In search of mechanisms to explain ventricular expansion in communicating hydrocephalus.

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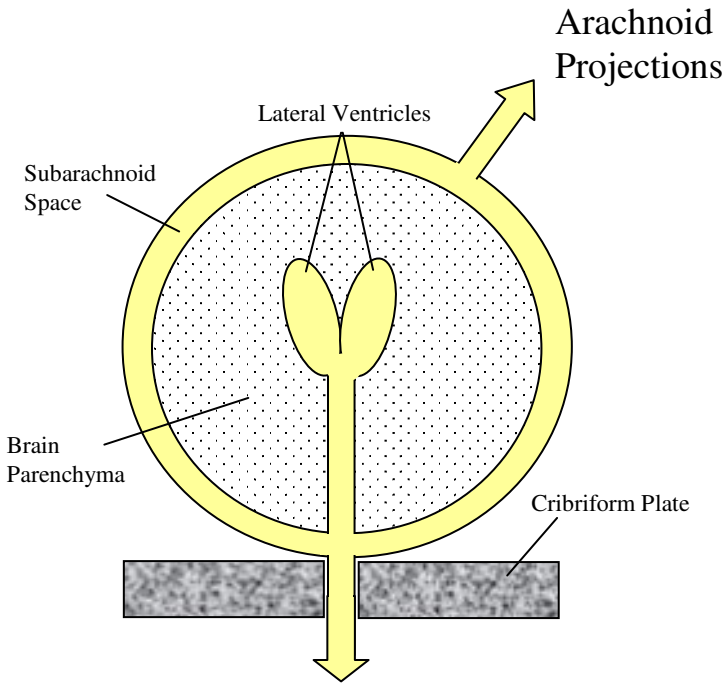
Pathways for CSF absorption

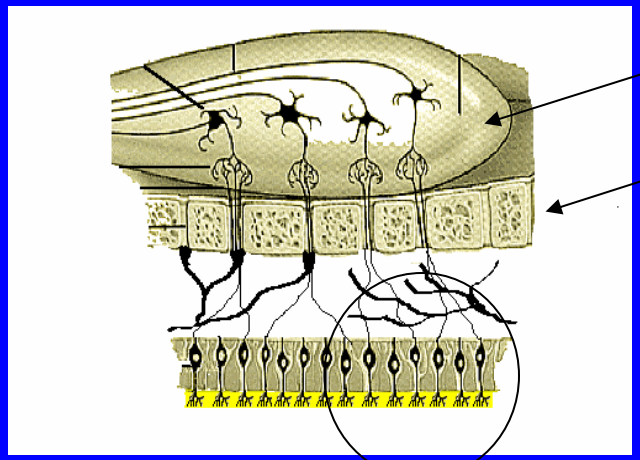


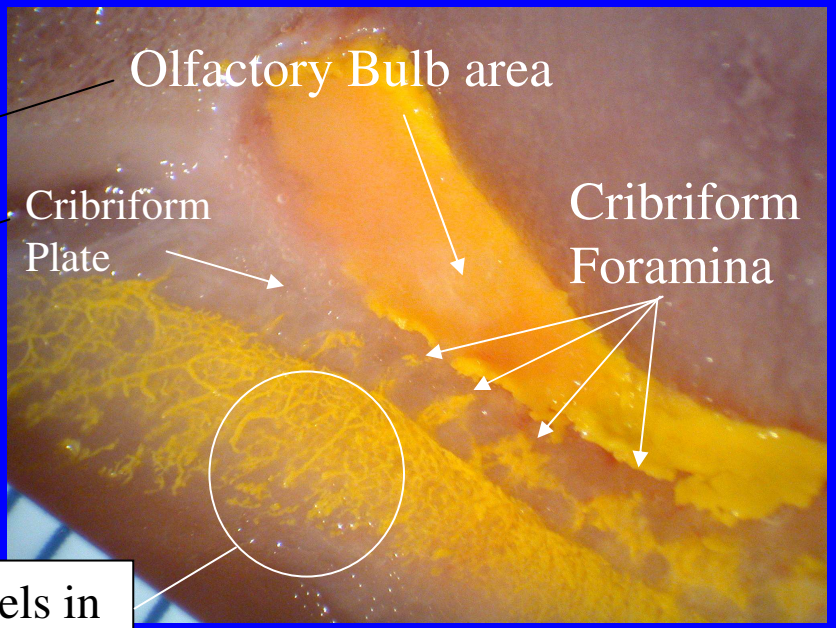
CSF absorption into extracranial lymphatic vessels in the olfactory turbinates

- Physiology
- Lymphatics
  - -quantitative
  - -qualitative

The concept

sheep





Lymphatic vessels in olfactory submucosa

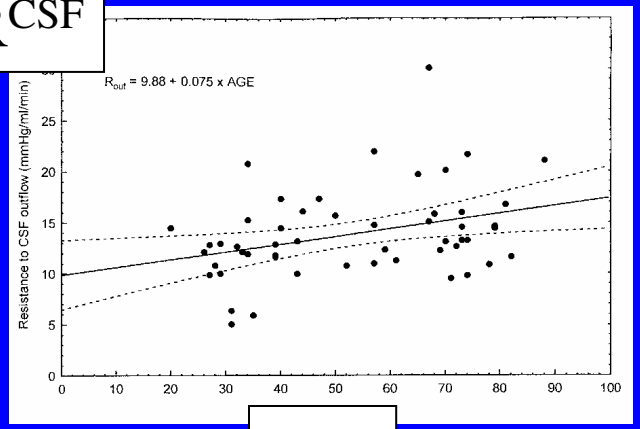
Near term fetal pig

Do lymphatics contribute to CSF disorders ?

- Ageing
- Kaolin hydrocephalus

Impact of ageing on CSF absorption in rats

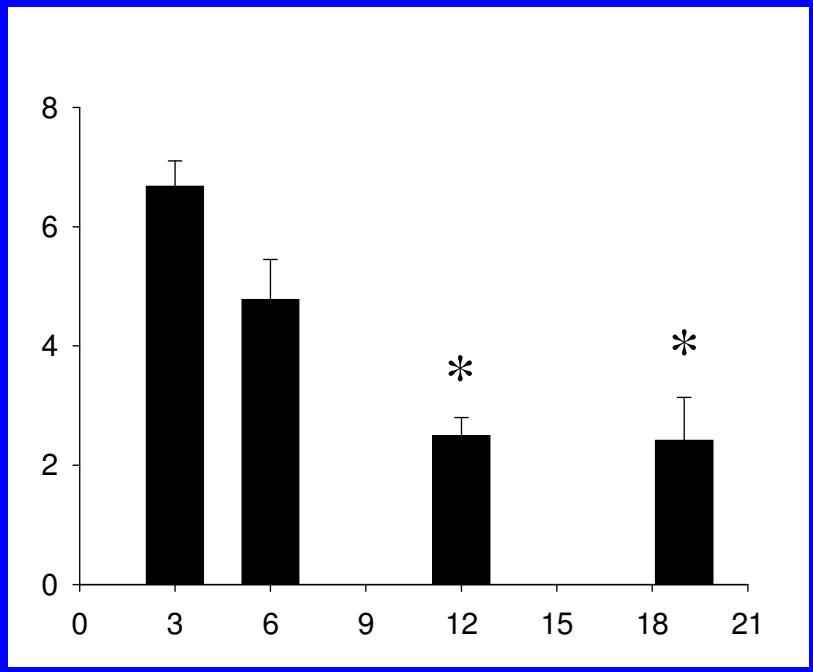
R^{CSF}



Age

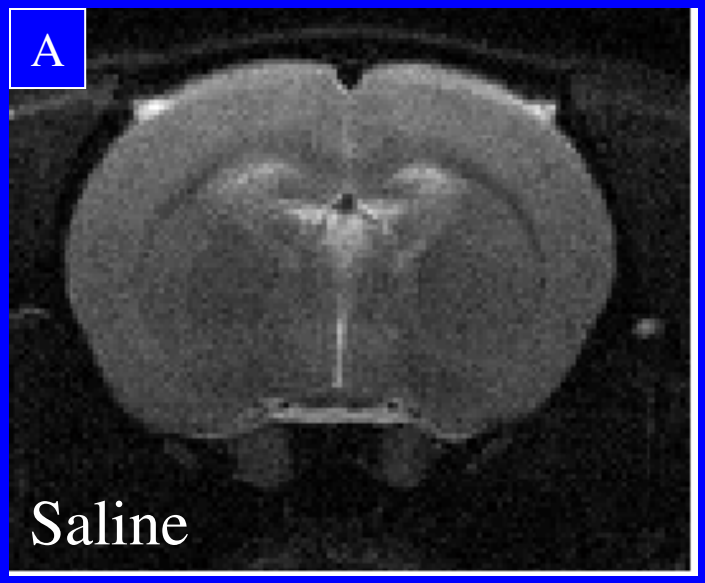
Albeck et al., J Neurosurg 89: 275-278, 1998

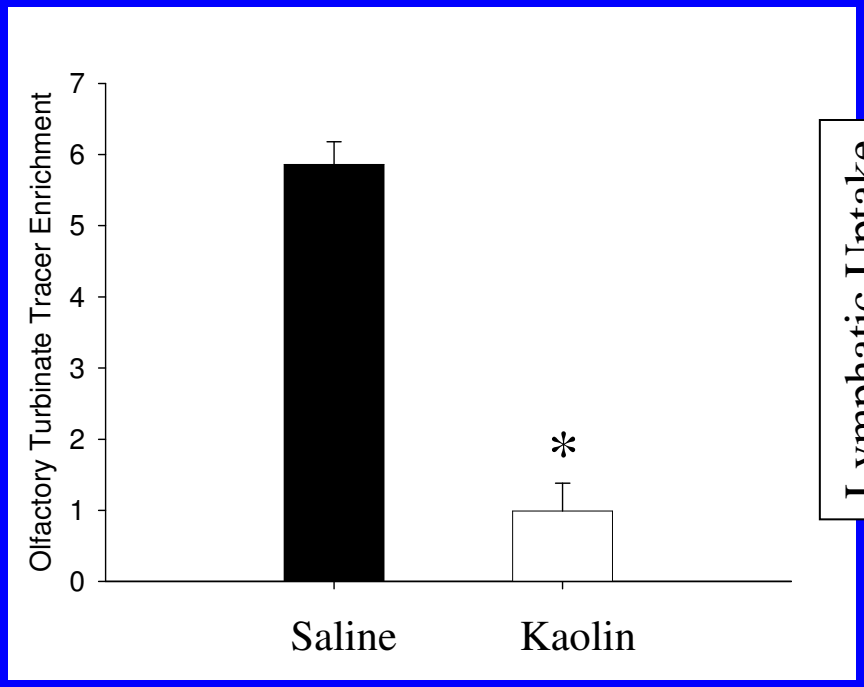
Fisher 344 rats

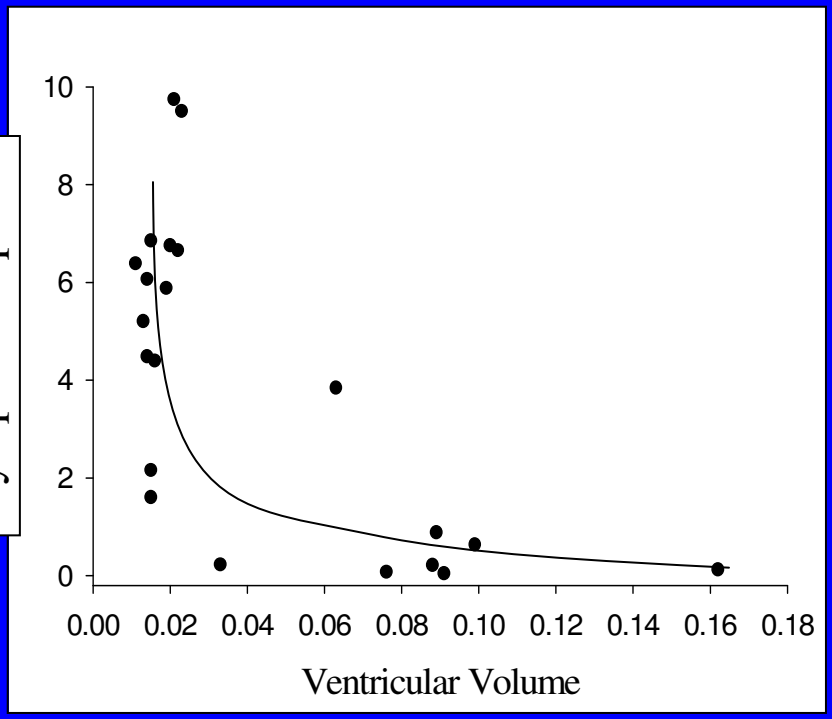


The movement of radioactive HSA across the cribriform plate is impaired in aged rats

Nagra et al., Neuropathol Appl Neurobiol, 2007, in Press



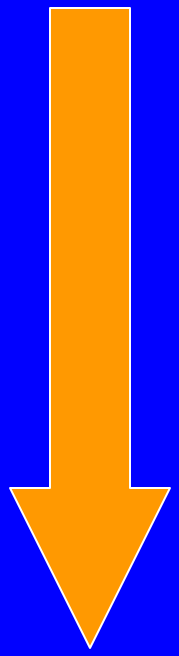




Nagra et al., 2007, in preparation

Lymphatic/arachnoid projection CSF absorption deficit and hydrocephalus?

- What is the mechanism responsible for the reduction in lymphatic CSF absorption?
- What is the relationship between CSF absorption and hydrocephalus?
- How are the pressure gradients formed to induce ventricular dilation?
- What is the magnitude of the gradient?
- Over what period must the gradient exist?

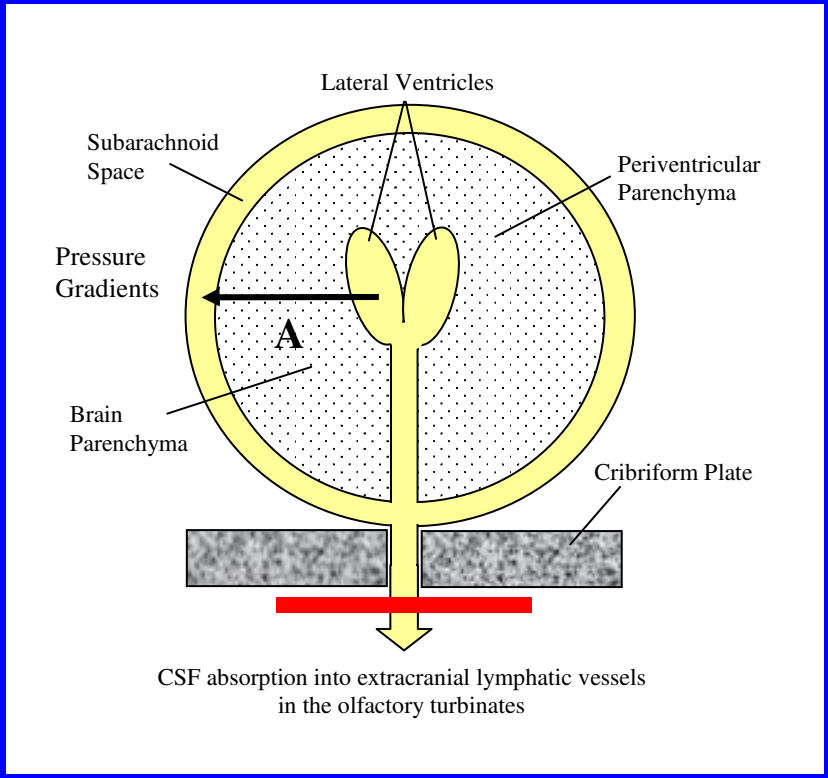


From a lymphatic perspective:

It is difficult to envisage how a CSF transport deficit through the cribriform plate can generate a transmantle pressure gradient (A).

Elevated ICP

May change compliance and contribute to redistribution of pulsatility ?

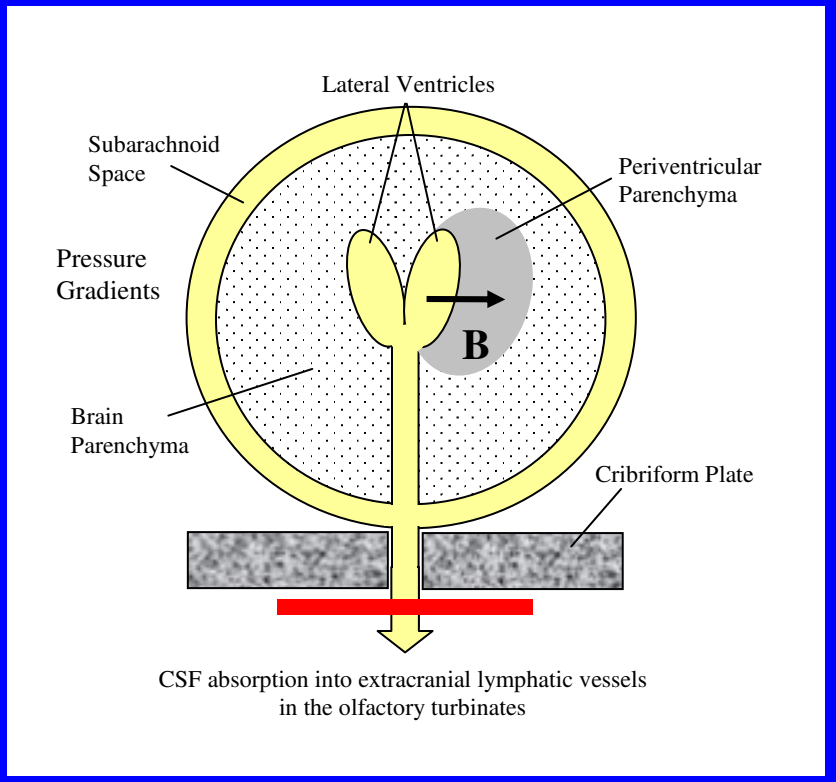


Issues to consider

A CSF absorption deficit may enhance (facilitate) other mechanisms that are responsible for ventricular expansion

Relative reduction in parenchymal interstitial fluid pressure in conjunction with changes in the matrix may contribute to a trans-parenchymal pressure gradient (B).

How might this occur ??

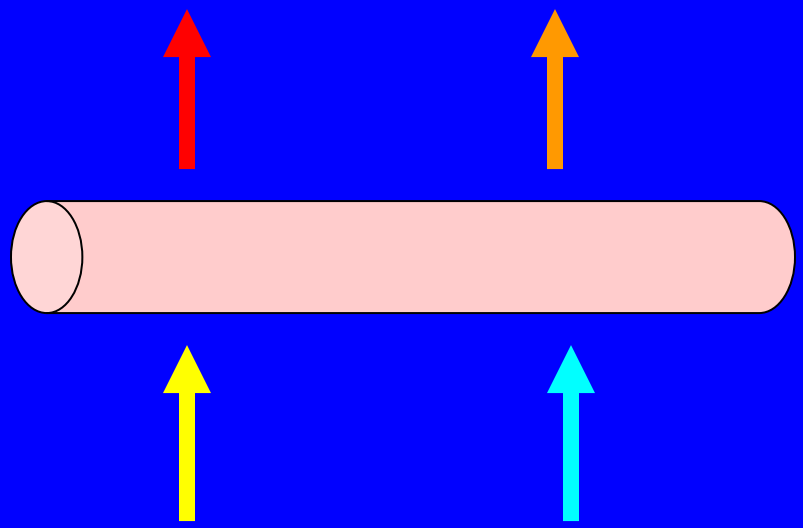


Pena et al., Acta Neurochir Supp 81: 59 (2002)

Work of Professor Reed and colleagues: Interstitial matrix actively contributes to regulation of P(i)

- Lund et al., Am J Physiol 255:H1069, 1988
- Reed and Rodt, Am J Physiol 260: H1985, 1991
- Koller and Reed. J Appl Physiol 72: 53, 1992
- Reed et al., Circ Res 71: 978, 1992

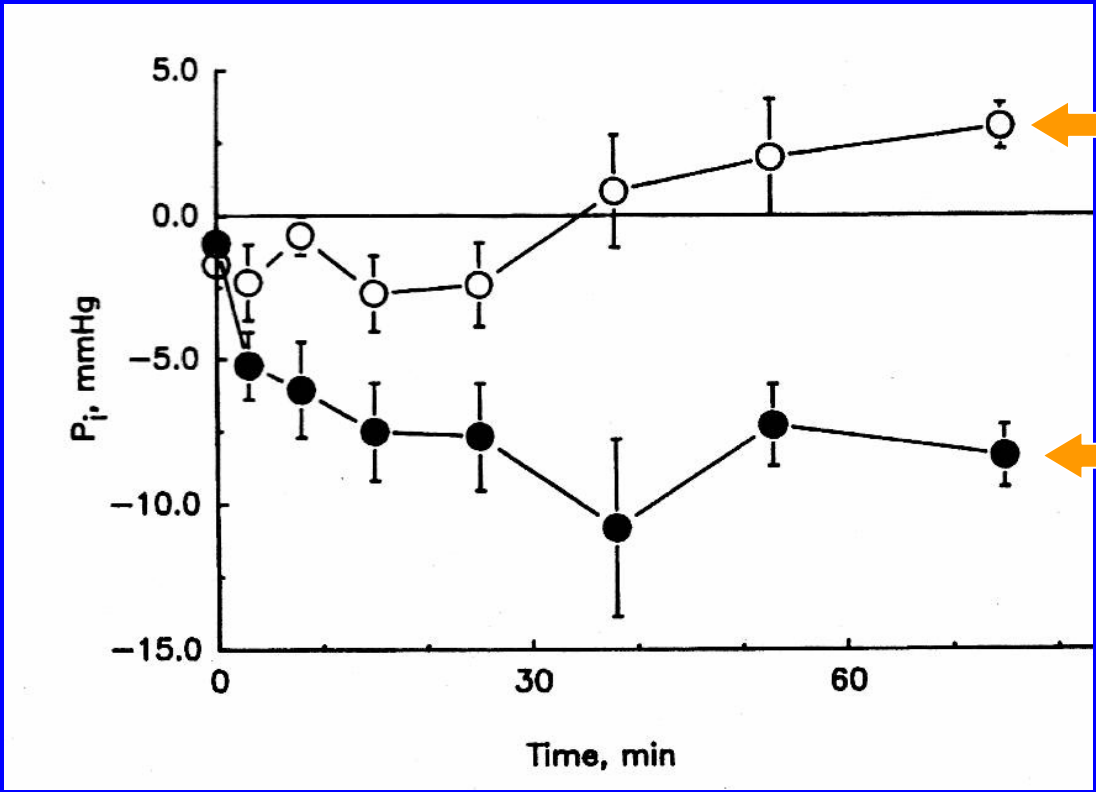
Starling Forces



$$Q = K\,(Pmv - Pi) - \delta(\pi mv - \pi i)$$

Problem – in inflammation, the measured accumulation of interstitial water was often much greater than that estimated from calculated values based on steady-state data

Effect of dextran anaphylaxis in P(i) in rat paw skin

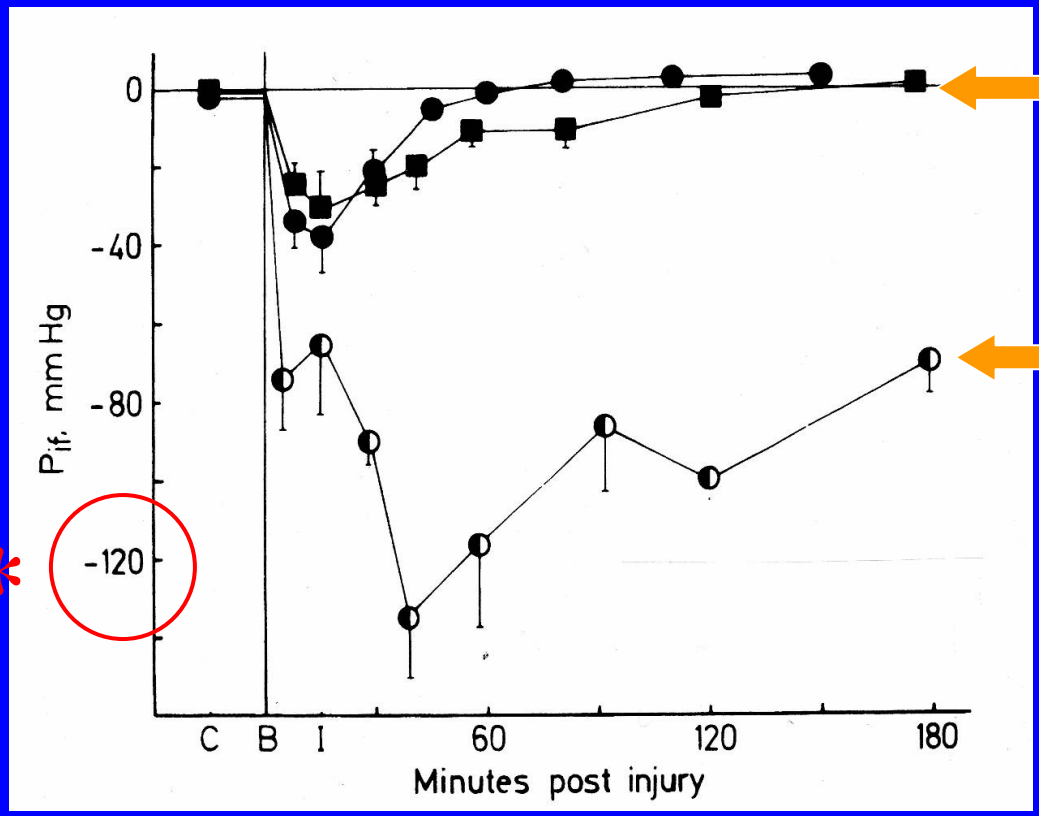


Intact circulation

Circulatory arrest

Circulatory arrest limits the increased capillary fluid filtration associated with the anaphylactic reaction. This increased filtration will otherwise raise interstitial volume and thereby p(i) and cause an underestimation of a potential increased negativity of p(i).

Impact of full thickness burn injury on P(i) in rat skin



Intact circulation

Circulatory arrest

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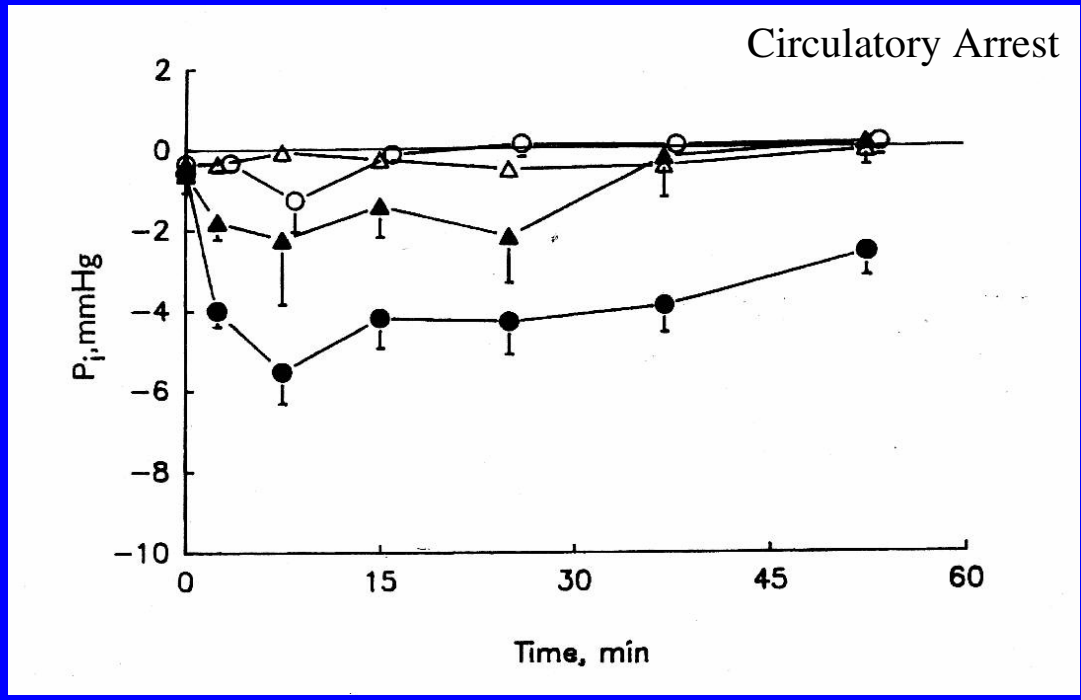
Effect of anti-beta1 integrin antibodies on P(i) in rat skin

Δ Anti fibronectin IgG

○ Pre-immune IgG

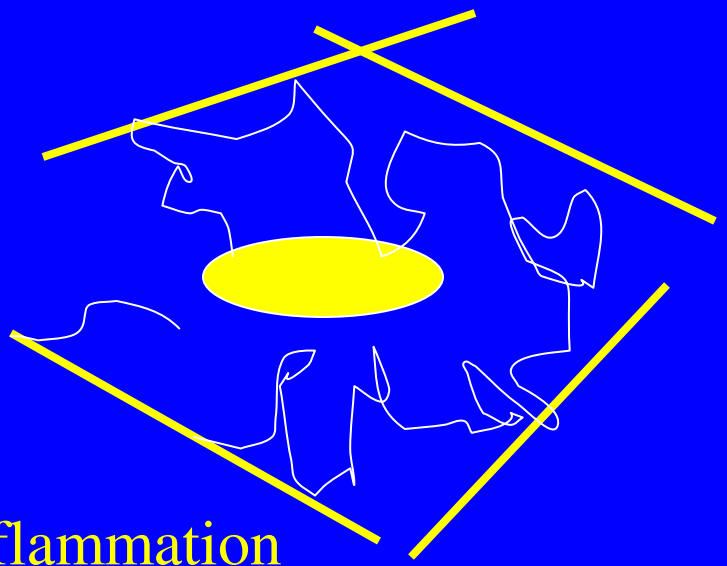
▲ RGD sequence peptide

● Anti beta1 integrin

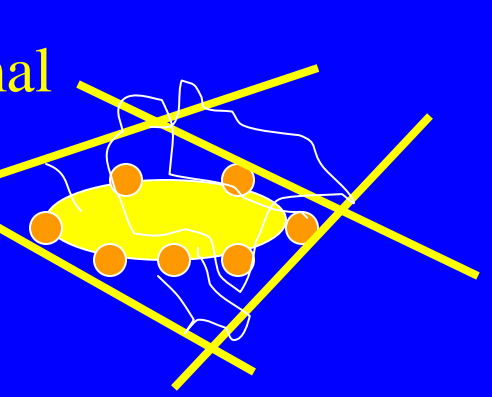


Concept

Increased negativity of P(i) relates to perturbation of Beta-1 integrins with release of contact between connective tissue cells and matrix fibres allowing matrix to expand



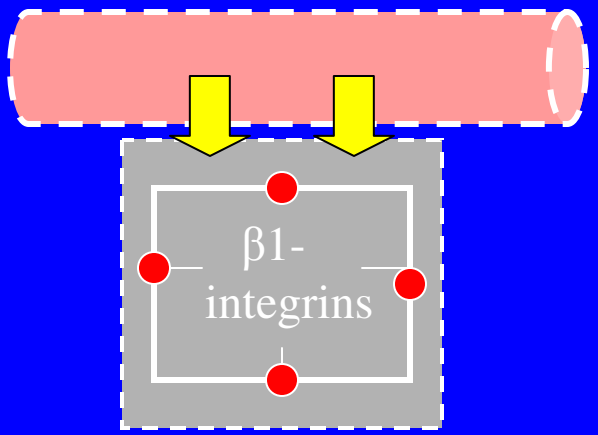
Inflammation

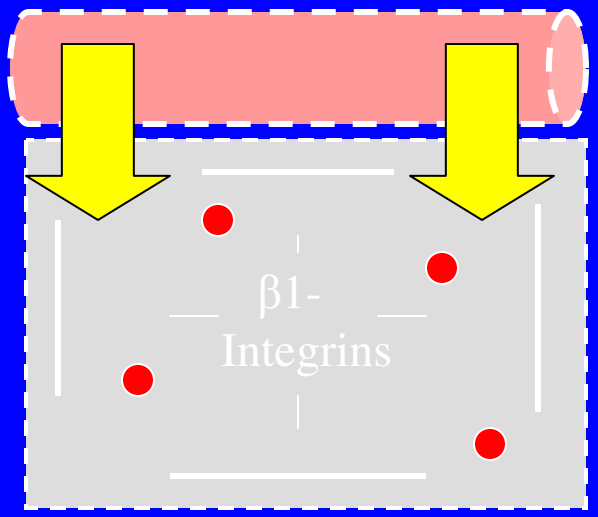


Normal

This lowers P_i until water moves into the tissues in an attempt to balance the Starling forces.

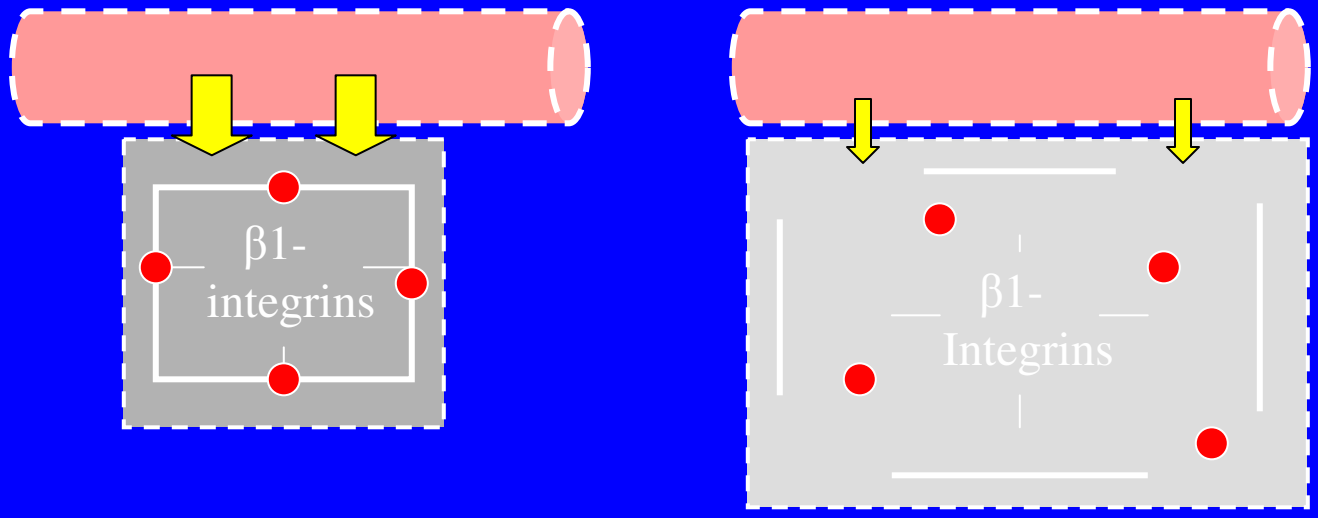
Matrix elements play an active role in the regulation of interstitial fluid pressure





Intact

Matrix elements play an active role in the regulation of interstitial fluid pressure

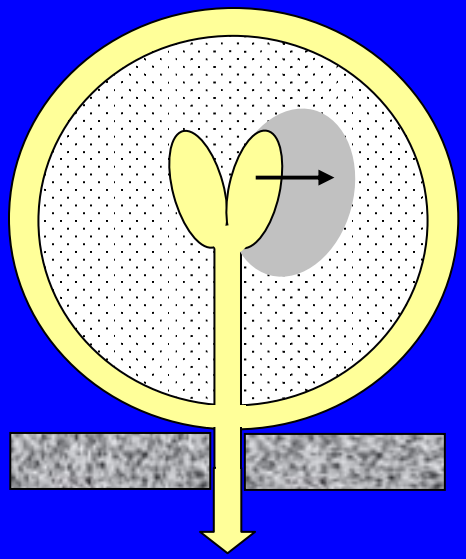


Circulatory arrest

$$Q = K\,(Pmv\text{-}Pi) - \delta(\pi mv\text{-}\pi i)$$

Gradient larger than predicted

Can a similar phenomenon occur in the brain – Hydrocephalus ??



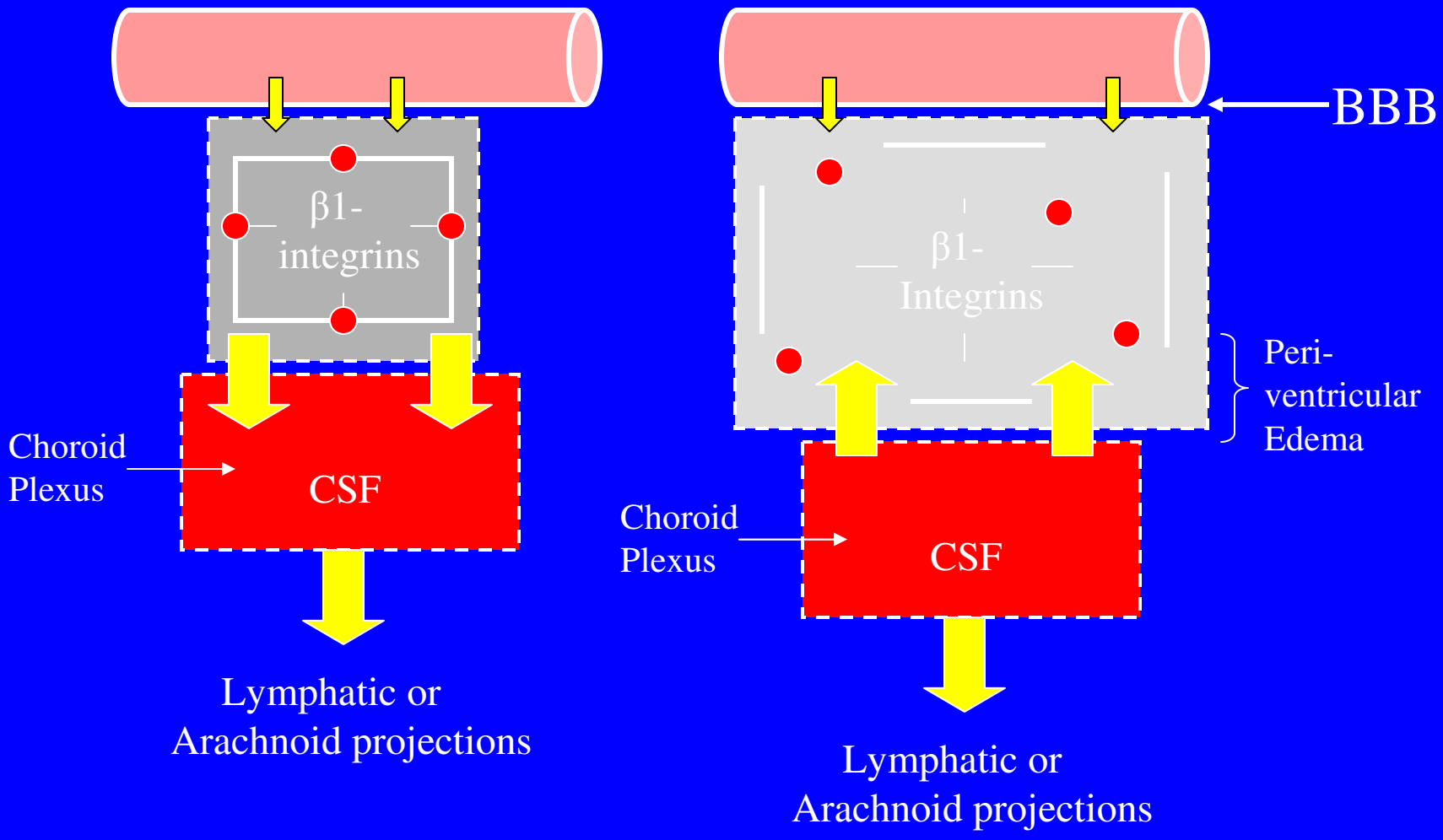
B1-integrin expression in brain

-blood vessel walls
- pineal gland
- periventricular region and ependyma
- choroid plexus
- grey matter
- cerebral cortex
- associated with astrocytes

Integrin expression affected by:

-Inflammation
--cytokines and prostaglandins
- Cerebral ischemia
- genetic ??

Can a similar phenomenon occur in the brain – Hydrocephalus ??

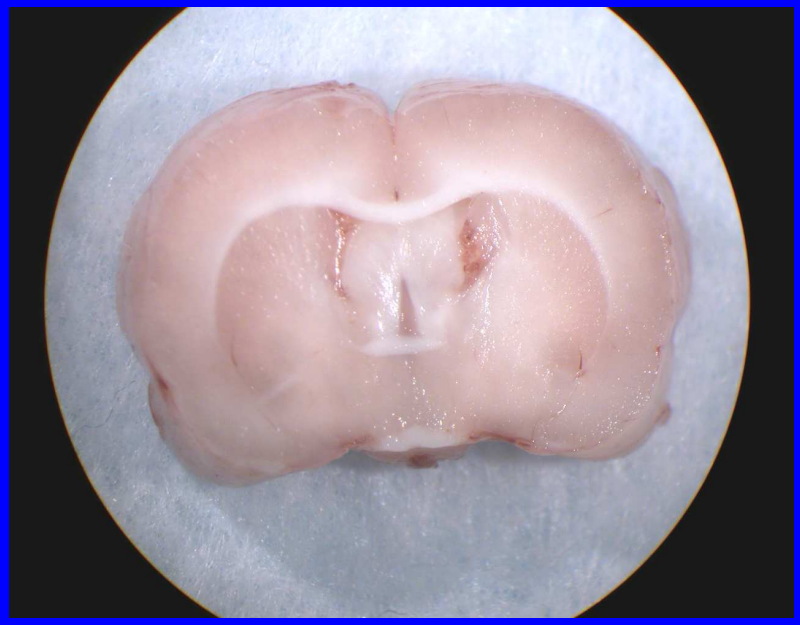


What happens if we inject anti beta1 antibodies into a lateral ventricle ?

Impact of anti-integrin antibodies in adult rats (assessed 2 weeks after injection into one lateral ventricle)

1 - beta 1 Ab (50µl)	ventricular enlargement
2 - beta 1 Ab (50µl)	normal
3 - beta 1 Ab (100µl)	normal
4 - beta 1 Ab (100µl)	mild expansion (+/-)
5 - beta 1 Ab (100µl)	ventricular enlargement
6 - beta 1 Ab (50µl)	normal
7 - beta 1 Ab (50µl)	ventricular enlargement
9 - alpha2, beta1 Ab (25µl)	ventricular enlargement
10 - alpha2, beta1 Ab (50µl)	ventricular enlargement
11 - alpha2, beta1 Ab (25µl)	ventricular enlargement
12 - alpha2, beta1 Ab (100µl)	ventricular enlargement
13 - alpha2, beta1 Ab (100µl)	ventricular enlargement
14 - alpha2, beta1 Ab (100µl)	ventricular enlargement
15 - alpha2, beta1 Ab (100µl)	ventricular enlargement
16 - alpha2, beta1 Ab (100µl)	ventricular enlargement

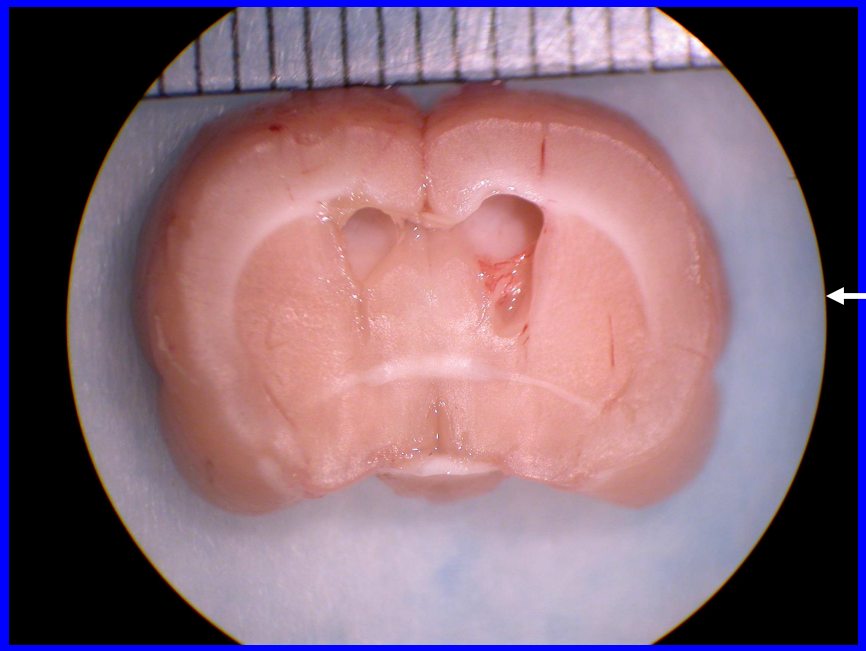
Ventricular expansion following injection of anti-β1 antibodies into a lateral ventricle

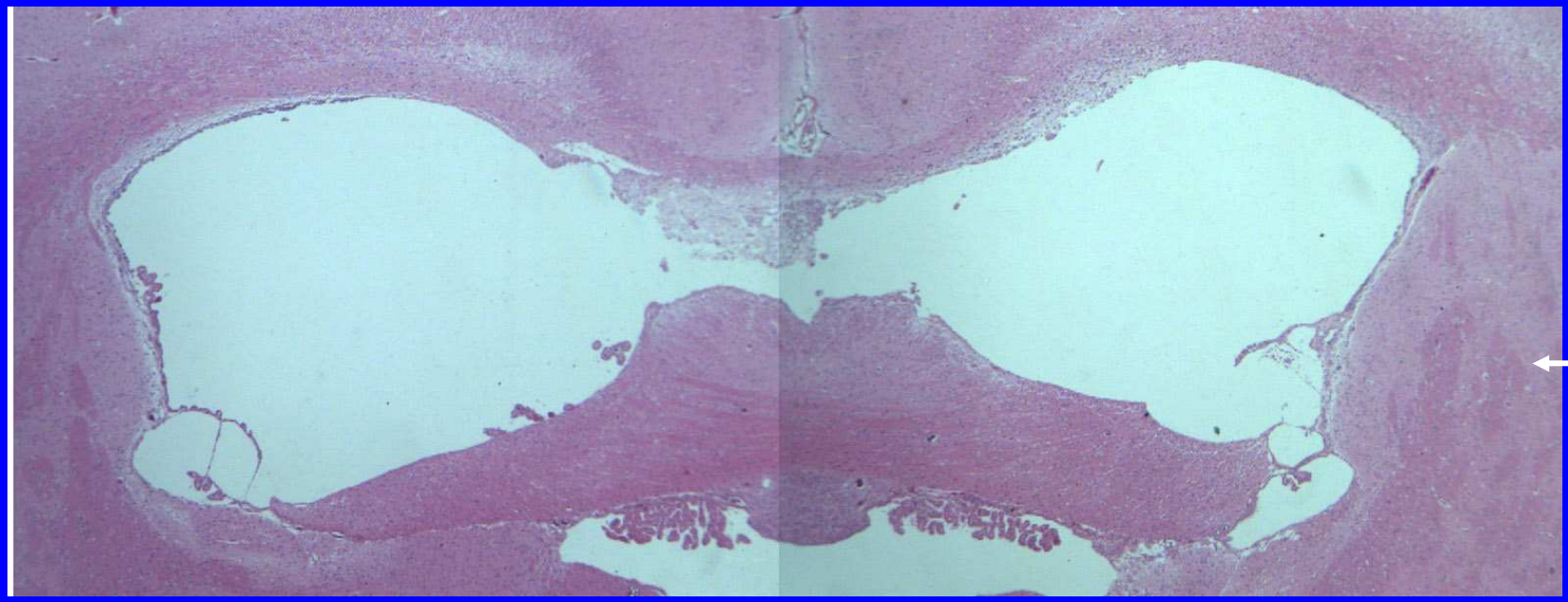


Control

Anti alpha2-β1 integrin antibodies

Anti-β1 integrin antibodies injected into lateral ventricle

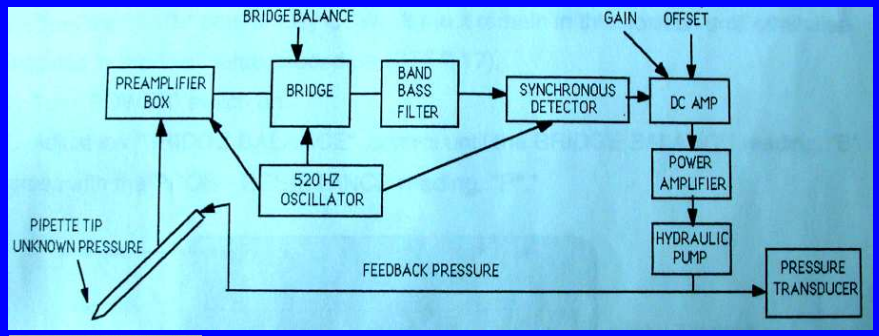




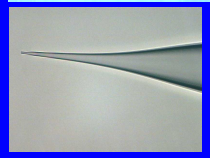
Next Step:

Attempt to measure trans-parenchymal pressure gradients while manipulating beta 1 integrin function

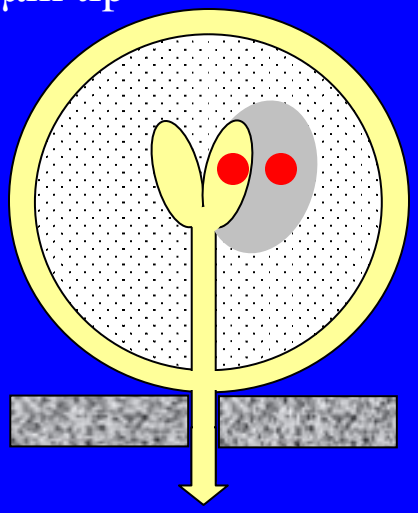
-antibodies (beta1, alpha2-beta1)
-kaolin



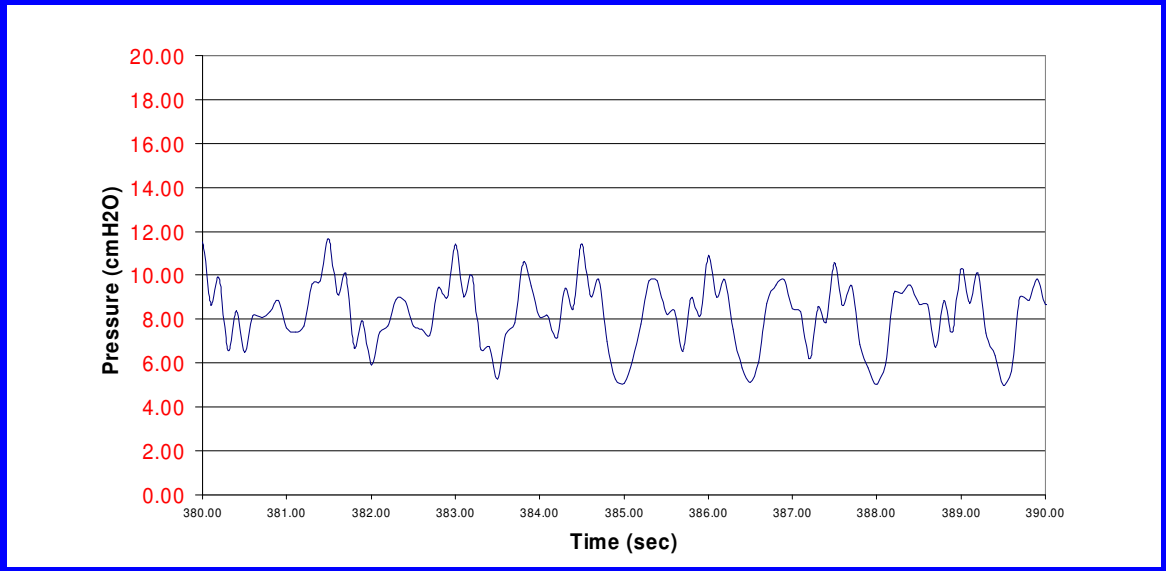
Servo-null method



2 μm tip



Measurement of periventricular pressure in a rat



Summary

Working towards the development of a 'two-hit' hypothesis

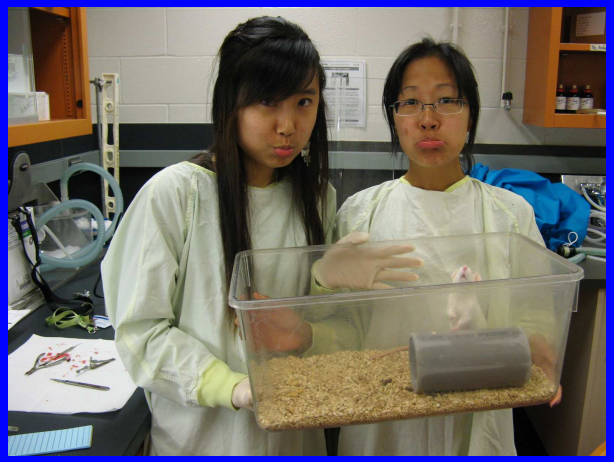
- disruption of beta1 integrins (decreased tissue pressure)
- impaired CSF absorption (lymphatics?)

Leads to ventricular enlargement

Reed found that an anti-inflammatory drug α-trinositol (given IV) inhibited the edema formation and lowering of P(i) that was induced after injection of anti β1 integrin antibodies.

*** Therefore, potential may exist for pharmacological strategies to reverse effect.

Contributors



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Research funded by MRC/CIHR and the BrainChild Foundation