RESPIRATION AND THE CEREBROSPINAL FLUID

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INTRODUCTION
It has long been known that changes in the hydrogen ion concentration ([H⁺]) and carbon dioxide tension (Pco₂) of the blood affect respiration. These alterations in ventilation are probably produced by a chemical stimulus at more than one site (Lambertsen et al., 1961). The presence of arterial chemoreceptors in relation to the carotid sinus and aortic arch is well known. Recently, Mitchell et al. (1963) have demonstrated another chemosensitive region in the anterolateral surface of the medulla which responds rapidly to changes in [H⁺] and Pco₂ in the cerebrospinal fluid (c.s.f.). Because of the blood-brain and blood-c.s.f. barriers, changes in the [H⁺] of the c.s.f. are not necessarily the same, nor do they occur at the same rate, as in the blood. This is important in understanding the consequences of ventilatory disturbances produced by anaesthesia, artificial respiration and disease.

This article reviews the following:
(i) The evidence that acid-base changes in the c.s.f. affect pulmonary ventilation.
(ii) The possible mechanisms whereby these effects are produced.
(iii) The c.s.f. changes which follow respiratory and metabolic acid-base disturbances.
(iv) The mechanisms whereby the [H⁺] of the c.s.f. is maintained constant in a variety of acid-base disturbances of the body.

Finally, the possible clinical and physiological applications of these findings are discussed.

METHOD OF PRESENTATION OF ACID-BASE DATA
The [H⁺] of the c.s.f. is determined, as in the plasma, by the ratio of the concentrations of carbonic acid to bicarbonate ([HCO₃⁻]). The concentration of the carbonic acid is directly proportional to the Pco₂ so that for simplicity we may express the Henderson-Hasselbalch equation as follows:

\[ [H^+] = K'_a \frac{Pco_2}{[HCO_3^-]} \]

where \( K'_a \) is a constant. (The above expression is only an approximation but is quite adequate for the purposes of this review. Many readers will be familiar with the above formula in its logarithmic form where the constant is pK'. In plasma this has a value of about 6-10, while in c.s.f. it is 6-13. For further details the reader is referred to the paper of Alexander, Gelfand and Lambertsen (1961).) It can be seen from the above expression that a rise in Pco₂ or fall in [HCO₃⁻] (or both) will lead to a rise in [H⁺] which is equivalent to a fall in pH.

EFFECT OF CHANGES IN C.S.F. [H⁺] AND Pco₂ ON PULMONARY VENTILATION
In 1950 Leusen reported that changes in [H⁺] of the c.s.f. affected pulmonary ventilation; and this observation has led to an extensive study of c.s.f. [H⁺] as a factor in the chemical control of ventilation. Mitchell et al. (1963) have located in animals the areas in the central nervous system where these effects are produced. They found bilateral chemosensitive regions on the anterolateral surface of the medulla bounded by the pons rostrally, the pyramidal tract medially, and by the roots of the 7-11th cranial nerves laterally. These workers have shown that filter paper pledgets saturated with "mock c.s.f." and equilibrated with 100 per cent carbon dioxide at 38°C produce a respiratory response within 3 seconds when applied to this area, whereas all other areas are unresponsive. Acetylcholine and nicotine applied to these areas stimulated ventilation whilst lobeline, procaine, cyanide and cold suppressed it.

These experiments identified the actual chemosensitive area, but gave only a qualitative guide to the respiratory changes produced by alteration of the acid-base composition of the c.s.f. To measure the magnitude of these respiratory changes it was necessary to produce a steady state; this was achieved by perfusing the cisterna magna with c.s.f. of known [H⁺]. By this method the [H⁺] of the c.s.f. can be kept quite constant over
the chemosensitive regions for as long as required, and ventilation measured accurately when a steady state has been achieved. The [H⁺] of the c.s.f. is then altered by changing the [HCO₃⁻] of the perfusate but keeping the Pco₂ constant, and the changes in ventilation recorded. If the [HCO₃⁻] of the c.s.f. is lowered in this way the [H⁺] increases and ventilation rises. These experiments were carried out on anaesthetized animals (Mitchell et al., 1963). Studies on unanaesthetized animals were made by Heisey, Held and Fencl (1964). In the latter experiments, the respiratory responses of healthy unanaesthetized goats to perfusion of the ventriculo-cisternal system with "mock c.s.f." were studied. Nylon guide tubes were implanted permanently into the lateral ventricles and cisterna magna. The goats tolerated respiratory masks satisfactorily and measurements were repeated over a period of several months. Heisey et al. found that, at a constant Pco₂ in the c.s.f., alveolar ventilation (per 40-kg goat) increased from 4.6 to 11.5 litres per minute when the c.s.f. [HCO₃⁻] was reduced in the perfusate from 22 to 16 m.equiv/l.

Further experiments by Heisey and his colleagues have shown that approximately 40 per cent of the increase in ventilation on carbon dioxide breathing can be attributed to the rise in c.s.f. [H⁺]; the remaining 60 per cent being the result of changes in Pco₂ or associated [H⁺] changes elsewhere, e.g. the arterial chemoreceptors or the respiratory centre. This information was obtained in the following way. The change in ventilation associated with carbon dioxide breathing was first measured when the [H⁺] of the c.s.f. was allowed to increase as it does when the Pco₂ rises in the normal way. The measurements were then repeated but the [H⁺] of the c.s.f. kept constant by perfusing the ventriculo-cisternal system with c.s.f. of constant composition. The difference between the rise in ventilation in these two conditions is a measure of the increase in ventilation due to changes in c.s.f. [H⁺] alone.

POSSIBLE MECHANISMS BY WHICH C.S.F. [H⁺] AFFECTS VENTILATION

Two possible explanations have been put forward. Firstly, it has been suggested that changes in c.s.f. [H⁺] do not affect the respiratory centre directly but act on a superficial chemosensitive area which may contain chemoreceptors. Part of the evidence for this is that respiratory changes following application of agents to the chemosensitive area occur very rapidly, within a few seconds. Others, however, believe that the composition of c.s.f. might influence pulmonary ventilation by penetration of ions from the c.s.f. to primary respiratory neurones in reticular tissue. This would alter the chemical environment of the neurones which might lead to changes in respiration.

CHANGES IN THE C.S.F. IN RESPIRATORY AND METABOLIC ACID-BASE DISTURBANCES

Between blood and brain, and between blood and c.s.f., there is a barrier to charged ions such as hydrogen and bicarbonate but no barrier to molecular carbon dioxide (fig. 1(a)). It is this barrier which, under certain circumstances, leads to changes in c.s.f. [H⁺] which are opposite to those in the blood. These paradoxical changes are important, not only in the chemical control of ventilation, but also because the barrier affects the distribution of those drugs which are weak acids or bases between blood, c.s.f. and brain (Stabenau, Warren and Rall, 1959).

Acute respiratory acidosis.

As the blood-c.s.f. barrier is permeable to carbon dioxide the Pco₂ of blood and c.s.f. will rise in a respiratory acidosis. The consequent increase in carbonic acid in the blood will be buffered by haemoglobin but in the c.s.f., where there is little protein, the increase will be unbuffered (fig. 1(b)). Thus for an equal change in Pco₂ there will be a greater rise in [H⁺] in the c.s.f. than in the blood. Although the blood-c.s.f. barrier is freely permeable to carbon dioxide this does not mean that the rate of rise in Pco₂ is as rapid in the c.s.f. as in the blood. This was shown in experiments where the rate of rise of Pco₂ was compared in arterial blood, jugular venous blood and cisternal c.s.f. during carbon dioxide breathing (Bradley, Semple and Spencer, 1963). The rise in Pco₂ in the c.s.f. was both delayed and then slower than in the arterial and jugular venous blood; it was anticipated that it would take some 30-40 minutes for the rise in c.s.f. Pco₂ to be complete after the start of carbon dioxide administration. This relatively slow rise in c.s.f. Pco₂
a) Normal acid-base balance

\[
\begin{align*}
\text{Blood-csf. barrier} \\
\text{Blood (capillary)} & \xrightarrow{\text{H}^+} \text{cs.f.} \\
[H^+] &= k_b' \cdot PCO_2 \\
\text{PCO}_2 &= k'_b' \cdot [H^+] \\
\text{HCO}_3^- &\rightarrow [HCO_3^-] \\
\text{PCO}_2 &\rightarrow [H^+] \\
[HCO_3^-] &\rightarrow [HCO_3^-]
\end{align*}
\]

b) Respiratory acidosis—short term

\[
\begin{align*}
\text{Blood-csf. barrier} \\
\text{Blood (capillary)} & \xrightarrow{\text{H}^+} \text{cs.f.} \\
[H^+] &= k_b' \cdot PCO_2 \\
\text{PCO}_2 &\rightarrow [H^+] \\
\text{HCO}_3^- &\rightarrow [HCO_3^-] \\
\text{PCO}_2 &\rightarrow [H^+] \\
[HCO_3^-] &\rightarrow [HCO_3^-]
\end{align*}
\]

c) Respiratory acidosis—long term (several hours)

\[
\begin{align*}
\text{Blood-csf. barrier} \\
\text{Blood (capillary)} & \xrightarrow{\text{H}^+} \text{cs.f.} \\
[H^+] &= k_b' \cdot PCO_2 \\
\text{PCO}_2 &\rightarrow [H^+] \\
\text{HCO}_3^- &\rightarrow [HCO_3^-] \\
\text{PCO}_2 &\rightarrow [H^+] \\
[HCO_3^-] &\rightarrow [HCO_3^-]
\end{align*}
\]

d) Metabolic acidemia—short term

\[
\begin{align*}
\text{Blood-csf. barrier} \\
\text{Blood (capillary)} & \xrightarrow{\text{H}^+} \text{cs.f.} \\
[H^+] &= k_b' \cdot PCO_2 \\
\text{PCO}_2 &\rightarrow [H^+] \\
\text{HCO}_3^- &\rightarrow [HCO_3^-] \\
\text{PCO}_2 &\rightarrow [H^+] \\
[HCO_3^-] &\rightarrow [HCO_3^-]
\end{align*}
\]

e) Metabolic acidemia—long term

\[
\begin{align*}
\text{Blood-csf. barrier} \\
\text{Blood (capillary)} & \xrightarrow{\text{H}^+} \text{cs.f.} \\
[H^+] &= k_b' \cdot PCO_2 \\
\text{PCO}_2 &\rightarrow [H^+] \\
\text{HCO}_3^- &\rightarrow [HCO_3^-] \\
\text{PCO}_2 &\rightarrow [H^+] \\
[HCO_3^-] &\rightarrow [HCO_3^-]
\end{align*}
\]

Fig 1

Change in [H^+], PCO_2 and [HCO_3^-] in blood and cs.f. in some acid-base disturbances. The magnitude of the changes shown are only qualitative. For simplicity, the effects of renal compensation for the acid-base disturbances have been omitted. K_b' and K_b" are constants. For details see text.

is presumably due to the time needed to saturate the brain and cs.f. with carbon dioxide.

Chronic respiratory acidosis and alkalosis.

After about an hour changes in PCO_2, whether produced by an alteration in ventilation or by carbon dioxide administration have a marked effect on cs.f. [HCO_3^-] (Michel, 1963). A rise in PCO_2 leads to a rise in [HCO_3^-] and the reverse occurs when PCO_2 falls. Initially, therefore, the [H^+] of the cs.f. will rise with the increase in PCO_2 but when the cs.f. [HCO_3^-] starts to rise the [H^+] will tend to return to its original concentration (see fig. 1 (b and c)).

During a respiratory alkalosis the reverse will occur. This has been shown in man when a respiratory alkalosis is produced by hypoxia at high altitude (Severinghaus et al., 1963). The increase in alveolar ventilation leads to a fall in cs.f. PCO_2 and [H^+]; after a few days there is also a drop in cs.f. [HCO_3^-] proportional to the fall in PCO_2 so that the [H^+] returns to the original concentration at sea level. The fall in the cs.f. [HCO_3^-] is greater than the fall in either the [HCO_3^-] or the standard bicarbonate of the plasma (fig. 2). Thus after a few days at high altitude plasma [H^+] remains low but the [H^+] of the cs.f. is normal. The mechanism by which the cs.f. [HCO_3^-] is lowered will be discussed later, but it is almost certainly due to active transport of one or more ions between the blood and cs.f. or between the blood and brain tissue.

Acute metabolic acid-base disturbances.

In metabolic acidosis the plasma [HCO_3^-] is low and plasma [H^+] raised. This acidemia leads to a rise in ventilation probably due to stimulation of the aortic and carotid chemoreceptors with a consequent fall in blood and cs.f. PCO_2. Because of the blood-brain barrier there will be no change
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Bicarbonate changes in blood and c.s.f. during acclimatization at a height of 3,800 m. Standard bicarbonate of blood is the plasma bicarbonate concentration in blood equilibrated at 37° at a Pco₂ of 40 mm Hg and Po₂ over 100 mm Hg. (From Severinghaus, Mitchell, Richardson and Singer (1963), J. appl. Physiol., 18, 1155. Reproduced by kind permission of the authors and the Editors of J. appl. Physiol.)

in c.s.f. [HCO₃⁻] but there will be a drop in Pco₂ (as in the blood). This will lead to a fall in [H⁺] in the c.s.f. in spite of an increase in blood [H⁺] (fig. 1(d)). The reverse occurs in an acute metabolic alkalosis. Thus in acute metabolic acid-base disturbances, changes in the [H⁺] of the c.s.f. are in the opposite direction to those occurring in the plasma.

Chronic metabolic acid-base disturbances.

In a chronic metabolic acidosis the Pco₂ of the c.s.f. is low for the same reason as in an acute acidosis. Now, it was pointed out in the section on respiratory acid-base disturbances that a fall in c.s.f. Pco₂ leads to a drop in [HCO₃⁻], and this occurs in a chronic metabolic acidosis. Again, because the drop in c.s.f. [HCO₃⁻] is proportional to the fall in Pco₂, the c.s.f. [H⁺] returns to normal (fig. 1(e)). It is important to notice that the drop in c.s.f. [HCO₃⁻] in a chronic metabolic acidosis is due to the associated fall in Pco₂ and not due to the lowered plasma [HCO₃⁻]. This is illustrated by the acid-base changes which have been found in patients with a chronic metabolic acidosis due to renal failure (Bradley and Semple, 1962). In this condition the fall in c.s.f. [HCO₃⁻] is less than that in the plasma, and this fall is proportional to the drop in c.s.f. Pco₂. The result is that the [H⁺] of the c.s.f. is normal in spite of a severe acidemia.

POSSIBLE MECHANISM WHEREBY THE [H⁺] OF THE C.S.F. IS MAINTAINED CONSTANT

In the acid-base disturbances described above, the [H⁺] of the c.s.f. has changed initially but thereafter returned to normal. A rise in the Pco₂ of the c.s.f. in respiratory acidosis initially produces a rise in [H⁺] but after a few hours the [HCO₃⁻] increases and the [H⁺] returns towards normal. In chronic metabolic acidosis the fall in c.s.f. [HCO₃⁻] is proportional to the fall in Pco₂ so that the [H⁺] is unchanged. What is the mechanism whereby c.s.f. [HCO₃⁻] is altered and [H⁺] remains constant during these acid-base disturbances? Why is it that changes in c.s.f. Pco₂ are so accurately matched by changes in [HCO₃⁻]?

At present these questions cannot be answered with certainty because the factors governing the composition of the c.s.f. are not completely known. It is probable that the c.s.f. is secreted at a constant composition in spite of quite wide variation in the level of the electrolytes in the plasma. The composition of the c.s.f. is then modified after secretion by exchange of ions and water between brain tissue and c.s.f. (Bradbury et al., 1963). Thus, changes in the [HCO₃⁻] of the c.s.f. may be secondary to those occurring in brain extracellular fluid. If this is so, then it is important to know the mechanisms which govern the [HCO₃⁻] of the brain when the Pco₂ is changed.

When the Pco₂ of the brain is raised, bicarbonate will be formed (as in blood) in quantities dependent on the physico-chemical buffer capacity of the brain. It is unlikely that this alone could account for the [HCO₃⁻] changes observed and there is evidence that another mechanism is involved. Siesjö (personal communication) measured the changes in the standard bicarbonate of brain tissue of rats exposed to 7-8 per cent carbon dioxide for periods of 1-48 hours. (The standard bicarbonate of the brain is the [HCO₃⁻] at a fixed Pco₂ and is therefore independent of alterations in
Pco₂ outlined above. This is a similar technique to the measurement of the standard bicarbonate in blood.) The results showed that the standard bicarbonate increased with the time of exposure to carbon dioxide. Siesjö (personal communication) concluded that the rise in carbon dioxide tension had led either to the extrusion of hydrogen ions or accumulation of bicarbonate ions by brain tissue. [A preliminary paper on the passive fluxes of hydrogen and bicarbonate ions has already been published by Siesjö (1964).] Whatever is the exact explanation of these results the implication is clear, namely that there is active transport of one or more ions between blood and brain. In this way it is possible to account for the magnitude of the changes in c.s.f. [HCO₃⁻] when Pco₂ changes.

In metabolic acidemia there is usually an increase in ventilation and a fall in Pco₂, and hence a drop in [HCO₃⁻] of brain and c.s.f. It is unlikely that changes in plasma [HCO₃⁻] in metabolic acid-base disturbances produce much change in brain and c.s.f. directly because of the blood-brain and blood-c.s.f. barriers. Therefore the changes in c.s.f. [HCO₃⁻] in a metabolic acidemia are more likely to be due to the concomitant changes in Pco₂ rather than the plasma [HCO₃⁻]. Evidence for this was obtained by Mitchell, Bainton, Vernon-inghaus and Edelist (1964) in some long-term experiments in conscious trained dogs. After removing the carotid and aortic chemoreceptors there was no significant overventilation during a moderate metabolic acidemia and no change in c.s.f. Pco₂, [HCO₃⁻] or [H⁺]. However, in a more severe acidosis induced in the same dogs there was an increase in ventilation with a drop in c.s.f. Pco₂ and [HCO₃⁻] with a small rise in [H⁺] in the c.s.f. In the opinion of these workers the [H⁺] of the c.s.f. is regulated by an active transport mechanism which in a severe acidemia fails to maintain the [H⁺] constant.

In summary then, it is probable that the constancy of the [H⁺] of the c.s.f. in acid-base disturbances is due to active transport of one or more ions. This transport may be between blood and brain extracellular fluid which in turn leads to changes in the c.s.f. by passive diffusion of water and ions. Alternatively the active transport may be between blood and c.s.f. or between brain and c.s.f. In my view it is not possible at present to be certain whether the active transport of these ions occurs at one or more of the sites mentioned above.

**CLINICAL AND PHYSIOLOGICAL APPLICATIONS**

**Chemical control of ventilation.**

The presence of a chemosensitive region in the surface of the medulla, separated from the blood by a barrier and affected by changes in [H⁺] and Pco₂ of the c.s.f., gives a rational explanation for the timing and magnitude of respiratory changes in acid-base disturbances. This is illustrated in the following two examples. Firstly, it has been shown that changes in ventilation are not complete till some 30 minutes after the start of carbon dioxide administration in man. This is considerably longer than the time taken to complete the rise in arterial and jugular venous Pco₂ (Bradley, Semple and Spencer, 1964, unpublished data). The rise in c.s.f. Pco₂ in the cisterna magna is much slower, taking some 30-40 minutes to complete, which may explain this slow rise in ventilation on carbon dioxide administration. Secondly, in a metabolic acidosis it has been shown by Nielsen (1936) that for equivalent changes in plasma [H⁺] the rise in ventilation is smaller than that produced by carbon dioxide administration. One possible explanation for the difference may be that during metabolic acid-base disturbances there is no significant increase in the [H⁺] of the c.s.f.; while during the short-term administration of carbon dioxide the [H⁺] of the c.s.f. increases because carbon dioxide diffuses into the c.s.f. In addition, it is likely that during metabolic acid-base disturbances changes in the c.s.f. will lag behind those in the blood. This may explain the fact that overventilation in diabetic acidosis is well known to persist for some time after plasma [HCO₃⁻] and [H⁺] have been corrected.

**Respiratory alkalosis produced by overventilation.**

This may be produced by overventilation of paralyzed patients under anaesthesia, during artificial ventilation, and by hypoxia at high altitudes. It was pointed out earlier that over-ventilation produced a fall in c.s.f. Pco₂ followed later by a fall in c.s.f. [HCO₃⁻]. When over-ventilation stops or when carbon dioxide is added to the inspired air, the Pco₂ of the c.s.f. will rise again. But now the c.s.f. [HCO₃⁻] is lower than it
was before the period of overventilation so that for any given Pco$_2$ level the [H$^+$] will be greater (see introduction). This will lead to stimulation of the medullary chemosensitive area and ventilation will be maintained at a higher level than before the period of overventilation. This overventilation will persist until the c.s.f. [HCO$_3^-$] has returned to its original level. This may explain why those who have become acclimatized to high altitude maintain a high ventilation and low arterial Pco$_2$ for some time after returning to sea level. It has also been observed that patients receiving artificial ventilation whose arterial Pco$_2$ has been kept at a low level, will often maintain a low arterial Pco$_2$ by their own efforts after the cessation of artificial ventilation (Smith, Spalding and Watson 1962).

It is customary for some anaesthetists to maintain a high level of ventilation in paralyzed patients undergoing surgery. If this overventilation lasts for longer than an hour there will be a significant reduction in the [HCO$_3^-$] of the c.s.f. This may help to maintain ventilation at a high level when Pco$_2$ rises postoperatively in face of the many other influences tending to produce hypoventilation at this time. Equally, carbon dioxide accumulation (even with high concentrations of inspired oxygen) during surgery and a rise in c.s.f. [HCO$_3^-$], may contribute to alveolar hypoventilation observed during the postoperative period.

REFERENCES