Cerebral blood flow in liver failure

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Nothing to disclose
Liver failure complications that may influence CBF

- Hepatic encephalopathy
- High ICP
- **Hyperventilation** - low PaCO2
- hypoglycemia
- Systemic vasodilatation
- **sepsis**
- Hypoxia / ARDS
- renal failure (ATN, HRS)
- Low sodium and phosphate
- coagulopathy
- thrombocytopenia
- Lactate acidosis
Main regulatory mechanisms of CBF

CBF to metabolism coupling

Roy & Sherrington 1893

Seymour S. Kety

Magistretti
CBF in liver disease

• Global CBF reduced in HE
• Cognitive impairment correlates with rCBF in
  • basal ganglia and limbic cortex
  • cerebellum
  • frontotemporal regions
• Reversible after liver transplantation

- Larsen et al. Hepatology 1995
- Dam, J Hepatology 1998
- Lockwood et al. Metabol Brain Dis 2001
- Bjerring PN et al. J Clin Exp Hepatol. 2018
CBF in acute liver failure with hepatic encephalopathy

- A wide CBF variation (14 to 240 ml/100g/min) in spite
- CMRO2 ~ 1.0 ml/100g/min

- Cerebral vasodilation develops during liver failure (Kindt, J Neurosurgery 1986; Larsen, J Hepatol 1997)

- CBF is higher in patients with oedema than in those without (Larsen. Sem Liv Dis 1999)

- Cerebral hyperperfusion is reversed by hepatectomy (Ejlersen, Larsen & Secher. Transpl Proc 1994)
Severe hyperammonemia
Cerebral mechanisms in HE: astrocyte swelling

Ammonia is metabolised in brain astrocytes by glutamine synthetase:

\[
\text{Glutamate + ATP + NH}_3 \rightarrow \text{Glutamine + ADP + phosphate}
\]

Intra-cellular glutamine is osmotically active and draws H2O into astrocytes

Although ammonia is important in pathogenesis, levels do not necessarily correlate with severity

Other factors can precipitate HE without high ammonia concentrations

- Hyponatraemia
- Benzodiazepines (sedatives)
- Inflammatory cytokines etc
- Induce astrocyte swelling \textit{in vitro}
- Different neurotoxins may contribute to astrocyte swelling and precipitate HE

\(^1\text{Haussinger et al, Gut, 2012.}\)
\(^2\text{Haussinger et al, J Hepatol, 2000; 32(6):1035–8.}\)
Hyperammonemia increases CBF

Chung et al. Hepatology 2001
Larsen et al. J Hepatol 2001
Why ?
Cerebral microdialysis in patients with liver failure

Tofteng, Larsen. Hepatology 2002
Glutamine causes mitochondrial failure in the brain in liver failure?

Bjerrings et al. Neurocritical Care 2008
The higher LP ratio the higher hypoxanthine in the brain during liver failure: A microdialysis study

Bjerring & Larsen. J Hepatol 2010;53:1054–58
Adenosine and CBF in liver failure: Biosensor study

CBF in severe liver failure - interpretation

- **NH₃**
- **CMRO₂**
- **[lactate]e**
- **CBF**
Main regulatory mechanisms of CBF II

Vasoreactivity

EH Starling

WM Bayliss

1903, London
Main regulatory mechanisms of CBF - II


Niels A Lassen
Definition of CBF autoregulation in 1959
CBF autoregulation is impaired in liver failure

Larsen FS & Secher N. J Hepatol 1995, CCM 1997
Tofteng & Larsen. J CBF & M 2004

Strauss & Larsen. Hepatol 1997 and J Hepatol 1998

Jalan et al. Hepatology 2001
What impairs CBF autoregulation in liver failure?

Which mediator?!
Loss of liver mass and liver function

Paracetamol intoxication - pooled data, plateau

\[ y = 0.4858x + 52.077 \]

\[ R^2 = 0.207 \]

PHx 90% - pooled data, plateau

\[ y = 0.7735x + 41.733 \]

\[ R^2 = 0.2312 \]
Systemic inflammation and CBF autoregulation: Effect of LPS and TNFα

![Graph showing the relationship between CPP change and CBF change with the equation y = 0.31x + 71.64.](image)
Additional effect of systemic inflammation on CBF autoregulation

- - - = Corresponding group without LPS

**Graph: PHx90 + LPS - pooled data**

- Equation: $y = 0.85x + 22.27$

- Data points and trend line representing the relationship between CPP change (%) and CBF change (%).
New method needed to detect adenosine in vivo - not microdialysis

- Bilateral cranial windows on anaesthetized rats
- Brain surface perfusion was evaluated with speckle contrast imaging.
- 30 min topical exposure to 10 mM NH₄Cl and aCSF
Biosensors to measure adenosine in real-time in rats exposed to NH3

Perivascular adenosine signal
CBF autoregulation is impaired by high NH3

![Graph showing the relationship between Mean Arterial Pressure (mmHg) and Arbitrary Flow Units. The graph includes data points for Ammonium, aCSF, and Ammonium + ZM, with the autoregulatory index values indicated for each condition. The left lower limit is 37.73 mmHg, with an autoregulatory index of 0.63, and the right lower limit is 39.73 mmHg, with an autoregulatory index of 0.45. There is a significance marker (*) indicating a difference between conditions.]
CBF mapping of autoregulation in various brain areas (per pixel)
Inhibition of adenosine receptor A2a by ZM 241385 prevents a high CBF during experimental hyperammonia
Impaired CBF autoregulation in experimental liver failure is mediated true adenosin receptors
Cerebral microcirculation in hyperammonemia

- Cerebral microcirculation is disturbed by topical NH3 exposure.
- NH3 exposure leads to increased perivascular adenosine tone.
- Adenosine receptor antagonism can restore the regulation of microcirculation during arterial hypotension.
Conclusion - 1

- CBF fluctuates in liver failure
- CBF autoregulation is impaired
- Cerebral vasodilation evolves due to
  - loss of liver mass
  - hyperammonemia
  - sepsis / systemic inflammation
Conclusion - 2

The mediator of cerebral vasodilation and loss of autoregulation is **Adenosine**

Antagonism of **Adenosine** receptor A2a restores CBF and CBF autoregulation

**Perspective**

Clinical use of Theophyllamine, ZM or just Coffee
Thanks to

- Prof. Niels Secher
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- Dr. John Hauerberg
- Dr. Flemming Tofteng
- Prof. Andres Blei
- Prof. Kirsten Møller
- Dr. Hans-Jørgen Frederiksen
- Prof. Julia Wendon
Hyperammonemia also causes brain edema and death

Clemmesen JO, Larsen fs & Ott P.
Hepatology 1999;29:648-653

Bernal W Hepatology 2007