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Oscillations and Concentration Dynamics of Brain Tissue Oxygen in Neonates and Adults

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Abstract

The brain is a metabolically demanding organ and its health directly depends on brain oxygen dynamics to prevent hypoxia and ischemia. Localized brain tissue oxygen is characterized by a baseline level combined with spontaneous oscillations. These oscillations are attributed to spontaneous changes of vascular tone at the level of arterioles and their frequencies depend on age. Specifically, lower frequencies are more typical for neonates than for adults. We have built a mathematical model which analyses the diffusion abilities of oxygen based on the frequency of source brain oxygen oscillations and neuronal demand. We have found that a lower frequency of spontaneous oscillations of localized brain tissue oxygen can support higher amplitudes of oxygen concentration at areas distant from a source relative to oscillations at higher frequencies. Since hypoxia and ischemia are very common events during early development and the neurovascular unit is underdeveloped in neonates, our results indicate that lower frequency oxygen oscillations can represent an effective passive method of neonatal brain protection against hypoxia. These results can have a potential impact on future studies aiming to find new treatment strategies for brain ischemia.

Keywords

Arterioles; Vasomotion; Ischemia; Hypoxia; Fluctuations; Model

1 Introduction

The dynamics of oxygen in brain tissue is one of the most important fundamental questions in neuroscience and medicine. The brain is a metabolically demanding organ and its health

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Conflict of interest

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directly depends on maintaining tissue oxygen to prevent hypoxia. As the many pathological effects of hypoxia become better understood, the need to characterize the relationship between oxygen supply and demand in the tissue grows more compelling. The oxygen level throughout the whole brain is controlled by global cerebrovascular autoregulation in response to fluctuations in arterial pressure (for review see (Willie et al. 2014)). More focal changes in oxygen demand in response to sensory signals, motor output, etc. are supported by transient increases in cerebral blood flow (CBF) via the hemodynamic response. The hemodynamic response occurs due to the coupling between neurons and vessels. The prevailing view on brain tissue oxygen regulation is that neuronal signaling via neurotransmitters, either directly or through astrocytic pathways, is responsible for driving CBF responses (Attwell et al. 2010). The oxygen level in brain tissue is therefore the product of oxygen delivery through local blood flow, oxygen consumption, primarily by neurons, and oxygen diffusion to neighboring tissue and venous system. Oxygen regulation has been shown to be consistent among human and laboratory mammals (Dagal and Lam 2009; Masamoto and Tanishita 2009; Ndubuizu and LaManna 2007).

Neurovascular interactions control not only the direct oxygen response to neuronal activity, but also spontaneous changes in the brain tissue oxygen levels. It has been shown in a number of studies, including our own, that localized (within approximately 100 μm area) brain tissue oxygen, measured directly with oxygen microelectrodes, is characterized by continual spontaneous oscillations, predominantly at frequencies of 0–20 cycles per minute (0–0.333 Hz) (Linsenmeier et al. 2016; Manil et al. 1984; Aksenov et al. 2018) depending on the age. These oscillations are attributed to spontaneous changes of vascular tone (i.e., vasomotion) at the level of arterioles (Hudetz et al. 1998; Aalkjaer et al. 2011; Mateo et al. 2017) and are important to prevent localized hypoxic damage of brain tissue (Goldman and Popel 2001; Tsai and Intaglietta 1993). Interestingly, the frequency of brain tissue oxygen oscillations is different in neonates and adults (Linsenmeier et al. 2016; Aksenov et al. 2018) so that brain tissue oxygen oscillations in awake neonatal brain have lower frequency (0–7 cpm (0–0.117 Hz) with a peak frequency near 1–2 cpm (0.0167–0.0333 Hz)), in contrast to the adult brain in which higher frequencies (0–20 cpm (0–0.333 Hz) with a peak frequently near 10 cpm (0.167 Hz)) appear more common. The reasons for this difference are not clear. It is known that neonates have higher tolerance to hypoxia than adults through different mechanisms (Singer 1999) because hypoxia is a typical event during early development. We hypothesize that the slower brain tissue oxygen oscillations in neonates can potentially represent one of the mechanisms to resist hypoxia. To test this hypothesis we developed a model which compares the diffusion abilities of oxygen based on the frequency of source brain oxygen oscillations and neuronal demand.

The models of oxygen diffusion in tissue have been developed for more than 100 years (Popel 1989). However, the localized oxygen oscillations were not analyzed previously in the context of comparing developmental differences. Our work can have a potential impact on future studies aiming to find different mechanisms of brain ischemia and improve treatment of this pathology.

2 Methods

Diffusion Equation

The concentration dynamics of particles over a surface from a source is governed by Fick's second law. In the case of oxygen diffusing over brain tissue from arterioles, we assume a constant proportional leakage into veins and neighboring tissue, giving us the following diffusion equation

$$\frac{\delta c}{\delta t} = D \frac{\delta^2 c}{\delta x^2} - Lc \quad (1)$$

where D is the diffusion coefficient and L is the leakage constant. By symmetry, we only consider the case when $x \geq 0$. Since we expect $c(x) \rightarrow 0$ as $x \rightarrow \infty$, we get the steady state solution

$$c(x) = c_0 \exp\left(-\sqrt{\frac{L}{D}}x\right) \quad (2)$$

where c_0 denotes the steady concentration of oxygen coming from the source. Introducing sinusoidal oscillations at the source, by Eq. (1) we expect the steady state solution to take the functional form,

$$c(x, t) = c_0 \exp\left(-\sqrt{\frac{L}{D}}x\right) + \phi_{x,f} \sin(2\pi f t + \gamma_{x,f}) - N \quad (3)$$

where f is the frequency (Hz). The function $\phi_{x,f}$ is the amplitude with respect to distance, and $\gamma_{x,f}$ is the lag rate, i.e. the shift in steady state oscillations with respect to distance. Furthermore, we introduce the exogenous variable N (mmHg), which represents neuronal activity within the brain tissue, a constant decrease over all points. We are using a diffusion coefficient of $1000 \mu\text{m}^2/\text{s}$ representing oxygen diffusion in the brain (Suwa 1992). Note that the diffusion could be slower in different brain regions, depending on cellular environment (density of neurons, dendrites, orientation of fibers, etc.).

Numerical Simulation

To assist solving for Eq. (3), we used Matlab (2017a, Mathworks, Inc.) to simulate the diffusion of oxygen particles. Starting with a lattice, we chose a point acting as the source where we oscillated the concentration above a baseline, and iterated the system by propagating 25% of the concentration at each point into adjacent points. At the end of each iteration, a percentage of the concentration from each point was removed, representing our leakage constant introduced in Eq. (1). The simulation is run until there is stability in the oscillations of concentration at all points.

3 Results

Running the simulation, we see that the amplitude of oscillations decreases exponentially with distance (Fig. 1). Furthermore, we see that Fig. 1A decays substantially faster

compared to Fig. 1B, indicating that a slower frequency of source oscillations implies higher amplitudes of oscillations at all points.

It follows that $\phi_{x,f}$ is an exponential function. Furthermore, we assume that $\gamma_{x,f}$ is a linear function with respect to x , so that $\gamma_{x,f} := \gamma x$. Applying the condition of Eq. (1) to Eq. (3), we get

$$\begin{aligned} \phi_{x,f} 2\pi f \cos(2\pi f t - \gamma x) &= D \left(\frac{\delta^2 \phi_{x,f}}{\delta x^2} \sin(2\pi f t - \gamma x) \right. \\ &+ 2 \frac{\delta \phi_{x,f}}{\delta x} \gamma \cos(2\pi f t - \gamma x) - \phi_{x,f} \gamma^2 \sin(2\pi f t - \gamma x) \\ &\left. - \phi_{x,f} L \sin(2\pi f t - \gamma x) \right) \end{aligned} \quad (4)$$

Making the substitutions $\phi_{x,f} := ae^{Bx}$ and $z := 2\pi f t - \gamma x$, and rearranging Eq. (4), gives us the equation,

$$\begin{aligned} 2\pi f a e^{Bx} \cos(z) - 2DaBe^{Bx} \gamma \cos(z) + Da e^{Bx} \gamma^2 \sin(z) \\ + La e^{Bx} \sin(z) = Da B^2 e^{Bx} \sin(z) \end{aligned} \quad (5)$$

Finding the values of B and γ such that the sine and cosine terms cancel themselves out, gives us a system of equations whose solution is,

$$B = -\sqrt{\frac{L + \sqrt{L^2 + (2\pi f)^2}}{2D}} \quad (6)$$

$$\gamma = \frac{-\pi f}{\sqrt{D(L + \sqrt{L^2 + (2\pi f)^2})}} \quad (7)$$

We denote B as the amplitude decay rate, for our exponential amplitude function in Eq. (3). Fig. 2 shows the relationship between the absolute value of the amplitude decay rate and frequency, under different leakage rates.

Since we can assume symmetry, the solution to the steady state concentration with oscillations is,

$$c(x, t) = \begin{cases} c(x, t) = c_0 e^{-\sqrt{\frac{L}{D}}x} + a e^{Bx} \sin(2\pi f t + \gamma x) - N & x \geq 0 \\ c(x, t) = c_0 e^{\sqrt{\frac{L}{D}}x} + a e^{-Bx} \sin(2\pi f t - \gamma x) - N & x < 0 \end{cases} \quad (8)$$

where a is the amplitude of oscillations at the source.

Applying Eq. (8) to fixed parameters, we see that a slower frequency has a non-trivial effect on the amplitude of oscillations at every distance from the source (Fig. 3A and 3B). Furthermore, varying neuronal activity demonstrates that this amplitude difference can be sufficient to maintain oxygen above the necessary threshold (Fig. 3C and 3D).

4 Discussion

The function of the brain directly depends on the delivery of oxygen and glucose because the oxidative metabolism of glucose provides nearly all of the ATP used by brain (Dienel 2019). If the delivery of oxygen is insufficient (e.g. due to obliteration of vessels), it can result in neuronal death within the area of ischemia. The size of this area depends on the size of affected vessels and compensatory abilities of collaterals (Sharma et al. 2018). Similar processes can be observed at the level of small arteries and arterioles (Pantoni et al. 2014) which are responsible for brain tissue oxygen oscillations (Hudetz et al. 1998; Aalkjaer et al. 2011; Mateo et al. 2017). If some of these small vessels are not able to provide adequate blood flow and neighboring vessels cannot deliver sufficient oxygen, it will lead to neuronal death within a localized region. The frequency of brain tissue oxygen oscillations can affect the diffusion dynamics of oxygen. Figures 1 and 2 illustrate the positive dependence between the amplitude decay rate and frequency of oscillations. This effect generally indicates that lower frequencies of oxygen oscillations can ensure lower amplitude decay rate even if the oxygen concentration gradient is high. Untypically high oxygen concentration gradient can occur under conditions of localized hypoxia/ischemia, for example, when a vessel is obliterated but neighboring vessels are still able to supply oxygen which can diffuse to the hypoxic region. Specifically, the results show that spontaneous oscillations of brain tissue oxygen at lower frequency of 1 cpm (e.g., .0167 Hz) can support higher amplitude of oxygen concentration at areas, distant from a source, than oscillations at higher frequencies (Fig. 3A and 3B).

The oxygen dynamics in the brain tissue depends not only on the delivery but also on the neuronal oxygen consumption. If the balance between oxygen delivery and consumption is affected due to the insufficient oxygen pressure in the vessels, neuronal activity can deplete the brain tissue oxygen and that will cause hypoxia and possible neuronal death. Indeed, our results further show that the level of neuronal activity greatly impacts oxygen concentration but lower frequency spontaneous oxygen oscillations can potentially provide periodic higher-than-zero oxygen concentration even under hypoxic conditions (Fig. 3C and 3D). These periodic increases in oxygen concentration can be sufficient to prevent neuronal death until the end of hypoxic state (Larson et al. 2014; Zeiger et al. 2010). Thus, spontaneous oscillations of brain tissue oxygen at lower frequency can have a better protective effect against ischemia in case of a misbalance between oxygen delivery and consumption than higher frequency oxygen oscillations.

Lower frequency oscillations of localized brain tissue oxygen are typical for neonates as have been shown in the previous study (Aksenov et al. 2018). It is known that neonatal brain hypoxia-ischemia (NHI) is a very common event during early development. The major reason for NHI is a fetal or neonatal asphyxia, however, the variability in the extent of brain damage can be explained by the presence of collaterals and redistribution of blood flow (Choy et al. 2006; Charriaut-Marlangue and Baud 2018). NHI is the most often cause of death and disability in human neonates, accounts for 23% of infant mortality (Millar et al. 2017). For comparison, the incidence rate of ischemic strokes in adults depends on the age, however the average mortality due to ischemic stroke in adults is below 5% of total death cases (Collaborators 2018). In neonate animals hypoxia is also the primary reason for death

accounting for up to 60% of neonate mortality (Munnich and Kuchenmeister 2014). These numbers indicate that HI is a serious problem specific for neonates and point to a possibility that lower frequency oscillations of brain tissue oxygen provide better chances for neonates to resist temporary hypoxia than higher frequency oscillations.

The mechanisms of the developmental transition between “neonate” and “adult” oxygen oscillation frequencies are related perhaps to the development of the neurovascular unit. The neurovascular unit consisting of neurons, astrocytes, endothelial cells, myocytes, pericytes and extracellular matrix components (Muio et al. 2014) can participate not only in the control of vascular response but also in spontaneous vasomotion. It has been directly shown that spontaneous vasomotions at the level of arterioles phase lock to ultra-slow variations in the envelope of the γ -band of local field potential activity (Mateo et al. 2017) which suggests the possible direct neuronal involvement in the control of spontaneous vasomotion. The neonatal neurovascular unit is underdeveloped in humans and animals (Kozberg and Hillman 2016), unable to provide high magnitude vascular response to stimulation and even may not be functional until a few weeks after birth (Andreone et al. 2015). Thus, lower frequency oxygen oscillations can represent an effective passive method of neonatal brain protection against hypoxia under absence of sufficient neuro-vascular regulation.

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Fig. 1. Relationship between amplitude of oxygen oscillations and distance from the source. Oscillations at the source lead to an exponential decay of amplitude with respect to distance. Fig. A shows the decay at a source oscillation of 10 cpm (0.167 Hz), while Fig. B shows the decay when the source oscillates at 1 cpm (0.0167 Hz). The slower decay rate of Fig. B indicates dependence on the frequency of oscillations. The simulation is run using $D = 1000 \mu\text{m}^2/\text{s}$.

Fig. 2. Relationship between frequency and amplitude dynamics of brain tissue oxygen. The amplitude decay rate increases with respect to frequency. A higher leakage constant ($L = .9$) causes the amplitude of oscillations to decrease more rapidly compared to a lower leakage constant ($L = .05$), which are represented as dashed and solid lines, respectively. The amplitude decay rate is calculated using $D = 1000 \mu\text{m}^2/\text{s}$.

Fig. 3.

Relationship of oxygen concentration oscillations, distance from source, and neuronal activity. We compare the dynamics at 0 microns, 75 microns, and 125 microns from the source under different rates of neuronal activity. Figures 3A and 3C respectively show the PO2 levels with no neuronal consumption and neuronal activity corresponding to oxygen consumption of 10 mmHg ($N=10$) when the source oscillates at 1 cpm (0.0167 Hz). Figures 3B and 3D show the PO2 levels with no neuronal consumption and neuronal activity corresponding to oxygen consumption of 10 mmHg ($N=10$) when the source oscillates at 10 cpm (0.167 Hz). Under oxygen consumption, there is zero oxygen concentration 125 microns away from the source for the faster oscillation, while being higher than zero for the slower oscillation. The fixed parameters are $c_0 = 28$ mmHg, $a = 7$ mmHg, $L = .05$ a.u., $D = 1000 \mu\text{m}^2/\text{s}$.