Control of Cerebral Blood Flow by Blood Gases

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Cerebrovascular reactivity can be measured as the cerebrovascular flow response to a hypercapnic challenge. The many faceted responses of cerebral blood flow to combinations of blood gas challenges are mediated by its vasculature’s smooth muscle and can be comprehensively described by a simple mathematical model. The model accounts for the blood flow during hypoxia, anemia, hypocapnia, and hypercapnia. The main hypothetical basis of the model is that these various challenges, singly or in combination, act via a common regulatory pathway: the regulation of intracellular hydrogen ion concentration. This regulation is achieved by membrane transport of strongly dissociated ions to control their intracellular concentrations. The model assumes that smooth muscle vasoconstriction and vasodilation and hence cerebral blood flow, are proportional to the intracellular hydrogen ion concentration. Model predictions of the cerebral blood flow responses to hypoxia, anemia, hypocapnia, and hypercapnia match the form of observed responses, providing some confidence that the theories on which the model is based have some merit.

Keywords: cerebral blood flow, mathematical model, hypercapnia, hypoxia, anemia, hypocapnia

INTRODUCTION

The mathematical model proposed here is concerned with the physiological mechanisms regulating cerebral blood flow (CBF) in response to anemia, hypoxia, and hypercapnia and hypocapnia. Cerebral blood flow increases in anemia (Brown et al., 1985; Borzage et al., 2016; Zheng et al., 2016); as well as during acute alterations in arterial blood gases (Willie et al., 2012) such as hypoxia (Cohen et al., 1967; Mardimae et al., 2012), and hypercapnia (Battisti-Charbonney et al., 2011). The model is tested by comparing its predictions to observations.

Cerebral blood flow is largely controlled by changes in the vascular resistance in parenchymal arterioles. The large pial arteries on the surface of the cortex contain multiple layers of vascular smooth muscle cells (Wei et al., 1980). These pial vessels branch into penetrating arterioles containing a single layer of vascular smooth muscle cells (Nishimura et al., 2007), and enter the cortical parenchyma, where micro vessels covered by pericytes but do not control microregional CBF (Hill et al., 2015). Vascular smooth muscle is the final CBF control effector in: (i) Autoregulation which mitigates against variations in brain perfusion pressure (Tan and Taylor, 2014; Tzeng and Ainslie, 2014), and (ii) Neurovascular Coupling which increases local blood flow
in response to increased neuronal metabolic demand (Attwell et al., 2011, 2016; Phillips et al., 2016; Hosford and Gourine, 2019; Hoiland et al., 2020).

Acute changes in arterial blood gases also affect CBF, independently of these regulatory mechanisms (Willie et al., 2012). Hypoxia (Cohen et al., 1967; Mardimae et al., 2012) and hypercapnia (Battisti-Charbonney et al., 2011; Hoiland et al., 2019), as well as decreases in hemoglobin (anemia) (Borzage et al., 2016; Duffin et al., 2020) increase CBF, while hypocapnia decreases CBF (Battisti-Charbonney et al., 2011; Hoiland et al., 2019). It is the increase in CBF during hypercapnia that is the basis of cerebrovascular reactivity (CVR) testing.

In the presence of hypoxia and anemia, vascular tone decreases to increase CBF and maintain an adequate O₂ supply (Duffin, 2020). Long term changes in CBF occur in chronic anemia (Brown et al., 1985) including sickle cell anemia (Bush et al., 2016), altitude acclimatization (Woff, 2000) and chronic hypoxia (Powell and Fu, 2008), and are accompanied by a multitude of adaptive changes orchestrated via the HIF 1 alpha pathway (Poellinger and Johnson, 2004). Over the long term the cerebral vasculature remodels to provide larger diameter vessels and accommodate higher CBF (Hulbert et al., 2017).

Vascular smooth muscle tone depends on intracellular [H⁺]; contracting in alkalosis and relaxing in acidosis (Austin and Wray, 1993; Aalkjaer and Peng, 1997) to consequently alter CBF. Changes in intracellular [H⁺] alter intracellular [Ca²⁺] (Swietach et al., 2013) and consequently smooth muscle tone (Boedtkjer, 2018), with the relaxation produced by hypercapnic acidosis, as in CVR testing, mediated by a reduction of [Ca²⁺] (Peng et al., 1998), although, rapid acute acidification can cause a transient increase in intracellular [Ca²⁺] that leads to contraction (Jensen et al., 1993).

Intracellular [H⁺] is the key intracellular regulated ion (Boedtkjer and Aalkjaer, 2012; Boedtkjer, 2018; Rasmussen and Boedtkjer, 2018), with a typical resting intracellular [H⁺] in vascular smooth muscle cells of about 50–80 nM/L (Boedtkjer et al., 2012). This regulation requires a net acid extrusion to maintain normal intracellular acid–base homeostasis, and it is this regulation that is challenged during CVR hypercapnia, producing a vasodilation and increased CBF (Kontos et al., 1977; Peng et al., 1998).

Stewart (Stewart, 1983; Hughes and Brain, 2013) has suggested an insightful approach to understanding acid-base changes in biological systems. In this system, intracellular [H⁺] is determined by CO₂ tension, the balance of concentrations of the strongly dissociated ions (the strong ion difference [SID]), and the requirement for electroneutrality. Consequently, the regulation of intracellular [H⁺] depends on cell membrane ion exchangers (Aalkjaer, 1990; Hughes and Brain, 2013; Boedtkjer, 2018; Garneau et al., 2020) to control intracellular [SID]. These membrane ion exchangers are energy dependent (Garneau et al., 2020) so that reductions in O₂ availability (Hoiland et al., 2016) (blood O₂ content, CaO₂) to the cerebral vasculature smooth muscles reduces the ability of these membrane ion exchangers to control intracellular [SID], and hence intracellular [H⁺], smooth muscle tone and CBF. Thus, changes in arterial CO₂ tension (PaCO₂) override intracellular [H⁺] regulation to produce vasodilation and vasoconstriction. Similarly, decreases in CaO₂ caused by decreases in arterial O₂ tension (PaO₂, i.e., hypoxia) or hemoglobin concentration ([Hb] i.e., anemia) degrade the efficiency or capacity of membrane ion exchangers that control [SID] producing an increase in intracellular [H⁺], which causes vasodilation and results in an increase in CBF. This model is pictured in Figure 1.

**MATERIALS AND METHODS**

The model equations are presented in the following assumptions using these symbols:

\[ [\text{H}^+] = \text{intracellular hydrogen ion concentration (nM/L).} \]
\[ PCO_2 = \text{intracellular CO}_2 \text{ tension = arterial CO}_2 \text{ tension (mmHg).} \]
\[ [\text{SID}] = \text{intracellular [strongly dissociated cations]} - \text{[strongly dissociated anions]} \text{ (mM/L).} \]
\[ \text{CBF} = \text{cerebral blood flow (ml/min/100 ml).} \]
\[ CaO_2 = \text{arterial O}_2 \text{ concentration/content (ml/ml).} \]

The equation parameters were empirically derived from observed responses to the various disturbances.

**Assumption 1:** Cerebrovascular smooth muscle intracellular [H⁺] is a function of PCO₂ and [SID] (Stewart, 1983) (see Appendix):

\[ [\text{H}^+] \text{ (nM/L)} = \text{ Function of } \{\text{PCO}_2, [\text{SID}]\} \]  
\[ (1) \]

**Assumption 2:** [H⁺] is regulated by a feedback alteration of [SID] proportional to the deviation of [H⁺] from its regulated value of \([H^+]_n = 40 \text{ nM/L} \) according to the following eq.

\[ [\text{SID}] = 5.5 + \text{Gain}^*([H^+] - 40) + 2 \]  
\[ (2) \]
Assumption 3: Smooth muscle tone is assumed to be limited to a maximum vasoconstriction and vasodilation so that CBF is a sigmoid function of intracellular $[\text{H}^+]$ according to the following eq. 3, which is illustrated in Figure 3:

$$\text{CBF} = 25 + 100/(1 + \exp(-(|[\text{H}^+] - 40.2]/0.34)) \quad (3)$$

Assumption 4: The regulation of $[\text{H}^+]$ by [SID] is oxygen dependent with the Gain of eq. 2 a function of arterial oxygen content, $\text{CaO}_2$, according to eq. 4, as illustrated in Figure 4:

$$\text{Gain} = 12.6 - 0.5/\text{CaO}_2; \quad (4)$$

$\text{CaO}_2$ is calculated from $\text{PaCO}_2$, $\text{PaO}_2$, and $[\text{Hb}]$ using previously published equations (Duffin, 2005; Balaban et al., 2013).

The system equations are solved using an iterative approach (LabVIEW, National Instruments, Austin, TX, United States) outlined in the block diagram of Figure 5.

RESULTS

The model performance was assessed by its CBF responses to changes in $\text{PCO}_2$, $\text{PO}_2$ and $[\text{Hb}]$ as shown in the following figures (Figures 6–8), which compare the model responses with examples of observed responses.

DISCUSSION

The model predictions for CBF responses match the form of the observed responses, providing some confidence that the theories on which the model was based are realistic. Of course, such a model does not prove the theories are correct, merely that they are feasible physiological mechanisms, and the interaction of the flow determinants are generally aligned to that of the model.

It must be emphasised that the model does not attempt to accurately predict the experimental examples provided but is a generic prediction of the form of the responses to test the hypotheses. For example, the midpoint of the sigmoidal response to $\text{CO}_2$ from a TCD experiment in Figure 6 is lower than that of the model response. However, it is not beyond the bounds of observed midpoints in other experiment using different methods. For example, the midpoints in the TCD experiments (means of 35–36 mmHg) differ from those derived from the vascular resistance which varied over a range of 38–48 mmHg (Duffin et al., 2018). A similar observation may be made for the responses to $[\text{Hb}]$ in Figure 8 where the model responses exhibit considerable curvature as $[\text{Hb}]$ decreases compared to the experimental observations. We note that there is considerable variability in the experimental observations, and while the authors chose to fit a linear response, the data indicates that curvature is present, as we showed in Duffin et al. (2020). Another confounding factor in the experimental observations is the variability of $\text{PCO}_2$ in the experiments where $\text{PCO}_2$ was uncontrolled compared to the model where isocapnia was maintained. In summary, there is no doubt that the model can be improved by adjusting the parameters and the relations used, such as the linear one between [SID] and $[\text{H}^+]$ which is almost certainly a simplification and awaits experimental measurements.
FIGURE 5 | Implementation block diagram of the feedback control of cerebral blood flow (CBF) by \( \text{PaCO}_2 \), \( \text{PaO}_2 \), and \([\text{Hb}]\).

FIGURE 6 | Cerebral blood flow (CBF) responses to \( \text{PCO}_2 \) at \( \text{PO}_2 = 150 \text{ mmHg} \) (solid line) and \( \text{PO}_2 = 50 \) (dashed line). (A) Model response. (B) Example transcranial Doppler (TCD) measurements of middle cerebral artery blood flow velocities (Battisti-Charbonney et al., 2011).

FIGURE 7 | Cerebral blood flow (CBF) responses to \( \text{PO}_2 \). (A) Model responses at \( \text{PCO}_2 = 35 \text{ mmHg} \) (dotted line), \( \text{PCO}_2 = 40 \text{ mmHg} \) (solid line) and \( \text{PCO}_2 = 50 \text{ mmHg} \) (dashed line). (B) Example transcranial Doppler (TCD) measurements of middle cerebral artery blood flow velocities at \( \text{PCO}_2 = 30 \text{ mmHg} \) (squares), \( \text{PCO}_2 = 40 \text{ mmHg} \) (diamonds) and \( \text{PCO}_2 = 50 \text{ mmHg} \) (triangles) (Mardimae et al., 2012).
There are several assumptions underlying the model, and, as reviewed in the introduction, some are supported by experimental evidence. That cerebrovascular smooth muscle attempts to maintain a constant intracellular [H⁺] by some regulatory process appears to be supported (Boedtkjer, 2018). Furthermore, that [H⁺] acts via alterations in [Ca²⁺] to control vascular smooth muscle tone and consequently CBF also appears to be substantiated (Aalkjaer and Peng, 1997). The physico-chemical theory of acid-base described by Stewart (Stewart, 1981) and illustrated in Hughes and Brain (2013) dictates that intracellular [H⁺] and bicarbonate [HCO₃⁻] are dependent variables, with CO₂ and [SID] independent variables that determine them. Therefore, the model assumption that [H⁺] is regulated by controlling [SID] in the face of a CO₂ disturbance is an obvious conclusion. That [SID] must be adjusted by membrane transport processes is well known (Garneau et al., 2020). The simple equation proposed to describe this regulation process is one of many that could be used to describe the relation between [SID] and the error signal, deviation of [H⁺] from a normal resting value. The equation form assumes that maximum vasoconstriction occurs at the hypocapnic limit of vasoconstriction (PCO₂ = 10 mmHg where [SID] = 5.5 mM/L attempting to restore [H⁺] to 40 nM/L). This assumption has the result that at a normal resting PCO₂ of 40 mmHg the regulation of [SID] is active and consequently subject to degradation by a lack of O₂.

The assumption that a decrease of CaO₂ affects intracellular [H⁺] by degrading the [SID] regulation is a major hypothesis of the model and is testable. That CBF is related to CaO₂, whether changed by anemia or hypoxia is well documented and the subject of a previous model (Duffin, 2020). Furthermore, it was previously demonstrated that brain tissue PO₂ was not a viable choice as a sensed variable controlling CBF (Duffin et al., 2020). Consequently, CaO₂ was the obvious choice of variable to represent a decreased O₂ supply affecting the supply of energy to the membrane transporters of strongly dissociated ions thereby degrading the [SID] regulation of [H⁺]. However, there does not currently appear to be supportive experimental evidence for this assumption, and it requires investigation.

Other mechanisms by which CaO₂ may change CBF involving nitric oxide (NO) have been proposed. Some (Holland et al., 2020) are linked to neurovascular coupling control of CBF (Attwell et al., 2011) rather than the control of blood O₂ supply. Others involve release of NO from red blood cells (Holland et al., 2016) or endothelial cells (Iadecola, 1992; Kisler et al., 2017). However, experiments show that NO does not appear to be involved in responses to changes in blood gases (White et al., 1998; Ide et al., 2007). Furthermore, these mechanisms for CBF control independent of CO₂, whether involving NO or not, do not agree with the observations of the interaction of CaO₂ and CO₂ in the control of CBF. For example, in hypocapnia, where vasoconstriction lowers CBF, a decrease in CaO₂ would be expected to increase CBF at least as much as is observed in normocapnia, but does not (Mardimae et al., 2012). The model proposed does so, exhibiting the interaction between CaO₂ and CO₂ observed (Figure 5).

CONCLUSION

This model can be used to predict the effects of hypoxia, hypercapnia and anemia, alone and in combination, on CBF. It therefore has practical usefulness for intensive care and intra-operative management where these conditions apply, as well as for drugs that affect carbonic acid dissociation and elimination, and shift the oxyhemoglobin dissociation curve.

The hypothetical basis of the model is not only supported in part by the experimental evidence used in its formulation, but also by the success of the model predictions of experimental observations. Thus, the hypothesized mechanisms merit
consideration as realistic possibilities, deserving of experimental investigation to determine their correctness. We suggest that the physiological mechanism described in this model for the response to CO₂ has widespread application as a general principle. It has already been used to describe the responses of the carotid body glomus cells to CO₂ (Duffin, 2020) and may also be applicable to the central chemoreception of CO₂ (Guynet et al., 2019). It is an aspect of a physico-chemical view of acid-base control pioneered by Stewart (1981) that should enable a better understanding of the mechanisms involved which in turn may inspire intervention opportunities that apply to clinical care.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the Local Legislation and Institutional Requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JD: conception and programming. JF, JF, and DM: drafting and revising of the article and final approval of the manuscript. All authors contributed to the article and approved the submitted version.

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APPENDIX

The acid-base control of intracellular [H⁺] was calculated using an iterative approach that solved eq. 1–4 to enforce electrical neutrality by minimizing R.

\[
[HCO_3^-] = KC \cdot \frac{PCO_2}{[H^+]} \tag{1}
\]

\[
[CO_3^{2-}] = K3 \cdot \frac{[HCO_3^-]}{[H^+]} \tag{2}
\]

\[
[OH^-] = Kw/[H^+] \tag{3}
\]

\[
R = [SID] + [H^+] - [HCO_3^-] - 2[CO_3^{2-}] - [OH^-] \tag{4}
\]

where:

- \(PCO_2\) (mmHg) is an input.
- \([SID]\) = [strongly dissociated cations] – [strongly dissociated anions] (mM/L) is an input.
- \([HCO_3^-]\) (mM/L)
- \([CO_3^{2-}]\) (mM/L)
- \([OH^-]\) (nM/L)
- \(KC = 2.45 \times 10^{-11}\)
- \(K3 = 1.16 \times 10^{-10}\)
- \(Kw = 2.39 \times 10^{-14}\)