Mapping Human Cerebral Vascular/Metabolic Activity Coupling at High-Resolution

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Introduction: The blood-brain barrier protects cerebral parenchymal cells. In parallel, the exquisite neurogliovascular unit [NGVU] has evolved to include the microvasculature in intimate maintenance of brain cellular metabolic activity (1,2). Fortunately, the mean brain capillary water molecule lifetime [τ_b] can be readily mapped with high-resolution from a straightforward DCE-MRI experiment (3-5). It has been shown that the unidirectional rate constant for *equilibrium* capillary water efflux, k_{po} [$\equiv \tau_b^{-1}$], is dominated by the capillary wall permeability coefficient, $P_W^{\dagger}$, not the capillary radius (4). Furthermore, the water exchange flux employs a trans[endothelial]cellular pathway, with less than 5% using the tight junction route (4). Here, we show that k_{po} tracks brain metabolic activity.

Methods: Healthy [2M/4F, 30 (±10 y)] and RRMS [2M/4F, 46 (±7 yr)] subjects gave informed consent. A 7T MRI instrument [Siemens], with quadrature transmit and 24-channel phased-array receive head RF coils, was used. The DCE-MRI acquisitions employed the single-slice IR turboflash technique detailed in (4,5). The transverse slice had nominal (2x2x10) mm^3 [40 μL] resolution.

Results: **Figure 1** shows resting-state axial parametric maps of a 22 y F control subject. The biomarkers are: [a] R_{1exv}, [b] v_b, and [c], k_{po}: R_{1exv} is the intrinsic extravascular ^1H_2O longitudinal relaxation rate constant, and v_b is the blood volume fraction [$\equiv \rho^{\dagger}\bullet V$, the capillary number density•volume product] (4,5). The R_{1exv} and v_b maps are accurate (4) and important biomarkers reflecting well-known brain tissue properties. R_{1exv} is greater in white matter [WM] than gray matter [GM] because of the greater WM macromolecular content. v_b[GM] > v_b[WM] [~0.03 to ~0.01] because of the greater GM $\rho^{\dagger}$. The new k_{po} map exhibits greater values in *centrum semiovale* [CSO] WM than in cortical GM.

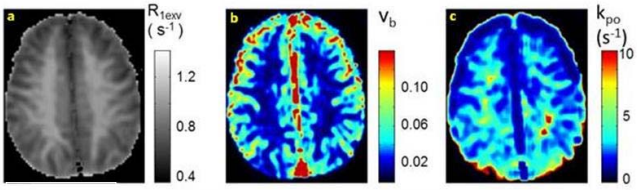

Figure 1.

Figure 2 shows the pixel-by-pixel k_{po} *vs.* v_b scatter plot of much of the Fig. 1b,c data. Pixels were chosen from 2500 in a square ROI centered on and covering ~75% of the image slice: they were assigned from the R_{1exv} histogram. The 649 pixels with R_{1exv} from 0.80 to 0.92 s^{-1} were identified as WM [pink points]. The 670 pixels from 0.62 to 0.72 s^{-1} are labeled GM [olive points]. Interestingly, the WM points exhibit a mostly vertically oriented cluster, while the GM points are mostly horizontally clustered. **Table 1** gives the population-averaged v_b and k_{po} values for ~3.6 mL "pure" WM and GM ROIs.

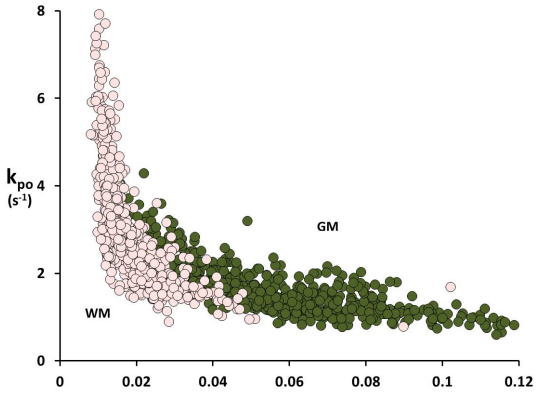

Figure 2.

Discussion: Because of active trans-membrane water cycling, the unidirectional equilibrium *cellular* water efflux rate constant [k_{io}] tracks the cell membrane Na^+,K^+ ATPase [NKA] turnover (6) – perhaps the cell's most vital enzyme flux. Table 1 shows k_{po} to be directly and inversely proportional, respectively, to literature ATP and Na^+ tissue concentrations, suggesting it too is metabolic. However, these are thermodynamic properties. Since k_{po} is a kinetic quantity, it must be finally validated with a flux measurement. The gold standard is CMR_{oxphos} measured by ^{31}PMRSI-MT (9), itself electroencephalographically validated (10). But k_{po} is a unique kinetic parameter [mol(H_2O)/s/capillary], being independent of the *intensive* $\rho^{\dagger}$ (4). [It is *supra-intensive*.] Since v_b is intensive [capillary volume/μL(tissue)], the $k_{po}\bullet v_b$ product can be compared with CMR_{oxphos}, an *ordinary* intensive property [pmol(ATP)/s/μL(tissue)]. Table 1 shows the $k_{po}\bullet v_b$ GM/WM ratio [2.0] in good agreement with the CMR_{oxphos} ratio [3.2], measured by the quite different ^{31}PMRSI-MT method [requiring ^1H_2O segmentation] (9). The synaptic proximities and synergistic metabolic co-operativities of polar brain NGVU endothelial, neuroglial, and neuronal cells make plausible a cascade mechanism (4) whereby a chain of NGVU k_{io} changes is communicated to k_{po}, making it a measure of NGVU NKA turnover. For a 44 μL rat brain ROI *in vivo*, k_{io} was measured as 1.8 s^{-1} using a very invasive intracerebroventricular CA infusion (11). This is similar to the Table 1 k_{po} values, consistent with the chain mechanism (4).

Table 1. The Biomarker k_{po} Measures Metabolically Activity						
	SSP DCE-MRI (^1H_2O)		^{31}PMRSI	^{23}NaMRSI	SSP DCE-MRI (^1H_2O)	^{31}PMRSI-MT
	v_b	k_{po} (s^{-1})	[ATP$_i$] (mM)	[Na$_i$] (mM)	$k_{po}\bullet v_b$ (s^{-1})	CMR_{oxphos} (pmol(ATP)/s/μL)
Controls						
WM	**0.014** (±0.002)	**3.2** (±0.56)	**2.43**	**19**	**0.045**	**50**
GM	**0.031** (±0.004)	**2.9** (±0.59)	**1.62**	**31**	**0.090**	**160**
GM/WM					**2.0**	**3.2**
RRMS						
NAWM	**0.019** (±0.002)	**2.2** (±0.20)	**2.11**	**27**	**0.042**	
NAGM	**0.045** (±0.004)	**2.0** (±0.13)	**1.29**	**36**	**0.090**	
References	this work [n = 6] (±SEM)		7	8	this work	9

The essentially vertical Fig. 2 pink point cluster suggests that in CSO WM v_b [probably $\rho^{\dagger}$] is tightly regulated near 0.015, but a range of NGVU NKA activity is present. This may reflect increased metabolic activity in common tracts shared by fluctuating resting-state neural circuits [Fig. 1c]. In contrast, the essentially horizontal Fig. 2 olive point cluster suggests that in cortical GM k_{po} is regulated near 1.8 s^{-1} for "pure" GM [with v_b near 0.03]. Larger v_b values are likely due to partial-volume-averaging of larger vessels near the cortical surface [Fig. 1b]. Though k_{po} is $\rho^{\dagger}$–independent, it does depend on the mean vascular volume [V] factor, but to only the $V^{-1/2}$ power (4), which likely causes the slight k_{po} decline at large v_b. For 6 relapsing-remitting MS patients, the averaged normal-appearing WM and GM ROI supra-intensive k_{po} values are each decreased 31 % from normal (Table 1), strongly suggesting whole-brain involvement. However, the $k_{po}\bullet v_b$ products remain completely unchanged. The $\rho^{\dagger}$ quantity seems recruited up to maintain constant intensive tissue NKA activity in this early disease stage. Therefore, neither the ^{31}PMRSI-MT nor the $^{15}OH_2$ PET [measuring the $P_W^{\dagger}\bullet S$ product: S is the intensive vascular surface area/μL(tissue)] intensive methods could detect this. Only the supra-intensive k_{po} senses this metabolic decline.

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