Chapter 2
Role of Ammonia in the Pathogenesis of Hepatic Encephalopathy

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Introduction

There is consensus that excess of gut-derived ammonia which is not cleared from the blood plays an important role in the pathogenesis of HE. However, as discussed elsewhere in this book, a growing body of evidence suggests significant contribution of other factors, such as proinflammatory cytokines and hyponatremia. Moreover, there is a long list of gut-derived toxins that accumulate in the body when the detoxifying capacity of the liver is compromised, many of which may enter the brain [1]. It thus appears worthwhile to distinguish the specific roles of ammonia in inducing HE. This will be done in five discrete sections. The first issue addressed in this chapter is the degree of correlation between blood ammonia levels and severity of HE as graded by the West Haven scale (assignment to grades I–IV). The impact of changes in the rate of ammonia generation in the peripheral tissues is briefly accounted for. Next, the contribution of ammonia to the specific pathophysiological manifestations of advanced stages of HE is analyzed. The key parameters under evaluation are brain edema, which is the major cause of death in patients with HE accompanying acute liver failure (ALF), and increased cerebral blood flow (CBF), which is a causative factor in brain edema. Further, the role of ammonia in the development of cognitive and motor impairment is assessed. Wherever the net effect of ammonia could not be directly evaluated in a clinical setting, its distinct role is demonstrated in experimental animals with "simple" hyperammonemia not complicated by liver

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damage or asymptomatic animals with experimentally induced chronic liver failure subsequently given ammonia bolus. The effectiveness of therapeutic interventions specifically aimed at reducing blood ammonia level in HE patients or experimental animals is taken as further support to the relative contribution of ammonia.

The section "Cellular and Molecular Mechanisms Underlying Ammonia-Induced Impairment of Brain Function" describes the molecular and biochemical effects of ammonia on the different cell types of the central nervous system (CNS) and on the interactions between these cells. It focuses on the events which can be causally linked to brain edema and to the growing imbalance between neural inhibition and excitation. Progression towards neural inhibition is mainly seen in Type C HE. Distinct contributions of ammonia itself and its direct metabolite, glutamine are emphasized.

Correlation Between Ammonia Levels in Blood and/or Its Rate of Production in the Periphery and the Advancement of HE

Most of the studies carried out in the last few decades have demonstrated a rather good correlation between blood ammonia and severity of HE. Occasional deviations from this rule are now interpreted as reflecting methodological inaccuracies and/or incompatibilities of the procedures used in different medical centers [2]. One major controversy of the past was whether arterial or venous blood should be taken for the measurements. It has been argued that when the liver becomes dysfunctional, detoxification of ammonia mainly occurs in the muscles, disproportionally lowering venous blood ammonia as compared to the arterial blood ammonia. It has also been suggested that partial pressure of ammonia correlates better with the HE grade than blood ammonia. Recently, Ong et al. [3] compared arterial and venous ammonia content, and arterial and venous partial pressure of ammonia, in a carefully selected group of 121 patients with liver cirrhosis, and demonstrated that blood ammonia measured with any of these four methods correlated equally well with the severity of HE.

Ammonia delivered from the peripheral tissues to blood is mainly derived from glutamine following its degradation by phosphate-activated glutaminase (PAG). There is evidence that the risk of progression of cirrhotic patients to advanced HE is associated with increased ammonia production from glutamine in the intestines [4] and kidney [5]. Similarly, it has been demonstrated that enhanced response to oral glutamine challenge test can identify cirrhotics with increased risk of transition to higher grades of HE [6]. More recently, mutation in the promoter region of PAG has been identified in in vitro tests which accelerates the transcriptional activity of this gene, i.e., enhances production of PAG molecules [7]. Cirrhotic patients carrying this mutation show an increased preponderance to develop symptomatic HE [7].

Although intracellular ammonia levels in the brain are not amenable to direct testing in HE patients, it is safe to assume that the increase in blood ammonia will lead to a proportional increase in brain ammonia. The current view is that not only ammonia base but also ionized ammonia penetrates the blood–brain barrier (BBB) [8]. Experiments in an animal model of hyperammonemia revealed a substantially increased extraction of blood ammonia by the brain [9].

The Role of Ammonia in Alterations of Cerebral Blood Flow and Development of Cerebral Edema Associated with HE

Brain edema is a frequent complication of ALF and a major cause of death in these patients because it leads to increased intracranial pressure (ICP) and herniation. Both clinical and animal model studies have brought about compelling evidence favoring a direct role of ammonia in inducing brain edema. In a retrospective study, death of ALF patients due to cerebral herniation closely correlated with the arterial ammonia levels [10], and a recent prospective study by the same group revealed a good correlation in time and magnitude between arterial hyperammonemia, cerebral accumulation of osmotically active amino acids and ICP [11]. Brain edema seen in ALF patients was reproduced in rats with ammonium acetate-induced hyperammonemia not complicated by liver failure [12, 13] and in portacaval-shunted rats which received an ammonia bolus [14]. Astrocytic swelling is not only associated with ALF [15] but also with low-degree brain edema accompanying Type C HE [16]. This phenomenon could also be induced by ammonia in cultured astrocytes [17] and cerebral cortical slices in vitro [18].

While the effects of ALF on CBF in a clinical setting varied in different studies, patients with increased CBF developed brain edema more frequently than those with decreased or unchanged CBF, suggesting causal relation between the phenomena [19]. The role of hyperammonemia in evoking changes in CBF and the role of CBF changes in the development of brain edema were documented in animal model studies. While cerebral hyperemia and brain edema were found absent in asymptomatic portacaval-shunted rats, they were precipitated by subsequent infusion of ammonia [20, 21]. The sequence in which brain edema and hyperemia occur has not been finally established. The current view is that the primary signals (nitric oxide and other as yet not well-defined factors) are derived from the swollen brain cells (astrocytes) which by inducing hyperemia elicit a self-amplifying pro-hyperemic signaling train [20, 21]. Pharmacological decrease of CBF in hyperammonemic rats attenuated brain edema, bespeaking the increased CBF as a causative factor [22].

Recent evidence suggests the role of a vasogenic component of ammonia-induced brain edema. Studies with the magnetic resonance imaging technique revealed stage- and brain region-dependent development of vasogenic brain edema in rats with acute hyperammonemia [23] and ALF [24]. The above studies also have demonstrated that regions with vasogenic edema show increases of BBB permeability associated with increased activity of the matrix metalloproteinase 9 (MMP-9). MMP-9 was earlier found to contribute to BBB dysfunction in ALF by disrupting the brain endothelial tight junction proteins, but the specific role of ammonia was not investigated in this study [25]. A challenging question for future investigations is whether and to what degree the subtle BBB disruption underlying vasogenic brain edema reflects direct toxic action of ammonia on the endothelial cells of the BBB similar to the effects of ammonia on astrocytes or neurons.

Ammonia and Impairment of Cognitive and Motor Functions

HE is associated with impairment of learning and memory. The complexity of the changes makes it difficult to gauge the degree of contribution of ammonia and other pathogenic factors to a given neuropsychological symptom. Nonetheless, in animals, experimentally induced hyperammonemia not complicated by liver impairment have been shown to evoke alterations in some basic learning and cognition tests similar to those noted in animals with HE [26]. Cyclic GMP (cGMP) is a molecule critically involved in the different aspects of learning and memory, and the activity of NMDA receptor/NO/cGMP pathway is a marker of the cognitive functions. Both impairment of cognitive functions coupled with decrease of cGMP in the brain, and restoration of these functions upon pharmacological elevation of cGMP, are observed in cirrhotic patients and animals with HE and in animals with induced hyperammonemia in the absence of liver failure [26, 27].

HE in cirrhotic patients is associated with impaired motor activity and coordination. These changes are due to the altered functioning of neuronal circuits involving basal ganglia and the cerebral cortex, including altered modulation of these circuits by the metabotropic glutamate receptor (mGluR) activity. The altered response to mGluR activation and the motor function changes observed in rats with chronic liver failure were mirrored in rats with induced hyperammonemia in the absence of liver failure. For example, activation of mGluR1 by excess glutamate in the substantia nigra/ventral tegmental area axis is thought to be responsible for hypokinesia in chronic hyperammonemic rats [28].

Effectiveness of Blood Ammonia-Reducing Therapies as an Indicator of the Role of Ammonia in HE

As discussed elsewhere in this book, nonabsorbable disaccharides (lactulose) and antibiotics (rifaximin) are the routinely employed ammonia lowering treatment modalities based on the principle of combating gut flora. Although the improvement of the status of patients treated with these drugs supports the role of ammonia in the development of HE, the effects of these drugs on specific pathophysiological manifestations of HE have not been assessed quantitatively. More precise information was recently derived from the experiments with a newly invented drug, ornithine phenylacetate (OP). OP has a two-hit mechanism of action, where L-ornithine acts as a substrate for glutamine synthesis from ammonia in skeletal muscles, while phenylacetate combines with ammonia-derived glutamine to form phenylacetyl glutamine, which is subsequently excreted in the kidneys. Treatment of cirrhotic (bile duct ligated) rats with OP for a few hours reduced the originally increased arterial blood ammonia almost back to the control level, and the reduction was correlated with an equally effective attenuation of brain edema [29].

Cellular and Molecular Mechanisms Underlying Ammonia-Induced Impairment of Brain Function

Ammonia that enters the brain is metabolized in astrocytes to glutamine in an ATP-consuming reaction catalyzed by glutamine synthetase (GS). Astrocytes that are in a close topographical contact with the cerebral vascular endothelial cells forming the BBB are the primary victim of excess ammonia. The metabolic and molecular changes evoked by ammonia on astrocytes affect the astrocytic–neuronal interactions which impact on neuronal function. However, ammonia also affects the neurons directly. It is beyond the scope of this chapter to discuss the multiple ways in which ammonia affects the general metabolism of astrocytes and/or neurons: in most general terms, astrocytic and neuronal dysfunction under excessive ammonia load is critically coupled to decreased energy metabolism [30]. The text later focuses on two issues: (a) the mechanisms by which ammonia specifically contributes to astrocytic swelling and subsequent brain edema and (b) how the effects of ammonia on astrocytes and neurons are translated into the shift of balance of neurotransmission to net neural inhibition, which progresses with the advancement of HE.

Role of Ammonia in Astrocytic Swelling and Brain Edema

The current view is that the major metabolic impairments and cell membrane dysfunctions produced in astrocytes by ammonia evolve from astrocyte swelling by a vicious cycle of oxidative/nitrosative stress (ONS) and intracellular osmotic imbalance [16]. Swelling of cultured astrocytes treated with ammonia is invariably associated with intracellular accumulation of reactive oxygen and nitrogen species (RONS), including the highly toxic peroxynitrite [20]. One contributor to the increased RONS formation in ammonia-treated astrocytes or brain slices is excessive nitric oxide (NO) synthesis which may be associated with the overactivation of NMDA receptor, in a self-amplifying mechanism involving excessive glutamate release from astrocytes [16]. In an in vivo model of hyperammonemia, reduction of brain edema could be achieved upon administration of an NMDA receptor antagonist, memantine to the rat [31]. Excess of NO activates cGMP synthesis and subsequently increases protein kinase G activity, which also contributes to ammonia-induced astrocytic swelling [32]. The other contributing factor is the accumulation of reactive oxygen species, mainly the superoxide anion ($^{\bullet}O_2$) generated by NADPH oxidase [16]. Natriuretic peptides (NPs) (atrial natriuretic peptide, C type natriuretic peptide), which are natural components of the brain tissue, reduce RONS production in ammonia-treated astrocytes by reducing NADPH oxidase expression and activity [33]. This antioxidative effect is specifically mediated by the natriuretic peptide clearance receptor (NPR-C). These NPs and the NPR-C may act as targets for therapy development for HE in future. Pharmacological studies demonstrated increased activity of MAP kinases and NFκ-B. These act as carriers of downstream signals

critical for the translation of RONS accumulation to astrocytic swelling [34]. Ammonia may also contribute to astrocytic swelling by directly interfering with the cell membrane ion and water transport. The phosphorylation-dependent activation and/or increased expression of Na–K–Cl co-transporter 1 (NaKCC1) mediates astrocytic swelling in ammonia-treated astrocytes [35] and brain edema in rats with experimentally induced ALF [36].

There is compelling evidence for increased glutamine accumulation in ammonia-exposed astrocytes which is a key factor mobilizing the vicious circle of ONS and osmotic imbalance associated with HE. Early studies have shown that astrocytic swelling and cerebral edema in rats with hyperammonemia become reduced or even disappear upon co-administration of glutamine synthetase inhibitor, L-methionine-D/L-sulfoximine (MSO) [13]. In the clinical setting, increased ICP in ALF patients awaiting liver transplantation was found to correlate almost perfectly with the glutamine (Gln) content measured in the cerebral microdialysates collected from the patients at the bedside [12]. The role of glutamine in brain edema has long been interpreted to exert exclusively by its intracellular osmotic effect. The finding that glutamine is able to induce mitochondrial permeability transition (mPT) and swelling in isolated mitochondria dependent on uninterrupted glutamine uptake to mitochondria [37] stimulated studies in this field. The essence of the hypothesis, nicknamed the "Trojan horse" hypothesis, is that a portion of newly synthesized glutamine is transported from astrocytic cytosol to mitochondria and is degraded back to ammonia: the glutamine derived-ammonia would be responsible for astrocytic swelling and brain edema [38]. Recently, the paradigm of directly blocking the entry of glutamine to brain mitochondria (by the amino acid histidine) was successfully employed to ameliorate brain edema in a rat model of ALF [39]. Of note, ammonia also promotes astrocytic swelling by upregulating the peripheral benzodiazepine receptor (PBR); recently renamed the 18-kDa translocator protein (see also section "Ammonia and the Neurotransmitter Imbalance in HE" for its other roles) [40]. Since PBR is located on the outer mitochondrial membrane, it could be an easily accessible target for the glutamine-derived, mitochondrial pool of ammonia.

In summary, it is currently accepted that both the osmotic and the "Trojan horse" mode of action of glutamine contribute to its role as a mediator in ammonia-induced astrocyte swelling and brain edema.

Ammonia and the Neurotransmitter Imbalance in HE

Progression of HE through its different stages from normality excitation to coma is notable in ALF. In contrast, evolution to coma in chronic liver disease is much more a gradual increase in neural inhibition. This shift from neural excitation to inhibition mainly involves changes in the amino acid neurotransmitter systems: the excitatory glutaminergic and the inhibitory GABAergic system, along with some evidence implicating the serotoninergic system as swaying the balance further towards inhibition. Studies in hyperammonemic models in vivo and analysis of the effects of

in vitro treatment of astrocytes or neurons strongly suggest that ammonia is largely responsible for the neurotransmission imbalance in HE and disclosed some clues to details of the underlying mechanisms.

The Glutamatergic Transmission

Administration of ammonia to rats results in increased activation of NMDA type of glutamate receptor, which is the primary cause of neuronal damage in these animals [23]. Ammonia instantly increases extracellular accumulation of glutamate, which may reflect ammonia-induced depolarization as a triggering factor for a vicious circle of glutamate-induced NMDA-receptor-dependent glutamate release. Induced hyperammonemia is also associated with increased glutamate exocytosis in astrocytes [41] and decreased astrocytic glutamate uptake [42], which may partly engage the astrocytic NMDA receptors [16], and which further contributes to the increase of extracellular glutamate. Extracellular gluatamate remains elevated under prolonged exposure to elevated ammonia levels, which eventually leads to NMDA receptor inactivation [43]. This leads to the depression of the excitatory neurotransmission in different brain regions and to the cognitive impairment associated with the decrease of the NO/cGMP pathway. Reduction of cGMP synthesis may also be due to excessive accumulation of glutamine, which limits the availability of arginine for NO synthesis [44]. As mentioned earlier, hypokinesia, a typical locomotor dysfunction accompanying advanced HE, is associated with overactivation of mGluR1 by excess glutamine. The underlying mechanism appears related to altered modulation of the microtubule-associated protein 2 (MAP-2) phosphorylation by mGluR1 in the neurons [28].

The GABAergic Transmission

Hyperammonemia is associated with an increased GABAergic tone. The underlying mechanism is associated with the increased density of PBR, which are located in astrocytes and control the synthesis of pregnenolone-derived neurosteroids, some of which are positive modulators of the GABA (A)-benzodiazepine receptor complex. Increase of PBR binding coupled with increased synthesis of pregnenolone and its neuroactive derivatives were measured in hyperammonemic mice [45]. Increased concentrations of pregnenolone and its highly active derivative allopregnenolone were also found in the brain of cirrhotic patients who died in hepatic coma [46]. Recently, chronic hyperammonemia in rats was observed to specifically increase the GABAergic tone in cerebellum, and this effect was associated with concerted increases of (a) extracellular GABA, (b) a neurosteroid positively modulating the GABAA receptor activation, and (c) the amounts of relevant GABAA receptor subunits. Most interestingly, pharmacological blockade of GABAA receptors restored the previously reduced ability of cerebellum to synthesize cGMP in response to NMDA receptor stimulation and the cerebellar aspect of learning in these hyperammonemic rats [47]. The latter study highlights the role of imbalance between glutamatergic and GABAergic transmission in HE.

The Serotoninergic Transmission

Serotonin, the tryptophan-derived inhibitory monoamine, is involved in regulation of sleep, circadian rhythmicity and locomotion. Increased serotoninergic tone has been implicated in the derangement of the above parameters in HE patients and experimental animals. In addition, increased serotonin accumulation and turnover in the brain were positively correlated with the degree of hyperammonemia [48]. Increased serotonin synthesis in HE-affected brain is associated with increased tryptophan uptake from the circulation, which occurs by exchange with glutamine. Increased tryptophan/glutamine exchange was verified in the rat cerebral capillaries treated with ammonia in vitro or derived from hyperammonemic rats [49].

Concluding Comments: Gaps in the Knowledge of Ammonia Neurotoxicity

The data reported in this chapter strongly support the key role of ammonia in the development of major HE symptoms and elucidate many of the underlying biochemical and molecular mechanisms. In general terms, the pattern of responses to ammonia noted in the CNS cells or brain slices in vitro and in the brain of animals with hyperammonemia corresponds relatively well with the changes observed in patients or experimental animals with HE. However, in light of the recent finding that hyperammonemia evokes an inflammatory response in the CNS engaging the CNS microglia [50], data obtained with cultured astrocytes or neurons will have to be interpreted with caution. Moreover, there may be a need for reinterpretation of some older studies in which the brain was regarded as a homogenous entity. As discussed in this chapter, studies of the last few years disclosed a remarkable brain region variability of the responses to ammonia concerning edema [23] or molecular mechanisms underlying cognition [47]. However, the contribution of ammonia to some of the common manifestations of HE still remains to be established beyond doubt. Events such as alterations of the dopaminergic or cholinergic transmission, and changes in the accumulation or intercellular fluxes of inhibitory neuromodulators: sulfur amino acid taurine, and serotonin metabolites kynurenic acid and oxindole, which frequently accompany HE, have not been analyzed in great detail. This needs to be done under the conditions mimicking hyperammonemia and in the absence of other factors precipitating HE. Answers to the above questions are needed to fully appreciate the specific role of ammonia in HE.

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