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## **Ammonia: this is not the end but rather the end of the beginning.**

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Hepatic encephalopathy (HE) represents a wide spectrum of neurological or neuropsychological symptoms due to liver disease and/or portosystemic shunts. The major role of hyperammonemia in association with systemic inflammation and oxidative stress has progressively emerged as key players in the pathogenesis of HE. However, the cascading downstream effects due to these pathogenic factors remain unresolved. The underlying abnormalities which have been described to cause HE include modification of glutamatergic and GABAergic neurotransmission, mitochondrial dysfunction, energy impairment, lactate dyshomeostasis, increased blood-brain barrier permeability, brain edema/astrocyte swelling as well as accumulation of toxic compounds (manganese, bile acids, indols) [1]. Abnormal cerebral blood flow (CBF) and cerebral metabolic rate of oxygen (CMRO<sub>2</sub>) have also been described and extensively discussed in their involvement in the pathogenesis of HE [2,3].

Due to the high metabolic activity of the brain, it demands close to 20% of whole body's total oxygen consumption, with a large proportion of CMRO<sub>2</sub> being used to maintain and restore membrane potentials. CMRO<sub>2</sub> can be calculated using <sup>15</sup>O-oxygen positron emission tomography (PET) and 3.5-5 mL/100g brain tissue/min is the physiological range measured in healthy individuals [4]. CBF, corresponding to the quantity of blood supplied to the whole brain in a determined period of time, can be assessed using <sup>15</sup>O-water PET. Magnetic resonance imaging (MRI) techniques can also, indirectly, estimate CBF but with a lower reproducibility. In healthy individuals, CBF is approximately 50 mL/100g brain

1 tissue/min [5]. It is also possible to evaluate the regional cerebral blood perfusion with both  
2 <sup>15</sup>O-water PET and MRI, arterial spin labelling sequences or functional MRI, the former using  
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4 blood oxygenation level dependent (BOLD) effect to evaluate regional consequences on  
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6 perfusion of a specific cognitive task [5]. Cerebral autoregulation is the maintenance of  
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8 constant CBF despite changes in systemic blood pressure where a cerebral vascular tone  
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10 adaptation exists which adjusts the regional blood perfusion following increased oxygen  
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12 demand in certain areas of the brain. Thus, in a healthy adult (normotensive), CBF does not  
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14 alter following changes in mean arterial pressure (MAP) between 50 to 150 mmHg. As  
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16 suggested by Poiseuille's law, CBF is inversely related to the radius of vessels to the power  
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18 four, therefore, this physiological response occurs merely with a minor adjustment in the  
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20 vascular resistance/tone, and thus in the diameter of large arteries and parenchymal arteries.  
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22 Outside the range of autoregulation (MAP <50 mmHg or > 150 mmHg) the CBF is  
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24 compromised and can consequently cause cerebral anoxia-ischemia or vasogenic (cerebral)  
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26 edema (posterior reversible encephalopathy syndrome) [6]. Several cellular mechanisms and  
27  
28 factors have been proposed to be implicated in the conservation of CBF autoregulation:  
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30 sympathetic and parasympathic innervation, levels of PaCO<sub>2</sub> and PaO<sub>2</sub>, release of H<sup>+</sup>, K<sup>+</sup>,  
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32 endothelial vasoactive factors such as nitric oxide, calcitonin related peptide and adenosine  
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34 [7].

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43 With <sup>15</sup>O-water PET, it has been shown that CBF does not significantly differ between  
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45 cirrhotic patients and healthy subjects. However, in cirrhotic patients with overt HE CBF was  
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47 found to be significantly less (approximately 66% of normal values) [2,8] which was  
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49 demonstrated in patients with minimal HE [9]. More specifically, reduced regional CBF has  
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51 been reported in the parietal cortex, occipital cortex and thalamus in overt HE patients [8]. In  
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53 this context, it appears a reduction in CBF is solely associated with overt HE as CBF in  
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55 patients with minimal HE was similar to cirrhotic patients (without HE) and healthy controls  
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[9]. However, increased regional CBF has been demonstrated using MRI in the basal ganglia and thalamus in patients with minimal HE when compared to healthy controls which was interpreted as a redistribution of CBF from the cortex to the diencephalon [10]. Interestingly, in patients having received a transjugular intrahepatic portosystemic shunt (TIPS), a decrease in CBF was found in patients that developed overt HE [11]. Using functional MRI, it was demonstrated that cirrhotic patients with minimal HE had abnormal regional CBF in several brain regions when performing different cognitive tasks (as reviewed by Keiding [4]). Parallel with CBF, similar findings were found with CMRO<sub>2</sub> using <sup>15</sup>O-oxygen PET and a positive relationship between CMRO<sub>2</sub> and CBF was shown during and after recovery from HE within individual patients [2,12]. Patients with overt HE had decreased CMRO<sub>2</sub>, about 66% normal values, compared to cirrhotic patients without HE or healthy controls [8]. Regional differences were also demonstrated in CMRO<sub>2</sub> with reduction in the occipital and parietal cortex, and in areas of the thalamus, striatum, frontal cortex, temporal cortex and frontal parts of the cingulate cortex. Previously, it was suggested that a decrease in CMRO<sub>2</sub> was a result of a reduced oxygen supply. However, more recent studies have showed that the reduced CMRO<sub>2</sub> in patients with HE is not caused by limitation of the oxygen supply but rather reflects a decline in oxidative metabolism with a secondary reduction in CBF. Additionally, analysis of flow-metabolism coupling indicated that CBF declined in HE as a consequence of reduced brain energy metabolism implied by the calculation of increased mitochondrial oxygen tensions that patients with HE were unable to utilize [12]. Therefore, it is understood that there is no oxygen delivery limitation in HE [12]. A possible inverse relationship between CMRO<sub>2</sub> and cerebral ammonia uptake has been previously suggested. However, this was challenged when it was demonstrated that an increase in CMRO<sub>2</sub> occurred following recovery from HE with no significant change in the cerebral metabolic rate of ammonia (CMRA). Furthermore, neither CMRO<sub>2</sub> nor CBF were related to the arterial ammonia concentration or

1 CMRA within individual patients [2]. Nevertheless, these findings using PET with only  
2 limited number of patients, does not exclude ammonia as a causal agent of energy impairment  
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4 as it has been recently demonstrated that patients with HE have altered levels of glutamine  
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6 and alpha-ketoglutarate in the cerebrospinal fluid [14].  
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9 In this issue of the journal, Bjerring et al. [15] elegantly demonstrated using cranial  
10 windows in anesthetized rats that exposing the brain to ammonium chloride leads to an  
11 increase in flow velocities of cerebral arterioles (using speckle contrast imaging), arteriolar  
12 surface area with an increase in periarteriolar concentration of adenosine (using biosensors  
13 inserted in the cortex). Furthermore, ammonia exposure also impaired preservation of flow  
14 (cerebral autoregulation) during hemorrhagic hypotensive challenge. Applying ZM241385  
15 (adenosine receptor antagonist) leads to restoration of cerebral autoregulation flow partially  
16 restoring to baseline values. Adenosine is a nucleoside present in the cerebral extracellular  
17 space that is mainly formed by ATP degradation that can directly activate four membrane  
18 receptors subtypes: A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub> and A<sub>3</sub> and is implicated in cyclic AMP production [16].  
19 The activation of A<sub>1</sub> could be neuroprotective through a specific action on neurons by  
20 blocking the excitotoxic glutamate release and the intracellular increase in calcium levels.  
21 A<sub>2A</sub> is constitutively expressed in the central nervous system and acts by activating adenylate  
22 cyclase, enhancing glutamate release and GABAergic activity in striato-pallidal neurons  
23 [16,17]. A<sub>2A</sub> receptor could interact with dopamine receptor D<sub>2</sub> and as a result, currently  
24 blocking A<sub>2A</sub> receptor strategies are being evaluated for a treatment in Parkinson disease [18].  
25 A<sub>1</sub>, A<sub>2A</sub> can be activated only by micromolar concentration of adenosine which only arise  
26 during pathological conditions; it can increase up to a thousand fold following cerebral  
27 ischemia or hypoxia (20).  
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55 The results from the study of Bjerring et al., suggest that even if CMRO<sub>2</sub> is not  
56 directly linked to ammonia levels, elevated ammonia is able to increase flow velocities and  
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perhaps CBF via an increase in adenosine tone. These findings are in accordance with results showing that systemically administered adenosine had a direct cerebral vasodilatory effect and altered cerebral autoregulation in an induced hypotension pig anesthetized model which both resolved following adenosine removal [21]. Administration of  $A_{2A}$  adenosine receptor antagonist, ZM241385, has also been shown to be able to shift the lower limit of cerebral autoregulation to higher blood pressure and to suppress the vasodilation of pial arteries in response to hypotension [22]. Bjerring and colleagues elegantly demonstrated the importance of adenosine in CBF. However, the mechanisms through which ammonia triggers adenosine release remain unknown. It could be speculated that ammonia toxicity could impact on adenosine metabolism (generation and breakdown), possibly implicating ATP utilization. It is important to note, the animal models involved in the above studies are not models of liver failure or disease and therefore more extensive data arising from animal models of liver failure/disease are highly warranted.

The paper from Bjerring et al., describes another important issue proposing that  $A_{2A}$  receptor antagonist ZM241385 could be used to treat HE. Most treatment strategies for HE target a blood-derived factor, especially ammonia [23]. Centrally acting drugs that directly target the brain are sparse and except for flumazenil [24], none have been extensively used in patients. This could largely explain some limitations in the treatment strategies in HE. Recently, a  $GABA_A$  receptor modulating steroid antagonist (GAMSA), has been developed and act as antagonists to the positive  $GABA_A$  receptor, thereby modulating the effects of the neurosteroids. The reduction in the activity of the inhibitory GABAergic system may benefit arousal and cognition [25]. However, targeting the brain requires crossing the blood-brain barrier as well as avoiding any peripheral action (unwanted secondary effects) due to the use of major systemic drug concentration [26]. Interestingly, a very common  $A_{2A}$  receptor

1 antagonist, caffeine, has been used with interesting results in simulated hyperammonemia in  
2 cirrhotic patients [27,28].  
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4 Patients with cirrhosis can be exposed to hypotensive insults; upper gastrointestinal  
5 bleeding (GIB) as well as perioperative conditions during liver transplantation. GIB  
6 constitutes a major risk factor for HE and preventive treatment strategies are being proposed.  
7 Liver transplantation is the solid-organ transplantation that is associated with the highest  
8 frequency of neurological post-operative complications (approximately 1/3 of transplanted  
9 patients) due to different factors including perioperative hypotension [29,30]. Indeed, it could  
10 be assumed that hyperammonemia could have an additive or even a synergistic effect with  
11 hypotension in these patients.  
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23 Hyperammonemia leads to increased brain ammonia and subsequently neurotoxicity  
24 which is induced through a different cellular pathways and mechanisms, including adenosine  
25 release and activation as described by Bjerring and al., in this issue. Therefore, lowering  
26 ammonia remains the primary treatment strategy. Recent developments of ammonia lowering  
27 agents are primarily being tested and used for the acute treatment of overt HE [31,32].  
28 However, long-term studies are required to evaluate whether attenuating hyperammonemia  
29 could reduce the incidence of overt HE after GIB or the incidence of post-operative  
30 neurological complications after liver transplantation. Interestingly, ammonia has recently  
31 been identified as a prognostic factor in patients with end-stage liver disease [33,34].  
32 Furthermore, ammonia has been shown to be involved in the development of sarcopenia [35]  
33 as well as possibly playing a role in acute-on-chronic liver disease [36].  
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51 Therefore, realizing the toxic effects of ammonia are not specific to the brain [37] and  
52 that ammonia can act as a metabolic stressor [38], the implication of hyperammonemia in the  
53 onset of complications in cirrhosis is just beginning.  
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Figure

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