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REVIEW

Down the road towards hepatic encephalopathy. Urea synthesis - the liver workhorse of nitrogen metabolism

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Abstract

Urea synthesis is an irreversible, essential for maintenance of health and life, and highly regulated liver function with a very high capacity for production of the end-product urea-nitrogen. The set-point of urea synthesis in relation to its overall substrate, the prevailing blood concentration of L-α-amino acids, contributes to determine whole-body nitrogen balance and the size and composition of the plasma free amino acid pool. Ammonia is definitively eliminated from the body by urea synthesis. Ammonia is released by all tissues as part of their nitrogen metabolism and accumulation of ammonia to supranormal levels is toxic, particularly to the brain where it gives rise to the devastating complication to liver diseases, hepatic encephalopathy. The first line ammonia scavenging has an efficiently high clearance several times over hepatic blood flow and close to cardiac output, under normal conditions securing rapid neutralization of ammonia by synthesis of amino acids and glutamine. This scavenging has a much lower capacity than urea synthesis. Maintenance of the scavenging system, therefore, relies on subsequent definitive depletion and elimination of amino- and amide-nitrogen to urea-nitrogen. In liver diseases, the capacity for urea synthesis is deficient due to reduced functional liver mass and dysregulation, which eventually delays the scavenging so that ammonia overflows. Considering the key role of ammonia in hepatic encephalopathy, this indirect relationship implies that deficient urea synthesis is a prerequisite for development of hyperammonemia and hepatic encephalopathy. This is in accordance with the definition of hepatic encephalopathy as being caused by liver insufficiency, where the insufficiency more specifically likely is deficiency of the urea synthesis.

Keywords Urea synthesis · Functional hepatic nitrogen clearance · Ammonia metabolism · Hepatic encephalopathy · Liver cirrhosis

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Introduction

In this paper, after a historical introduction, we will review quantitative static and dynamic aspects of in vivo urea synthesis in health and liver disease. The recurring theme is that urea synthesis is a low clearance, high-capacity one-way process that runs exclusively in the liver, whereas ammonia scavenging is a high clearance, low-capacity metabolic loop to which all organs contribute, and by which ammonia-nitrogen (N) is indirectly fed into the urea cycle. Delayed definitive drainage of the ammonia scavenging system due to deficient urea synthesis as occurring in liver disease leads to ammonia accumulation, taken to be the pivotal event for development of hepatic encephalopathy (HE). In this way we intend to contribute towards the understanding of the relationship between liver disease with metabolic liver function loss, and HE. This review views and deals with urea synthesis as a collective metabolic hepatocyte and liver function, encompassing the numerous processes involved in the complete urea synthesis. Thus, the intricate biochemistry and enzymatical steps of the urea cycle are not detailed here.

History

Urea, also known as Harnstoff, carbamide, carbonyldiamide etc., is the smallest known complete organic molecule with a molecular weight of only 60 g/mol. Urea is a true metabolic end-product, as mammalian organisms contain no urease. Urea distributes rapidly in the total body water. Scientifically, urea has a long lifeline of nearly 300-years, which is associated with a number of eminent researchers. The first one was dutchman Herman Boerhaave who in 1727 collected his own urine for a whole year and evaporated it. What was left he called Harnstoff (German for urine material). Ninety years later, Englishman William Prout did the same for a shorter period of time. He found what it was composed of and coined the name urea. A decade later, in 1828, a huge breakthrough for science was made by the German scientist Friedrich Wöhler, who synthetized urea from inorganic material. This marked the end of 'Vitalism', the ruling belief till that time that nothing happens in organic life without divine intervention. So, urea was the vehicle for the transition from natural philosophy and theology to science. The source of urea remained a matter of debate. Despite its appearance in urine, in 1858 difficult experiments by Dutchman Adrianus Heynsius for the first time indicated it to originate from the liver, but not until nearly one hundred years later, in 1924, American clinical researcher Jesse L. Bollman demonstrated that urea is produced exclusively by the liver, through experiments in nephrectomized and hepatectomized animals. In 1932, Hans A. Krebs and Kurt Henseleit, after a long series of experiments, solved the mystery of how the urea cycle works. The key was the addition of the amino acid citrulline, derived from melons that finally made the cycle run in the laboratory. Krebs got the Noble Price for describing the tricarboxylic (citric) acid cycle ('Krebs' cycle'), but their solution of the urea cycle was no less remarkable and important.

In phylogenetic terms, urea and its enzymatic machinery has a history much longer than and different from the scientific timeline, dating back into the origin of species (Withers 1998). Urea then served as the osmotic filler and water retainer that allowed organisms to move out of the water and live on land.

Functions of urea synthesis

In mammalian species urea synthesis has a key function as metabolic regulator of N turnover and balance in health and disease, serving as the one and only way of ultimate, irreversible, and need-responsive metabolic elimination of N from the body. This implies that regulation of the urea cycle is important to determine whole-body and organ N balances. It is a formidable task, but urea synthesis is capable of it due to its huge capacity, responsivity to metabolic need and substrate, and diverse and sophisticated regulation. The resulting regulatory set-point of urea synthesis rate determines the level of free plasma amino acids and in this way influences organ amino acid fluxes and balance between protein build-up and -break down.

In vivo, the overall physiologic substrate for urea synthesis is blood α-amino-N (AAN). Free ammonia is not a significant or immediate substrate for urea synthesis (Keiding et al. 2005) but is primarily scavenged by carbon skeletons in the synthesis of amino acids, to a large extent of glutamine by amidation of glutamate. This happens in all organs, but particularly down-stream liver sinusoidal glutamine synthetase, inducible by ammonia, plays an important role in capturing free ammonia that passes the hepatocytes with urea cycle enzymes. AAN and glutamine amide-N feed ammonia-N into the urea cycle and serve as 'metabolic scavenging loops' before final elimination of ammonia-N by urea-N synthesis. In this way, there is no direct or linear kinetic ammonia-urea relationship. As important and necessary elimination of ammonia-N is, this function thus remains subsidiary to both the quantitative and regulatory aspects of urea synthesis. On the other hand, and because urea is the only final metabolic ammonia-N outlet function in Man, deficient urea synthesis unavoidably leads to delayed scavenging and accumulation of ammonia.

Urea synthesis is an essential liver function. It runs in its complete form only in the liver, it is prioritized over other liver

functions, and health and survival cannot be sustained without it. There is only one report in the literature of a person without measurable urea in the body fluids. That was in 1929 in a patient with fatal 'acute yellow atrophy of the liver' (Rabinowitch 1929).

The high priority of urea synthesis - and its relation to HE - is illustrated by the different rates of recovery of various liver functions in a case of acute liver failure (Fig. 1) (Vilstrup 1989). The capacity of urea synthesis was the first to recover, likely securing survival of that patient, and at the same time the patient woke up from HE.

Measuring urea synthesis rate and its capacity

To progress in the understanding of the urea cycle it is paramount to be able to reliably measure in vivo urea synthesis rates in quantitative and dynamic terms and in clinical settings. This is possible by simple means because the urea produced in higher organisms is an end-product, rapidly equilibrates between liver, blood, and total body water, and is excreted into the urine. However, most intestinal bacteria contain urease so that a correction for recycling of gut urea hydrolysis derived ammonia into urea synthesis is necessary (Fig. 2).

Such measurements of urea synthesis rates are low-tech but tedious in time and sampling of body fluids. Still, no other methods are as rapid and reliable, including tracer techniques. This is likely the main reason why only few measurements of urea synthesis rate in patients with HE are reported.

To determine the kinetic relationship between urea-N synthesis rate (UNSR) and blood alpha-amino-N concentration (AAN), amino acid solutions can be infused to control UNSR (Vilstrup 1980). In healthy persons, it emerges that UNSR increases linearly with AAN concentration increasing to very high levels and without sign of saturation of urea synthesis. Also, in patients with cirrhosis, the configuration is linear but down- and right-shifted so that for any given AAN, UNSR is lower (Fig. 3).

This whole-body kinetics can be described by its slope, i.e. the ratio between UNSR and AAN. In enzymatic terms this is akin to first order part of a Michaelis–Menten kinetics.

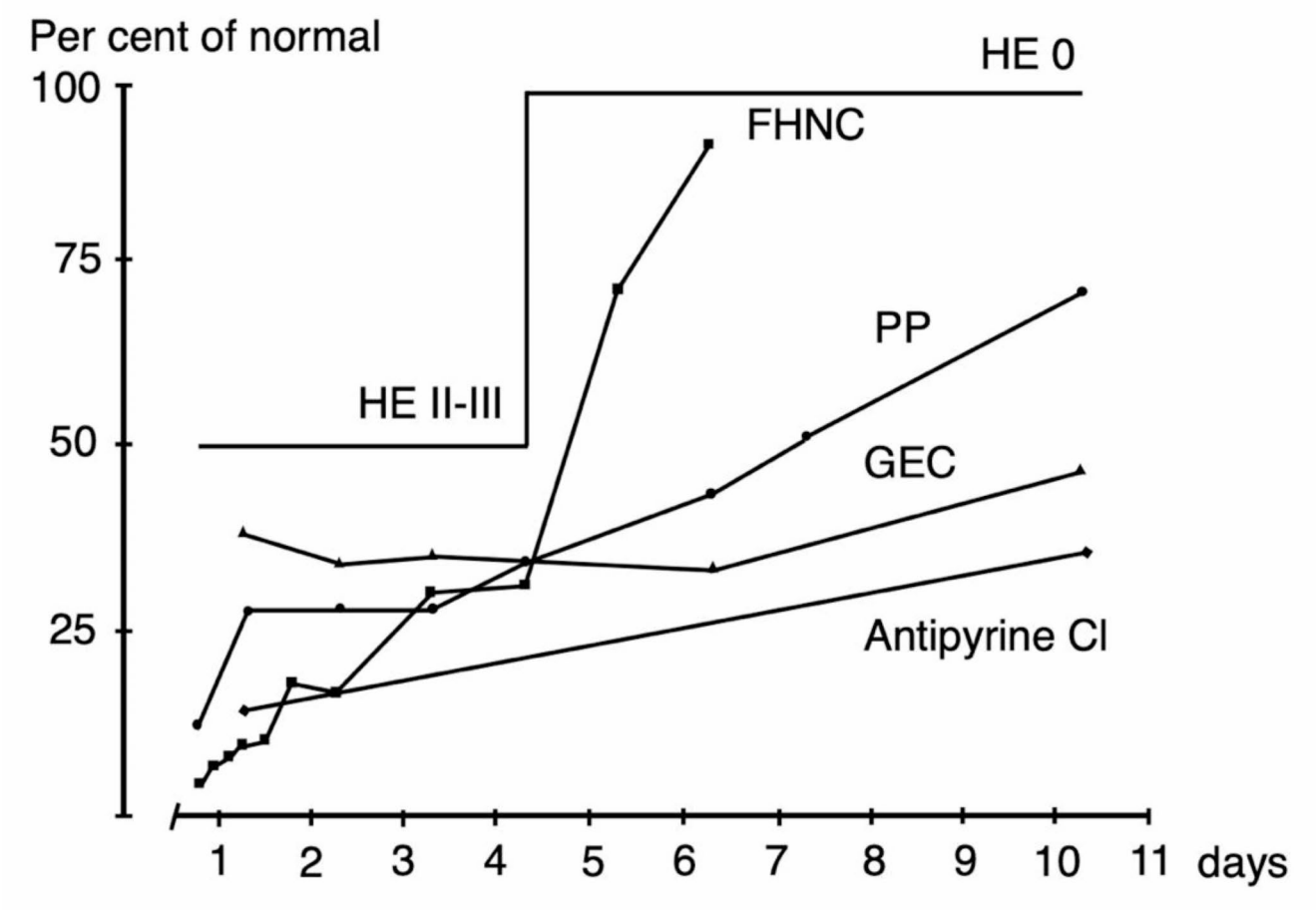

Fig. 1 Priority of recovery of metabolic liver functions and hepatic encephalopathy after acute liver failure. Liver functions measured as the Functional Hepatic Nitrogen Clearance (FHNC, a measure of the capacity for urea synthesis, cf. text mention), prothrombin-proconvertin ratio (PP, coagulation factors II, VII, X), Galactose Elimination Capacity (GEC) and Antipyrine Clearance (Cl) in per cent of normal after spontaneous reversal of acute liver failure (Adapted from Vilstrup 1989)

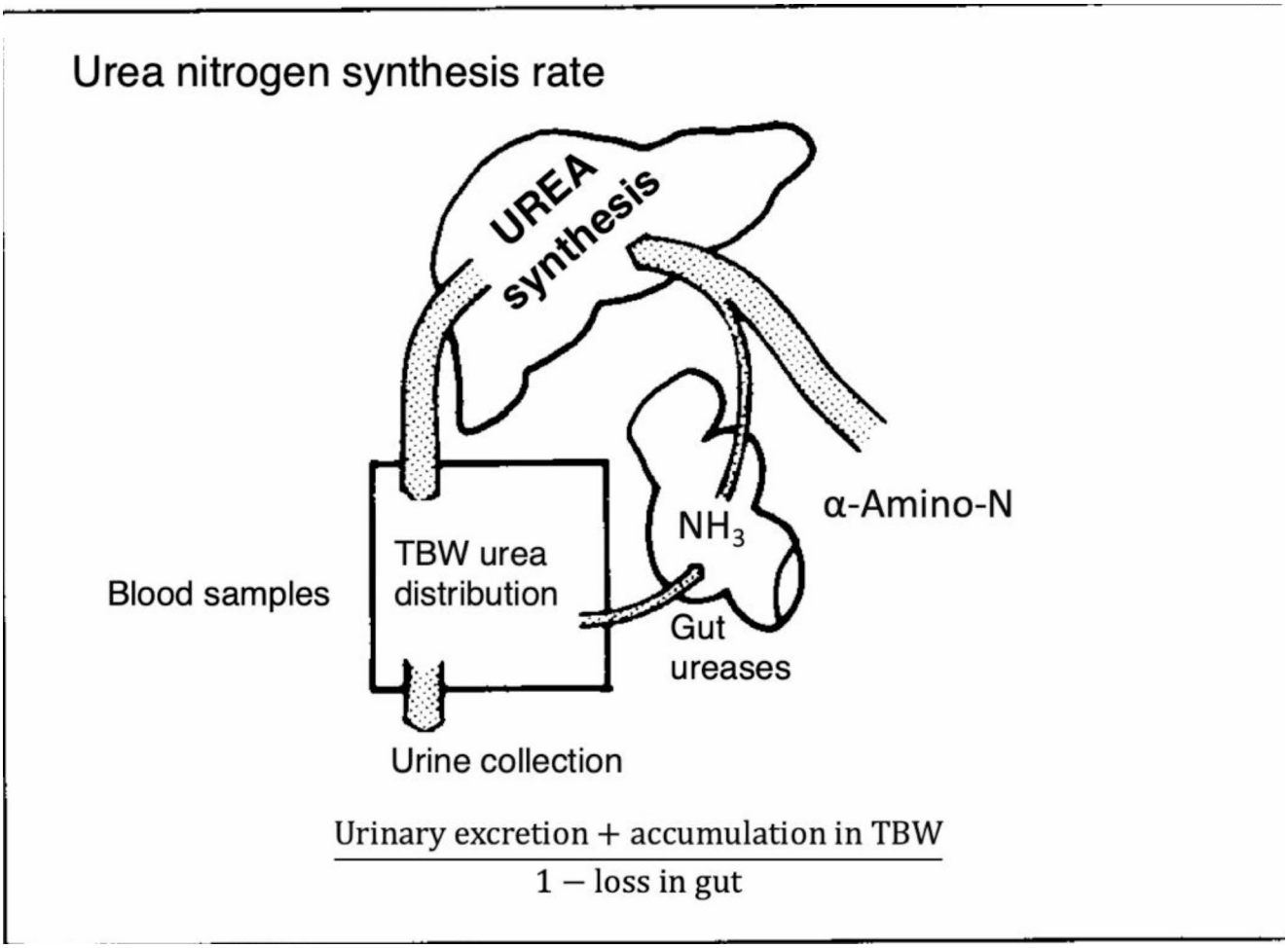

Fig. 2 Urea nitrogen synthesis rate measured in vivo. Method for measuring the urea nitrogen synthesis rate (UNSR). Each rate determination of UNSR requires >1 hour of system stability. TBW: total body water, α-Amino-N: alpha-amino nitrogen, NH_3: ammonia (Adapted from Vilstrup 1989)

The unit of the slope is a flow rate which is the clearance rate of conversion of AAN into urea-N, and the term adopted for this measure is the 'Functional Hepatic Nitrogen Clearance' (FHNC). The linear configuration implies that the FHNC is a meaningful measure of the capacity for urea synthesis in humans. It is already evident that the FHNC is decreased by cirrhosis, but it is also changed and regulated under many other conditions. The strongest up-regulating hormone is glucagon (Vilstrup et al. 1990), an effect impaired by glucagon resistance (Hamberg and Vilstrup 1994) in liver diseases ranging from steatotic liver disease (Lykke Eriksen et al. 2019; Winther-Sørensen et al. 2020) to acute liver failure (Vilstrup et al. 1986). Numerous other hormones, cytokines, substances, and drugs up- or down-regulate urea synthesis (Wolthers et al. 1997, 2000; Sandahl et al. 2011; Thomsen et al. 2010; Aagaard et al. 2004; Fabbri et al. 1995). Dehydration and hypokalemia both down-regulate ureagenesis (Ivarsen et al. 2001; Mikkelsen et al. 2021), the former likely as a remnant of the original osmotic role of urea.

Urea synthesis in liver disease– deficient urea synthesis

Deficient urea synthesis is measurable by decreased FHNC and can be related to decreased functional liver mass in chronic (cirrhotic) or acute liver failure. Likewise, the liver architecture and perfusion can be disturbed by shunting and fibrosis, resistance to regulation and toxicity to urea cycle genes, the last effect e.g. seen in steatotic liver disease (De Chiara et al. 2018). Also, several relatively rare congenital urea cycle defects exist, caused by genetic disorders affecting urea cycle enzymes or transporters and not described in this review.

Figure 4 shows some of the liver disease cohorts previously studied and how the capacity for urea synthesis as measured by the FHNC is deficient in steatotic liver disease, alcohol-related liver cirrhosis, Hepatitis C Virus cirrhosis, alcoholic hepatitis, and acute liver failure (Vilstrup 1980; Vilstrup et al. 1986; Glavind et al. 2016; Lykke Eriksen et

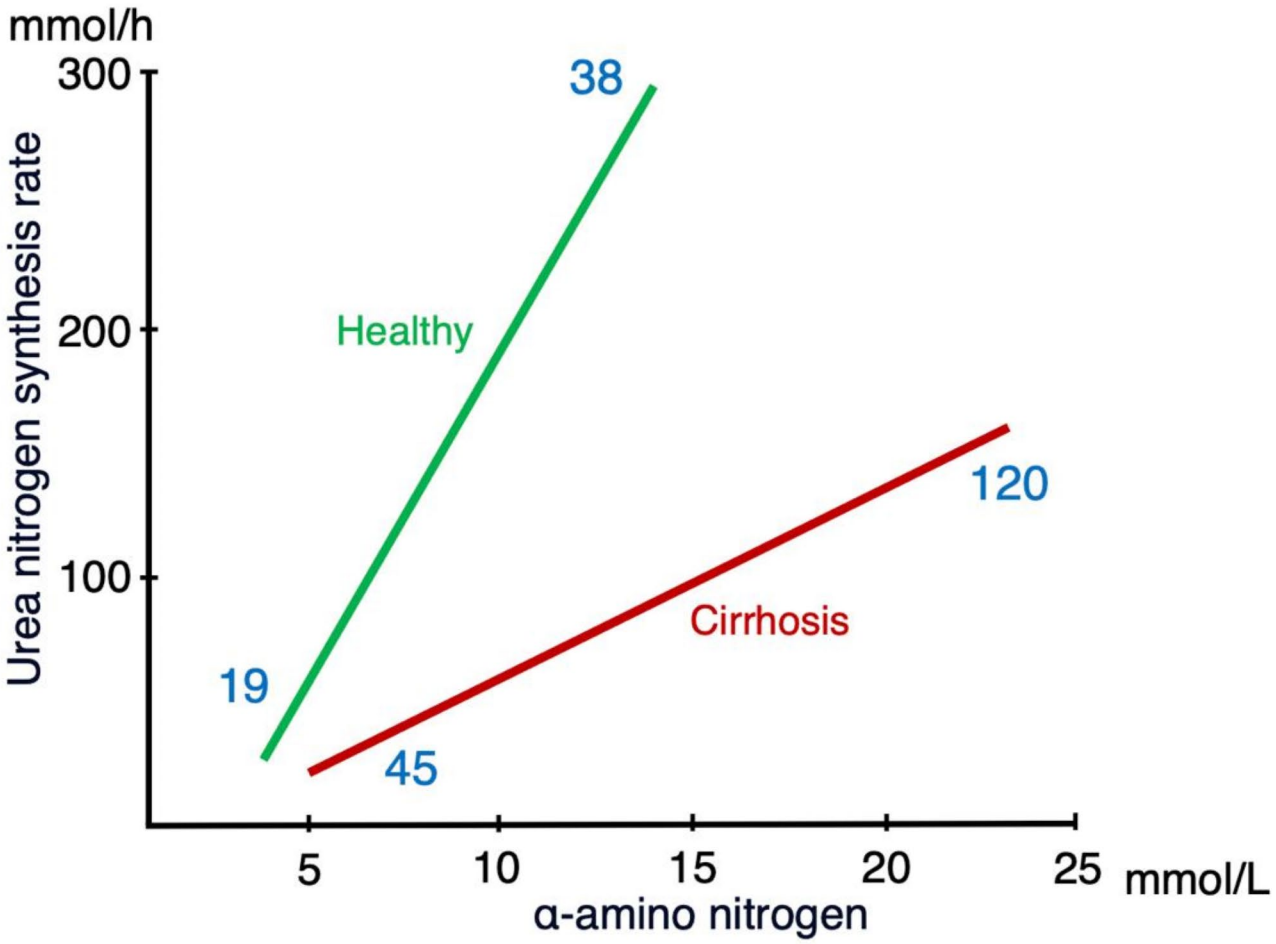

Fig. 3 Urea nitrogen synthesis rate vs. blood amino acid nitrogen concentration during infusion of amino acids. Graphical representation of the Functional Hepatic Nitrogen Clearance (FHNC, the slope of the shown linear kinetic relationship obtained by constant amino acid infusion in healthy persons). The lines represent mean values of several persons (green line, FHNC range in the quoted paper 16-29 l/h), and patients with cirrhosis (red line, FHNC range 6-24 l/h). Ammonia concentrations before and at the end of amino acid infusion are shown (cf. mention in text, blue, µmol/L) (Adapted from Vilstrup 1980)

al. 2019; Laursen et al. 2020). Thus, the liver's capacity for urea synthesis is indeed reduced when the liver is sick. The degree of reduction can be very marked with the most serious liver diseases, but the urea cycle never completely stops, as long as the liver is alive.

Urea synthesis and ammonia dynamics–quantitative aspects

Urea synthesis is a low clearance system with an enormous capacity. The low clearance means that the FHNC is not generally determined by the hepatic blood flow. Urea synthesis is a large metabolic machinery, and its extreme variability and diverse regulation secures it can maintain nitrogen related body functions in the most extreme situations. As an example, during a protein or amino acid load, a normal urea synthesis can reach a rate of at least 300 mmol N per hour without signs of saturation, corresponding to a daily intake of more than 3.5 kg of meat. So, even a large gastrointestinal bleed or another increase in intestinal ammonia release will cause no significant or lasting ammonia accumulation in persons without liver disease.

In contrast, the scavenging of free ammonia from the blood is a high clearance low-capacity system in which ammonia emerging from all organs is rendered harmless by the mentioned metabolic 'scavenging loops' in the form of amino- and amide-N, until it reaches urea synthesis for final elimination (Table 1 and Fig. 5). The functional consequences of these kinetic differences are detailed below.

The differences between urea and ammonia can initially be considered in terms of the sizes of their body fluid pools that illustrate the differences between the large urea machinery and the much smaller ammonia scavenging. The urea-N pool is measured in mmol whereas the amount of ammonia

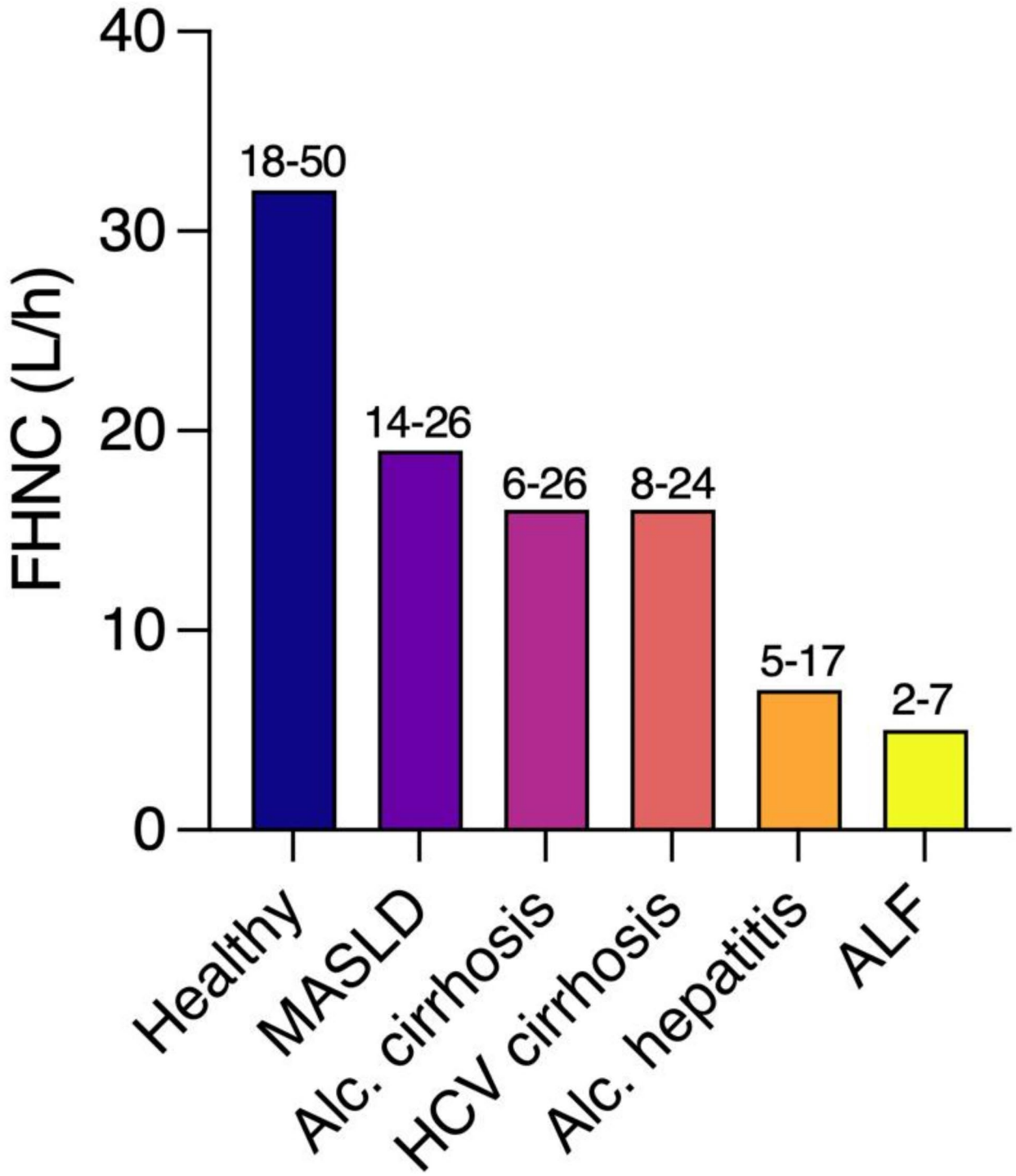

Fig. 4 The Functional hepatic nitrogen clearance in liver diseases. The Functional Hepatic Nitrogen Clearance (FHNC) in various liver diseases (MASLD: metabolic dysfunction-associated steatotic liver disease; Alc. cirrhosis: alcohol related cirrhosis; HCV cirrhosis: hepatitis C cirrhosis; Alc. hepatitis: alcohol related hepatitis; ALF: acute liver failure) compared to healthy individuals. Data are presented as means with 95 % CI's

Table 1 Metabolic dynamics of the two-step ammonia elimination, consisting of urea synthesis following ammonia scavenging from blood

	Ammonia scavenging	Urea synthesis
Organs	All	Liver
Clearance	High	Low
Capacity	Low	High
Elimination	Temporary	Final

in the body is measured in µmol. The body pool of urea-N amounts to about 600 mmol N and that of ammonia is much smaller at about 200 µmol, i.e. only 0.3‰ of the urea-N pool. As to the potential ammonia-N scavenging pool into glutamine, there is a total of about 10 mmol of glutamine in the body and much less glutamate, so that this pool is 17‰ of the urea-N pool. The total size of the ammonia scavenging pools thus is below 2% of the urea-N pool.

More importantly, also in dynamic terms there are large differences between urea synthesis and ammonia scavenging. The amino-N to urea-N clearance, the FHNC, recalculated from Fig. 3, is normally about 0.53 L/min, which is only about 40% of the hepatic blood flow. Our recent publication on ammonia clearance and release measured directly by means of ammonia infusion to healthy persons and patients with cirrhosis (Eriksen et al. 2023) for the first time provides direct quantitative data on ammonia dynamics. In contrast to urea synthesis, the ammonia clearance is much higher at about 3.4 L/min which is more than six-fold higher than the FHNC, nearly three-fold higher than the hepatic blood flow, and as high as 70% of the cardiac output. This confirms that the initial scavenging clearance of ammonia from the blood is not by the liver via elimination by urea synthesis (Table 1; Fig. 5).

These clearances can be converted into metabolic substance rates by multiplication by prevailing concentrations, which may give a clearer picture of the differences. As shown in Fig. 3, the UNSR can vary from about 40 mmol/h or less under basal conditions to at least 300 mmol/h during amino acid stimulation. The ammonia metabolic scavenging rate is much lower. Under basal conditions, it is 2.5 mmol/h and under exogenous ammonia load 25 mmol/h (Eriksen et al. 2023). These ammonia loops thus are only 6–8% of the UNSR. This explains why ammonia under normal conditions is ultimately and effortlessly cleared by urea synthesis despite ammonia having a much higher clearance than urea synthesis.

The high scavenging clearance of ammonia obviously cannot continue for longer periods or indefinitely. Unless amino- and amide-N is definitively eliminated via urea synthesis the necessary immediate ammonia receiver sites rapidly saturate so that ammonia overflows. If FHNC is decreased, any needed UNSR requires a higher substrate drive due to the previously described shift to the right of the linear relationship in Fig. 3, forcing the ammonia loaded receiver structures– particularly amino acids– to increase, making fewer ammonia receiver sites available and thereby decreasing ammonia clearance, and ultimately making ammonia accumulate. All this happens until a new balanced metabolic homeostasis at a higher ammonia and amino acid level is established. In this way, deficient urea synthesis and hyperammonemia are inseparably albeit indirectly linked.

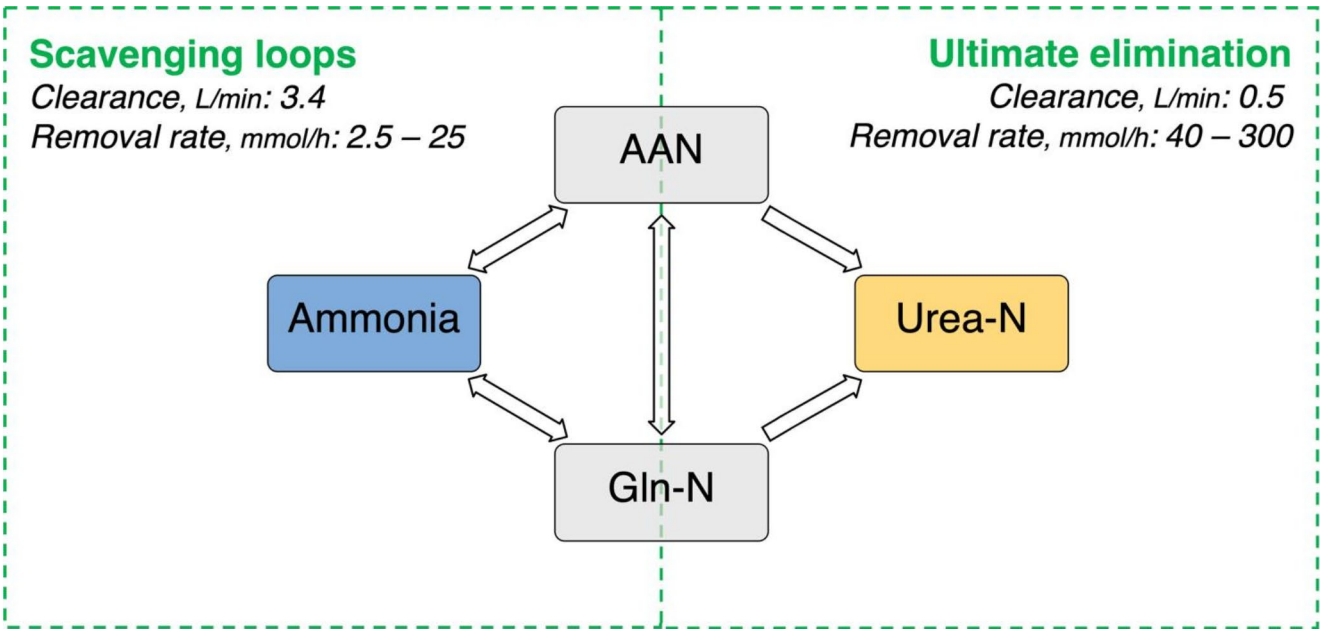

Fig. 5 The ammonia scavenging loops and elimination via urea synthesis. Alpha-amino nitrogen- (AAN), glutamine nitrogen- (Gln-N) and ammonia metabolism via scavenging loops and final elimination via urea formation. Metabolic rate = clearance × concentration

Urea synthesis, ammonia, and hepatic encephalopathy

There are few if any simultaneous measurements of UNSR and ammonia in HE but we have a few observations in healthy persons and cirrhosis patients without HE (Vilstrup 1980). Figure 3 shows how healthy persons at the basal state have low ammonia that only doubles during the unphysiologically high increase in amino acids during infusion. Patients with cirrhosis at the basal state exhibit hyperammonemia which rises much more in response to the amino acid infusion and reaches values three times higher than in the healthy persons. This confirms that there is a relationship between deficient urea synthesis capacity and hyperammonemia. As mentioned above, the relationship is indirect in reflecting passage of scavenged ammonia-N to urea synthesis.

In liver disease, FHNC is decreased not only because of reduced functional liver mass but also because of inappropriate regulation or influence from other factors. As regards the first mechanism, glucagon resistance is mentioned above. Any intervention further decreasing the FHNC will place the patient in increased risk of hyperammonemia, as observed by e.g. alcohol, hypokalemia, and dehydration (Ivarsen et al. 2001; Aagaard et al. 2004; Mikkelsen et al. 2021). Conversely, interventions supporting the FHNC will tend to protect from the risk of developing hyperammonemia. A recent example is from patients with steatotic liver disease undergoing bariatric surgery leading to hepatic de-fattening. This is associated with a 30% increase in FHNC and a 50% reduction in ammonia (Kjærgaard et al., personal communication). High protein feeding increases the FHNC and the effect remains, albeit weakened, in patients with cirrhosis (Hamberg et al. 1992). Another example is zinc supplementation which can improve the FHNC in patients with cirrhosis (Marchesini et al. 1996).

Because urea synthesis in the end frees the organism from ammonia-N, it is a reasonable notion that there exists a relationship between urea synthesis and HE. Already in 1954, German clinical researcher Dieter Müting (Müting 1954) suggested that in patients with cirrhosis more than normal amounts of amino acids appear into their urine because their urea cycle could not metabolize the blood amino acids– and the deficient urea synthesis was seen as a cause of HE. Later, in the 1970s, American clinical researchers Rikkers and Ansley described a linear relationship between a standardized rate of urea excretion and different cognitive measures and electro-encephalographs in patients with cirrhosis, which today is known as minimal HE (Rikkers et al. 1978). As mentioned above, the right- and down-shift of the UNSR vs. AAN relationship (Fig. 3) in liver disease requires a higher plasma AAN for maintenance of a given UNSR. Whole-body neutral N balance with a UNSR sufficient to relieve the body of ingested protein-N not used for protein synthesis is only possible with a higher-than-normal substrate drive on urea synthesis. This larger plasma amino acid pool in cirrhosis patients contains more aromatic amino acids (AAA) and fewer branched-chain amino acids (BCAA) due to altered hepatic metabolism (Vilstrup et al. 1982). This imbalance has been implicated in the pathogenesis of HE. The high AAA could lead to inhibited neuronal synthesis of excitatory dopamine, and the low BCAA could inflict astrocytic energy production via depletion of TCA cycle intermediates. However, these hypotheses have been refuted (Johansen et al. 2007) and the clinical effect of treatment with tailored amino acid solutions is now ascribed to their effect on muscle metabolism, decreasing muscle ammonia release (Dam et al. 2011). The recent understanding is that the link between FHNC and HE is the propensity for ammonia accumulation due to compromised scavenging of ammonia as a backward failure resulting from the compromised final elimination of ammonia-N via urea synthesis.

Conclusion

Liver diseases lead to decreased urea synthesis capacity which in turn, together with increased organ ammonia release, leads to ammonia accumulation. So, can HE occur with intact urea synthesis? Assuming that the precipitating prerequisite for HE is hyperammonemia, it is a pathophysiologically and mechanistically tenable contention that HE ultimately results from deficient urea synthesis. But there is still not any definite answer to this basically important question. Anyway, HE is defined as being caused by liver insufficiency (and/or porto-systemic shunts) (Vilstrup et al. 2014). Considering the dependency of ammonia scavenging on urea synthesis capacity outlined above, it is plausible that the liver insufficiency mentioned in the definition more specifically is insufficiency of the urea synthesis.

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Declarations

Competing interests The authors declare no competing interests.

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