Metabolic Brain Disease (2025) 40:48
https://doi.org/10.1007/s11011-024-01435-3

REVIEW

Down the road towards hepatic encephalopathy. The elusive ammonia– what determines the arterial concentration?

Peter Ott[1] · Peter Lykke Eriksen[1] · Kristoffer Kjærgaard[1] · Michael Sørensen[1,3] · Karen Louise Thomsen[1] · Hendrik Vilstrup[1,2]

Received: 14 June 2024 / Accepted: 25 October 2024

Abstract
Elevated arterial ammonia is associated with several complications of liver disease as it predicts mortality for in-patients and decompensation, hospitalization and death in out-patients with cirrhosis. In this review, our aim was to estimate how the individual organs contribute to arterial ammonia based on published data from human studies. The brain removes ammonia from arterial blood in a concentration-dependent fashion. Ammonia that is released from the gut to portal blood is mainly from metabolism of glutamine in the enterocytes using this as a source of energy. Ammonia produced by bacterial metabolism of urea and proteins only partially reach portal blood and is likely recycled into bacterial proteins. In general, the liver efficiently removes ammonia from arterial or portal blood in proportion to the delivered concentration. As a result,– and in some contrast to conventional wisdom–, the hepato-splanchnic region only contributes marginally to arterial ammonia; even during a simulated upper GI bleed. The only exception is acute liver failure where hepatocyte necrosis allows large quantities of portal ammonia to pass. The kidneys release ammonia from glutamine metabolism into systemic blood. The renal ammonia release increases during a simulated upper GI bleed or hypokalemia where it becomes a major source of elevated arterial ammonia. In the resting state, muscles remove ammonia in a concentration-dependent manner and muscles are the primary ammonia lowering organ in most situations with elevated arterial ammonia. During strenuous exercise, muscles produce large amounts of ammonia into systemic blood. Thus, the complete pattern of ammonia metabolism is very dynamic and illustrates the difficulties in designing ammonia lowering therapies.

Keywords Ammonia metabolism · Ammonia concentration · Hepatic encephalopathy · Liver cirrhosis

Introduction– Ammonia and its relation to organ dysfunction in liver disease

Ammonia has been of interest for hepatologists since the description of elevated ammonia and hepatic encephalopathy (HE) in portacaval shunted dogs (Nencki 1895). However, a number of recent reports suggest that elevated ammonia may have more widespread consequences in chronic liver disease. Thus, in acute-on-chronic liver failure, ammonia levels predict 30-day mortality (Verma et al. 2021; Chiriac

Peter Ott and Peter Lykke Eriksen shared co-first authorship.

✉ Peter Ott
peterott@rm.dk

Peter Lykke Eriksen
ple@clin.au.dk

Kristoffer Kjærgaard
krikje@clin.au.dk

Michael Sørensen
michsoer@rm.dk

Karen Louise Thomsen
karethom@rm.dk

Hendrik Vilstrup
vilstrup@clin.au.dk

[1] Department of Hepatology and Gastroenterology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, Aarhus N DK-8200, Denmark

[2] Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

[3] Department of Internal Medicine, Viborg Regional Hospital, Viborg, Denmark

Published online: 02 December 2024

et al. 2021; Hu et al. 2020; Patwardhan et al. 2016); Elevated ammonia is related to in-hospital mortality in patients with alcoholic hepatitis (Ravi et al. 2017); and in patients with cirrhosis admitted to hospital for other reasons, elevated ammonia was related to the failure of multiple organs (liver, coagulation, kidneys, and lungs) (Shalimar et al. 2019). Even in stable out-patients with cirrhosis, elevated ammonia is associated with subsequent liver related complications, hospitalizations and mortality (Tranah et al. 2022; Balcar et al. 2023).

So, while the clinical utility of measuring plasma ammonia has been questioned (Deutsch-Link et al. 2022), arterial ammonia seems to be a key factor in the development of complications in cirrhosis of the liver. Accordingly, ammonia is now linked to a broad range of pathophysiological complications in liver disease including not only brain edema and the neuropsychiatric syndrome of HE, but also stellate cell activation with hepatic fibrosis, risk of liver cancer, compromised immune function, hypotension with hyperdynamic circulation, and possibly in extreme cases also renal and pulmonary injury (Dasarathy et al. 2017; Thomsen et al. 2023).

Since the culprit in these cases is the *arterial* ammonia concentration, it is fundamental to understand the dynamics of ammonia metabolism; the origin of arterial ammonia and its removal in different situations. In the following we will try to explore these questions by looking at the contribution of different organs to the arterial ammonia concentration.

Ammonia is truly elusive in the sense that it can be both synthetized and metabolized in most cells and thus recirculate intra- and intercellularly. The focus of this review is the sum of these processes expressed as the resulting (net-) *release of ammonia* from the organs into systemic blood or *removal* of ammonia from the systemic blood. The removal rate depends on the arterial concentration and may also be expressed as a *clearance* (removal rate/arterial concentration).

We aim to describe how the individual organs contribute in different situations. To provide this overview we recalculated values to release- and removal rates in µmol/min per person and if necessary, a standard body weight of 70 kg was used. In most studies, ammonia was measured in plasma, so we specify only if that was not the case and full blood was used. We also used literature values for flow rates: Portal vein 750–1000 ml/min fasting, superior mesenteric vein (SMV) 600 mL/min, Inferior mesenteric vein (IMV) 150 ml/min, and for perfusion of jejunum (300 mL/min), ileum (300 mL/min) and colon (150 mL/min) (Bjorck and Bergqvist 2006; Burkart et al. 1993; Naganawa et al. 1994). We only used studies in humans.

Whole-body ammonia metabolism

A novel methodology enabled us to quantify whole-body *release* of ammonia into and *clearance* from systemic blood in vivo (Eriksen et al. 2023). In that study, arterial ammonia in fasted, resting patients with cirrhosis was 4 times higher than in healthy individuals. This difference was caused by a ~ 3-fold increase in ammonia *release* into arterial blood and a 25% lower *clearance* of arterial ammonia in patients with cirrhosis (Fig. 1). These findings will constitute the basis of this paper, in which we present and discuss the primary organs responsible for these metabolic alterations and how they may be affected in health and disease.

The inter-organ trafficking of ammonia is mainly a result of three important metabolic processes. First, the immediate detoxification of ammonia mediated by the glutamine synthetase reaction:

$$\text{Glutamate} + NH_4^+ + \text{ATP} \rightarrow \text{Glutamine} + \text{ADP} + P_i + H^+ \quad (1)$$

Second, the glutaminase reaction that releases ammonia and is the reverse of Eq. 1:

$$\text{Glutamine} + \text{ADP} + P_i + H^+ \rightarrow \text{Glutamate} + NH_4^+ + \text{ATP} \quad (2)$$

These two reactions can simultaneously take place in most cell types, but with different weight. An important exception is the brain, where the glutamine synthetase reaction is absent in the neurons which therefore rely on astrocytic glutamine synthetase to remove ammonia.

As a third possibility, ammonia is produced in contracting muscles through the metabolism of adenosine monophosphate (AMP) to inosine phosphate (IMP), as explained below under *Muscle*.

Generally speaking, ammonia can be regarded as a waste product of protein metabolism after the carbon skeletons have been used for energy production. It is detoxified through the glutamine synthetase reaction. However, while that reaction helps the transient control of arterial ammonia, it does not provide a route of excretion. The only quantitatively important pathway for elimination of ammonia derived nitrogen is when glutamine (from Eq. 2) or other amino acids after transamination from glutamine enter the urea cycle and the subsequent urinary excretion of urea. The synthesis of urea (25 g/day ~ 460 µmol/min) exceeds the release of ammonia into arterial blood (Fig. 1). Thus, the total level of plasma nitrogen (including ammonia) is controlled by the urea synthesis, whilst the short-term regulation of ammonia is governed by Eqs. 1–2 and the dynamics explained below.

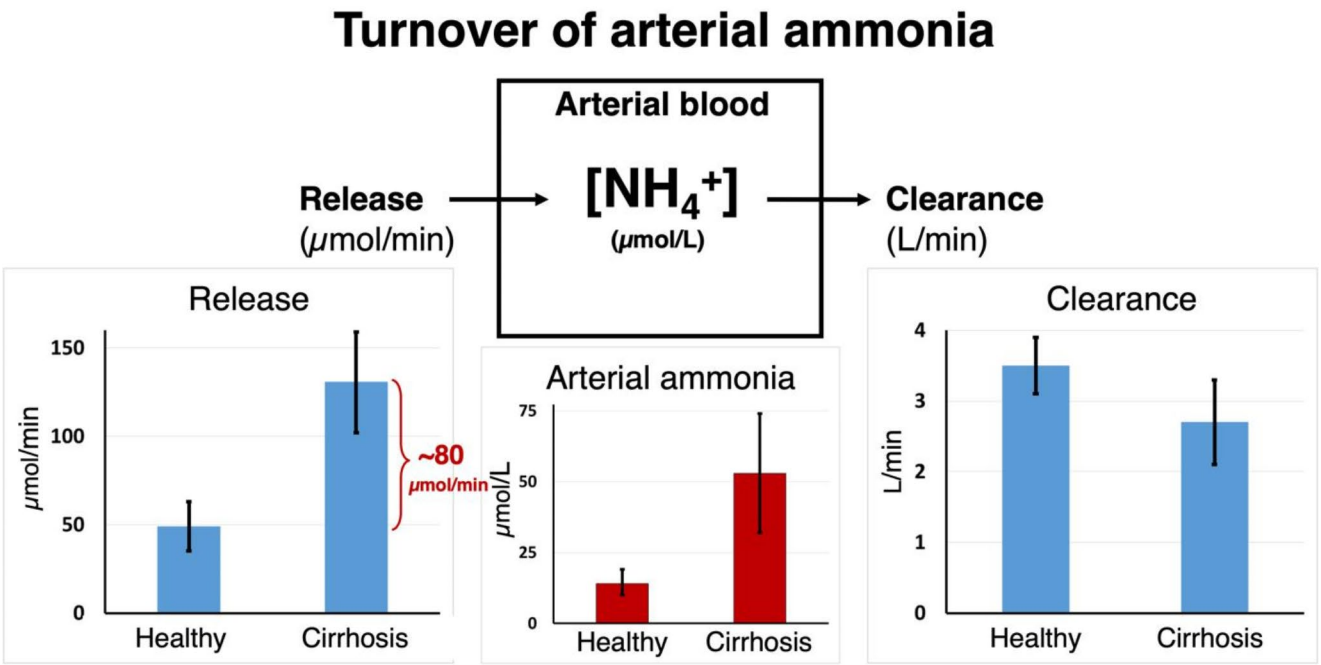

Fig. 1 A simple model of the turnover of arterial ammonia. In this context the release of ammonia is the sum of ammonia released from different organs into the arterial blood, and clearance is the net clearance of arterial ammonia by all organs

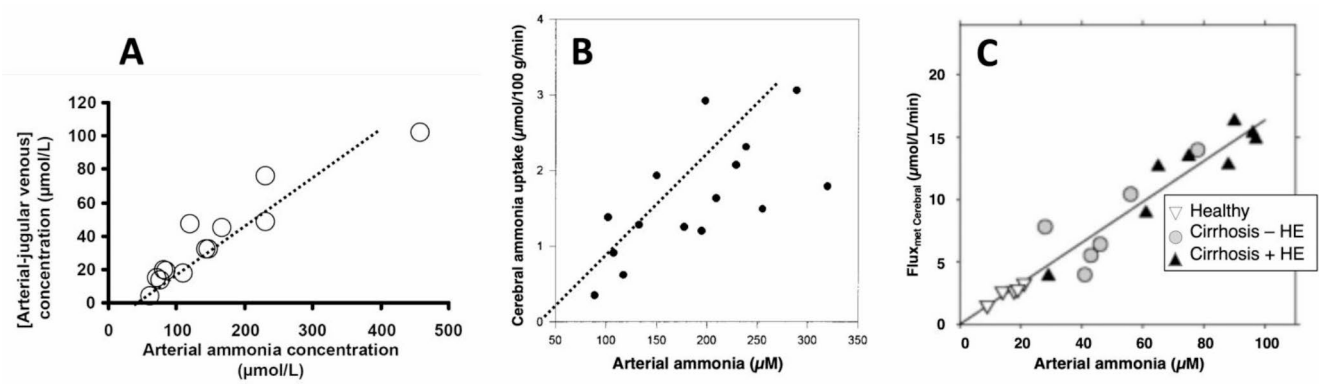

Fig. 2 The net cerebral uptake of ammonia increases linearly with arterial concentration in acute liver failure (Panel **A** and **B**), as well as in healthy persons and patients with or without hepatic encephalopathy (Panel **C**). As seen in Panel **C**, the correlation is identical in healthy persons and patients with cirrhosis with or without HE. References: Panel **A** (Clemmesen et al. 1999), **B** (Strauss et al. 2001), **C** (Keiding et al. 2006)

Brain

The brain is a net remover of ammonia. Reports from the 1990's suggested that the blood-brain-barrier permeability for ammonia was increased in cirrhosis but more recent PET studies showed no permeability difference between healthy controls and patients with cirrhosis with or without HE or patients with ALF (Keiding et al. 2006; Strauss et al. 2001; Clemmesen et al. 1999; Ott and Larsen 2004). In accordance, the cerebral uptake is proportional to the arterial ammonia concentration (Clemmesen et al. 1999; Keiding et al. 2006). As presented in Fig. 2, the net cerebral uptake increases linearly with arterial ammonia concentration. This linear relation is similar in healthy individuals, patients with cirrhosis, and patients with ALF (Fig. 2, Panel C).

The transport of ammonia across the BBB may both be mediated by diffusion of the gaseous form NH_3 and by carrier-mediated transport of NH_4^+ which constitutes 98% at physiological pH. Carrier-mediated transport is likely the most efficient, since change in pH does not affect ammonia permeability as would be expected if the diffusion was more prominent (Strauss et al. 2001; Sørensen 2013; Ott and

Larsen 2004). The most important transport proteins remain to be determined. Candidates include specific transport proteins for NH_4^+, such as members of the Rhesus glycoprotein C transporter family and non-specific transport via transporters of potassium, that has a similar size and charge as NH_4^+ (Ott and Larsen 2004).

Hyperammonemia is involved in both cerebral edema with risk of herniation and HE but the pathophysiological role of ammonia may be different in these two complications. In patients with acute liver failure, cerebral edema is clearly related to arterial ammonia: Levels > 100 µmol/L predicted cerebral edema (Bernal et al. 2007), and > 150 µmol/L predicted cerebral herniation (Clemmesen et al. 1999) as well as 28 day mortality (Drolz et al. 2013). The mechanism by which hyperammonemia causes HE is still under debate and beyond the scope of this paper.

The relationship between HE and arterial ammonia is related to the severity of the liver disease. In acute liver failure, the correlation between arterial ammonia and the clinical HE grade (Westhaven Criteria) is unambiguous (Kundra et al. 2005). In acute-on-chronic liver failure the association is somewhat weaker (Patwardhan et al. 2016; Chiriac et al. 2021; Verma et al. 2021). In hospitalized patients with cirrhosis the correlation is still present but with considerable overlap of ammonia levels between HE grades (Nicolao et al. 2003; Ong et al. 2003). In out-patients with compensated cirrhosis, it required 1868 patients to demonstrate a weak association between ammonia levels and minimal HE and a large proportion of patients with hyperammonemia did not exhibit cognitive impairment (Kimer et al. 2021; Thomsen et al. 2016; Lauridsen et al. 2011; Lauridsen, Schaffalitzky de Muckadell, and Vilstrup 2015; Gairing et al. 2023; Tsai et al. 2019; Nakai et al. 2022). Nevertheless, direct evidence for the role of ammonia in HE is supported by the effect of the ammonia-lowering glycerol phenylbutyrate, which caused simultaneous amelioration of blood ammonia concentration and HE (Rockey et al. 2014), while this has not been consistently shown for other HE treatments (Gluud et al. 2015; Goh et al. 2018; Morgan and Hawley 1987; Sharma et al. 2013). The likely explanation for these findings is that the pathophysiology of HE includes several components such as hyperammonemia, systemic inflammation, and oxidative stress (Häussinger et al. 2022).

As the brain is a net remover of ammonia from the systemic circulation, we produced quantitative estimates based on studies reporting arterio-jugular venous ammonia concentration differences (Clemmesen et al. 1999; Strauss et al. 2001; Keiding et al. 2006; Dam et al. 2013). Using a cerebral perfusion of 750 mL/ min and brain weight of 1200 g (Cosgrove et al. 2007), total removal of ammonia by the brain was calculated to be 0–15 µmol/min at arterial concentrations 0–50 µmol/ L, 11–30 µmol/min at arterial concentration of 100 µmol/L and 30–60 at arterial concentration of 200 µmol/L.

Gut

In this section we will examine the release of ammonia from the gut to portal blood. To contribute to the systemic ammonia concentration, portal ammonia should first pass through the liver or bypass it through portosystemic shunts. The resulting contribution of the splanchnic region (gut + liver) to systemic ammonia will be discussed in the next two sections: *Liver* and *Hepato-splanchnic region*. The data will question the current dogma that elevated arterial ammonia in patients with cirrhosis is gut-derived and primarily a result of bacterial metabolism in the colon.

To measure gut release of ammonia from the gut to the portal vein, portal blood sampling is required and only few human studies are available (van de Poll et al. 2008; van der Hulst et al. 1997; Olde Damink et al. 2003; Olde Damink et al. 2002; Plauth et al. 2000).

From these studies we calculated the following values for gut ammonia release to portal blood in the fasting state; in non-cirrhotic patients: 34 µmol/min (van der Hulst et al. 1997) and 37 µmol/min (van de Poll et al. 2008) and in stable cirrhotic patients with a transjugular intrahepatic portosystemic shunt (TIPS): 38.5 µmol/min (Olde Damink et al. 2002), 42 µmol/min (Olde Damink et al. 2003) and 37.5 µmol/min (Plauth et al. 2000). Thus, in fasting conditions the release of ammonia from intestines to portal blood is around 30–40 µmol/min, and comparable between healthy persons and patients with cirrhosis.

Changing circumstances may influence this value. Thus, in patients with cirrhosis, a simulated upper gastrointestinal (GI) bleed increased the release of ammonia from gut to portal blood from 42 ± 14 to 80 ± 28 µmol/min (Olde Damink et al. 2003). Feeding seems to have a similar effect; enteral administration of 40 g of amino acids including 6 g of glutamine, doubled the ammonia concentration difference between the superior mesenteric artery and -vein (Plauth et al. 2000).

Two hypotheses that do not exclude each other have been proposed as the source of gut-derived ammonia into portal blood: the intestinal epithelial glutaminase activity and luminal bacterial metabolism.

Deamidation of glutamine by glutaminase (Eq. 2) is an important source of energy for the enterocytes. In all studies quoted above (Olde Damink et al. 2003; Olde Damink et al. 2002; Plauth et al. 2000; van de Poll et al. 2008; van der Hulst et al. 1997) and a study including liver vein catheterization in healthy, stable cirrhosis, acute-on-chronic liver failure and acute liver failure groups (Clemmesen et

al. 2000), a correlation between intestinal glutamine uptake and ammonia release was observed as would be expected if the source of ammonia was metabolism of glutamine. In all these studies, intestinal glutamine consumption was sufficient to explain ammonia release. The use of glutamine as an energy source is supposed to be most important in the small intestines. In accordance, 85% of intestinal glutaminase activity is located in the small intestines and only 15% in the colon (James et al. 1998). In further support, the superior mesenteric vein that primarily drains small intestines, contributed with a significant fraction of intestinal glutamine consumption and ammonia release into portal blood in both persons without liver disease (van de Poll et al. 2008; van der Hulst et al. 1997) and in patients with cirrhosis (Olde Damink et al. 2002; Plauth et al. 2000).

These findings support that the intestinal release of ammonia is predominantly derived from the metabolism of glutamine in the enterocytes. The effects of meals (Plauth et al. 2000) and simulated upper GI bleed (Olde Damink et al. 2002) on portal ammonia are not in conflict with this view, since the increased ammonia release was followed stoichiometrically by an increase of glutamine removal.

Luminal bacterial metabolism includes urease activity and proteolysis. The bacterial hydrolysis of urea and deamination of intestinal protein produce ammonia. At the same time, ammonia is a powerful growth factor for the intestinal microbiota and used for synthesis of new proteins and bacterial replication. Accordingly, a certain degree of re-cycling takes place and it is in fact unclear to what extend intestinal luminal derived ammonia ever reaches the portal circulation (Magasanik 1993; Levitt and Levitt 2018).

Intestinal bacterial urease activity was earlier regarded as an important source of portal ammonia. Around 15% of the daily produced urea cannot be recovered in the urine and was assumed to be hydrolysed primarily by the colonic microbiota, (Levitt and Levitt 2018; Jackson et al. 1984; Hansen and Vilstrup 1985; Walser and Bodenlos 1959) even though bacterial overgrowth is common in cirrhosis (Maslennikov et al. 2018). This would correspond to ~80 µmol ammonia/min. In certain extreme situations like after administration of large amounts of urea into the rectum (Evans et al. 1966) or after ureterosigmoidostomy where total urea production reaches colon (Kaufman 1984), elevation of systemic ammonia have been reported.

However, it is unclear whether intestinal hydrolysis of urea is of quantitative important in patients with cirrhosis. The studies did not account for urea-derived nitrogen that could be recovered as bacterial proteins in the faeces. The colon is almost impermeable to urea (Wolpert et al. 1971) and the amount of urea that enters the colon from ileum is only around 3.5 mmol/day corresponding to a colonic release of ammonia of only 5 µmol/min, of which a fraction will be used for bacterial replication. The finding that 15% of injected urea could not be recovered in urine was unchanged in patients without a colon (Gibson et al. 1976). Finally, the urease hypothesis would predict that most ammonia originates from the colon while– as explained above– a substantial fraction of gut derived ammonia in portal blood in fact originates from the small intestines. In healthy persons, the ammonia concentration difference between systemic artery and colonic vein was 30.1 ± 9.2 µmol/L and assuming a colonic perfusion of 150 mL/min (Naganawa et al. 1994), the release of ammonia from the colon to portal blood would be 4–5 µmol/min which is much smaller than predicted by the hypothesis. Taken together the urease activity may not be as important for portal vein ammonia in patients with cirrhosis as previously thought.

Bacterial proteolysis is present in the intestines, again mostly in the colon. The nitrogen content in terminal ileum is higher than in faeces, and the colonic nitrogen loss was estimated to be 0.6 g/day, corresponding to 30 µmol nitrogen/min of which some may be released as ammonia to portal blood.

Taken together, our interpretation of present data is that most ammonia that is released from the gut to the portal blood originates from the small intestines, and that consumption of glutamine (Eq. 2) by enterocytes is the most prominent source of portal ammonia. In resting persons, with or without cirrhosis, the release from gut to portal blood is ~30–40 µmol/min. During simulated or actual upper GI bleed, this value may approximately double (Olde Damink et al. 2003).

The liver

The normal liver has a large potential for removal of ammonia which is affected by functional and circulatory changes associated with cirrhosis.

Ammonia is delivered to the liver via the hepatic artery (25% of the hepatic blood flow in healthy persons) at the systemic concentration and via the portal vein (75%) at a somewhat higher concentration. In the liver sinusoid, ammonia is taken up from blood in the perivenous zone through active transport of the NH_4^+-ion, mediated by the Rhesus glycoprotein B (Weiner et al. 2003) (Fig. 3). This part of the sinusoid contains high glutamine synthetase activity and detoxifies ammonia by the formation of glutamine (Eq. 1), which is then released to systemic blood via the hepatic veins. After systemic circulation, glutamine re-enters the liver via the hepatic artery and the portal vein, and is taken up in the periportal zone of the sinusoid to enter the urea cycle where the ammonia-nitrogen is finally eliminated through formation of urea and subsequent urinary

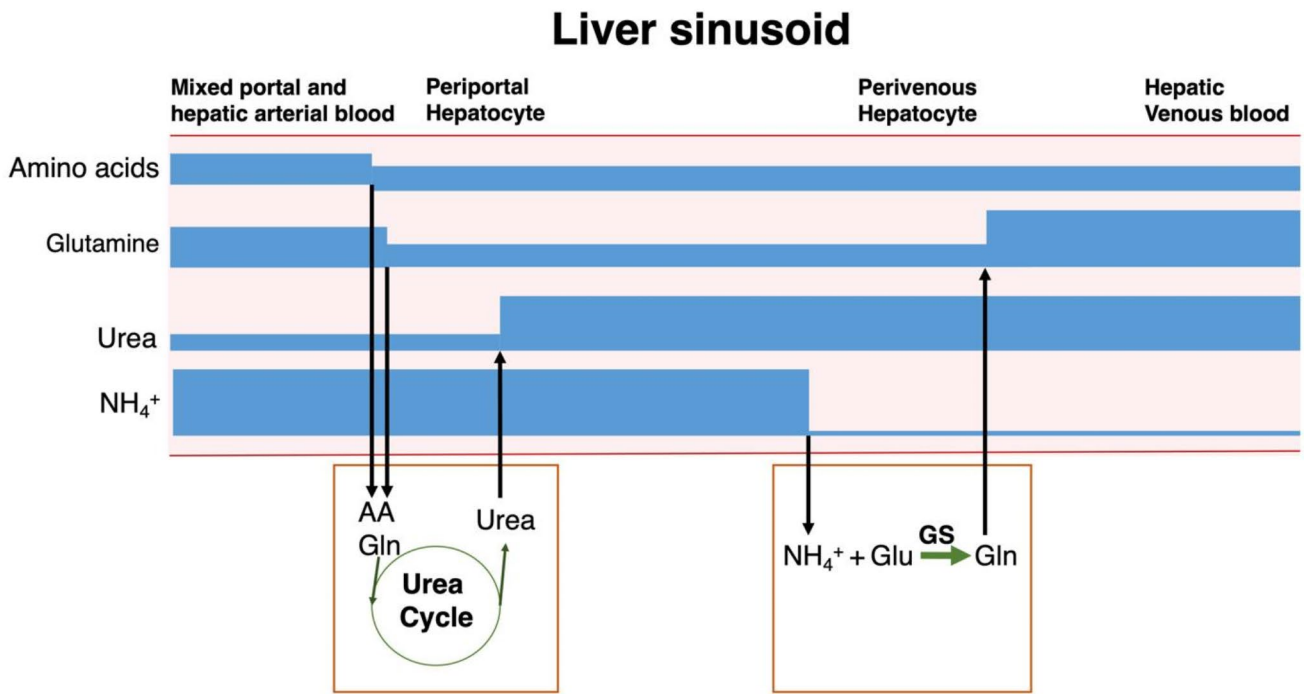

Fig. 3 Handling of ammonia and relevant metabolites in the liver sinusoid. The blue bars indicate the concentration of amino acids, glutamine, urea and ammonia (NH_4^+) in sinusoidal blood, which are utilized differently in the anatomical zones of the liver sinusoid. Ammonia and glutamine will enter the systemic circulation via the hepatic vein. AA: amino acids; Gln: glutamine; Glu: glutamate; GS: glutamine synthetase; NH_4^+: ammonia

excretion. Consequently, there is a continuous peri-portal removal of glutamine and peri-venous removal of ammonia. As explained in the accompanying paper (Vilstrup 2025), the rate of hepatic urea release is much higher than the rate of ammonia removal by the liver.

The hepatic removal of ammonia is highly efficient. The liver removes ammonia from portal blood so efficiently that the hepatic vein ammonia concentration is lower than arterial concentration in healthy persons, patients with compensated cirrhosis, patients with acute-on-chronic liver failure and in patients with a simulated or an actual upper GI bleed (Clemmesen et al. 2000; Olde Damink et al. 2002, 2003, 2009; van de Poll et al. 2008; van der Hulst et al. 1997). The only situation in which the liver becomes a net producer of ammonia and the concentration in the hepatic vein is higher than in systemic artery is in acute liver failure as reported in a single study of 22 patients with ALF in which the etiology was paracetamol in 13, hepatitis A-D in 4 and unknown in 5. (Clemmesen et al. 2000).

The effects of hepatic metabolism on arterial ammonia depend on the clinical situation. In acute liver failure with mean arterial ammonia of 182 µmol/L, the average release of ammonia to the blood stream was 100 µmol/min (Clemmesen et al. 2000). In most other situations, the liver is a net remover of ammonia, removing 0–10 µmol/min in healthy persons and patients with compensated cirrhosis (arterial ammonia: 46–61 µmol/L) and 39 µmol/min in patients with acute-on-chronic liver failure (arterial ammonia: 120 µmol/L) (Clemmesen et al. 2000). In patients with stable cirrhosis and a TIPS, the hepatic removal was 25 µmol/min (70% shunting) (Olde Damink et al. 2003) increasing to 40 µmol/min during simulated upper GI bleed (Olde Damink et al. 2003).

Thus, except for acute liver failure, portal vein ammonia only reaches the systemic circulation via portosystemic shunting. This is partly compensated by hepatic arterialisation and increased arterial delivery of ammonia to the liver for efficient removal. The combined effect will be discussed in the next section.

The hepato-splanchnic region

In this section we will summarize the combined effect of the hepato-splanchnic region on the arterial ammonia concentration by use of three different scenarios based on specific publications: Healthy persons (van de Poll et al. 2008), patients with stable cirrhosis and a TIPS and a simulated upper GI bleed (Olde Damink et al. 2003), and similar patients with stable cirrhosis (Olde Damink et al. 2002) (Fig. 4).

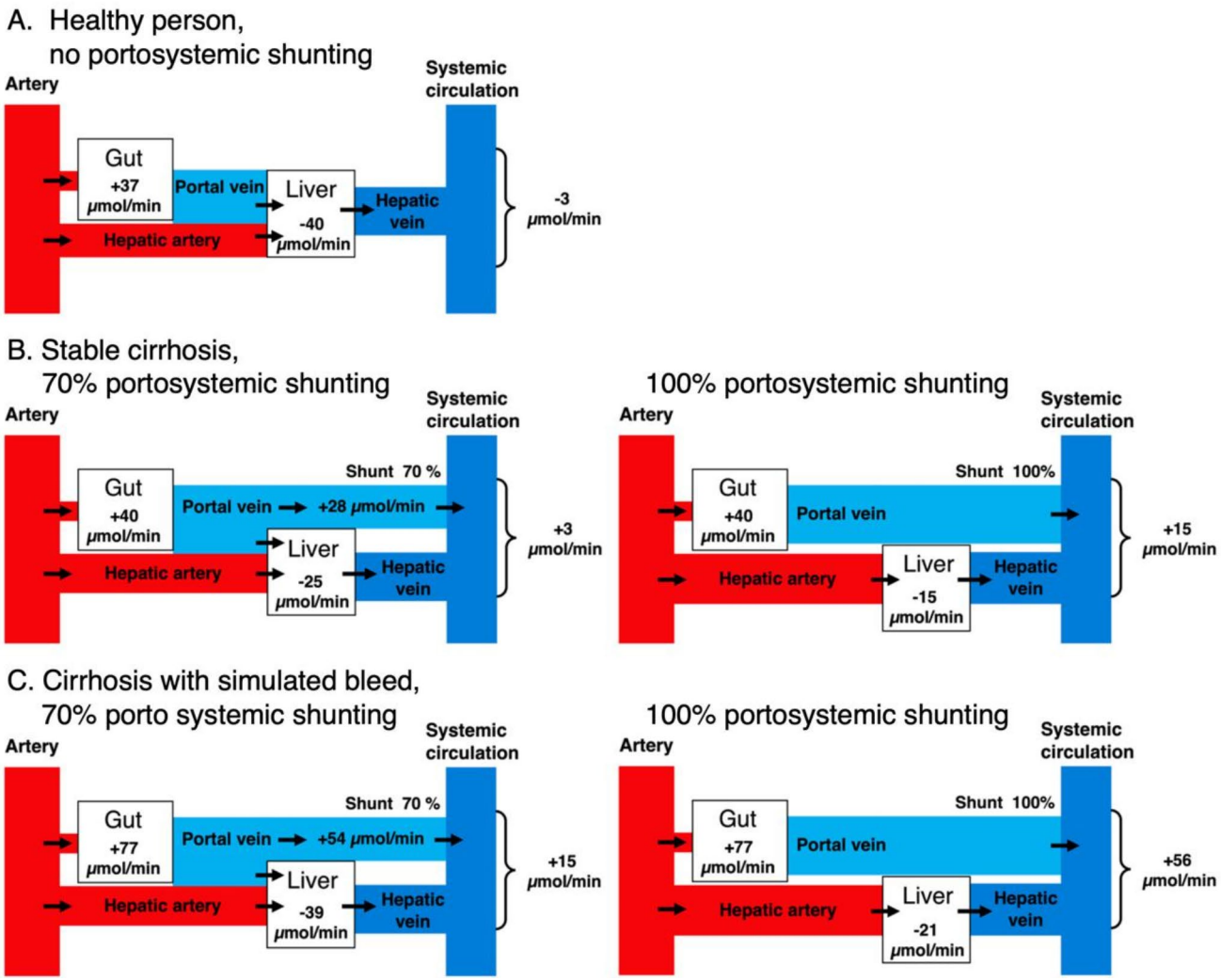

Fig. 4 The combined effect of the hepato-splanchnic region on systemic arterial ammonia concentration (µmol/L) illustrated by different scenarios. (**A**) The healthy situation (van de Poll et al. 2008). (**B**) Stable cirrhosis and a TIPS (Olde Damink et al. 2002) with the effect of either 70% and 100% of portal blood bypassing the liver through portosystemic shunts. (**C**) Stable cirrhosis and a TIPS during a simulated upper GI bleed (Olde Damink et al. 2003) at 70% and 100% portosystemic shunting, respectively

In the healthy persons (Fig. 4A), all blood from the portal vein passes through the liver, and ammonia that is released from the gut into portal blood is removed by the liver. Thus, the total exchange of ammonia from the hepato-splanchnic region into systemic blood is neutral or there is a net removal of systemic ammonia. The removal of ammonia by the liver is a clearance, so hepatic removal will increase with increasing influx concentrations. Consequently, gut production of ammonia has little or no effect on systemic concentration.

In patients with stable cirrhosis and a TIPS (Olde Damink et al. 2002) (Fig. 4B), the release of ammonia from the gut was the same as in healthy persons but calculations depended on the fraction of portal blood that bypassed the liver (van de Poll et al. 2008). Since this fraction was unknown, the authors provided calculations with both 70% and 100% of portal venous blood bypassing the liver through portosystemic shunts, including the TIPS. With 70% shunting, the contribution from the hepato-splancnic region was still neutral, and even with 100% shunting, the net release of ammonia into the systemic circulation was only 15 µmol/min, as compared to the release from gut to portal vein of 40 µmol/min (Olde Damink et al. 2002). When patients with stable cirrhosis and a TIPS were administered an oral 46 g mixture of amino acids similar to haemoglobin ("a simulated upper GI bleed", Fig. 4.C), the release of ammonia from gut to portal blood increased to 77 µmol/min. Still, hepatic removal reduced the hepato-splanchnic release of ammonia into the systemic circulation to 15 µmol/min with 70% shunt fraction, and 54 µmol/min with 100% shunting (Olde Damink et al. 2003). In the latter two studies, all patients with cirrhosis had a TIPS, which enabled sampling from the portal vein during TIPS phlebography.

In these patients, the fraction of portal blood bypassing the liver by flowing through the TIPS is within the 70–100% range. Mathematic modelling from literature data suggests that with shunt fractions below 50%, the hepato-splanchnic contribution to arterial ammonia would be close to zero in most cases (Levitt and Levitt 2018). Thus, in patients with cirrhosis without portosystemic collaterals, the hepato-splannic area will be a net remover of ammonia or neutral. In accordance, hyperammonemia was related to the magnitude of portosystemic collaterals (Tarantino et al. 2009) and the hepatic venous pressure gradient (Balcar et al. 2023). In 40 patients with cirrhosis without a TIPS, the mean shunt fraction was 62%, ranging from 0 to 100%. However, this fraction was higher in splenic than mesenteric portal blood (Groszmann et al. 1972). So, in patients with cirrhosis without a TIPS, a large percentage will have shunt fractions in a range where arterial ammonia concentration is not affected by the gut metabolism. Reports that a protein rich meal only marginally increases arterial ammonia in patients with cirrhosis further support that most portal ammonia is removed by the liver even in patients with cirrhosis (Bajaj et al. 2020).

These findings challenge conventional wisdom that the main source of hyperammonemia in cirrhosis is caused by increased release from the hepato-splanchnic region. In Sects. 7 and 8 we will consider other potential sources.

Kidney

The kidneys play a complex role in ammonia metabolism and generally release ammonia into the systemic circulation (Fig. 5).

In the epithelial lining cells of the proximal tubule, glutamine is degraded in a two-step fashion, first by the glutaminase reaction (Eq. 2) and subsequently by the glutamate dehydrogenase reaction (glutamate → α-ketoglutarate + NH_4^+) (van de Poll et al. 2004). At normal plasma pH, NH_4^+ produced in the proximal tubule is released with 1/3 to urine and 2/3 to blood. During acidosis, the ratio reverses to 2/3 to urine and 1/3 to blood (Olde Damink et al. 2009).

Specific ammonia transporters belonging to the Rhesus glycoprotein C proteins transport the NH_4^+ ion from blood to urine in the collecting duct (Harris et al. 2023). The transport of ammonia from blood to urine only partly counteracts the ammonia release to blood in the proximal tubule, so the kidneys are net releasers of ammonia from a systemic point of view. In studies including blood sampling from a renal vein, renal release of ammonia into the systemic circulation was 9 µmol/min in resting and fasting healthy persons (van de Poll et al. 2008). Similar values were obtained in fasting patients with compensated cirrhosis (Owen et al. 1960; Olde Damink et al. 2002).

Several factors may change this picture, including GI bleed and disturbances in pH or potassium levels.

During a simulated upper GI bleed, renal ammonia release increased from 7 ± 3 to 49 ± 10 µmol/min, which could be explained by increased renal removal of glutamine and metabolism (Eq. 2) (Olde Damink et al. 2003). A similar elevation of renal ammonia release was observed during an actual upper GI bleed (Olde Damink et al. 2003). In this situation, the kidneys were an important source of elevated ammonia, since the hepato-splanchnic region as a whole contributed with only ~ 15 µmol/min (70% shunting, Fig. 4).

Renal ammonia metabolism is also affected by hypokalemia which is common in cirrhosis (Mikkelsen et al. 2023; Maiwall et al. 2016). After a reduction of plasma potassium from 4.4 to 2.0 mmol/L in 9 patients with cirrhosis, arterial ammonia increased from 24 to 77 µmol/L (Gabduzda and Hall 1966). In two patients examined by use of renal vein catheterization, renal ammonia release increased by 35 µmol/min after a decrease in potassium from 4.5 to 3.7 mmol/L in one patient and by 120 µmol/min after a reduction in potassium from 5.0 to 2.5 mmol/L in another patient. In both cases, hyperammonemia was reversible by potassium supplementation (Baertl et al. 1963).

Muscle and adipose tissue

Muscle may both remove ammonia from the systemic circulation and release it.

At rest, muscle removes ammonia from arterial blood. Through the glutamine synthetase reaction (Eq. 1), ammonia is scavenged into glutamine and released to the blood. In PET tracer experiments, a single lower extremity removed 8.3 ± 2.6 µmol ammonia per/min, corresponding to ~ 46 µmol/min/person (leg muscle mass 18% of total muscle) in resting patients with cirrhosis, higher than the ~ 16 µmol/min/person in healthy persons (Dam et al. 2011). The removal of ammonia by muscles increases with elevated ammonia. During a simulated upper GI bleed, arterial ammonia concentration increased from 75 ± 6 µmol/L to 122 ± 6 µmol/L with a parallel increase in muscle ammonia removal from 15 to 42 µmol/min (Olde Damink et al. 2003). In acute liver failure, with an arterial ammonia of 182 ± 80 µmol/L, muscle removal amounted to ~ 110 µmol/min (Clemmesen et al. 2000). Thus, preserved muscle mass and quality is an important protective factor towards hyperammonemia in patients with cirrhosis. Still, ammonia is only temporarily trapped in glutamine that is released into the systemic circulation and may be re-metabolized to glutamate and ammonia in the gut and kidneys or provide

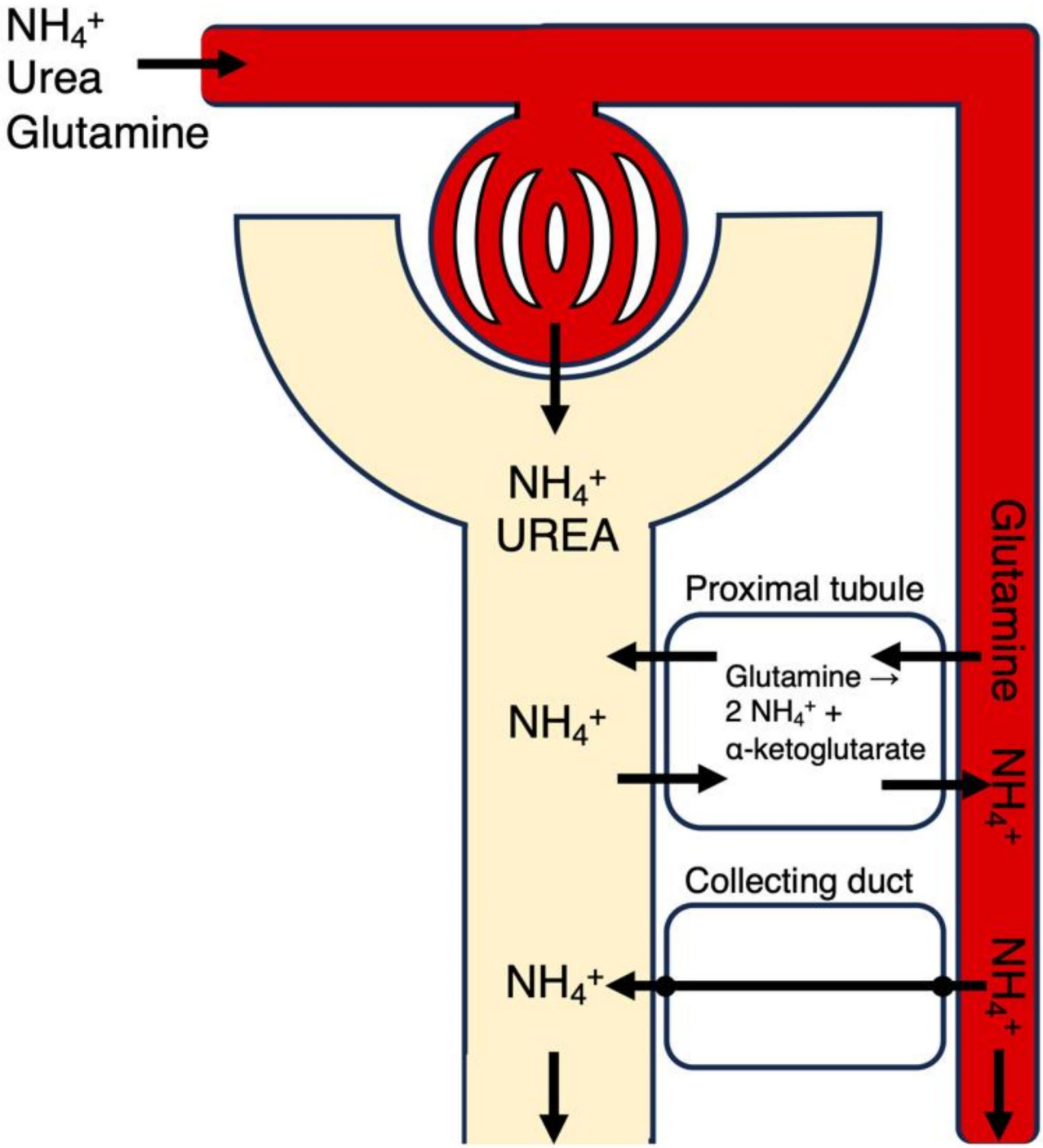

Fig. 5 Renal ammonia handling with the primary processes illustrated. In the proximal tubule, glutamine is degraded to ammonia (NH_4^+), which is excreted and reabsorbed depending on the homeostatic situation and to α-ketoglutarate. In the collecting duct, ammonia is secreted

nitrogen for urea synthesis and final elimination of ammonia associated nitrogen.

In contrast to its resting state, the working muscle releases ammonia into the systemic circulation due to degradation of AMP to IMP by AMP deaminase (Katz et al. 1986). Accordingly, short lasting exhaustive exercise may elevate ammonia to above 150 µmol/L, even in healthy persons (Eriksson et al. 1985; Esbjörnsson et al. 2006; Katz et al. 1986). In addition, muscle may also metabolize branched-chain amino acids to ammonia as an energy source during

prolonged endurance exercise. In one study, the muscle release of ammonia was 45.7 ± 15.3 µmol/min in healthy persons exercising at 75% VO2max intensity on bicycle ergometers in contrast to a minimal ammonia uptake at rest (Eriksson et al. 1985). In patients with cirrhosis, exercise resulted in higher arterial ammonia concentrations than in healthy controls on similar workloads (Dietrich et al. 1990; Volianitis et al. 2024), which was likely due to larger muscle release of ammonia at a given workload in patients with cirrhosis while hepatic clearance of ammonia was less affected (Volianitis et al. 2024).

Adipose tissue may also remove ammonia from blood through the glutamine synthetase reaction (Eq. 1). In a study of strenuous exercise in healthy persons, arterial ammonia reached ~220 µmol/L in men and ~120 µmol/L in women and the total body removal of ammonia by adipose tissue was estimated to ~50 µmol/min in both sexes (Esbjörnsson et al. 2006) with an equimolar release of glutamine (Esbjörnsson et al. 2006). In this way adipose tissue dampened the ammoniagenic effects of exercise. There was no exchange of ammonia between blood and adipose tissue at rest in healthy persons (Esbjörnsson et al. 2006). Patients with cirrhosis have not been studied.

A dynamic situation

To understand the origin of elevated ammonia in a given situation, one has to recognize the very dynamic nature of organ interaction in different situations. This is illustrated in Fig. 6 with 6 scenarios based on the reviewed data. The values should be taken as illustrative, not absolute.

The only situation in which the liver is not a net-remover of ammonia is during acute liver failure. In cirrhosis, elevated arterial ammonia is generally caused by increased renal release, especially during GI bleed or hypokalemia, whereas increased release of ammonia by portosystemic shunting likely plays a quantitatively less important role. In such situations, increased removal of ammonia by muscles is important, a kind of buffering effect that is likely weakened by sarcopenia. In contrast, during exercise muscles release ammonia which cannot be completely attenuated by increased hepatic uptake and the result may be high levels of ammonia.

Some questions arise from this review that could be the focus for future investigations. Our conclusions on the hepato-splancnic handling of ammonia rest to some extend on indirect evidence, so studies with sampling of arterial, portal and hepatic venous blood and simultaneous determination of the porto-systemic shunted fraction of portal blood would be of great interest. The role of intestinal urease is still intriguing. Better understanding of the role of

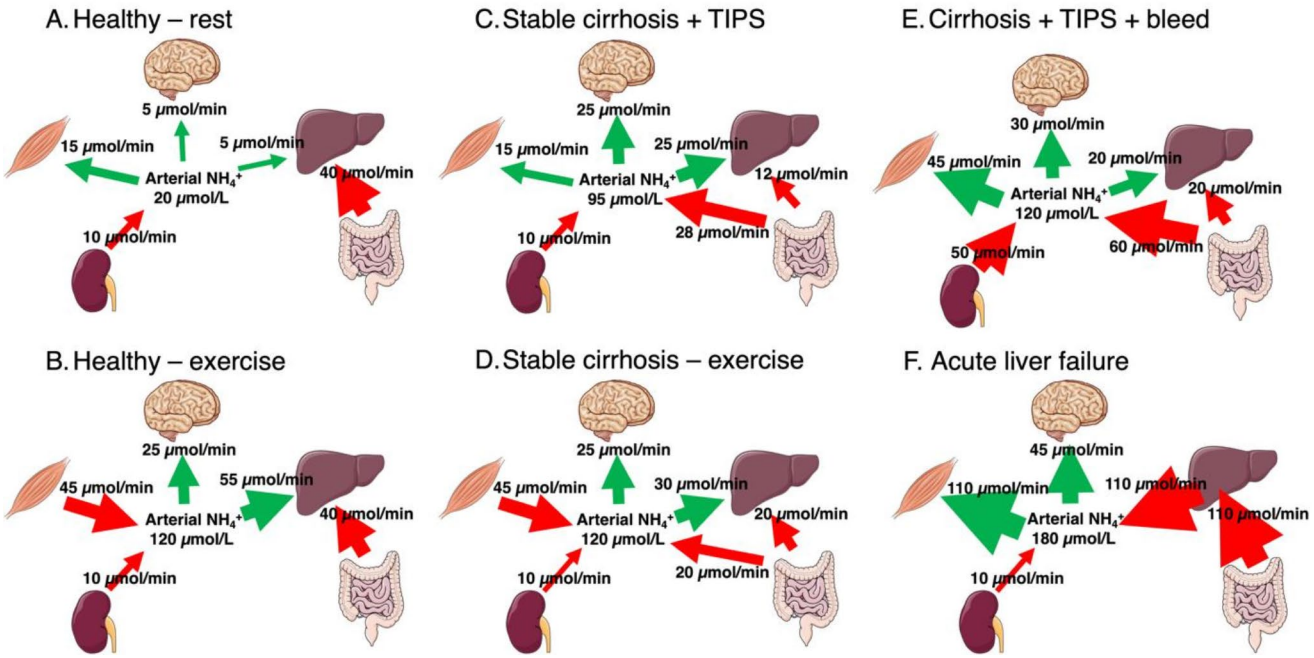

Fig. 6 Ammonia exchange rates (µmol/min) and arterial ammonia concentration (µmol/min) in different situations: Panel **A**, healthy persons at rest; **B**, healthy persons during exercise; **C**, patients with stable cirrhosis with a transjugular intrahepatic portosystemic shunt (TIPS); **D**, patients with stable cirrhosis during exercise; **E**, patients with cirrhosis with a TIPS and an upper GI bleed and **F**, in patients with acute liver failure. In E and F, a 70% shunt fraction was used. The red arrows indicate release of ammonia from the organ to the blood stream; the green arrows indicates removal of blood ammonia by the organ. Values are illustrative, not absolute

exercise on ammonia levels in patients with cirrhosis would be important, since exercise it self seems beneficial. The role of adipose tissue in removal of ammonia in patients with cirrhosis needs further study. These and similar fields of research will hopefully pave the way for prevention of the deleterious effects of elevated ammonia in patients with cirrhosis.

Author contributions Calculations and figure preparation were performed by Peter Ott and Peter Lykke Eriksen. The first draft of the manuscript was prepared by Peter Ott. Peter Ott, Peter Lykke Eriksen, Kristoffer Kjaergaard, Michael Sørensen, Karen Louise Thomsen and Hendrik Vilstrup all contributed to the editing and revision of the manuscript and approved the final version.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

References

Baertl JM, Sancetta SM, Gabuzda GJ (1963) Relation of acute potassium depletion to renal ammonium metabolism in patients with cirrhosis. J Clin Invest 42:696–706

Bajaj JS, Bloom PP, Chung RT, Hassanein TI, Padilla-Martinez M, Kayali Z, Rockey DC, Sasso R, Muthukumar AR, Lee WM, Denney WS, Gavis EA, Anderson C, Blankstein L, Brennan AM, Puurunen MK, Lawitz E (2020) Variability and lability of ammonia levels in healthy volunteers and patients with cirrhosis: implications for trial design and clinical practice. Am J Gastroenterol 115:783–785

Balcar L, Krawanja J, Scheiner B, Paternostro R, Simbrunner B, Semmler G, Jachs M, Hartl L, Stättermayer AF, Schwabl P, Pinter M, Szekeres T, Trauner M, Reiberger T, Mandorfer M (2023) Impact of ammonia levels on outcome in clinically stable outpatients with advanced chronic liver disease. JHEP Rep 5:100682

Bernal W, Hall C, Karvellas CJ, Auzinger G, Sizer E, Wendon J (2007) Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. Hepatology 46:1844–1852

Bjorck M, Bergqvist D (2006) Blood-flow of the inferior mesenteric and internal iliac arteries among patients undergoing open surgery for abdominal aortic aneurysm. Vasa 35:11–14

Burkart DJ, Johnson CD, Ehman RL (1993) Correlation of arterial and venous blood flow in the mesenteric system based on MR findings. 1993 ARRS Executive Council award. AJR Am J Roentgenol 161:1279–1282

Chiriac S, Stanciu C, Cojocariu C, Singeap AM, Sfarti C, Cuciureanu T, Girleanu I, Igna RA, Trifan A (2021) Role of ammonia in predicting the outcome of patients with acute-on-chronic liver failure. World J Clin Cases 9:552–564

Clemmesen JO, Larsen FS, Kondrup J, Hansen BA, Ott P (1999) Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. Hepatology 29:648–653

Clemmesen JO, Kondrup J, Ott P (2000) Splanchnic and leg exchange of amino acids and ammonia in acute liver failure. Gastroenterology 118:1131–1139

Cosgrove KP, Mazure CM, Staley JK (2007) Evolving knowledge of sex differences in brain structure, function, and chemistry. Biol Psychiat 62:847–55

Dam G, Keiding S, Munk OL, Ott P, Buhl M, Vilstrup H, Bak LK, Waagepetersen HS, Schousboe A, Møller N, Sørensen M (2011) Branched-chain amino acids increase arterial blood ammonia in spite of enhanced intrinsic muscle ammonia metabolism in patients with cirrhosis and healthy subjects. Am J Physiol Gastrointest Liver Physiol 301:G269–G277

Dam G, Keiding S, Munk OL, Ott P, Vilstrup H, Bak LK, Waagepetersen HS, Schousboe A, Sørensen M (2013) Hepatic encephalopathy is associated with decreased cerebral oxygen metabolism and blood flow, not increased ammonia uptake. Hepatology 57:258–265

Dasarathy S, Mookerjee RP, Rackayova V, Rangroo Thrane V, Vairappan B, Ott P, Rose CF (2017) Ammonia toxicity: from head to toe? Metab Brain Dis 32:529–538

Deutsch-Link S, Moon AM, Jiang Y, th Barritt AS, Tapper EB (2022) Serum ammonia in cirrhosis: clinical impact of hyperammonemia, utility of testing, and national testing trends. Clin Ther 44:e45–e57

Dietrich R, Bachmann C, Lauterburg BH (1990) Exercise-induced hyperammonemia in patients with compensated chronic liver disease. Scand J Gastroenterol 25:329–334

Drolz A, Jäger B, Wewalka M, Saxa R, Horvatits T, Roedl K, Perkmann T, Zauner C, Kramer L, Ferenci P, Fuhrmann V (2013) Clinical impact of arterial ammonia levels in ICU patients with different liver diseases. Intensive Care Med 39:1227–1237

Eriksen PL, Djernes L, Vilstrup H, Ott P (2023) Clearance and production of ammonia quantified in humans by constant ammonia infusion - the effects of cirrhosis and ammonia-targeting treatments. J Hepatol 79:340–348

Esbjörnsson M, Bülow J, Norman B, Simonsen L, Nowak J, Rooyackers O, Kaijser L, Jansson E (2006) Adipose tissue extracts plasma ammonia after sprint exercise in women and men. J Appl Physiol (1985) 101:1576–1580

Evans WB, Aoyagi T, Summerskill WH (1966) Gastrointestinal urease in man. II. Urea hydrolysis and ammonia absorption in upper and lower gut lumen and the effect of neomycin. Gut 7:635–639

Gabduzda GJ, Hall PW 3rd (1966) Relation of potassium depletion to renal ammonium metabolism and hepatic coma. Medicine (Baltimore) 45:481–90

Gairing SJ, Mangini C, Zarantonello L, Gioia S, Nielsen EJ, Danneberg S, Gabriel M, Ehrenbauer AF, Bloom PP, Ripoll C, Sultanik P, Galle PR, Labenz J, Thabut D, Zipprich A, Lok AS, Weissenborn K, Marquardt JU, Lauridsen MM, Nardelli S, Montagnese S, Labenz C (2023) Prevalence of minimal hepatic

encephalopathy in patients with liver cirrhosis: a multicenter study. Am J Gastroenterol
Gibson JA, Sladen GE, Dawson AM (1976) Protein absorption and ammonia production: the effects of dietary protein and removal of the colon. Br J Nutr 35:61–65
Gluud LL, Dam G, Les I, Córdoba J, Marchesini G, Borre M, Aagaard NK, Vilstrup H (2015) Branched-chain amino acids for people with hepatic encephalopathy. Cochrane Database Syst Rev Cd001939
Goh ET, Stokes CS, Sidhu SS, Vilstrup H, Gluud LL, Morgan MY (2018) L-ornithine L-aspartate for prevention and treatment of hepatic encephalopathy in people with cirrhosis. Cochrane Database Syst Rev 5:Cd012410
Groszmann R, Kotelanski B, Cohn JN, Khatri IM (1972) Quantitation of portasystemic shunting from the splenic and mesenteric beds in alcoholic liver disease. Am J Med 53:715–722
Hansen BA, Vilstrup H (1985) Increased intestinal hydrolysis of urea in patients with alcoholic cirrhosis. Scand J Gastroenterol 20:346–350
Harris AN, Skankar M, Melanmed M, Batlle D (2023) An update on Kidney Ammonium Transport along the Nephron. Adv Kidney Dis Health 30:189–196
Häussinger D, Dhiman RK, Felipo V, Görg B, Jalan R, Kircheis G, Merli M, Montagnese S, Romero-Gomez M, Schnitzler A, Taylor-Robinson SD, Vilstrup H (2022) Hepatic encephalopathy. Nat Rev Dis Primers 8:43
Hu C, Huang K, Zhao L, Zhang F, Wu Z, Li L (2020) Serum ammonia is a strong prognostic factor for patients with acute-on-chronic liver failure. Sci Rep 10:16970
Jackson AA, Picou D, Landman J (1984) The non-invasive measurement of urea kinetics in normal man by a constant infusion of 15N15N-urea. Hum Nutr Clin Nutr 38:339–354
James LA, Lunn PG, Middleton S, Elia M (1998) Distribution of glutaminase and glutamine synthetase activities in the human gastrointestinal tract. Clin Sci (Lond) 94:313–319
Katz A, Broberg S, Sahlin K, Wahren J (1986) Muscle ammonia and amino acid metabolism during dynamic exercise in man. Clin Physiol 6:365–379
Kaufman JJ (1984) Ammoniagenic coma following ureterosigmoidostomy. J Urol 131:743–745
Keiding S, Sorensen M, Bender D, Munk OL, Ott P, Vilstrup H (2006) Brain metabolism of 13 N-ammonia during acute hepatic encephalopathy in cirrhosis measured by positron emission tomography. Hepatology 43:42–50
Kimer N, Gluud LL, Pedersen JS, Tavenier J, Møller S, Bendtsen F (2021) The psychometric hepatic Encephalopathy Syndrome score does not correlate with blood ammonia, endotoxins or markers of inflammation in patients with cirrhosis. Transl Gastroenterol Hepatol 6:8
Kundra A, Jain A, Banga A, Bajaj G, Kar P (2005) Evaluation of plasma ammonia levels in patients with acute liver failure and chronic liver disease and its correlation with the severity of hepatic encephalopathy and clinical features of raised intracranial tension. Clin Biochem 38:696–699
Lauridsen MM, Jepsen P, Vilstrup H (2011) Critical flicker frequency and continuous reaction times for the diagnosis of minimal hepatic encephalopathy: a comparative study of 154 patients with liver disease. Metab Brain Dis 26:135–139
Lauridsen MM, Schaffalitzky de OB, Muckadell, Vilstrup H (2015) Minimal hepatic encephalopathy characterized by parallel use of the continuous reaction time and portosystemic encephalopathy tests. Metab Brain Dis 30:1187–1192
Levitt DG, Levitt MD (2018) A model of blood-ammonia homeostasis based on a quantitative analysis of nitrogen metabolism in the multiple organs involved in the production, catabolism, and excretion of ammonia in humans. Clin Exp Gastroenterol 11:193–215
Magasanik B (1993) The regulation of nitrogen utilization in enteric bacteria. J Cell Biochem 51:34–40
Maiwall R, Kumar S, Sharma MK, Wani Z, Ozukum M, Sarin SK (2016) Prevalence and prognostic significance of hyperkalemia in hospitalized patients with cirrhosis. J Gastroenterol Hepatol 31:988–994
Maslennikov R, Pavlov C, Ivashkin V (2018) Small intestinal bacterial overgrowth in cirrhosis: systematic review and meta-analysis. Hepatol Int 12:567–576
Mikkelsen ACD, Thomsen KL, Vilstrup H, Aagaard NK (2023) Hypokalaemia - an active contributor to hepatic encephalopathy? Metab Brain Dis 38:1765–1768
Morgan MY, Hawley KE (1987) Lactitol vs. lactulose in the treatment of acute hepatic encephalopathy in cirrhotic patients: a double-blind, randomized trial. Hepatology 7:1278–1284
Naganawa S, Cooper TG, Jenner G, Potchen EJ, Ishigaki T (1994) Flow velocity and volume measurement of superior and inferior mesenteric artery with cine phase contrast magnetic resonance imaging. Radiat Med 12:213–220
Nakai M, Suda G, Ogawa K, Yoshida S, Hosoda S, Kubo A, Tokuchi Y, Kitagataya T, Yamada R, Shigesawa T, Ohara M, Sho T, Morikawa K, Sakamoto N (2022) Efficacy of rifaximin against covert hepatic encephalopathy and hyperammonemia in Japanese patients. PLoS ONE 17:e0270786
Nencki M, Pawlow JP, Zalenski J (1895) Über den Ammoniakgehalt des Blutes und der Organe und die Harnstoffbildung bei Säugethieren. Archiv für experiementelle Pathologie und Pharmakologie 37:26–51
Nicolao F, Efrati C, Masini A, Merli M, Attili AF, Riggio O (2003) Role of determination of partial pressure of ammonia in cirrhotic patients with and without hepatic encephalopathy. J Hepatol 38:441–446
Olde Damink SW, Jalan R, Redhead DN, Hayes PC, Deutz NE, Soeters PB (2002) Interorgan ammonia and amino acid metabolism in metabolically stable patients with cirrhosis and a TIPSS. Hepatology 36:1163–1171
Olde Damink SW, Jalan R, Deutz NE, Redhead DN, Dejong CH, Hynd P, Jalan RA, Hayes PC, Soeters PB (2003) The kidney plays a major role in the hyperammonemia seen after simulated or actual GI bleeding in patients with cirrhosis. Hepatology 37:1277–1285
Olde Damink SW, Jalan R, Dejong CH (2009) Interorgan ammonia trafficking in liver disease. Metab Brain Dis 24:169–181
Ong JP, Aggarwal A, Krieger D, Easley KA, Karafa MT, Van Lente F, Arroliga AC, Mullen KD (2003) Correlation between ammonia levels and the severity of hepatic encephalopathy. Am J Med 114:188–193
Ott P, Larsen FS (2004) Blood-brain barrier permeability to ammonia in liver failure: a critical reappraisal. Neurochem Int 44:185–198
Owen EE, Tyor MP, Flanagan JF, Berry JN (1960) The kidney as a source of blood ammonia in patients with liver disease: the effect of acetazolamide. J Clin Invest 39:288–294
Patwardhan VR, Jiang ZG, Risech-Neiman Y, Piatkowski G, Afdhal NH, Mukamal K, Curry MP, Tapper EB (2016) Serum ammonia is associated with transplant-free survival in hospitalized patients wth acutely decompensated cirrhosis [corrected]'. J Clin Gastroenterol 50:345–350
Plauth M, Roske AE, Romaniuk P, Roth E, Ziebig R, Lochs H (2000) Post-feeding hyperammonaemia in patients with transjugular intrahepatic portosystemic shunt and liver cirrhosis: role of small intestinal ammonia release and route of nutrient administration. Gut 46: 849–55
Ravi S, Bade KS, Hasanin M, Singal AK (2017) Ammonia level at admission predicts in-hospital mortality for patients with alcoholic hepatitis. Gastroenterol Rep (Oxf) 5:232–236

Rockey DC, Vierling JM, Mantry P, Ghabril M, Brown RS Jr., Alexeeva O, Zupanets IA, Grinevich V, Baranovsky A, Dudar L, Fadieienko G, Kharchenko N, Klaryts'ka I, Morozov V, Grewal P, McCashland T, Reddy KG, Reddy KR, Syplyviy V, Bass NM, Dickinson K, Norris C, Coakley D, Mokhtarani M, Scharschmidt BF (2014) Randomized, double-blind, controlled study of glycerol phenylbutyrate in hepatic encephalopathy. Hepatology 59:1073–83

S Eriksson L, Broberg S, Björkman O, Wahren J (1985) Ammonia metabolism during exercise in man. Clin Physiol 5:325–336

Shalimar MF, Sheikh RP, Mookerjee B, Agarwal SK, Acharya, Jalan R (2019) Prognostic role of Ammonia in patients with cirrhosis. Hepatology 70:982–994

Sharma BC, Sharma P, Lunia MK, Srivastava S, Goyal R, Sarin SK (2013) A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. Am J Gastroenterol 108:1458–1463

Sørensen M (2013) Update on cerebral uptake of blood ammonia. Metab Brain Dis 28:155–159

Strauss GI, Knudsen GM, Kondrup J, Møller K, Larsen FS (2001) Cerebral metabolism of ammonia and amino acids in patients with fulminant hepatic failure. Gastroenterology 121:1109–1119

Tarantino G, Citro V, Esposito P, Giaquinto S, de Leone A, Milan G, Tripodi FS, Cirillo M, Lobello R (2009) Blood ammonia levels in liver cirrhosis: a clue for the presence of portosystemic collateral veins. BMC Gastroenterol 9:21

Thomsen KL, Macnaughtan J, Tritto G, Mookerjee RP, Jalan R (2016) Clinical and pathophysiological characteristics of cirrhotic patients with Grade 1 and minimal hepatic encephalopathy. PLoS ONE 11:e0146076

Thomsen KL, Eriksen PL, Kerbert AJ, De Chiara F, Jalan R, Vilstrup H (2023) Role of ammonia in NAFLD: an unusual suspect. JHEP Rep 5:100780

Tranah TH, Ballester MP, Carbonell-Asins JA, Ampuero J, Alexandrino G, Caracostea A, Sánchez-Torrijos Y, Thomsen KL, Kerbert AJC, Capilla-Lozano M, Romero-Gómez M, Escudero-García D, Montoliu C, Jalan R, Shawcross DL (2022) Plasma ammonia levels predict hospitalisation with liver-related complications and mortality in clinically stable outpatients with cirrhosis. J Hepatol 77:1554–1563

Tsai CF, Tu PC, Wang YP, Chu CJ, Huang YH, Lin HC, Hou MC, Lee FY, Liu PY, Lu CL (2019) Altered cognitive control network is related to psychometric and biochemical profiles in covert hepatic encephalopathy. Sci Rep 9:6580

van de Poll MC, Soeters PB, Deutz NE, Fearon KC, Dejong CH (2004) Renal metabolism of amino acids: its role in interorgan amino acid exchange. Am J Clin Nutr 79:185–197

van de Poll MC, Ligthart-Melis GC, Olde Damink SW, van Leeuwen PA, Beets-Tan RG, Deutz NE, Wigmore SJ, Soeters PB, Dejong CH (2008) The gut does not contribute to systemic ammonia release in humans without portosystemic shunting. Am J Physiol Gastrointest Liver Physiol 295:G760–G765

van der Hulst RR, von Meyenfeldt MF, Deutz NE, Soeters PB (1997) Glutamine extraction by the gut is reduced in depleted [corrected] patients with gastrointestinal cancer. Ann Surg 225:112–121

Verma N, Dhiman RK, Choudhury A, Taneja S, Duseja A, Singh V, Al Mahtab M, Devarbhavi H, Shukla A, Ning Q, Hamid SS, Butt AS, Jafri W, Tan SS, Hu J, Zhongping D, Treeprasertsuk S, Lee GH, Ghazinyan H, Lesmana LA, Sood A, Midha V, Goyal O, Kim DJ, Eapen CE, Goel A, Tao H, Shaojie X, Yuemin N, Dokmeci AK, Sahu M, Singh A, Arora A, Kumar A, Kumar R, Prasad VGM, Shresta A, Sollano J, Payawal DA, Shah S, Rao PN, Kulkarni A, Lau GK, Sarin SK (2021) Dynamic assessments of hepatic encephalopathy and ammonia levels predict mortality in acute-on-chronic liver failure. Hepatol Int 15:970–982

Vilstrup H, Eriksen PL, Kjærgaard K, Sørensen M, Thomsen KL (2025) Down the road towards hepatic encephalopathy: Urea synthesis - the liver workhorse of nitrogen metabolism. Metab Brain Dis

Volianitis S, Secher NH, Clemmesen O, Ott P, Nielsen HB (2024) Hepato-splanchnic fluxes during exercise in patients with cirrhosis-a pilot study. Physiol Rep 12:e16162

Walser M, Bodenlos LJ (1959) Urea metabolism in man. J Clin Invest 38:1617–1626

Weiner ID, Miller RT, Verlander JW (2003) Localization of the ammonium transporters, rh B glycoprotein and rh C glycoprotein, in the mouse liver. Gastroenterology 124:1432–1440

Wolpert E, Phillips SF, Summerskill WH (1971) Transport of urea and ammonia production in the human colon. Lancet 2:1387–1390