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Dead Spaces Hinder Diffusion and Contribute to Tortuosity of Brain Extracellular Space

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1. Introduction

Brain cells are surrounded by the extracellular space (ECS). The ECS is comprised of narrow, connected spaces where signaling molecules, nutrients, metabolites and drugs are transported. All these processes are primarily mediated by diffusion.

The diffusion properties of the ECS can be summarized by two macroscopic parameters, volume fraction α, and tortuosity λ [1], which can be estimated from the diffusion analysis of an inert, small, and membrane impermeable marker. The volume fraction determines a percentage of the total tissue volume accessible to the diffusing molecules ($\alpha = V_{ECS}/V_{tissue}$). The tortuosity describes the average hindrance of a complex medium relative to an obstacle-free medium; $\lambda = (D/D^*)^{1/2}$, where D is a free diffusion coefficient and D^* is an effective diffusion coefficient in tissue. In a healthy isotropic brain, α is about 0.2 and λ is about 1.6 (Fig. 1), but both parameters change during brain activity and in pathological conditions [1,2]. In principle, two mechanisms could account for the measured value of tortuosity: geometry alone or in a combination with high viscosity of the extracellular fluid. Here we summarize our recent work suggesting that complex geometry of the ECS alone is sufficient to explain λ.

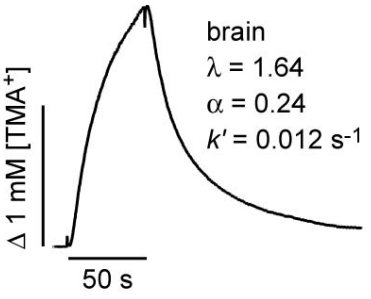

Fig. 1. Diffusion curve of tetramethylammonium (TMA^+, *MW* 74) in brain.

2. Monte Carlo simulations of diffusion process

Tao and Nicholson [3] constructed several virtual 3D models of brain tissue. These models, based on the morphological studies employing electron microscopy, depicted the ECS as interconnected spaces of uniform size that surround convex elements (Fig. 2A). The diffusion in the ECS of these models was simulated using *MCell* [4], and the geometrical tortuosity, λ_g, was calculated [3]. Tao and Nicholson [3] obtained a simple relationship between the two ECS parameters ($\lambda_g(\alpha) = ((3-\alpha)/2)^{1/2}$) giving an upper limit of 1.225 for λ_g. Interestingly, Maxwell derived the same formula from the study of electric conductivity of a medium containing a dilute suspension of spheres [3]. In brain, however, α and λ are

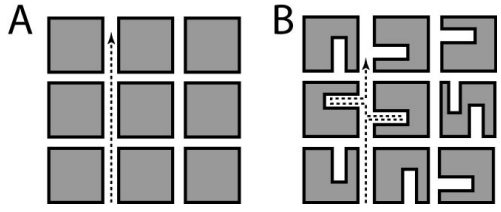

Fig. 2. A section through 3D models composed of convex (A) and concave (B) cells.

independent parameters, and $\lambda > \lambda_g$ [3,5]. The 3D models built from convex cells thus did not capture all the critical structural features of brain ECS.

In subsequent work, concave elements were incorporated into the 3D model [6,7] (Fig. 2B). The ECS of such media is composed of well-connected spaces (λ_0, α_0) and dead spaces within concave elements (α_d), which delay diffusing molecules by transiently trapping them. Geometrical tortuosity increased to about 1.6 when α_0:$\alpha_d \approx 60$:40. Simulations confirmed the semi-quantitative diffusion model that predicted $\lambda_g = \lambda_0 ((\alpha_0+\alpha_d)/\alpha_0)^{1/2}$ [6].

We conclude that dead spaces can increase λ_g of the 3D media to the value measured in brain.

3. Experiments in brain tissue support dead-space hypothesis

Our recent experimental findings indicate that dead spaces are present in ischemic tissue [8,9]. During ischemia (a loss of oxygen and nutrient supply to brain), λ increases from about 1.6 to 1.9, but drops to 1.5 when dextran macromolecules (*MW* 70,000) are added to the tissue and distribute in the ECS. The decrease in λ is accompanied by a reduction in α from 0.14 to 0.10. It was proposed that cells swell during ischemia, thereby blocking off some of the intercellular gaps and forming a number of dead-end pores. A diffusing molecule entering such a dead space becomes delayed, causing an increase in λ (Fig. 3A). When dextran macromolecules are present, however, they become selectively trapped in the dead-spaces so that many of these spaces are eliminated, decreasing both λ and α (Fig. 3B). Dead spaces are thus implicated in the high extracellular hindrance in ischemia.

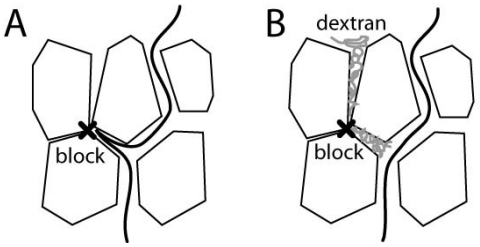

Fig. 3. High λ in ischemia (A) is reduced by dextran (B). Modified from [9].

4. Conclusion

We put forward a concept of dead spaces, the geometrical elements that contribute significantly to the hindrance of brain tissue. At present, the experimental evidence comes from ischemia. Future work will address the presence of dead spaces in a healthy brain. The presence of dead spaces in the ECS would have fundamental implications for intercellular communication and drug delivery over both short and long distances.

References

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