**Exercise and the brain: a mechanical model for pulsation on flow of cerebrospinal fluid**

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Short title: Delivery of molecules to brain neurons by CSF.

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**Abstract.**

Exchange of molecules between cerebrospinal fluid (CSF) and brain cells appears to contribute to brain function and protection from dementia, but the route by which CSF solutes are brought close enough to the neural tissue to be exchanged by extracellular diffusion is not clear. Exogenous molecules injected into CSF are carried along channels outside the larger blood vessels and reach the pericapillary basal lamina of the dense capillary network. The lamina is about 0.xx um thick, and composed of a gel of macromolecules. Transport of solutes by diffusion along the basal lamina would be too slow; bulk flow in a static geometry would require unphysiologically high pressures. However, it is known that the pulsation of blood aids transport of CSF, and we hypothesized that this is because the pulsation intermittently squeezes the pericapillary lamina. In a primitve mimicry of this, we have tested whether intermittent squeezing (pulsation) increases flow in a silicone tube filled with an agar gel. In all of xxx tests pulsation caused a reversible increase in flow, in some cases by a factor of 100 or more. Even without pulsation, flow rate varied with time (over tens of minutes). There was a significant peak in the increase for frequencies in the range 3 - 9 Hz. The results suggest one reason why exercise that increases blood pulsation slows the aging of the brain.

**1. Introduction.**

*1.1. The details of how CSF irrigates brain tissue are unknown.*

Blood supplies the main molecules required for brain metabolism, glucose and oxygen. Arterioles penetrating into the brain from the surface carry blood to a dense capillary network drained by venules (Fig. 1A). Glucose and oxygen can escape across the capillary wall and then diffuse the short distances (typically less than 13 um ref) to the neurons and glial cells. A second, complementary, source of certain other necessary molecules, including vitamins and DNA precursors, is cerebrospinal fluid (CSF) (reviewed by Spector et al. (2015a)). CSF can also carry away molecules, such as amyloid beta, whose accumulation in the brain is associated with Alzheimer's disease (refs). CSF is secreted into the brain ventricles by the choroid plexuses which synthesize, or transport from blood, a palette of molecules. By injecting marker molecules visible in microscopy it has been shown that CSF flows through ducts connecting the ventricles to the surface of the brain at the cisterna magna and from there is distributed to the surface of the cortex (Key and Retsius, 1875; Rennels et al., 1985; Kida et al., 1993; Iliff et al., 2012, 2013b; Coles et al., 2015, Smith et al., 2017; see Fig.1(b,c)). ) Although they have been discussed for over a century (Cathelin 1903; Weed ), the pathways that bring CSF close enough to the neurons and glial cells for molecules to be exchanged between them are still debated. One suggestion is that CSF enters the brain interstitium from the periarteriolar space, flows through the interstitium and leaves to the perivenular space (the 'glymphatic' theory: Iliff 2012; Mestre et al. 2021; see objection by Smith et al. 2017). Another is that amyloid beta and other macromolecules are transported to the brain surface along the walls of the penetrating arteries (Carare ). Several authors have observed CSF markers in a pericapillary space (Fig. 1B, Bowsher, 1957; Rennels; Iliff.....Abbott) and it has been suggested that CSF may flow along a pericapillary route from the arterioles to the venules (Fig. 1C, Cathelin 1903; Rennels? Abbott). The CSF is then carried along perivenular space to the brain surface and, at normal intracerebral pressures, most of it leaves the cranium through channels associated with blood vessels or nerves (Zakharov 2004; Ma et al 2017). If the pericapillary space contained only fluid, calculation suggests that sufficient CSF could flow along it with a small steady pressure gradient in the order of those present in the brain (Supp Mat1). However, the pericapillary 'space' is a basal lamina composed of a gel of macromolecules such as laminin (Hannocks et al. 2018) which would not allow sufficient flow with a static geometry under a steady pressure gradient. Rennels, Hadjarek and others observed that transport of CSF into the brain parenchyma was reduced when blood pulsation was reduced, which suggests that pulsation contributes to the transport of CSF. In support of a role for blood pulsation, artificial perfusion of the brain with a steady, rather than pulsating, flow of blood, is associated with brain damage (Wright & Sanderson 1972). And mathematical models have suggested that oscillation of the diameter of an artery could transport macromolecules along its periarterial space (Nedergaard) or its wall (Carare). Outside the brain, spread of dye through the extracellular space of skin is increased when the blood flow pulsates (McMaster & Parsons 1938;1950). These observations have led us to hypothesize that pulsation of CSF pressure at the proximal ends of brain capillaries, or a pulsating pressure on the pericapillary basal lamina, might account for the repeated observation that CSF markers can reach the pericapillary 'space'.

We find no report of the effect of lateral pressure changes on longitudinal flow through a gel so we have started with the experimentally most simple arrangement, namely repetitive lateral pressure (pulsation) on an elastic tube filled with a gel. In over xxxx tests we invariably found that pulsation reversibly increased the flow, often by a factor of ten or more. We have examined the dependence on frequency, static pressure head, and degree of compression of the tube. We conclude that in the presence of a pulsating blood flow, CSF may well flow through pericapillary space, as has been suggested previously (Cathelin 1903, ..Abbott 2018). The effect of blood pulsation may be one reason why physical exercise benefits the brain.

**Fig.1. A.** A cast of the blood vessels in the cortex of a rat brain (from Motti, 1986). **B.** A CSF marker dye in a space surrounding a capillary (Iliff et al 2012, with permission). **C.** Scheme of the pathway of CSF in the cortex proposed by Cathélin (1903); Rennels et al (1986); Coles et al, 2017; Hannocks et al. (2018) showing flow of CFS along a pericapillary space. **D.** Minimal portayal of the experimental set-up (see Supp Mat for setails). **E**. Flow of fluid through gel columns of different lengths L with a static pressure gradient. **F**. The mean flow rates (Q) for the linear parts of (E) plotted against 1/L [G The same data with 1/Q plotted against L]

**Brief Methods (Very detailed methods are given in Supplementary Material)**

Silicone tubing, i.d. 1.0 mm, o.d. 3.0 mm, was cut into 40 - 80 mm lengths, filled with agar agar, 1% by weight prepared, and stored in, 0.15M NaCl. Five mm of gel was flushed from each end of a length of tube and it was connected upstream to a pressure head of 20 -50 cm H2O and downstream to a microburette consisting of polyethylene tubing, i.d. 0.38 mm, held against a 200 mm scale (Fig. 1D). A small bubble was introduced so that the movement of fluid could be measured. The gel-filled tube was held under a solenoid-driven piston, diameter 3.5 mm, that could pummel the tube at a frequency controlled by a microcomputer (Raspberry Pi) instructed by wifi from a laptop. The solenoid was mounted on a micromanipulator with vernier scale so that the approximate indentation of the silicone tube could be controlled

**Results**

In all of xxx tests, pulsation reversibly increased the flow through the agar gel.

**Control Experiment 1: Flow through an agar gel without pulsation.** The rate ofprogression of the bubble along the microburette was approximately constant, usually after a delay of up to XX (Fig. 1E). Over the tested range of 20 - 50 cm H2O flow rate was proportional to the pressure head (the slope was not significantly different from 1. (Fig. A)? At a pressure head of 40 cm H2O the mean specific hydraulic conductivity (Darcy's permeability coefficient, see Levick, 1987) was YYYY m2 for a 1% agar gel in 0.15M NaCl. The flow (normalized for length of gel column) varied from one experiment to another, and often varied considerably over time (Fig 3B). Therefore, in describing the effects of pulsation we have normalized [the effects to control conditions].

**Control Experiment 2: Periodic squeezing slows the flow of water through a fluid-filled elastic tube.**

Water with a head of about 30 cm flowed through a horizontal silicone tube, i.d. 1.0 mm, which passed beneath a small solenoid (S.M. 2, Fig.1). The flow was adjusted with a control valve to about 0.1 ml/sec. The water was switched to a coloured solution (CuSO4) and changes in the optical density at a point downstream of the solenoid was monitored using an LED and a photodiode. Squeezing the tube at 2 - 5 Hz with the solenoid slightly reduced the flow, as might be expected as the lumen of the tube was constricted for part of the time. Squeezing produced no marked difference in the time course of the progressive increase in optical density caused by the arrival of the solute (CuSO4).

**Experiment 1. Periodic squeezing speeds the transport of water through a column of agar contained in an elastic tube.** Water from a raised reservoir flowed through a microburette (polyethylene tubing i.d. 0.38 mm, sellotaped on a ruler) and was delivered via a syringe needle to a column of agar in a silicone tube i.d. 1.0 mm (Fig. 3). As for Experiment 1, the silicone tube passed under a solenoid. To measure the flow rate, a bubble of air was admitted (through tap B in Fig.3) and its progress along the microburette was timed. Flow rates with and without periodic squeezing by the solenoid were compared. In a preliminary/typical/exemplary experiment, the solenoid was driven at 5 Hz. the head of water was 305 mm, the length of the agar column was 21 mm, giving a pressure gradient of 14.5 mmH2O/mm. The mean speed of the water through the microburette was 3.3 um/s without squeezing and 21.8 um/sec with squeezing. This corresponds to bulk flow through the agar at 0.476 and 3.145 um/sec.

**2. Derivation of a model for CSF flow through mouse cortex.**

Recent studies on movements of CSF and ISF in the brain cortex have been done mainly on mice, in which real-time in vivo imaging with optical resolution is possible (e.g. Iliff et al. 2012; Smith et al. 2017), so, as far as they are available, parameters measured in mice have been used.

*2.1. Flow through paracapillary space.*

If all CSF secreted by the choroid plexuses is distributed to flow equally through the paracapillary spaces (PCS) of all capillaries, then the flux through each PCS is

*f* = *F*/*N*  (1)

where *F* is the total secretion by the choroid plexuses, and *N* is the number of capillaries in the brain. Literature values are available for the total length *L* of capillary per unit volume of brain, and for the mean length *l* of each capillary, which give the number, *n*, of capillaries per unit volume of brain:

*n* = *L*/*l.*  (2)

Hence

*f* = *F*/((volume of brain) x *L*/*l*). (3)

Taking literature values for mouse listed in Table 1,  *F* = 0.37 µL/min, brain volume = 430 mm3, and (see Table 2) *L* = 1 m.mm-3, and *l* = 0.1 mm (from Motti et al. 1986, for rat) gives

*f* = 86.0 fL/min = 1.43 fL/sec (4)

What pressure gradient along a capillary would be required to drive this flux?

**Discussion**

*K* decreases with P Johnson & Dean1996

Table 2. Angioarchitecture

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Species | Total length of capillaries per unit volume of brain  (m.mm-3) | Length of individual  caplllaries ± SD (µm) | Capillary internal diameter (µm) | Space occupied by microvessels (%) | Thickness of pericapillary  'space' (µm) |
| Mouse | 1.1 (Boero et al., 1999); 0.88 (Tsai et al., 2009); |  | 2.8 (Boero et al., 1999); 4.0 (Tsai et al., 2009);3 (Nishimura et al., 2016) | 0.74 (Tsai et al., 2009).  2 (Vérant et al., 2007) | ≈ 2 um (Iliff et al., 2012;Rangroo Thrane et al., 2013) |
| Rat | 1.0 (Hudetz, 1997) | 112 ± 55 (Motti et al.,1986) | 7.3 ± 0.8 (Motti et al., 1986) |  |  |
| Cat | 0.94 (Pawlik et al., 1981) |  |  | 2.2 (Pawlik et al., 1981; Hudetz, 1997) |  |
| Human cortex |  | 57.4 (Cassot et al., 2006) | 5.9 (Cassot et al., 2006) |  |  |
| Model 'mouse cortex' | 1 | 100 | (outer diameter = 4 µm) | 1 | 2 |

*2.2. Hydrodynamics of flow through paracapillary space****.***

Although published images (e.g. Fig. 3(c), or Fig 2f in Rangroo Thrane et al., 2013) show the capillary located eccentrically in the pericapillary space, for simplicity we treat the case of a capillary located at the centre of a cylindrical space.

If flow of a Newtonian fluid in the *x* direction between two parallel plane surfaces at *z* = 0 and *z* = *h* is laminar and driven by a constant longitudinal pressure gradient *G* (= ∂*p*/∂*x*) then the speed of flow *v* varies with *z* as

*v*(*z*) = *G* *z*(*h* - *z*)/2 (5)

where is the viscosity. Integrating from *z* = 0 to *z* = *h* gives the quantity of flow per unit width of the plane surfaces:

Flow per unit width = *G* *h*3/12 (6)

With sufficient accuracy, we can ignore the curvature of the thin annular perivascular space, and calculate the paravascular flow, *f*, as

*f* = π*rG* 3/6 (7)

where *r* is the mean radius of the pericapillary space and ** is its thickness as in Fig. 3c. That is:

*r*  = (outer diameter of capillary + **

Rearranging Eq. (7):

*G* = 6*f*/π*r* 3 = 1.91*f*/*r* 3 (9a)

*2.2.1. Numerical values.*

*f*: from Eq. (4), *f* = 1.43 fL s-1 = 1.43 x 10-18 m3s-1.

**: the viscosity of CSF is very close to that of water (Bloomfield et al., 1998) soat 37 ºC, * =* 6.91 x 10-4 Pa.s.

**: this is the most uncertain quantity. The width of the labelled space in fixed tissue appears to be at least 2 µm in images such as Fig. of Iliff et al (2012) shown here as Fig. 3(c). Rangroo Thrane et al. (2013) show an in vivo image (their Fig. 2f) of a space filled (according to the legend) with the hydrophilic compound rhod-2 (Minta et al., 1989) that is also about 2 µm.

*r*: published values for the mean internal diameter of capillaries in the mouse cortex range from 2.7 µm (Boero et al 1999) to 4.0 µm (Tsai et al 2009) in fixed tissue or 3 µm in vivo (Nishimura et al., 2016). Talking 4 µm as the outer diameter of the capillary, Eq. (8) gives *r* = 3.0 x 10-6 m.

Then Eq.( 9) becomes:

*G* = 1.91 x 6.91 x 10-4 Pa.s x 1.43 x 10-18 m3 s-1 x (3 x 10-6 m x 8 x 10-18 m3)-1

= 78.6 Pa m-1 (9b)

I.e., the pressure drop along the 100 µm length of a capillary, *Gc*, is

*Gc* = 7.86 x 10-3 Pa = 5.895 x 10-5 mmHg (10)

**3. Speed of flow.**

The mean speed of the fluid movement along the paracapillary space is:

(Flow rate)/(area of annular PCS) = *f*/2*r* where *r* is defined in Eq. (8)

Using the values given in 2.2.1,

Mean speed = 1.43 µm3s-1 (2 x 3.142 x 3 x 2 µm2 )-1

= 2.275 µm/min.

This means that a molecule would take about 44 min to travel the 100 µm length of the capillary. This is comparable to the delay between labelling of PVS in descending arteries and ascending veins of 30 - 45 min observed by Iliff et al. (2013).

A paravascular transport that has been better observed in real time is that from the cisterna magna to the para-arterial spaces of the cortex (Iliff et al. 2012; 2013b). Some of this pathway is through spacious cisternae in the ventral leptomeninx, but then the pathway follows spaces adjacent to surface arteries (Fig. 1(b)). Guided by Fig. 1(c) we approximate the channels adjacent to a surface artery by two tubes of radius . Volume flow by Poiseuille's formula is

*Q* = 4. (11)

Defining a mean speed, *v* = *Q*/2,

*v*/2. (12)

6.91 x 10-4 Pa.s. From the largest vessel in Fig. 2(c), is roughly 10 µm = 10-5 m

The length of the path taken by CSF to move from the cisterna magna through the ventral cisternae and the para-arterial channels to the cortical leptomeninx is about 15 mm, and this transport takes about 5 min (Iliff et al., 2012; 2013b) so

*v* = 15/5 mm/min

Inserting the numerical values in Eq.(12),

*dp/dx* = 2.764 x 103 Pa m-1  (12b)

This gradient is about 35 times that (78.6 Pa m-1) calculated for the paracapillary space. Over the 15 mm path length from cisterna magna to cortical meninges, a pressure difference of about 41.46 Pa (= 0.311 mmHg) will be required. This pressure difference is small compared to measured values of intracranial pressure, typically about 5 mmHg (see Appendix A), and merits discussion of its physiological feasability.

**4. Discussion**

*4.1. Limitations of the calculation*s

The calculations were done on the hypothesis that CSF flows through a paravascular space free of obstacles. The dimensions and fluid speed are small and Reynolds number is in the order of 10-7, some 10-10 times the value at which turbulence occurs, so the assumption of laminar flow is well justified. However, the possibility that the narrow pericapillary ‘space’ contains an extracellular matrix cannot be excluded (Hannocks et al., 2018), in which case some form of Darcy’s Law would apply (Philip, 1970). Besides bulk flow driven by a longitudinal pressure gradient, molecules are transported by diffusion, and, if the width of the perivascular space changes in time, also by mixing (Hladky and Barrand, 2014). Since technical difficulties have so far prevented measurement of possible pressure gradients along paracapillary spaces, or changes in their volume, the available data on CSF pressure and CSF flow in macroscopic brain structures will be considered.

*4.2. Time-averaged pressure gradients of CSF within the cranium*

Transport of markers from the cisterna magna to the cortical meninges in mice is rapid and independent of their molecular weight and so must depend on bulk flow (Iliff et al., 2012; Iliff et al., 2013a). For mice, there appear to be no experimental data on the time-averaged pressure gradients in the CSF circuit. For rats, several papers have reported values in the ventricles, the cisterna magna and the superior SAS, but never all in the same experiment. For what it is worth, the mean values given for CSF pressure in the ventricles reported in the papers listed in Appendix A have an overall mean of 6.9 mmHg, S.D. 2.1 mmHg, and in the cisterna magna of 5.0 ± 2.3 mmHg. The difference between these means (1.9 mmHg) is large compared with the pressure differences calculated from the flow from cisterna magna to calvarial SAS (0.3mmHg), and along a paracapillary space (0.00006 mmHg). And indeed, since brain tissue is compliant, time-averaged pressure *gradients* (outside the mechanically constrained blood compartment) cannot be large, and the clinical approximation that there is a single intracranial pressure is justified. However, when outflow from the ventricles is blocked, as has been done experimentally in dog (Dandy, 1919), and occurs in non-communicating hydrocephalus in humans, pressures sufficient to enlarge the ventricles or even the entire head are generated (Scarff, 1970; Rachel, 1999; Hellwig et al., 2005). The simplest hypothesis, that flow from the cisterna magna to the parietal SAS is driven by secretion from the choroid plexuses appears unobjectionable as, indeed, is its extension to flow along paracapillary space, but tissue movements should also be considered.

*4.3. Pulsating pressures and tissue movement*

Intracranial pressure oscillates with components at the frequencies of cardiac pulsation and respiration and, in principle, in the compliant tissue of the brain, transient pressure gradients could be larger than constant ones. Uldall et al. (2014) made simultaneous continuous measurements of pressure in a lateral ventricle and immediately under the skull in rat, and found no significant difference between the two sites in the amplitudes of the oscillations. However, a pressure gradient adequate to drive the observed flow from ventricles to meninges would be less than the uncertainty in these measurements. Nevertheless, in humans and other animals with large brains, phase-contrast MRI shows that cardiac pulsation and respiration produce major to-and-fro movements of CSF through the aqueduct of Sylvius, indirectly showing movement of brain tissue (Picard and Zanardi, 2015; Dreha-Kulaczewski et al., 2017). (And, with care, the expected, relatively small, net flow, outward from the ventricles, can be measured (Feinberg and Mark, 1987; see Coles et al., 2017 for other references)).

On a smaller scale, cardiac pulsation of the vessel diameter has been measured in brain arterioles and venules of mice by Iliff et al. (2013b) and they suggest that this causes synchronous changes in the width of perivascular space that drives CSF in the direction of the blood flow by a peristaltic mechanism. However, such vectorial peristaltic pumping is unlikely to make a significant contribution, because the wavelength of the vascular pulse is too long: from the data of Yeh et al. (2012), the wavelength on a 30 µm arteriole is about 30 mm. Pulsatile perfusion of the arterial tree has nevertheless been shown (in the peripheral tissue of a rabbit ear) to enhance spread of dye through interstitial space (McMaster and Parsons, 1938). A similar effect in brain might explain why pulsatile blood flow increases the spread of dye through the brain (Hadaczek et al., 2006) and preserves the integrity of brain tissue better than does continuous flow (Sanderson et al., 1972). The spread of extracellular dye in rabbit ear is also increased when the pulsatile pressure is applied directly to the tissue (Parsons and McMaster, 1938; McMaster and Parsons, 1939). Presumably these effects result from increased mixing, as in a sponge that is repeatedly squeezed and released (see also Hladky and Barrand, 2014).

*4.4. Conduits for CSF along capillaries and in the leptomeninx*

*4.4.1. Exchange between blood and neural tissue, and CSF and neural tissue*

The evidence for transport of CSF along paravascular conduits, and in particular along capillaries, must be reconciled with the existence of major molecular fluxes across the capillary endothelium between blood and neural tissue, and for control of vessel diameter by signals from astrocytes and other neural cells (Peppiatt et al., 2006; Fernandez-Klett et al., 2010). In those cross-sectional images of parenchymal vessels that show some perivascular space, the vessel is apparently always seen to be apposed to the wall of the surrounding neural tube, as in Fig. 3(b). The wall appears not to be homogeneous, e.g. Ma et al. (2001) and Mathiisen et al. (2010) show pericytes covering only part of the capillary circumference. It seems possible that where there is apposition there is transfer of metabolites between blood and brain and signalling, and where there is a conduit for CSF there is exchange between CSF and ISF.

*4.4.2. Channeling of CSF flow in the leptomeninx*

CSF arrives in the calvarial leptomeninx in channels that accompany surface arteries and then descends the paravascular space of arterioles that penetrate the cortex (Fig.1(c)). If it flows upwards along paravenular space then, presumably, it reaches other channels in the leptomeninx (Krisch et al., 1983) that carry it away, perhaps to lymph vessels in the pachymeninx (Andres et al., 1987), or perhaps to the foraminae of the cribriform plate (Fig. 1(d)). In either case, major questions remain: how does CSF circumvent the arachnoid barrier membrane to reach the lymph vessels (Raper et al., 2016)? Or how does an efflux through the cribriform plate occur in foraminae that also support rapid influx of particles (Clark, 1929)?

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**Appendix A**

Reported values of CSF pressure in *Murinae.*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Species | Site | Mean  Pressure (mmHg) | S.D.  (mmHg) | Remarks | Reference |
| Mouse | Ventricle | 7.0 | 2.4 | 2,2,2-tribromoethanol | Oshio et al., 2005, http://www.fasebj.org/cgi/doi/10.1096/fj.04-1711fje. |
| Mouse | Calvarial epidural | 5.1 | 1.2 | Midazolam + fentanyl + medetomidin | Feiler et al., 2010, J. Neurosci. Meth. 190  (2) 164-170. |
| Mouse | Parietal SAS | 3.81 | 1.14 | Careful description of method | Moazen et al., 2016, J. Biomech. 49 (1) 123-126. |
| Rat | Ventricle | 4.71 | 0.78 | Unrestrained | Mandell & Zimmermann (1980) Physiol. Behav. 24, 399–402. |
| Rat | Ventricle or CM | 2.5 | 0.3 | Pentobarbitol | Jones et al.,1987, Dev. Brain Res. 33: 23-30. |
| Rat | Ventricle | 9 |  |  | Nakamura et al.,1987, Hypertension, 10, 635-641. |
| Rat | Ventricle | 8.4 | 3.9 | Daytime, unrestrained | Starcevic et al., 1988, Brain Res. 462, 112-117. |
| Rat | Ventricle  Cisterna magna | 9.6  11.7 |  | Unrestrained | Sanchez-Valverde et al., 1995, Neurosci. Res. 24 (1) 103-107. |
| Rat | Ventricle | 9.1  4.2 | 3.2  2.2 | Loose restraint.  Anesthesia | Jiang & Tyssebotn, 1997, Undersea Hyperbaric Med., 24 (1) 39-43. |
| Rat | Ventricle  Cisterna magna | 8  6 |  | Halothane | Zwienenberg at al., 1999, J. Neurotrauma, 16 (11) 1095-1102. |
| Rat | Ventricle | 9.2-9.3 | 5.0 | Unrestrained  Circadian range | Lin & Liu, 2010, Invest. Ophthal. Vis. Sci. 51 (11) 5739-5743. |
| Rat | Ventricle | 4.05 | 1.1 | Conscious | Chowdhury et al., 2013, PLoS ONE 8: e82151 |
| Rat | Ventricle | 5.7 | 4.2 | Isofluorane | Uldall et al., 2014, J. Neurosci. Meth., 227, 1-9. |
| Rat | Cisterna magna | 6.2 |  | Ether. Dietary  deficiency | Rokkones, 1955, Int. Z. Vitaminforsch. 26, 1-10. Cit. by Mandell and Zimmermann, 1980. |
| Rat | Cisterna magna | 2.5 | 1.8 | Pentobarbarbitol | Hayes & Corey, 1970, J. Appl. Physiol. 28, 872–873. |
| Rat | Cisterna magna | 2.9 |  | Halothane/N2O | Melton & Nattie, 1984, Am. J. Physiol. 246 (4) R533-541. |
| Rat | Cisterna magna | 2.7 |  | Pentobarbitol | Jones & Gratton, 1989, J. Neurosurg. 71, 19-123. |
| Rat | Cisterna magna | 6 |  | Conscious | Kotwica et al., 1991, Res. Exp. Med. 191 99-104. |
| Rat | Cisterna magna | 4.1 |  | Ketamine | Barth et al.,1992, Neurosurgery 30, 138-140. |
| Rat | Cisterna magna | 7 | 1 | Halothane | Morimoto et al.,1996, Stroke 27 (8) 1405-1409. |
| Rat | Cisterna magna | 9.1  4.2 | 3.2  2.2 | Loose restraint  Fentanyl+fluanizone+  midazolam | Jiang & Tyssebotn, 1997, Undersea Hyperbaric Med., 24 (1) 39-43. |
| Rat | Calvarial SAS | 6.0 | 2.1 | Conscious | Guild et al., 2015, J. Appl. Physiol. 119 (5) 576-581. |
| Rat | Spinal SAS | 5.9 – 7.4 |  | Conscious | Mann et al., 1978, Ann. Neurol. 3, 156-165. |

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