exercise.

Lactate production by adipose tissue

As emphasised earlier, white adipose tissue is an important site of lactate production in whole-body terms. Lactate has been described as a major metabolite of glucose in adipocytes, particularly in large fat cells(12,13). Indeed, there is a strong correlation between fat cell size and the relative conversion of glucose to lactate, with between 50 and 70% of glucose being converted to lactate in adipocytes from the obese(13–15). Thus lactate production in adipose tissue increases in obesity, with raised concentrations of the metabolite in the tissue(13,16,17). It is suggested that the enlarged white adipose tissue mass in obese subjects may lead to a 5- to 8-fold
increase in lactate release from the tissue relative to lean subjects, and there is a correlation between plasma lactate and BMI\(^1\). The increased lactate production by adipose tissue in obesity, with the raised proportional conversion of glucose to lactate, may be primarily a consequence of local hypoxia within the tissue. Studies in mouse models have demonstrated that hypoxia occurs in adipose tissue with obesity, oxygen tension being up to 3-fold lower than in lean animals\(^{16,17}\). Limited hypoxia has also been reported in the tissue in obese humans\(^{18,19}\), although a recent report has cast doubts on this\(^{20}\). In cell culture studies, hypoxia has been shown to lead to an increase in glucose uptake by adipocytes, this involving recruitment of the GLUT1 facilitative GLUT\(^{21,22}\). These changes occur together with increased expression and secretion of a number of inflammation-related adipokines, including vascular-endothelial-growth-factor, IL-6, leptin and Angptl4\(^{23-26}\).

In parallel with the hypoxia-induced increase in glucose uptake, lactate release from adipocytes is also augmented and this again involves the recruitment of a specific transporter, namely monocarboxylate transporter-1\(^{27}\).

The hypoxia-induced elevation in lactate release by adipocytes in obesity would be predicted to augment the inhibition of lipolysis, by maximising the anti-lipolytic effect of insulin. This could in turn increase the rate at which lipid accumulates in adipocytes in obesity, perpetuating the expansion of adipose tissue mass. However, a loss of insulin sensitivity is characteristic of adipose tissue in the obese state, with hypoxia itself leading to the rapid induction of insulin resistance\(^{22,28}\). Additional factors are, of course, also implicated in the development of insulin resistance, including fatty acids and specific adipokines, but its induction is likely to provide a counter-regulatory brake on continuing net lipid deposition in adipocytes.

In a recent clinical study, the ability of insulin to inhibit lipolysis was found to be positively correlated with the oxygen tension of adipose tissue\(^{19}\). This is consistent with the concept that adipose tissue hypoxia leads to an impairment in the suppression of lipolysis by insulin and the dysregulation of the local lactate autocrine/paracrine loop. An attenuation of the local anti-lipolytic action of lactate in adipose tissue may underlie raised NEFA release and circulating levels in obesity.

**Lactate and fuel utilisation during exercise**

The relative contribution of lipid and carbohydrate as energy sources during exercise is dynamic. It is widely accepted that at rest, lipid is the predominant fuel for muscle ATP synthesis and that as exercise intensity increases, there is a shift in fuel utilisation towards a greater reliance on carbohydrate. This was described in the 1990s by Brooks & Mercier\(^{29}\) as the ‘cross-over concept’. Although the thesis was initially much debated\(^{30-32}\), the evidence for a reduction in fat oxidation as the intensity of exercise increases is generally accepted. However, identification and acceptance of an integral metabolic ‘switch’ responsible for the shift from lipid to carbohydrate as the principal fuel during exercise has been the subject of extensive discussion over many years.

Historically, early studies by Randle et al\(^{33}\) described what is commonly referred to as the ‘glucose–fatty acid’ cycle. Their early experiments in isolated rat cardiac and diaphragm muscle identified specific reactions in glycolysis that are inhibited by the presence of high fatty acid concentrations. Key sites of inhibition include the pyruvate dehydrogenase complex and phosphofructokinase, subsequent to elevated levels of acetyl CoA and citrate, respectively. Studies in the 1990s\(^{34-36}\) in which human participants performed exercise at varying intensities of between 25 and 85\% of their VO\(_{2}\)\(_{\text{max}}\) were not able to completely replicate the findings of Randle. In these more recent studies, plasma NEFA levels were artificially raised through intravenous infusion of lipid and heparin emulsions, and while total fat oxidation was increased and relative carbohydrate oxidation reduced, this was largely due to slight reductions in glucose transport and glycogenolysis in skeletal muscle.

Central to the debate on shifting fuel utilisation during exercise has been the need to identify a locally derived factor of either carbohydrate or lipid metabolism which may specifically inhibit the oxidation of the other. Another hypothesis that has originated from studies in cardiac muscle\(^{37}\) proposed that a reduction in fat oxidation at high intensities was a result of the inhibition by malonyl CoA of fatty acid transport into the mitochondrial matrix mediated by carnitine palmitoyl transferase-1. In brief, as glycolytic rates increase with increasing carbohydrate catabolism, excess pyruvate production and subsequent mitochondrial acetyl CoA production leads to an accumulation of acetyl CoA in the muscle cytosol, where a muscle-specific isofrom of acetyl CoA carboxylase converts this to malonyl CoA. Once again, however, confirmation of this cycle in humans is not evident\(^{38}\).

The exponential rise in muscle lactate production accompanying muscle glycogen utilisation and coinciding with a decrease in fatty acid oxidation, has been largely ignored by those investigating the mechanisms of shifting fuel utilisation. Particularly, if it is accepted that excess fatty acid availability can result in an accumulation of acetyl CoA and subsequent inhibition of pyruvate dehydrogenase, then some resultant increase in lactate – the other metabolic pathway for pyruvate – would be expected. The role of lactate accumulation in muscle as exercise intensity increases has been largely considered in the debates centred on proton production and muscle acidosis-based mechanisms of fatigue\(^{39-44}\). Any potential role of lactate as a regulator of fuel utilisation has been discussed more as a potential endocrine factor regulating adipose tissue lipolysis, and hence as a key feature in restricting NEFA availability for contracting muscles.

**Rising plasma lactate and decreasing plasma NEFA availability during exercise**

The release of NEFA from subcutaneous adipose tissue during exercise follows an inverted parabolic relationship. That is, as intensity increases from rest, NEFA release into the systemic blood supply increases until intensities of approximately 50–60\% of VO\(_{2}\)\(_{\text{max}}\), at which point the release rates plateau and subsequently decline as intensity continues to increase.
This has been described across a number of studies and is classically represented in figures by Brooks\textsuperscript{31,32}. The reduction in NEFA availability has been suggested to drive the observed decline in fat oxidation as exercise intensity increases. However, the evidence suggests that this is only part of the explanation, and that other intracellular muscular events are also at play\textsuperscript{30}, such as the role of malonyl CoA described previously. Two widely discussed mechanisms, described to explain the change in NEFA release from adipose tissue as exercise intensity increases, have centred on: (i) changes in adipose tissue blood flow\textsuperscript{45–47} in which elevated flow has accompanied elevated NEFA release at low–moderate intensity exercise, and (ii) alternatively, increasing plasma lactate levels\textsuperscript{48,49} in which elevated plasma lactate is associated with reduced NEFA release.

In 1974, men performing low-intensity exercise were infused with lactate such that the plasma level was elevated almost 9-fold above that observed without infusion\textsuperscript{48}. For the same given exercise intensity, plasma NEFA and glycerol levels were significantly reduced in the presence of elevated plasma lactate. A year later, this finding was closely replicated in dogs running on treadmills\textsuperscript{49}. These reports established the basis for the view that muscle-derived lactate may act in an endocrine manner to inhibit adipose tissue lipolysis.

While a specific mechanism was not obvious, speculation pointed towards reduced fatty acid turnover resulting from increased re-esterification\textsuperscript{49}. It is important to note, however, that this view is not without contradiction. A study by Ferrannini \textit{et al.}\textsuperscript{50} referred to earlier is often cited as showing lactate infusion to have no effect on lipolysis. However, its relevance in the context is doubtful since plasma lactate levels were less than 3 mM (compared to approximately 9 mM in the study of Boyd\textsuperscript{48}) and infusion of lactate occurred during both a resting state and/or a euglycaemic–hyperinsulinaemic clamp (compared to 90 min of exercise at 40\% \textit{VO}_{2\text{max}} in the Boyd study\textsuperscript{48}).

More recently, with the discovery of the lactate-binding receptor (GPR81) in adipocytes\textsuperscript{33}, a mechanism by which muscle-derived lactate could regulate adipose tissue lipolysis was potentially realised. This was investigated using mice running on treadmills, and although plasma lactate levels of 10 mM were obtained together with a suppression of plasma NEFA\textsuperscript{43}, a comparison between wild-type and GPR81-deficient knockout mice provided strong evidence against GPR81 as the target for an anti-lipolytic affect of lactate during exercise.

The difficulty in collecting evidence for a direct mechanism, as opposed to associative data, by which elevated muscle-derived plasma lactate inhibits adipocyte lipolysis is not surprising. There are many competing tissues for circulating lactate during exercise, including the liver which can use it as a precursor for gluconeogenesis, as well as cardiac and oxidative skeletal muscle which may convert the metabolite back to pyruvate and use it as a fuel for oxidative phosphorylation. Furthermore, given that the increased cardiac output in exercise is generally accepted to direct blood flow towards the working muscle, a mode by which circulating lactate could be delivered to the adipose tissue would also need to be identified. Blood flow redistribution away from peripheral organs and the large influx of lactate into hepatic gluconeogenesis, or to other oxidative tissues, as more likely predominant sites of lactate action during exercise, make it difficult to accept an endocrine function of myocyte-derived lactate on adipose tissue. This is not to say, however, that lactate does not have the potential to act locally, in an autocrine manner to regulate fuel utilisation.

\textbf{An autocrine lactate loop in myocytes regulating fuel utilisation?}

It is important to note that the outcome measure used to identify an anti-lipolytic affect of lactate during exercise has been NEFA and/or glycerol in the circulation. However, an alternative view on the role of lactate in regulating fat metabolism during exercise may be surmised from the outcome of studies that measure fat oxidation \textit{per se} through indirect calorimetry.

In this case, the focus is not on lactate regulating plasma NEFA availability, but rather on lactate influencing what muscle can actually do with the NEFA. For example, a distinct correlation between rising plasma lactate levels and lowering rates of fat oxidation is evident\textsuperscript{50}; in this particular study, participants performed cycling exercise at a range of intensities between low (approximately 40\% \textit{VO}_{2\text{max}}) and maximal intensity, with plasma lactate concentration and whole body fat oxidation assessed by ventilatory gases at each work intensity. A major outcome was the relationship between the intensity at which the first rise in plasma lactate concentration is observed and the intensity at which maximal fat oxidation occurs, such that further increases in plasma lactate were associated with a subsequent decline in fat oxidation.

Until recently, a mechanism by which lactate could drive a reduction in fat oxidation in muscle was not evident. It can, of course, be argued that the reduced fat oxidation observed by Achten & Jeukendrup\textsuperscript{50} is secondary to the reduced fatty acid availability that occurs as intensity increases, or as the authors suggest, a result of acidosis-induced inhibition of carnitine palmitoyl transferase-1-mediated fatty acid transport into mitochondria. However, with identification of GPR81 as a lactate binding receptor on the plasma membrane of muscle, one can argue that lactate could act locally in the tissue. Activation by lactate of a muscle-specific GPR81 could result in local inhibition of the lipolysis of intramyocellular lipids which would thus further restrict NEFA availability at high intensities and hence drive a subsequent reduction in fat oxidation (see Fig. 1).

For this hypothesis to be applicable, in the first instance confirmation of the presence of the functional GPR81 receptor in muscle is required. While some recent reports have referred to GPR81 expression being ‘exclusively’ or ‘solely restricted’ to adipocytes\textsuperscript{33,51}, the original identification of lactate activation of GPR81 observed GPR81 gene transcripts in human, rat and mouse skeletal muscle, as well as protein expression in mouse muscle\textsuperscript{52}. It should be noted that the mRNA levels were substantially lower than those of adipose tissue and that the protein expression assays were not performed in either human or rat tissues. In addition, the protein detection
that was performed in mouse samples was in ‘crude plasma membrane homogenates’, and as such potential contamination from adipocytes in the homogenate cannot be ruled out. Indeed, lactate derived from muscle during exercise could have a powerful local action on those adipocytes associated with the musculo-skeletal system. Nevertheless, there is a priori evidence for investigations on GPR81 expression in muscle and its functions. It is tempting to speculate that lactate produced during exercise has a specific role in regulating muscle-specific fuel utilisation.

As described in an earlier section, isolated adipocyte studies have shown GPR81 activation to be intrinsically linked to the insulin-mediated inhibition of lipolysis and that this occurs through G-protein coupled (Gι) inhibition of adenyl cyclase. During exercise, insulin is not a major factor in regulating fuel utilisation as its release from the pancreas is inhibited. However, adenyl cyclase is central to the intracellular response to adrenaline and glucagon activation of their respective G-protein coupled receptors. Hence, GPR81 inhibition of adenyl cyclase could interfere with hormonal activation of pathways regulating fuel oxidation during exercise through suppressed cAMP-dependent protein kinase A (PKA) activation. PKA is essential for the activation of the muscle isoform of hormone-sensitive lipase, as well as of other key regulatory enzymes in glycogen metabolism.

If substantiated, identification of a lactate-activated GPR81 signalling pathway in muscle would provide two major outcomes for research in the nutritional biochemistry of exercise. In the first instance, it could provide evidence for another carbohydrate-derived factor directly limiting fat oxidation (through HSL inhibition, as seen in adipocytes). This would therefore reduce lipolysis of intramuscular lipid stores and restrict NEFA availability within muscle independent of plasma NEFA levels as exercise intensity increases. Secondly, if the signalling pathway is as identified in the adipocyte (Gι-induced suppressed cAMP), then the inhibited PKA activity could have more global ramifications for fuel utilisation and adaptation given the role of cAMP and PKA in other enzyme systems, including cAMP response element binding protein-mediated gene expression as well as glycogen phosphorylase and glycogen synthase regulation of glycogenolysis. Potentially, lactate may play a role as a negative-feedback loop limiting complete exhaustion of glycogen stores.

Fig. 1. Regulation of fuel utilisation in skeletal muscle during exercise. Adrenaline release and subsequent activation of a G-protein coupled receptor (ER) results in elevated cyclic AMP (cAMP) levels and activation of protein kinase A (PKA). Two key targets of PKA include glycogen phosphorylase and hormone-sensitive lipase, which result in elevated rates of glycogenolysis and lipolysis, respectively. Liberated NEFA can be oxidised within the mitochondria and contribute to ATP re-synthesis through oxidative phosphorylation (OxPhos). Liberated glucose-6-phosphate drives elevated rates of glycolysis, leading to elevated pyruvate production. Pyruvate can feed into mitochondrial OxPhos. As OxPhos approaches maximal rates, excess pyruvate production drives elevated rates of lactate production within muscle cells. Lactate is transported from myocytes through a specific monocarboxylate transporter (MCT) and accumulates in the plasma. Currently accepted theories suggest that the lactate can be taken up by the heart or other oxidative muscle for conversion to pyruvate and use in OxPhos; lactate can be utilised by the liver as a source for gluconeogenesis or may be transported to adipose tissue where it acts to inhibit adipocyte lipolysis (all shown in filled lines). The dashed lines represent the proposal that if skeletal muscle is shown to contain membrane bound GPR81, then it may facilitate an autocrine function of lactate whereby a negative-feedback loop is identified. In this instance, rising cellular lactate concentrations act as a signal by which fat utilisation is restricted (through reduced intramyocellular lipolysis) and carbohydrate oxidation becomes limiting (through reduced glycogenolysis). In the first instance, lactate serves as a metabolic switch between fat and carbohydrate oxidation as exercise intensity increases and then as a peripheral signal of fatigue through limiting complete exhaustion of glycogen stores.
Conclusions

The identification of a selective G-coupled lactate receptor, GPR81, which is principally expressed in adipose tissue has provided a mechanistic basis for a metabolic signalling role for lactate. Lactate inhibits lipolysis in adipocytes, and is the route through which the anti-lipolytic action of insulin is mediated. It is likely that the switch from lipid to carbohydrate as a fuel by muscle during exercise is not directly due to the lactate-induced inhibition of lipolysis in adipose tissue. However, it is conceivable that there is an autocrine loop in muscle in which lactate inhibits intramuscular lipid mobilisation through a GPR81 receptor in myocytes. The increased production of lactate by adipocytes in obesity as a consequence of adipose tissue hypoxia is unlikely to have a major effect on the anti-lipolytic action of insulin, since insulin resistance is a characteristic of the tissue in the obese. It is increasingly evident, nonetheless, that lactate is an important metabolic signal.

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