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REVIEW ARTICLE

Red cell 2,3-diphosphoglycerate and oxygen affinity

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The red blood cell can no longer be considered an *effete sac* or *passive carrier* of haemoglobin, since there exists within this cell an intrinsic *mechanism* for the control of the oxygen affinity of haemoglobin, which enables it to act as an oxygen donor under physiological conditions. This mechanism depends on the interaction of haemoglobin with intra-erythrocytic organic phosphates, approximately 80% of which are composed of 2,3-diphosphoglycerate (2,3-DPG) and adenosine triphosphate (ATP). In 1967[1,2] it was shown that 2,3-DPG alters the oxygen affinity of haemoglobin, such that an increase in the intra-erythrocytic 2,3-DPG concentration reduces the affinity of haemoglobin for oxygen and vice-versa. Therefore an increase in 2,3-DPG concentration improves tissue oxygenation whereas a decrease in 2,3-DPG concentration may lead to tissue hypoxia.

All phosphates exert an effect on oxygen affinity[2,3] but the di- and triphosphates are the most potent. Only 2,3-DPG and ATP are present in substantial concentrations in the erythrocyte.[1] 2,3-DPG is the most important, as the intra-erythrocytic molar concentration is about four times that of ATP and approximately equal to that of haemoglobin.[1,3] Erythrocytes are unique in having such a high concentration of 2,3-DPG.

This review discusses the role of 2,3-DPG as a mediator of oxygen delivery, in various conditions of interest to the anaesthetist and attempts to assess its clinical significance. It is necessary first of all to review the physiology and biochemistry of 2,3-DPG and its effect on the oxyhaemoglobin dissociation curve.

Biochemistry of 2,3-DPG

The synthesis and breakdown of 2,3-DPG is controlled in the phosphoglycerate cycle of Rapoport & Luebering[4] a side-shuttle off the main Embden–Meyerof pathway (Fig. 1). Approximately 20% of the glycolytic flux is via this shuttle.[5] Under normal physiological conditions, factors controlling the concentration of 2,3-DPG are:

(1) *The concentration of 2,3-DPG itself.* A negative feed-back mechanism inhibits the activity of the enzyme 2,3-DPG mutase[6] (Fig. 1).

(2) *Hydrogen ion concentration.* In alkalosis the rate of glycolysis is increased and the activity of 2,3-DPG phosphatase is inhibited. Therefore, 2,3-DPG concentration is increased.[7–8] In acidosis the concentration is reduced.[7–9]

(3) *Inorganic phosphate concentration.* In hypophosphataemia 2,3-DPG concentration is low[9] and in hyperphosphataemia it is high.[10]

In conditions such as hyperthyroidism, in which the rate of glycolysis is increased,[11] accumulation of 2,3-DPG occurs. Conversely, in hypothyroidism there is reduced 2,3-DPG concentration.[11] Blocks of the glycolytic pathway, above the level of the shuttle, e.g. hexokinase deficiency, reduce 2,3-DPG con-

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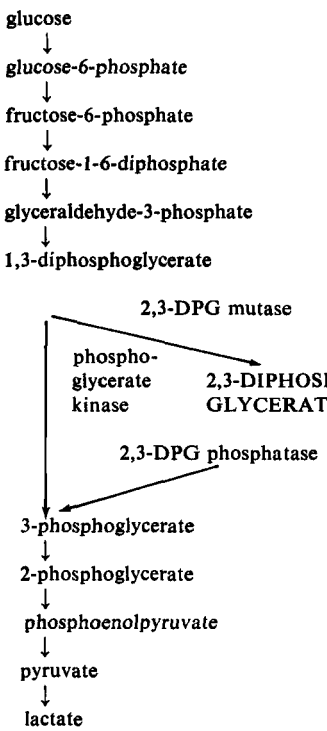

Fig. 1. An outline of the Embden–Meyerof Pathway, showing the phosphoglycerate cycle of Rapoport and Luebering.

centration,[12] whereas in blocks below the shuttle, e.g. pyruvate kinase deficiency 2,3-DPG accumulates[12] (Fig. 1).

DPG is a non-penetrating anion. Increases in the concentration of 2,3-DPG produce a fall in intra-erythrocytic pH via the Donnan Membrane equilibrium effect.[13,14] This slows down glycolysis, activates 2,3-DPG phosphatase and so reduces 2,3-DPG concentration. Therefore, the magnitude of any increase in red cell 2,3-DPG concentration is limited by this mechanism as well as by product inhibition.

Action of 2,3-DPG at molecular level: haemoglobinopathies

X-ray crystallographic studies have shown that 2,3-DPG binds specifically to deoxyhaemoglobin in the central cavity.[15] It stabilizes the tense, deoxy form of haemoglobin and so reduces oxygen affinity. The central cavity of relaxed oxyhaemoglobin is smaller and is therefore unable to accommodate 2,3-DPG.[3,16] It is thought that 2,3-DPG also binds non-specifically to the N-terminal amino-groups of the β-chains of both oxy and deoxyhaemoglobin.[17] Many haemoglobinopathies exhibit increased or decreased oxygen affinity which can be explained by altered binding of 2,3-DPG. Polycythaemia frequently occurs in high affinity haemoglobinopathies, e.g. Hb Rahere.[18] This is secondary to the increased erythropoietin production which usually accompanies increased oxygen affinity.[19] Likewise, in low affinity haemoglobinopathies normal tissue oxygenation may be achieved with a lower than normal haemoglobin concentration,[20] secondary to a decrease in erythropoietin production.[19]

Fetal haemoglobin (HbF) does not interact with 2,3-DPG[17] which explains the very high oxygen affinity of HbF. Consequently, fairly high saturations may be achieved at the low Po_2 levels encountered in the villous spaces of the placenta. Nevertheless 2,3-DPG still affects the oxygen affinity of HbF via its effect on intra-erythrocytic pH. In β-thalassaemia major or minor, oxygen affinity will depend on the relative proportions of HbF and HbA. In this type of haemoglobinopathy, 2,3-DPG concentration increases in response to anaemia, only in proportion to the amount of HbA present as it does not interact with the HbF.

In sickle cell disease or trait sickling occurs when the concentration of deoxy HbS reaches a critical level. Treatment with oral cyanate is now being used to prevent sickling and to reduce the incidence of crises in patients with sickle cell disease.[21] Following carbamylation which takes place at the N-terminal amino groups of the α-chains, the oxy form of HbS is stabilized.[21] The efficacy of cyanate therapy is thought to be independent of any effect on 2,3-DPG binding to haemoglobin S[22] although theoretically a low 2,3-DPG concentration, by increasing the oxygen affinity of HbS would be beneficial. However, in sickle cell trait or disease 2,3-DPG concentration is increased,[23,24] secondary to the concurrent anaemia rather than to the molecular pathology.[25] This may be a handicap in these people. Therapy, designed to lower 2,3-DPG concentration might be of value. The increased percentage of HbF found in sickle cell trait or disease is beneficial since HbF is a high oxygen affinity haemoglobin. In patients with sickle cell disease, irreversibly sickled cells are found to contain less HbF than others.[26]

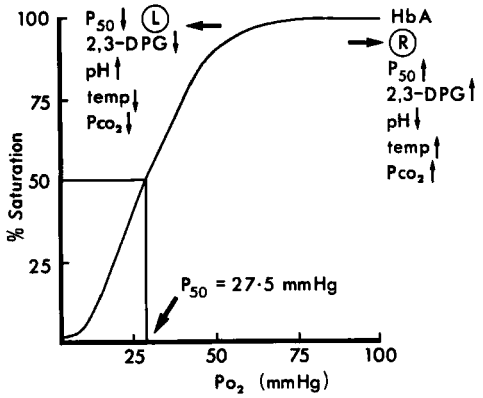

Fig. 2. Factors controlling the position of the oxy-haemoglobin dissociation curve.

2,3-DPG and the oxy-haemoglobin dissociation curve (Fig. 2)

The interaction of 2,3-DPG with haemoglobin and its subsequent effect on oxygen affinity means that changes in the concentration of 2,3-DPG will alter the position of the oxyhaemoglobin dissociation curve (ODC) which is usually denoted by the P_{50}, i.e. the partial pressure of oxygen when haemoglobin is 50% saturated. Increases in 2,3-DPG concentration increase the P_{50}[27] (ODC is shifted to the right) and decreases in 2,3-DPG concentration decrease the P_{50} (ODC is shifted to the left).[27] The P_{50} is increased by a fall in pH (Bohr effect) which also reduces 2,3-DPG concentration. Although this would appear to be contradictory both effects are important. The pH effect is immediate whereas the 2,3-DPG effect takes several hours to develop.[8] Therefore 2,3-DPG affects oxygen affinity not only by its direct effect on the P_{50} but also by control of the intra-erythrocytic pH.[13,14] Approximately 35% of the change in haemoglobin–oxygen affinity resulting from an alteration in 2,3-DPG concentration is explained by this effect of 2,3-DPG on the intra-erythrocytic pH.[8]

Carbon dioxide (CO_2) and 2,3-DPG compete for binding at the N-terminal amino groups of the β-chains. However, at a low pH 2,3-DPG binding is stronger, thus increasing the CO_2 component of the Bohr effect. A high pH reduces the CO_2 component of the Bohr effect.[28,29] The effects of temperature on the P_{50} are important only in pyrexia or in exercise when muscle temperature is high. Increases in temperature increase the P_{50}, but it has been suggested that the effect of 2,3-DPG in reducing oxygen affinity decreases with increasing temperature.[30]

Mean corpuscular haemoglobin concentration (MCHC) also affects oxygen affinity. Increases in the MCHC occurring in acidosis decrease oxygen affinity (P_{50} increases) and decreases in the MCHC increase oxygen affinity (P_{50} decreases). When a pH change occurs MCHC changes rapidly to ensure that the P_{50} remains relatively unchanged as 2,3-DPG concentration alters.[8]

Role of 2,3-DPG in response to hypoxia

2,3-DPG by its control of oxygen affinity has an important role to play in the physiological adaption to hypoxaemia which is classically divided into four types.

Stagnant hypoxaemia

Patients with congestive cardiac failure have an increased 2,3-DPG concentration[31,32] which parallels the reduction in cardiac output.[31] Within 24 hours of myocardial infarction 2,3-DPG concentration is increased[33] and this has been shown to increase the *in vitro* P_{50}. The rise in 2,3-DPG concentration in the patients studied was attributed to an increased deoxyhaemoglobin: haemoglobin ratio and to a metabolic alkalosis.[33] However, because of the alkalosis the *in vivo* P_{50} was modified.[33] 2,3-DPG concentration is also increased in patients with stagnant hypoxia secondary to peripheral vascular disease.[34]

Hypoxic hypoxaemia

Low inspired oxygen tension. An increased 2,3-DPG concentration is part of the physiological adaption to altitude.[35] When people resident at altitude return to sea level, their 2,3-DPG concentration also returns to normal.[35,36] At altitudes above 12,000 feet, the right-shifted ODC offers little advantage as it impairs oxygen loading in the lungs. The increase in 2,3-DPG concentration at altitude is thought to be due initially to alkalosis secondary to hypoxia-induced hyperventilation.

The continuing hypoxia and increased deoxyhaemoglobin concentration maintain the high levels, once the pH has returned to normal.[32,37]

In chronic lung disease normal 2,3-DPG concentrations have been found despite severe hypoxia.[38] Other workers[38,39] have found slightly increased 2,3-DPG concentrations which did not correlate well with saturation levels. Although 2,3-DPG concentrations correlate well with the *in vitro* P_{50}, there appears to be little overall effect on oxygen transport[40] because of the *in vivo* pH changes in chronic hypoxic lung disease.

Cyanotic heart disease. In adults and children, there is a rise in 2,3-DPG concentration[31] which produces a right-shifted ODC. It has been suggested that when corrective surgery is performed these changes disappear, but not if the surgery is only palliative.[32] It seems that if the mean Pao_2 is <60 mmHg, 2,3-DPG is elevated, but if the mean Pao_2 is >60 mmHg 2,3-DPG concentration remains normal.

Anaemic hypoxaemia

Although displacements of the ODC to the right, produced by increased concentrations of 2,3-DPG, may be of dubious value in situations with a low arterial Po_2 (e.g. lung disease, cyanotic heart disease) it is of tremendous advantage in anaemia where there is a normal arterial Po_2. The increased P_{50} is produced by an increase in 2,3-DPG concentration.[41,42] An increase in the 2,3-DPG concentration of 1 μ mole/ml red cells causes the P_{50} to increase by 1·23 mmHg[42] thus making normal oxygen delivery possible without such a large rise in cardiac output. This explains the exercise tolerance and lack of symptoms experienced by patients with mild anaemia. The rise in 2,3-DPG concentration seems to increase with the severity of the anaemia.[12] Thus patients with renal failure on maintenance haemodialysis can survive very low haemoglobin concentrations. In patients not on dialyses the rise in 2,3-DPG concentration is prevented by the accompanying acidosis.[43]

In children before puberty the increased inorganic phosphate leads to an increased 2,3-DPG concentration.[44] The resulting decreased oxygen affinity and increased oxygen delivery results in a lower erythropoietin drive from the kidney and hence a reduction in red cell mass and haemoglobin concentration. This explains the 'physiological anaemia' of childhood.[44] 2,3-DPG concentration appears to be increased in different types of anaemia, e.g. chronic renal failure[43,45] and cirrhosis of the liver.[46] In macrocytic anaemia the increase seems to be more variable than in iron deficiency anaemia.[24]

Histotoxic hypoxaemia

The hypoxaemia which occurs in septic shock is histotoxic in origin. Studies of 2,3-DPG concentration in septic shock have shown that the adaptive increase in 2,3-DPG concentration seen in other hypoxic conditions fails to occur. On the contrary, there is a steady decrease in 2,3-DPG concentration and the poor clinical condition of patients appears to correlate well with the decrease in 2,3-DPG.[47,48] It has also been suggested that the increased cardiac output and hyperdynamic peripheral 'shunting' typical of septic shock are secondary to the increased oxygen affinity produced by the low 2,3-DPG concentration.[47,48]

What is the mechanism of the increase in 2,3-DPG in response to hypoxia? It has been suggested that the concentration of 2,3-DPG is inversely related to that of haemoglobin even within normal levels[42,49] so that when the haemoglobin concentration falls as in anaemia, there will be an increase in 2,3-DPG concentration. This inverse relationship has not been substantiated by other workers,[24,37] and also the magnitude of the increase in 2,3-DPG concentration varies in different types of anaemia at the same haemoglobin concentration.[24,37] When hypoxia occurs there is an increased deoxyhaemoglobin concentration. As more 2,3-DPG is bound by this increasing quantity of deoxyhaemoglobin, product inhibition of 2,3-DPG mutase (Fig. 1) is removed leading to increased synthesis of *free* 2,3-DPG and so the *total* intra-erythrocytic concentration is increased.[50] Also, as the concentration of deoxyhaemoglobin increases the intra-erythrocytic pH rises which also encourages 2,3-DPG synthesis.[7–8] Unfortunately the deoxyhaemoglobin concentration cannot be measured. However, the mixed venous oxygen saturation gives a fair indication of the amount of deoxyhaemoglobin present. Direct correlation has been found between 2,3-DPG con-

centration and mixed venous oxygen saturation in anaemia.[37]

2,3-DPG concentration in stored blood

In 1954 Valtis & Kennedy[51] observed that the ODC of stored blood is shifted to the left. Serial estimations of organic phosphates in blood stored in acid-citrate-dextrose solutions show that there is a precipitous fall in 2,3-DPG concentration during the first 15 days of storage.[52] ATP decreases more slowly.[52] It is therefore apparent that the effect described by Valtis & Kennedy can be explained by the decrease in organic phosphate concentration.[47,53,54] 2,3-DPG concentration can be maintained when blood is stored in citrate phosphate dextrose solution (CPD) rather than ACD.[55] Also, if either CPD or ACD stored blood is supplemented with inosine, pyruvate, phosphate and adenine it can be stored for even longer periods with satisfactory oxygen transport function.[56] Super-normal concentrations of 2,3-DPG can also be obtained.[47,56] The main disadvantage of the addition of substrates is that inosine and adenine will lead to hyperuricaemia and renal damage in recipients.[57] The red cells therefore require to be washed prior to transfusion and this is an expensive process. Additives are also prohibited by law in the United Kingdom. However, it has been found that the 2,3-DPG concentration can be maintained if ACD or CPD blood is deep frozen within 24 hours of collection[55] and many blood transfusion centres offer this for special cases.

Following transfusion with stored blood, *in vivo* restoration of donor cell 2,3-DPG and ATP occurs.[47,58,59] The rate of restoration of 2,3-DPG will depend on the volume of blood transfused[56] and the physical condition of the recipients, e.g. acid–base status, cardio-respiratory function[56] and also the availability of phosphate.[60]

Hormonal control of 2,3-DPG concentration

The role of thyroid hormones has already been mentioned.[11] It has also been suggested that growth hormone and adequate pituitary function are required to maintain a normal 2,3-DPG concentration.[61] Androgens induce increases in erythrocytic 2,3-DPG.[62] Experiments in humans have shown that aldosterone plays a regulatory role in 2,3-DPG metabolism,[63] possibly by a direct influence on red cell glycolysis. Steroids have been used to manipulate 2,3-DPG levels in stored blood.[64]

Anaesthesia and 2,3-*DPG*

Any substance which alters the position of the ODC is of importance in anaesthesia. An experiment in dogs showed that halothane produced a shift of the curve but there was no change in 2,3-DPG concentration during or immediately following anaesthesia.[65] However, it has been shown that in other metabolic situations alterations of 2,3-DPG concentration develop over a few hours.[8]

It has been shown that both halothane and methoxyflurane at clinical concentrations are capable of localized and specific interactions with haemoglobin, resulting in a conformational change in the structure.[66] It is therefore possible that the binding of 2,3-DPG to haemoglobin will be altered by anaesthesia and consequently the relationship of anaesthesia, possible changes in 2,3-DPG concentration and displacement of the ODC merit further investigation.

Clinical implications of alterations in 2,3-DPG concentration

Preparation of anaemic patients for anaesthesia and surgery

The adaptive increase in 2,3-DPG concentration in anaemia compensates for the decrease in the oxygen flux by enhancing the ability of the erythrocytes to unload oxygen. Thus tissue oxygenation can be maintained in anaemia without such a large rise in cardiac output. This explains why patients with anaemia frequently do not experience symptoms until the haemoglobin concentration is about two-thirds normal. Transfusion of the anaemic patient with ACD blood, will be a hazardous procedure since the subsequent reduction in the patient's 2,3-DPG concentration will impair tissue oxygenation.

Old people (over 70 years) have an increased 2,3-DPG concentration[24] possibly in response to tissue hypoxia secondary to arteriosclerosis and the lower arterial oxygen saturation encountered in old age.[67] Transfusion of the

elderly anaemic patient with ACD stored blood not infrequently leads to cardiac failure. It is suggested that this is not due to fluid overload but to myocardial ischaemia secondary to the reduction in 2,3-DPG concentration and the subsequent increased oxygen affinity. All too often, in order to obtain an anaesthetically acceptable haemoglobin concentration, patients are hurriedly transfused the evening prior to surgery, instead of having their anaemia properly investigated and treated. If pre-operative blood transfusion is indicated in anaemic or elderly patients this should be administered *at least* 48 hours prior to surgery and where possible, fresh or 2,3-DPG-rich blood should be used. It is now the author's practice to send patients home following such transfusions if at all practicable, and to return the following week for their elective surgery. Objections from surgical colleagues can be scientifically overcome!

Experimental work in rabbits, has shown that wound healing is apparently normal in chronic anaemia.[68] This is possibly because of the decreased oxygen affinity. Reduction of the vital 2,3-DPG concentration by hasty pre-operative blood transfusion may thus delay wound healing. It is much better that the patient should approach anaesthesia and surgery with adequate haemoglobin and 2,3-DPG concentrations.

In pregnancy 2,3-DPG concentration is increased by about 20%.[24,69] The low haemoglobin concentration, increased deoxyhaemoglobin concentration, and various biochemical changes of pregnancy encourage a high 2,3-DPG concentration[24] which will maintain normal maternal tissue oxygenation and will be beneficial to the fetus with its high-affinity HbF. It follows that transfusion of the anaemic pregnant patient with ACD blood is very hazardous since the resulting maternal tissue hypoxia may lead to fetal hypoxia. This explains why many such transfusions near term result in premature labour.[70]

Carboxyhaemoglobin concentration is raised in people who smoke and is not able to transport oxygen. Therefore, to maintain normal oxygen transport and tissue oxygenation, either haemoglobin or 2,3-DPG concentration must be increased. Anaemic or pregnant patients who smoke will suffer a further reduction of their functional haemoglobin concentration and may be unable to effect a greater increase in their 2,3-DPG concentration to compensate for this. Smoking should be positively discouraged in anaemic and pregnant patients.

2,3-*DPG and massive blood transfusion*

In open-heart surgery 2,3-DPG concentration decreases during bypass and may not return to normal until the third post-operative day.[71] The increase in oxygen affinity may be deleterious in these very ill patients.

Two groups of open-heart surgery patients were given 2,3-DPG-enriched blood (2,3-DPG = 150% normal), or CPD, anticoagulated fresh blood (2,3-DPG = 70% normal).[72] The group which received the 2,3-DPG enriched blood had an increased cardiac index at similar filling pressures and improved oxygen delivery without decreasing mixed venous Po_2[72] The high 2,3-DPG group also required fewer inotropic interventions. This is an excellent example of a high 2,3-DPG transfusion improving myocardial performance and suggests that the use of 2,3-DPG enriched blood would be beneficial in other situations, e.g. treatment of septicaemic shock and transfusion of anaemic patients.

Steroids are frequently used in the treatment of shock. *In vitro* experiments have shown that hydrocortisone sodium succinate is more effective than methyl-prednisolone in increasing 2,3-DPG concentration[64] suggesting that the former steroid may be the drug of choice *in vivo*. It must also be remembered that maintenance of a normal plasma pH will always permit a more optimal 2,3-DPG response to hypoxia.

Hypophosphataemia

Parenteral feeding, with solutions lacking added inorganic phosphorus (e.g. aminosol) leads to hypophosphataemia, low 2,3-DPG concentration and an increased oxygen affinity which can be accompanied by symptoms suggestive of tissue hypoxia.[9,73] Since patients having parenteral feeding are usually ill, this increase in oxygen affinity is not advisable. It has also been shown that use of intravenous infusions such as 5% dextrose or dextrose/saline, following surgery, leads to hypophosphataemia.[74] This may possibly result in a low 2,3-DPG concentration and increased

oxygen affinity, at a time when the arterial oxygen saturation will be low secondary to alterations in ventilation and perfusion following anaesthesia and surgery.[67] It has been suggested that the hypophosphataemia is caused by an alteration in the maximal tubular reabsorption capacity for phosphate.[74] Although the hypophosphataemia appears to be transient[74] the addition of inorganic phosphorus to routine post-operative intravenous fluids may be advisable; this is currently being investigated.

Disorders of acid–base balance

In chronic acidosis, e.g. uncontrolled diabetic keto-acidosis, the low pH results in a low 2,3-DPG concentration which balances the Bohr effect so that tissue oxygenation remains normal.[75] Rapid correction of the pH by intravenous bicarbonate removes the pH effect on the dissociation curve, revealing the low 2,3-DPG effect which produces a rapid fall in the P_{50}. Furthermore, in uncontrolled diabetic keto-acidosis 2,3-DPG concentration may take several days to return to normal because of changes in plasma phosphate.[75] Emergency treatment of diabetic keto-acidosis should not include intravenous bicarbonate. It may be advisable to add inorganic phosphorus to any intravenous fluids being used.

In chronic alkalosis the subsequent rise in 2,3-DPG concentration prevents increased oxygen affinity consequent upon the pH mediated shift of the ODC to the left.

Management of patients with sickle cell haemoglobinopathy.

Prior to anaesthesia and surgery it is frequently customary to induce a metabolic alkalosis in patients with sickle-cell disease, to increase oxygen affinity and decrease the likelihood of sickling.[76] When systemic alkinization is carried out with oral sodium bicarbonate, as has been recommended[76] there is time for the pH change to increase 2,3-DPG concentration[8] and counteract the pH effect on the ODC. Therefore the benefits of alkalinization are dubious.[77] Instead it is possibly better to concentrate on an anaesthetic technique which maintains a good peripheral blood flow and to avoid cooling and hypoxia. Intravenous alkalinization[76] will tide the patient over the intra and immediate postoperative period without causing changes in 2,3-DPG concentration.

What is the clinical relevance of the effects of 2,3-DPG on oxygen affinity?

It must be remembered that although there is a proven relationship between increases in 2,3-DPG and in the P_{50}, the *in vivo* P_{50} is frequently quite different from the *in vitro* P_{50} because of the effects of pH, P_{CO_2} and temperature on the position of the ODC. Consequently this has prompted the suggestion that the clinical significance of the effects of 2,3-DPG on oxygen affinity is minimal. Nevertheless, an understanding of the basic physiological processes controlling oxygen affinity has already led to beneficial therapeutic intervention, e.g. in the field of blood transfusion and storage. Iatrogenic manipulation of the ODC, e.g. with 2,3-DPG-rich blood, may be of importance in the management of acutely ill patients. Intelligent use of pre-operative blood transfusion in the management of the anaemic patient results from a knowledge of the role of 2,3-DPG in the physiological adaptation to anaemia.

The effects of hypophosphataemia on oxygen affinity means that constituents of solutions used for parenteral nutrition and routine intravenous fluids may require to include inorganic phosphorus. No longer can post-operative dextrose saline be considered 'innocuous'.[74]

In general, elucidation of physiological and biochemical processes ultimately benefits patients therapeutically.

Summary

The ease with which haemoglobin releases oxygen to the tissues is controlled by erythrocytic 2,3-diphosphoglycerate (2,3-DPG) such that an increase in the concentration of 2,3-DPG decreases oxygen affinity and vice versa.

This review article describes the synthesis and breakdown of 2,3-DPG in the Embden–Meyerof pathway in red cells and briefly explains the molecular basis for its effect on oxygen affinity. Interaction of the effects of pH, P_{CO_2}, temperature and 2,3-DPG on the oxyhaemoglobin dissociation curve are discussed. The role of 2,3-DPG in the intra-

erythrocytic adaptation to various types of hypoxaemia is described. The increased oxygen affinity of blood stored in acid–citrate–dextrose (ACD) solution has been shown to be due to the decrease in the concentration of 2,3-DPG which occurs during storage. Methods of maintaining the concentration of 2,3-DPG in stored blood are described.

The clinical implications of transfusion of elderly people, anaemic or pregnant patients with ACD stored blood to anaesthetically and surgically acceptable haemoglobin concentrations are discussed.

Hypophosphataemia in association with parenteral feeding reduces 2,3-DPG concentration and so increases oxygen affinity. Since post-operative use of intravenous fluids such as dextrose or dextrose/saline also lead to hypophosphataemia, the addition of inorganic phosphorus to routine post-operative intravenous fluid may be advisable.

Disorders of acid–base balance affect oxygen affinity not only by the direct affect of pH on the oxyhaemoglobin dissociation curve but by its control of 2,3-DPG metabolism. Management of acid–base disorders and pre-operative alkalinization of patients with sickle cell disease should take account of this.

It is known that anaesthesia alters the position of the oxyhaemoglobin dissociation curve, but it is thought that this is independent of any effects which anaesthetic agents may have on 2,3-DPG concentration.

In vitro manipulation of 2,3-DPG concentration with steroids has already been carried out. Elucidation of the role of 2,3-DPG in the control of oxygen affinity may ultimately lead to iatrogenic manipulation of oxygen affinity *in vivo*.

Key words

BLOOD; 2,3-diphosphoglycerate, haemoglobin, oxyhaemoglobin dissociation, stored.

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