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## Metabolic control of blood flow with reference to heart, skeletal muscle and brain

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### Introduction

The main aim of the circulation is to ensure a proper milieu for cells by supplying oxygen and substrates for tissue respiration and by removing waste metabolites. It follows that if blood supply is less than that required to meet functional demands of an organ/tissue, metabolism will be compromised by lack of oxygen and accumulation of metabolites, leading to cell dysfunction. Alterations in metabolic demand at the organ level are met by changes in the level of perfusion; for example, the proportion of cardiac output received by the skeletal muscle mass increases 3–4-fold upon change from rest to exercise (see Chapter 6). The idea of metabolic control of blood flow involves a feed-back system, in which blood vessels controlling organ perfusion are responsive to some metabolic error signal, presumably a substance or substances produced in the tissue as a result of mismatch between metabolic supply and demand. Metabolic control of blood flow relates not only to the way in which increases in metabolic need are met by appropriate changes in blood flow (functional hyperaemia), but also to situations in which oxygen/substrate supply is inadequate, e.g. by impairment of perfusion. As such, it ensures matching between supply and demand and is, therefore, evident not only in situations of functional hyperaemia but also in hypoperfusion where supply is compromised (reactive hyperaemia). It can also contribute to autoregulation, the maintenance of organ blood flow in the face of changes in perfusion pressure; for example, if perfusion pressure is increased, vasodilator metabolites would be 'washed out', leading to vasoconstriction.

Metabolic control is only one of the regulatory mechanisms which determine blood flow

and, therefore, interacts with neural, myogenic, hormonal and physical influences upon vascular smooth muscle. However, it plays an important role in determining the capacity of three important organs — heart, brain and skeletal muscle — to function under conditions of widely varying metabolic activity, and the study of these provides us with the opportunity to investigate what it is that actually couples blood flow to metabolism.

### Relationship between blood flow and metabolism in heart, brain and skeletal muscle

The ratio between the proportion of total body oxygen consumption required by individual organs and the proportion of cardiac output that each receives demonstrates that the closest matching between metabolic requirements for oxygen and blood flow occurs in heart, brain and skeletal muscle. In other organs, e.g. kidney and skin, flow is in excess of metabolic requirements and subserves other functions, such as filtration and heat dissipation. Resting levels of blood flow are higher in heart (approx. 70 ml/min per 100 g in humans) and brain (50–60 ml/min per 100 g) than in skeletal muscle (2–15 ml/min per 100 g), in proportion to resting oxygen consumption (8 and 3 ml/min per 100 g for heart and brain, respectively, and <1 ml/min per 100 g for skeletal muscle).

In the heart, the main determinants of oxygen consumption are contractility, heart rate and ventricular wall tension, and, since resting oxygen extraction is already high (75%), it is more-or-less totally dependent upon increases in flow (4–5-fold) to meet oxygen demand during activity, showing a good correlation

between blood flow and oxygen consumption [1]. The large mass of skeletal muscle (about 40% of body weight) also requires profound circulatory adjustments during muscle activity to accommodate up to 25-fold increases in blood flow. Resting oxygen extraction is lower than in the heart (around 25–30%) and increased oxygen consumption during muscle activity can, therefore, be met by increased oxygen extraction (up to 80–90%), in addition to increased flow. Although individual skeletal muscles display considerable heterogeneity in the metabolic profile of their constituent fibres and their vascular supply, the correlation between oxygen consumption and blood flow broadly holds [2]. In both heart and skeletal muscle, blood flow is subject to intermittent impedance by mechanical compressive forces, which occlude it particularly in the subendocardium during systole and in skeletal muscle during tetanic contractions (see Chapter 6).

Total brain blood flow is relatively constant, and it was not until the advent of methods for flow and metabolism measurement, with sufficient spatial resolution to detect regional heterogeneity, that the tight metabolic regulation of perfusion at the local level became apparent. Such methods include Kety-Schmidt inhalation of diffusible indicators, [ $^{14}\text{C}$ ]-antipyrine, radiolabelled microspheres, positron emission tomography and computer-assisted reconstruction, [ $^{14}\text{C}$ ]-2 deoxyglucose and quantitative autoradiography for glucose utilization as an index of metabolism. With these techniques it could be shown that, while there is little change in oxygen extraction over a range of blood flow, there is a close correlation between local metabolic rate and cerebral blood

flow in both experimental animals and humans. Localized increases in blood flow during different types of cerebral activity are accompanied by flow decreases in other areas [3].

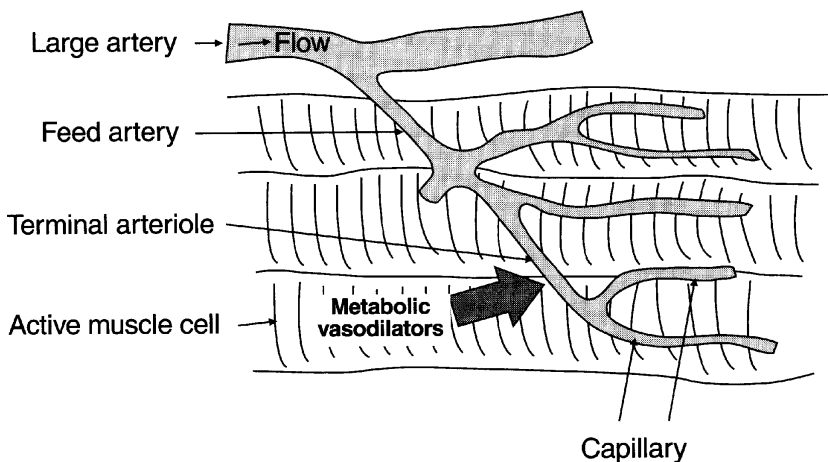
### **Possible factors involved in metabolic regulation of blood flow**

The basic idea of metabolic regulation of blood flow is that there are vasoactive products released from active cells which influence the smooth muscle cells of blood vessels. Possible substances linking metabolism and blood flow (oxygen,  $\text{K}^+$ , carbon dioxide, lactate, pH, adenosine, inorganic phosphate and osmolarity) have been described in several reviews of the subject (for example, see [4]). The search for one single factor linking metabolism to blood flow is clearly inappropriate because of the variability in degree to which metabolic control operates under different conditions, such as hypoxia, reactive hyperaemia and functional hyperaemia, and also because this presupposes that factors pertaining when the supply side is compromised (e.g. hypoxia, reduced perfusion) would necessarily be the same as when the demand side is increased (functional hyperaemia). It is also possible that different factors are involved in the initiation of vasodilatation from those which maintain it during prolonged metabolic activity.

The site of action of any of these metabolic products should ultimately be on smooth muscle cells of the arteriolar resistance vessels (Fig. 1) where there are several possible modes of action. There could be a local effect either on the vessel outer wall, or a local indirect effect by

**Table 1** Criteria for identification of possible couplers between cell metabolism and blood-flow

- There should be an adequate source of the substance occurring naturally in the tissue.
- The substance should have access to vascular smooth muscle.
- The concentration of the substance in interstitial fluid should be sufficient to produce and maintain dilatation.
- The substance should be shown to be a potent vasodilator *in vitro* and *in vivo*.
- Antagonists/inhibitors or potentiators of the substance should be shown to have the appropriate effects, i.e. blocking or enhancing, upon its exogenous and endogenous effects.



**Fig. 1. Site of action of metabolic vasodilator substances**

*It is generally assumed that the ultimate site of action of metabolic vasodilators must be on the smooth muscle of the terminal resistance arterioles which regulate capillary flow.*

interaction with neural elements, or a substance or substances released at a distance from the resistance vessels could act on them via the blood-stream or some other signalling means. The mechanism of vasodilator action is likely to be by influencing  $\text{Ca}^{2+}$  entry into smooth muscle cells via voltage-operated or receptor-operated channels — possibly involving ATP-sensitive  $\text{K}^+$  channels [5].

A list of criteria by which possible mediators of metabolic vasodilatation could be identified was originally proposed by Mellander and Johansson [6] and has since been refined [7] (Table 1). Although these criteria still remain as the basis for establishing a metabolic vasodilator coupler, there are some important considerations. The first two criteria are self-evident, but it should be noted that the second implies the presence of the substance in the interstitial fluid, not necessarily in venous effluent. The third criterion is more difficult to substantiate for technical reasons. In many cases it has been assumed that measuring the concentration of a substance in venous effluent is indicative of its presence and concentration in the interstitium, but this may not be the case if there is cellular uptake of the substance by tissue and/or endothelial mechanisms (e.g. for adenosine in heart), or variations in capillary permeability to released substances which may restrict venous efflux. The fourth criterion can be established

by several experimental means. The substance should produce vasodilatation when applied to isolated tissue or vessel preparations where pharmacological characterization of responses can be made; alternatively, observations of its direct effects on resistance vessels can be made *in vivo* in preparations such as the cranial window for pial vessels, trans- or epi-illuminated skeletal muscle preparations and even on epicardial surface vessels in the heart. If infused intra-arterially or intravenously, the substance should produce a comparable degree of vasodilatation with a similar time-course to that occurring naturally. However, such experiments may not accurately represent the effects of the substance in its interstitial compartment and should be interpreted in the light of factors which could affect its access to smooth muscle. The use of antagonists/inhibitors or potentiators of the substance in the intact organ can demonstrate its involvement but may be difficult to interpret if abolition of the effects of one substance expose the action of another.

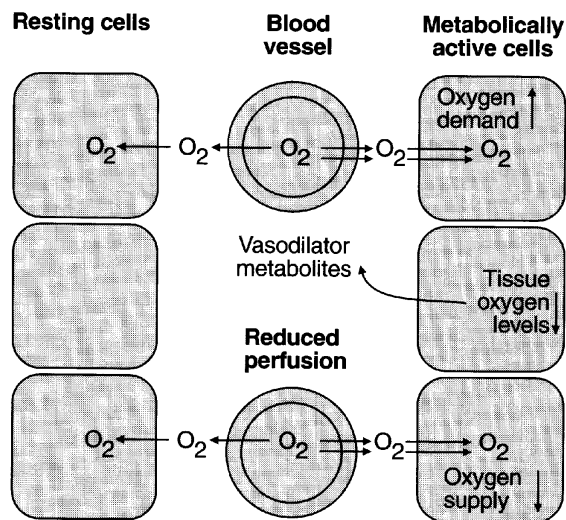
### **Evidence for the role of putative metabolic vasodilator substances**

#### **Oxygen**

Blood vessels show some intrinsic sensitivity to oxygen. For example, when arterial partial

pressure of oxygen ( $PO_2$ ) is reduced below about 40 mmHg, vascular resistance decreases in skeletal muscle, brain and heart. Responsiveness to hypoxia is observed in isolated vessels from the heart and skeletal muscles, and pial vessels dilate rapidly to either low  $PO_2$  or superfusion with cerebrospinal fluid (CSF) at low  $PO_2$ . Superfusion of pial vessels with a fluorocarbon solution at high arterial  $PO_2$  reduces the dilatation to low arterial  $PO_2$ , suggesting that oxygen lack can play a role in regulation of cerebral vessel tone. In addition, diameter changes in response to changes in superfusate  $PO_2$  have also been observed in resistance arterioles in skeletal muscle prepared for intravital microscopy.

Oxygen lack has been discounted as a metabolic vasodilator on the basis that arterial blood vessel walls are exposed to high arterial  $PO_2$  levels on their luminal surface. However, it could be the oxygen gradient that exists across the vessel wall between blood and tissue levels which is important (Fig. 2). Two critical ques-



**Fig. 2. Role of oxygen as a putative metabolic vasodilator**

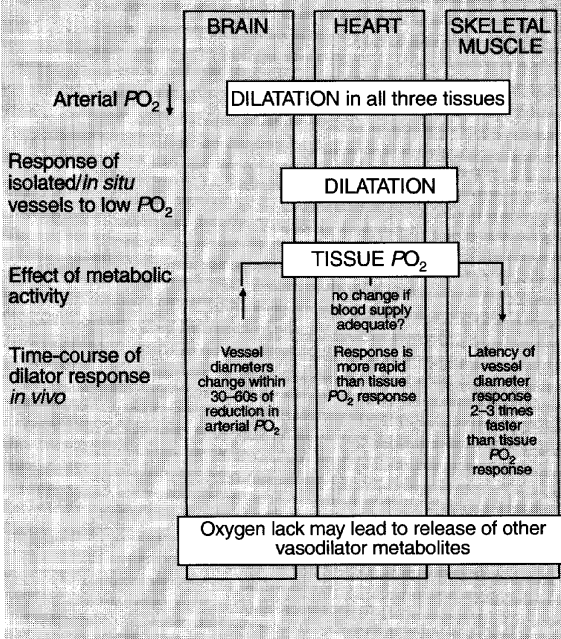
Smooth muscle cells in the blood vessels could be sensitive to tissue levels of  $PO_2$ . These would be altered by supply/demand mismatch. Metabolically active cells can increase their demand for oxygen and hence oxygen flux (double arrows). If this is not met by increased supply, for example, if perfusion is reduced, it would lead to reduced tissue levels of oxygen and subsequent release of vasodilator metabolites (curved arrow), or altered  $PO_2$  gradients between tissue and blood (large versus small  $O_2$  symbols).

tions have to be answered to establish a role for oxygen in metabolic vasodilatation. The first is whether the tissue  $PO_2$  levels to which smooth muscle cells would be exposed abluminally accurately reflect metabolic energy state and, secondly, if so, whether a lack of oxygen influences vessel tone by direct action on vascular smooth muscle or indirectly via release of vasodilator metabolites. When oxygen supply is compromised by arterial hypoxia, tissue  $PO_2$  measured directly by microelectrodes decreases in all three tissues — heart, skeletal muscle and brain — but a reduction in coronary perfusion pressure may only increase heterogeneity of tissue  $PO_2$  rather than reduce it overall. On the other hand, increases in metabolic activity have varied effects on tissue  $O_2$  — it has been shown to decrease in skeletal muscle during and after contractions, not to change in myocardium at different work levels achieved by moderate lowering and raising of heart rate, and to rise in brain when neuronal activity is increased by stimulation or seizures. Thus it is not clear that during increased metabolic activity, lack of oxygen at the tissue level occurs to a sufficient degree in heart or brain to initiate functional hyperaemia. The main evidence against a role for oxygen lack as a direct initiator of metabolic vasodilatation in skeletal muscle comes from observations that, during contractions, arteriolar diameters increased before any decrease in tissue  $PO_2$  was observed [8].

The time-course of changes in venous  $PO_2$  does not always correlate with that of vascular resistance in skeletal muscle undergoing either brief tetanic or prolonged contractions. This may be because a discrepancy exists between venous and tissue oxygen levels, especially at low arterial  $PO_2$ . A similar discrepancy is found in the heart, between the time-course of changes in vasodilatation and venous  $PO_2$ . For example, reactive hyperaemia is proportional to, but in excess of, the initial oxygen debt, persisting even after coronary sinus oxygen levels have approached arterial levels. Although coronary sinus  $PO_2$  has been taken to reflect tissue levels in the heart in some studies, others have observed a delay in venous  $PO_2$  changes relative to cardiac tissue  $PO_2$ . Further, coronary blood flow does not increase in response to a reduction in oxygen content of arterial blood if flow is maintained by high perfusion pressure and coronary sinus oxygen levels are above resting. This suggests that oxygen lack is not

the primary cause of vasodilatation, and is effective only under conditions of low flow. On the other hand, it has been reported that anoxic perfusion can produce a similar peak increase in flow as coronary occlusion [9].

- ▶ Although there is evidence of an intrinsic sensitivity of blood vessels to oxygen, it is unlikely that during increased metabolic activity tissue oxygen levels fall sufficiently and/or quickly enough to account for vasodilatation.
- ▶ Lack of oxygen does not appear to be directly involved in blood flow regulation unless flow is restricted. Under these circumstances, it is more likely that release of one or more vasodilator metabolites is involved.
- ▶ Hypoxia may modulate responsiveness of vessels to other metabolites.

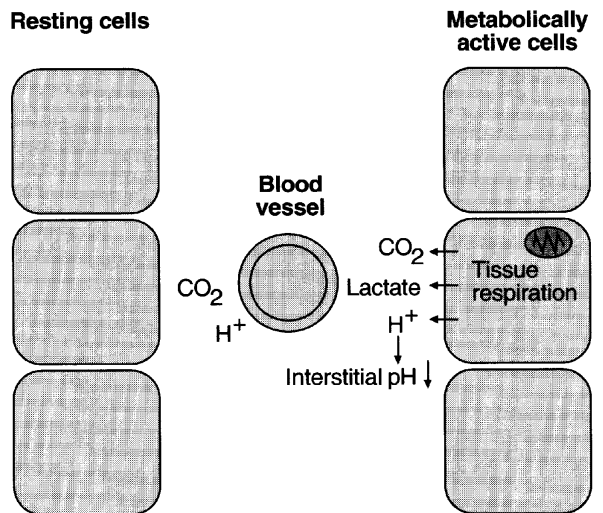


### Carbon dioxide, pH and lactate

Interstitial accumulation of carbon dioxide and lactate, and a fall in pH are consequences of increased cellular metabolic activity (Fig. 3) and they have been considered as potential candidates for metabolic coupling to blood flow.

Hypercapnia results in a decrease in vascular resistance, most notably in the cerebral circulation. In comparison, skeletal muscle blood flow seems to be relatively insensitive to changes in arterial  $PCO_2$ . Perfusion of hind-limb muscle with blood at high  $PCO_2$  has mini-

mal effects on blood flow, and carbon dioxide release from actively contracting muscle is not considered sufficient to account for functional hyperaemia. Similarly, the effects of changes in  $PCO_2$  on coronary circulation appear to be variable and inconclusive. In general, experiments in heart and skeletal muscle have not discriminated between direct effects of carbon dioxide on vessels, or indirect effects mediated by the associated reduction in interstitial pH, which could influence vascular smooth muscle activity by altering intracellular  $Ca^{2+}$  handling. However, elimination of tissue acidosis in the ischaemic myocardium did not alter arteriolar dilatation, indicating that acidosis does not play a major role in coronary reactive hyperaemia [10]. In active skeletal muscle, the change in hydrogen ion concentration  $[H^+]$  is considered too small to account for changes in vascular resistance during exercise (see Chapter 6) and there is a lack of correlation between the time-course of changes in venous or interstitial pH and muscle blood flow. Although significant increases in venous blood lactate occur in skeletal muscle during exercise, lactate infusion does not produce dilatation. The most often cited evidence against a role for either lactate, pH or



**Fig. 3. Carbon dioxide, pH and lactate as putative metabolic vasodilators**

*Mitochondrial respiration augments production of carbon dioxide, and anaerobic production of ATP in the cytoplasm results in formation of lactate acid and carbon dioxide, both of which diffuse out of the cell and cause an increase in  $[H^+]$  of extracellular fluid, decreasing its pH.*

carbon dioxide in muscle metabolic vasodilatation is from patients with McArdle's syndrome, who have an inborn deficiency of phosphorylase enzyme and, consequently, no muscle glycolysis. During muscle contractions there are no changes in venous lactate, pH or  $PCO_2$ , yet functional hyperaemia still occurs [11]. It is possible, however, that low pH in active muscle normally plays a facilitatory role by augmenting vasodilatation in response to, for example, low  $PO_2$  or by facilitating enzymes which produce vasodilator polypeptides. Moreover, in heavy exercise, when oxygen supply to tissues is compromised,  $H^+$  ions derived from lactate may be important for promoting oxygen diffusion to mitochondria by a combination of effects, via the Bohr shift and local microvascular dilation. Substances associated with acidosis in active muscles are also important as chemical stimuli to afferent nerve fibres involved in reflex cardiovascular adjustments to exercise, such as the rise in arterial pressure (see Chapter 6).

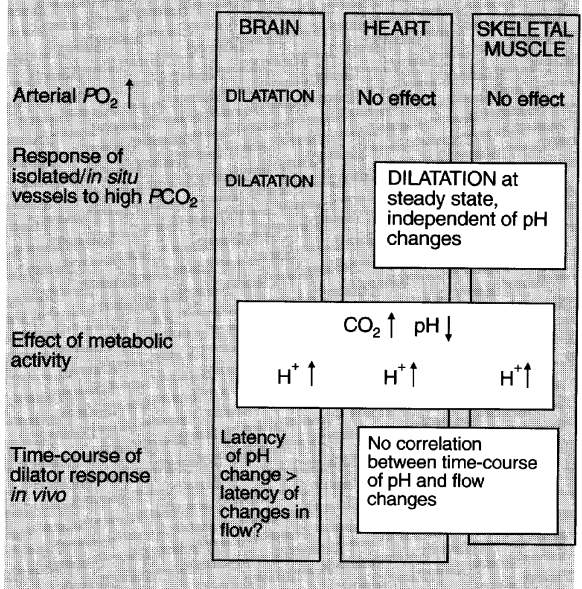
In contrast, cerebral vessel tone is profoundly affected by alterations in arterial  $PCO_2$ ; hypercapnia, as a result of inspiration of 5–7% carbon dioxide, increases blood flow by 50–100% and produces dilatation with rapid onset; pial diameter changes are detectable within 1–2 min of increasing inspired carbon dioxide. Several findings indicate that these responses are mediated via changes in extracellular  $[H^+]$  as a consequence of carbon dioxide readily crossing the blood–brain barrier. Blood flow is not changed significantly when arterial pH is altered independently of  $PCO_2$ , but dilatation does occur if pH is changed by altering bicarbonate ion concentration ( $[HCO_3^-]$ ). Also, pial arteries dilate and constrict to acid and alkaline cerebrospinal fluid, respectively, while alterations in  $[HCO_3^-]$  or  $PCO_2$  independently of pH have no effect.

To establish a role for extracellular  $[H^+]$  in cerebral functional hyperaemia, appropriate changes should be observed during increased metabolic activity. Although pH decreases and cerebral blood flow increases during increased neuronal activity due to electrical stimulation or pharmacologically induced seizures, there appears to be a time lag before the onset of pH changes which would rule out changes in  $[H^+]$  as an initiator of metabolic vasodilatation. Hence it is more likely to be important in flow regulation in later stages of neuronal activity.

Changes in extracellular  $H^+$  and lactate concentrations in the brain do not occur to a sufficient degree for these substances to play an important role in control of blood flow during either hypoxia or autoregulation [12].

► Neither carbon dioxide, pH nor lactate plays a significant role in metabolic vasodilatation in heart and skeletal muscle.

► In the cerebral circulation, carbon dioxide is a potent regulator of vascular tone via its effect on  $[H^+]$ , but the time-course of changes makes it unlikely to act as an initiator of functional hyperaemia.



### Potassium

Potassium ions are released from excitable cells with the passage of the action potential and, as such, represent a good candidate for the initiation of functional hyperaemia. On a longer term basis,  $K^+$  could be released via  $K_{ATP}$  channels and in association with anaerobic glycolysis in muscle (Fig. 4). *In vitro*, coronary vessels and isolated heart preparations show dose-dependent dilatation over the range of  $K^+$  concentration  $[K^+]$  found in tissue (4–16 mM) with a transient response. In the heart *in vivo*, the rate of release of  $K^+$  alters with changes in rate and force of contraction. However, tissue levels of  $K^+$  have not been found to correlate with coronary vasodilatation, and intracoronary infusions of  $K^+$  which markedly elevate plasma concentration increase coronary blood flow only modestly. While this evidence does not

