Case study 13.2 Nitric oxide transport and the control of regional blood flow

It has been known since at least the early 1960s, that the rate of local blood flow in mammals is related to the degree of oxygen saturation of haemoglobin in the blood. Figure A(i) shows the results of a classic experiment on dogs in which a progressive reduction in percentage oxygen saturation of haemoglobin (per centHbO_2) results in a progressive increase in the rate of blood flow. In Figure A(ii) these data have been replotted as the amount of oxygen available to the tissues. The data demonstrate that the increase in rate of blood flow maintains the supply of oxygen to the tissues as per cent HbO_2 declines. The change in rate of blood flow in response to a change in per cent HbO_2 is known as **autoregulation of blood flow**. Such regulation improves oxygen supply to the tissues when there is a fall in blood oxygen content.

The rate at which oxygen is delivered to tissues such as muscles, is in direct proportion to the rate of blood flow which in turn, is determined by the degree of dilation of blood vessels. As percentage saturation of the haemoglobin decreases, so rate of blood flow increases, and *vice versa*. Since the 1960s, it has been demonstrated that the transport of nitric oxide (NO) by the blood and its local availability play important roles in the process of increasing blood flow in response to falling levels of oxygen in the blood.

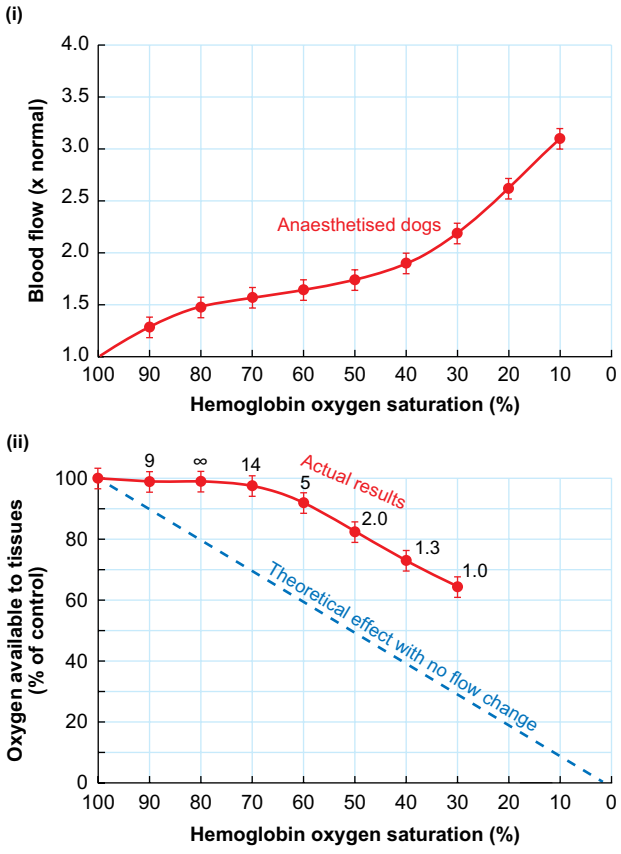

Figure A Relationship between blood flow to tissues and oxygen content of whole blood

(i) Step-reductions in percentage saturation of haemoglobin (%HbO_2) with oxygen caused a progressive increase in blood flow through the femoral artery to the leg. Pressure in the blood vessel remained constant. n = 8, vertical lines are ± SEM (ii) Plot of above data illustrating that the increase in blood flow maintained the supply of oxygen to the tissues in the face of falling oxygen content (%HbO_2). Numbers along the top curve are the calculated amplification of the local vasodilator control system

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The significance of the transport of nitric oxide (NO) by the blood is that NO is a free radical, characterised by the presence of an unpaired electron, which is signified by a dot next to the molecular formula (•NO). •NO is released from the endothelium of blood vessels and from blood platelets in response to increases in shear stress on the endothelial cell with increasing rate of blood flow. This release triggers vasodilation. •NO does not act independly; it is in equilibrium with more stable species derived from NO.

Nitric oxide acts mainly by binding covalently to cysteine thiols to form S-nitrosothiols (SNOs). NO can be transferred within the haemoglobin molecule of humans from the haem groups to cysteine 93 of the β—chains (Cysβ93) forming the SNO, S-nitrosohaemoglobin (SNO-Hb). There is a tendency for nitric oxide to combine with Cysβ93 in oxygenated blood and to be released from Cysβ93 in deoxygenated blood. The SNO is in equilibrium with the thiol pools in the plasma. This sequence is shown in Figure B(ii).

It has been proposed that nitric oxide combines with haemoglobin in the lungs, with SNO then being released from the red blood cells in the relatively oxygen-poor (hypoxic) tissues, where it causes dilation of the blood vessels and increased blood flow, as shown in Figure B. SNO is as powerful a vasodilator as •NO. This mechanism would be particularly important during exercise, when the active muscles require additional oxygen.

A therapeutically significant aspect of this system has been identified in blood stored for transfusion. Blood transfusion does not always lead to improved oxygen delivery, most likely because the concentration of SNO-Hb in fresh venous blood gradually decreases after storage. As vasodilation is strongly correlated with the concentration of SNO-Hb, the process of renitrosylation through exposure of the stored red blood cells to a solution of aqueous NO increases SNO-Hb content of the blood and restores its vasodilatory activity.

Find out more

Doctor, A and Stamler, JS 2011. Nitric oxide transport in blood: a third gas in the respiratory cycle. Comprehensive Physiology 1, 541–568.

Furchgott, RF 1999. Endothelium-derived relaxing factor: discovery, early studies and indentification as nitric oxide. Bioscience Reports 19, 235–251.

Reynolds, JD, Ahearn, GS, Angelo, M, Zhang, J, Cobb, F and Stamler, JS 2007. *S*-nitrosohemoglobin deficiency: a mechanism for loss of physiological activity in banked blood. Proceedings of the National Academy of Sciences of the United States of America 104, 17058–17062.

Ross, JM, Hilton, MF, Weldy, J and Guyton, AC 1962. Autoregulation of blood flow by oxygen lack. American Journal of Physiology. 202, 21–24

Sonveaux, P, Lobysheva, II, Feron, O and McMahon, TJ 2006. Transport and peripheral bioactivities of nitrogen oxides carried by red blood cell hemoglobin: role in oxygen delivery. Physiology 22, 97–112.

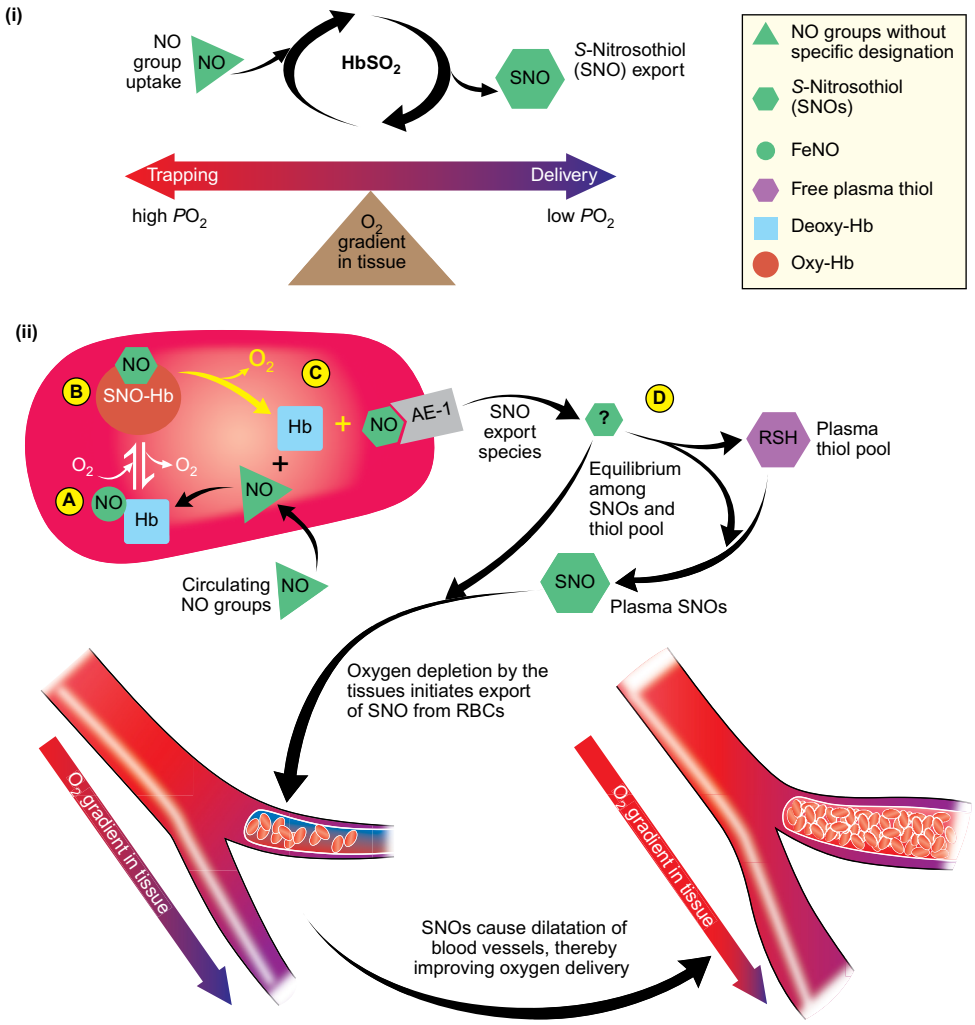

Figure B Role of red blood cells in the transport of nitric oxide

(i) The oxygen saturation of haemoglobin, $HbSO_2$, varies as it passes around the body. Nitric acid (NO) combines with well oxygenated haemoglobin at the gas exchange organ and forms S-nitrosothiol (SNO), which is as vasoactive as NO. SNO is released from poorly oxygenated haemoglobin in the tissues. (ii) Detailed sequence of events within a red blood cell, RBC, and the effects on the peripheral circulation. Circulating NO groups combine with Hb as it becomes oxygenated at the gas exhanger (A) to form a store of NO in the form of S-nitrosohaemoglobin, SNO-Hb (B). SNO is then transported from the RBCs via the membrane protein AE-1 (band 3 protein) (C) into the plasma in response to low oxygen levels in the tissues. The SNO is in equilibrium with the thio pool, RSH, in the plasma (D).

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