Exercise-Induced Hyperammonemia: Peripheral and Central Effects

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Abstract

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The intent of this paper is to review the recent literature on exercise-induced hyperammonemia (EIH) and to compare the current interpretations of ammonia accumulation during exercise with the recognized clinical symptoms of progressive ammonia toxicity. In doing so, we will speculate on possible exercise-induced symptoms of CNS dysfunction which could result from elevated ammonia during intense short-duration or prolonged exercise.

Ammonia is a ubiquitous metabolic product producing multiple effects on physiological and biochemical systems. Its concentration in several body compartments is elevated during exercise, predominantly by increased activity of the purine nucleotide cycle (PNC) in skeletal muscle. Depending on the intensity and duration of exercise, muscle ammonia may be elevated to the extent that it leaks (diffuses) from muscle to blood, and thereby can be carried to other organs. The direction of movement of ammonia or the ammonium ion is dependent on concentration and pH gradients between tissues. In this manner, ammonia can also cross the blood-brain barrier (BBB), although the rate of diffusion of ammonia from blood to brain during exercise is unknown. It seems reasonable to assume that exhaustive exercise may induce a state of acute ammonia toxicity which, although transient and reversible relative to disease states, may be severe enough in critical regions of the CNS to affect continuing coordinated activity. Regional differences in brain ammonia content, detoxification capacity, and specific sensitivity may account for the variability of precipitating factors and latency of response in CNS-mediated dysfunction arising from an exercise stimulus, e. g., motor incoordination, ataxia, stupor.

There have been numerous suggestions that elevated ammonia is associated with, or perhaps is responsible for, exercise fatigue, although evidence for this relies extensively on temporal relationships. Fatigue may become manifest both as a peripheral organ or central nervous system phenomenon, or combination of both. Thus, we must examine the sequential or concomitant changes in ammonia concentration occurring in the periphery, the central nervous system (CNS), and the cerebrospinal fluid (CSF) induced by any effector, not only exercise, to interpret and rationalize the diverse physical, physiological, biochemical, and clinical symptoms produced by hyperammonemic states. Since more is known about elevated brain ammonia during other diverse conditions such as disease states, chemically induced convulsion, and hyperbaric hyperoxia, some of these relevant data are discussed.

Key words

Ammonia, brain, central fatique, peripheral fatigue, purine nucleotides

Abbreviations

The following abbreviations are used in the text, figures, and tables.

AAA = aromatic amino acid
AcCoA = acetyl coenzyme A
ADP = adenosine diphosphate
AMP = adenosine monophosphate
Asp Ac = aspartic acid
ATA = atmospheres absolute of pressure
ATP = adenosine triphosphate
BBB = blood brain barrier
BCAA = branched-chain amino acid
BC-∝-keto acid dehydrogenase = branched-chain alpha-keto acid dehydrogenase
BC 2-oxo acid dehydrogenase = branched chain 2-oxo acid dehydrogenase
CSF = cerebrospinal fluid
CNS = central nervous system
GAD = glutamate decarboxylase
ECS = extracellular space

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EIH = exercise-induced hyperammonemia
EPEN = ependyma
FFA = free fatty acid
FG = fast-twitch glycolytic muscle
FOG = fast-twitch oxidative glycolytic muscle
GABA = gamma-aminobutyric acid
GLN = glutamine
GLU = glutamate
5-HT = 5-hydroxytryptamine
IMP = inosine monophosphate
ISOLEU = isoleucine
∝-KG Ac = alpha-ketoglutaric acid
Lac/Pyr = ratio of lactate to pyruvate
LEU = leucine
MAO = monoamine oxidase
∝-methyl-p-tyrosine = alpha-methylparatyrosine
NAA = neutral amino acid
NADH/NAD = ratio of reduced to oxidized nicotine adenine dinucleotide
NH_3 = ammonia
NH_4^+ = ammonium ion
NE = norephinephrine
OAA = oxaloacetic acid
OHP = oxygen at high pressure
PCr = phosphocreatine
PFK = phosphofructokinase
PHE = phenylalanine
PNC = purine nucleotide cycle
Pyr Ac = pyruvic acid
SO = slow oxidative muscle
Succ Ac = succinic acid
TRP = tryptophan
TYR = tyrosine
VAL = valine

Note: In this paper, NH_3 or ammonia are also used for the sum of NH_3 (ammonia) and NH_4^+ (ammonium ion), recognizing that NH_3 and NH_4^+ are in equilibrium ($NH_3 + H^+ \rightarrow NH_4^+$). The pK_a of this reaction is 9.3; thus, at physiological pH, most ammonia is present as NH_4^+.

General Ammonia Metabolism

Whatever the source or fate of metabolically produced ammonia, there always seems to be some spilled to the blood. Thus, ammonia formed in one organ may be distributed widely in the body via the circulation.

Ammonia generated in the gut (169, 176) from protein digestion and deamination of glutamine enters the portal venous circulation in the amount of several grams per day in normally active, well-nourished adults (152). Peripheral arterial concentration of ammonia is kept relatively low at rest, as shown in Table 1 (34), since the liver efficiently removes most gut-derived ammonia for excretion or recirculation as urea, creatinine, glutamine, and ammonium ion (60, 61, 62, 152).

Gut-derived nitrogen from the intestine appears in the circulation mainly as urea and glutamine, whereas labeled ammonia-nitrogen from tissue other than the gut appears in the amide group of glutamine (37, 148). The kidney releases NH_3 predominantly to the urine for excretion, although

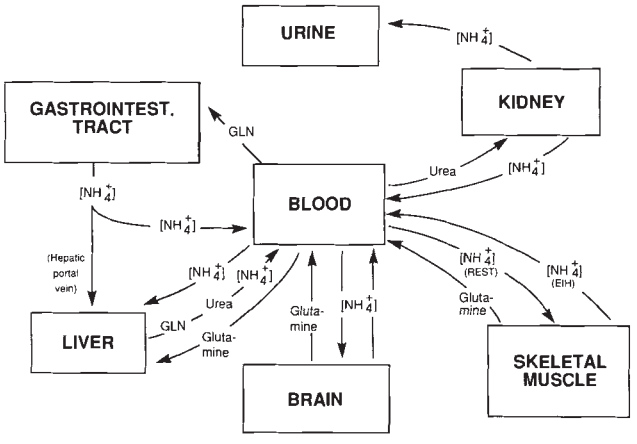

Fig. 1 Major organs of ammonia formation, utilization, and circulation either as free base NH_3, ammonia ion NH_4^+, or related nitrogenous by-products [modified from Kvamme (87), Fig.1, with permission].

Table 1 Normal concentrations of ammonia in human blood and CSF and in rat blood, CSF, and brain

	Ammonia concentration (μM)	Selected references
Human		
Arterial blood/plasma	22–113	42, 84, 91
Venous blood/plasma	20–25	5, 6, 24, 51, 153, 179
CSF	20–100	46, 162
Rat		
Brain	150–300	9, 32, 33, 41, 68, 70, 142, 144
Arterial blood/plasma	50–250	9, 33, 53, 70, 142, 144
Venous blood/plasma	50–80	39
CSF	100–300+	68, 70
Portal venous	350	34
Hepatic venous	40	34

(Some data are extrapolated from graphs. Tissue concentrations were interpreted as $\mu mol \cdot kg^{-1}$ wet weight, modified from ref. 34, Table 1, with permission.

some is also liberated to systemic blood via the renal vein (77). It may be noted that extrahepatic shunting of a hyperammonemic load to the systemic circulation is also evident in disease states of the liver, e. g., during the development of hepatic encephalopathy (4, 119). The extended life of metabolically produced ammonia is emphasized by the pathway of ammonia escaping the gut and liver to be metabolized by extrahepatic organs to glutamine. Thereafter, glutamine may again be taken up by the gut as an energy source until its remaining protein-nitrogen is excreted as urea, and its carbon skeleton as carbon dioxide and water (61, 62, 118).

To these evident intra organ exchanges must now be added the complex two-way interchange between the brain and systemic circulation. Lockwood et al. (91) have described ammonia transport into the brain (discussed later in this review). In addition, recent evidence, although is has been disputed (96), indicates that ammonia is returned to the circulation from the CSF either as glutamine (26, 79, 80, 81) or as ammonia (31, 34, 125).

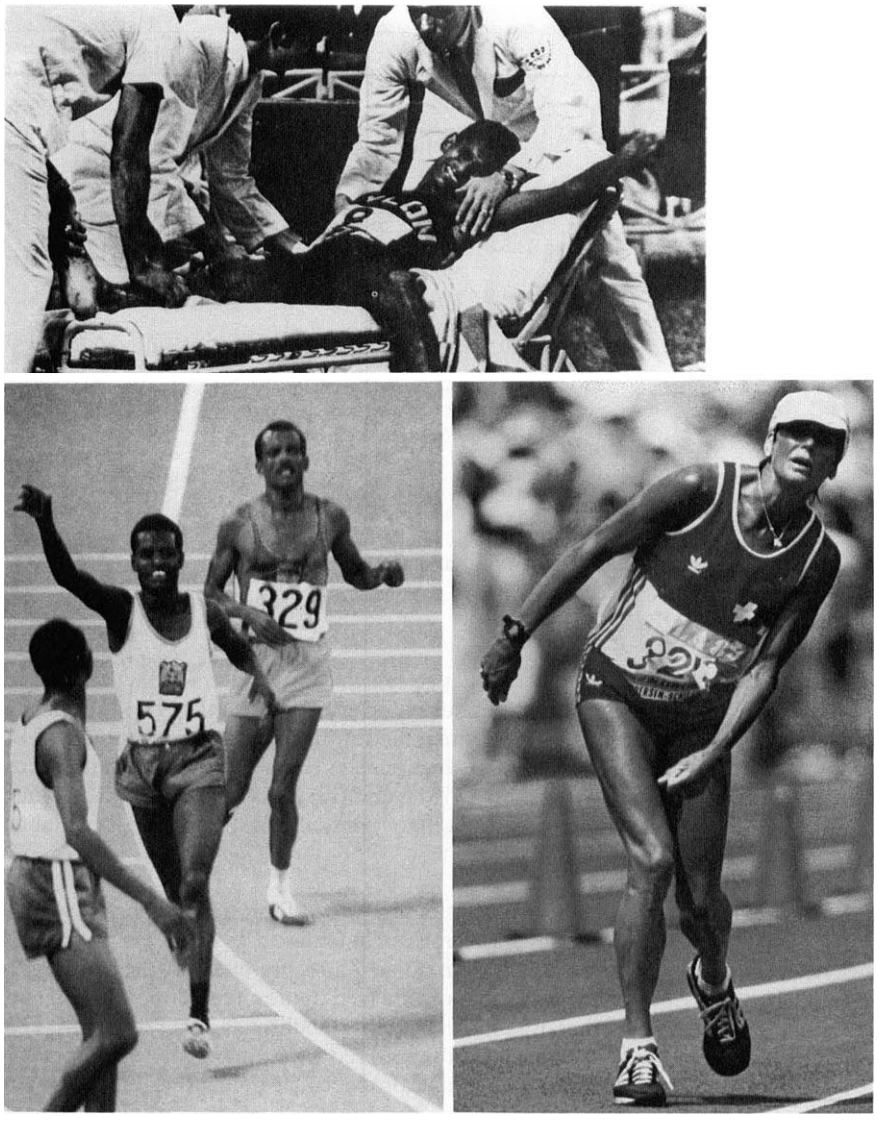

Fig. 2 Physical signs of peripheral and CNS fatigue resulting from the chronic sustained exhaustive effort of long-distance running under alien environmental conditions. Middle: at altitude, the left runner has been lapped, the middle runner who wins the race shows little physical distress, while the right runner shows fatigue and motor incoordination. Top left: at altitude, a runner suffers complete physical collapse and obvious pain. Right: the marathon runner demonstrates classical ataxia. Stupor is also reflected by the vacant facial expression.

This complex metabolism, intra organ shunting, and excretion of nitrogenous products is shown diagramatically in Fig. 1 (87).

At the cellular level, ammonia production in different tissues is principally from:

- Deamination of glutamine catalyzed by glutaminase (88, 161):
  L-glutamine + $H_2O \rightarrow$ L-glutamate + NH_3

- The reversible oxidative deamination of glutamate catalyzed by glutamate dehydrogenase (13,14, 154):
  glutamate + $NAD(P)^+ + H_2O \rightarrow$ ∝-ketoluarate + NAD (P)H + $H^+ + NH_3$

- Action of the PNC (principally in muscle but also in the brain and other organs) (92, 93, 136, 137, 157):
  AMP + $H_2O \rightarrow$ IMP + NH_3
  IMP + asparate + GTP → adenylosuccinate + GDP + Pi
  Adenylosuccinate → AMP + fumarate
  Equivalent to:
  Asparate + GTP + $H_2O \rightarrow$ fumarate + GDP + Pi + NH_3

- Deamination of other amino acids
  Transamination to an ∝-keto acid, followed by oxidative deamination

- Oxidative deamination of monoamine neurotransmitters by MAO (63, 115) which may be an important regional source of ammonia in the brain:
  $R\text{-}CH_2NH_2 + O_2 + H_2O \rightarrow R\text{-}CHO + NH_3 + H_2O_2$

Hyperammonemia of Exercise

In the exercise physiology literature, ammonia produced by exercising muscle has been associated with fatigue. Previous review of EIH (8, 105) have provided a historical perspective of the association of muscle-linked hyperammonemia to exercise-induced fatigue. Comprehensive recent reviews also clearly indicate the central role played by ammonia in the biochemistry and physiology of the brain (13, 14, 34, 39, 87). It would seem that, as a consequence of their shar-

Table 2 Exchange of NH_3 across the leg and splanchnic circulation at rest and during exercise

	Rest*	Submax exericse*			Maximum**
Relative work Intensity (%$\dot{V}O_2$max)	Basal	35±2	55±3	80±3	100
Exercise time (min)	0	15	30	45	4
Arterial plasma Ammonia ($\mu mol \cdot l^{-1}$)	21.8±1.7	27.4±2.1	45.6±5.8	84.4±12.1	112±17
Leg exchange ($\mu mol \cdot min^{-1}$)	−2.4±0.5	3.6±2.5	14.4±1.9	45.7±15.3	89±21
Leg blood flow ($l \cdot min^{-1}$)	0.49±0.03	2.31±0.15	3.55±0.14	4.74±0.18	6.32±0.25
Splanchnic exchange ($\mu mol \cdot min^{-1}$)	−12.4±1.8	−11.4±1.1	−13.7±1.3	−14.8±3.6	n. m.
Hepatic blood flow ($l \cdot min^{-1}$)	1.27±0.12	1.01±0.06	0.72±0.06	0.40±0.07	n. m.

Data from * ref. 42 and ** ref. 84, with permission. Values are reported as mean±SEM. nm=not measured. Negative sign for flux rates denotes net uptake.

ing a common circulation and a pervasive, blood-soluble, toxic metabolite, the overt features of so-called PERIPHERAL and CENTRAL FATIGUE, i. e., muscle weakness, motor incoordination, stupor, and ataxia, may be inextricably linked (Fig. 2).

During exercise a shift takes place both in the predominant source of metabolic ammonia production and also the blood supply to major organs (131). Active skeletal muscle now becomes a major source of ammonia (5, 6, 24, 35, 38, 100) by deamination of AMP to IMP in a cyclical process called the purine nucleotide cycle (PNC) (92). This cycle is also active in the brain (136, 137), although a change in its activity during exercise has yet to be investigated. There has been some argument about whether the kinetic characteristics of the enzymes catalyzing each step of the PNC in muscle are altered when physiological conditions deviate from those at rest. Meyer and Terjung have suggested that the deamination step of the PNC occurs preferentially during exercise, while the reamination of IMP to AMP procedes more favorably during recovery (102). Flow of AMP through the PNC may be affected by other metabolic reactions since AMP may also be degraded by dephosphorylation to adenosine. The potential for ammonia production from AMP in any particular fiber type depends on the ratio of the enzymes 5' nucleotidase (AMP phosphatase) to AMP deaminase, which varies as a function of the oxidative capacity of striated muscle (21, 100, 158). Tissues with a high potential for ammonia production, as estimated by high activity of AMP deaminase, appear to have a relatively low potential for adenosine production. The relative distribution of these enzymes in striated muscle is:

(1)AMP deaminase:
FG > FOG > SO > heart

(2)5' nucleotidase (AMP phosphatase):
heart > SO > FOG > FG

Other potential contributors to EIH include: (i) deamination of amino acids, possibly during long endurance performance which stimulates protein uptake and amino acid catabolism in skeletal muscle (91), particulary branched-chain amino acids, (ii) decrease in renal blood flow during exercise, which could reduce renal uptake and excretion of ammonia (131), and (iii) reduced liver blood flow and extra hepatic shunting of ammonia to the systemic circulation (42, 44, 84, 131).

It is evident, therefore, that hyperammonemia accompanying exercise in humans arises from several sources. During EIH the ammonia load represented by the above reactions may be temporarily held in the circulation before uptake by other organs for further catabolism and excretion, or it may remain permanently buffered in the blood by incorporation into other nitrogenous products.

Factors influencing the rate of ammonia production by skeletal muscle during exercise include relative muscle fiber composition (38, 170), exercise intensity, and exercise duration (5, 6, 24, 55, 175), which determine the demand for ATP formation as well as the extent of motor unit/muscle fiber recruitment (64).

Previous suggestions that production of ammonia may stimulate glycolysis (94, 150) and therefore lactate production have been challenged (55), as has been the role that ammonia may play in buffering hydrogen ion during exercise (84). Recent investigations have demonstrated clearly that EIH is not an obligatory adjunct to exercise-induced lactacidosis (55). The environmental PO_2 level appears to have paradoxical effects on EIH. Hyperoxia results in an elevated muscle and plasma ammonia (55) but less elevation of lactate (10, 55, 73, 155, 171, 177), whereas hypoxic acclimation reduces EIH, at least during submaximum exercise (179). These apparently contradictory results also contrast with initial experimental evidence that ammonia is produced predominantly from fast-twitch muscle, particularly during intense (anaerobic) exercise (38, 100, 101, 170).

Fate of Ammonia in EIH

Because of increased muscle NH_3 production during exercise, there is a shift from the net uptake of ammonia in skeletal muscle observed at rest to a large net efflux into the circulation during exercise in humans, which increases in magnitude as exercise intensity increases (Table 2) (42, 84). The important function of skeletal muscle in removing circulating ammonia at rest (72, 91) may therefore be reduced or reversed (42, 84), although nonacitve muscle may still provide a venue for the uptake of ammonia from the blood.

The mounting hyperammonemic load faced by the body during exercise is evident in a rising blood ammonia concentration, although the imbalance between ammonia production and removal may be interimly contained by the blood and exercise continued for a considerable period. The liver, which normally regulates blood ammonia, appears not to increase its rate of ammonia extraction ($\cong$ 12–15 $\mu mol \cdot min^{-1}$) during exercise, although the arteriovenous difference for NH_3 across the liver must increase since blood flow to the liver decreases during exercise (Table 2) (42, 84). Because the circulating ammonia concentration is increased, every area of the body is now exposed to a potential hyperammonemia.

What mechanisms restrain exercise hyperammonemia? The current literature attributes exercise-induced ammonia flux principally to the action of MUSCLE (production), BLOOD (circulation), and LIVER (detoxification). This appears inadequate either during submaximal or intense exercise. Thus, we view the blood as an important storage compartment with a role in temporarily accommodating and redistributing an acute or chronic ammonia load in plasma (33, 60, 61, 118). If existing modes of blood detoxification become limited during exercise either by reason of decreased blood flow to vital organs or by saturation of their detoxifying power, we speculate that little protection would then remain to the brain against a chronic and increasing ammonia load. It is evident that blood ammonia is elevated during exercise, and it is equally well documented that ammonia crosses the blood-brain barrier (from blood to brain) under the influence of both concentration and pH gradients. Lockwood et al. (91) suggest that in normal subjects (at rest) NH_3 is taken up from blood by liver, skeletal muscle, bladder, and brain, and that within the brain itself, ammonia uptake is greatest in grey matter, i. e., cell bodies. Currently little information is available on the accessibility of circulating blood ammonia to the brain during exercise in normal healthy individuals. We have found only one paper which reports elevated brain ammonia in rats during EIH (113). While the absolute values reported here in both blood and brain seem somewhat high, the pattern of their elevation is consistent with the observed elevation of blood and brain ammonia in other conditions (encephalopathy, hyperoxia, etc.; 52, 76, 133, 142, 144).

Pattern of Ammonia Accumulation in Organs

Exercise is one of a variety of stimuli effecting a transient or chronic hyperammonemia. The common pattern of clinical symptoms which signifies developing toxicity induced by such disparate conditions as chemical poisoning, electric shock disease, or hyperoxia seems to proceed from peripheral involvement to central (CNS) dysfunction (34, 43, 117, 120, 151). It seems unlikely, therefore, that the accompanying pattern of organ hyperammonemia differs markedly in response to the different stimuli. A hierarchical picture of exercise-induced ammonia accumulation in major organs may perhaps be inferred from experiments in which hyperammonemia has been induced by a different stimulus and specific tissue ammonia measured. Fig. 3 (144) shows the pattern of developing hyperammonemia at rest in animals in response to an incremental hyperbaric oxygen stimulus, sufficient eventually to produce convulsions, a condition reversible when the stimulus is removed. During such exposure, the liver is the first organ to show a sustained progressive ammonia elevation, followed by the heart, skeletal muscle, serum, and brain. Convulsive activity usually accompanied a brain ammonia concentration of 0.90–1.10 $\mu mol \cdot g^{-1}$. Confirmation of whether a similar temporal order of developing tissue hyperammonemia exists during an incremental exercise stimulus to exhaustion awaits development of adequate experimental techniques to determine brain ammonia flux during exercise in humans. However, the rise of blood ammonia above some critical level with other stimuli seems to signal the onset of CNS symptoms severe enough to curtail

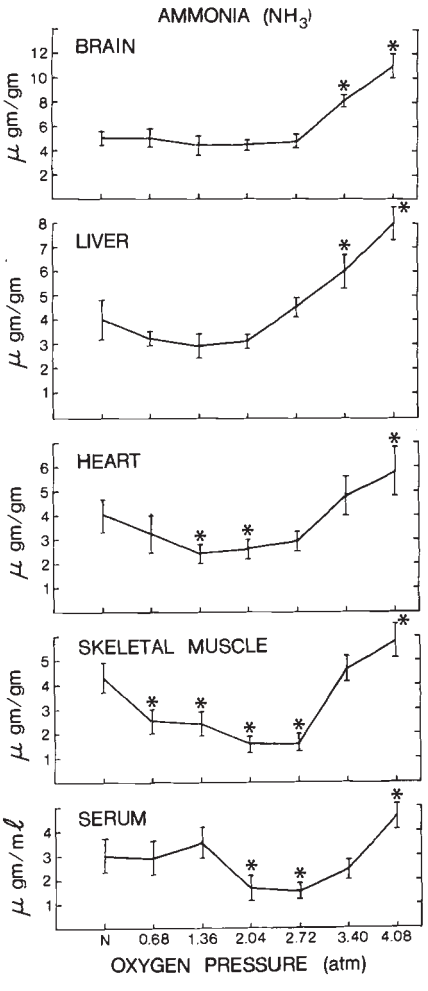

Fig. 3 The progressive hierarchical elevation of ammonia concentration in various rat tissues due to a hyperoxic stimulus in resting animals up to an oxygen pressure producing convulsion [from Singh and Banister (144), Fig. 1, with permission].

coordinated activity in animals and man. Thus, acute ammonia loading of rats with a preexisting low-grade hyperammonemia induces acute physical (106) and electrophysiological (22, 124) signs of CNS disruption.

Fate of Ammonia in the Brain

Ammonia is an important metabolite in endogenous brain metabolism. Under resting conditions the ammonia content of the brain is maintained at a relatively low concentration (Table 1) (34). Any substantial extraneous influx of NH_3 across the BBB may seriously unbalance its equilibrium. It is now acknowledged that ammonia has access to the brain from the blood predominantly as free base NH_3, but also as the NH_4^+ ion (31, 32, 34, 125). Its movement is directly dependent on concentration and pH gradients (32, 33, 91, 147, 167). When ammonia is presented to brain tissue in a large single dose, at a rapid rate, or in conjunction with an already established elevated condition, existing endogenous detoxification mechanisms are unable to contain the increased ammonia load, and the brain ammonia concentration rises rapidly (53, 67). Over a period of continuing hyperammonemic challenge, the toxic central effect of ammonia becomes magnified and manifest via the CNS causing widespread rather than local dysfunction, as noted in the previous section.

The glutamate-glutamine system (14, 15) is a principal detoxification pathway for ammonia in the brain. Evidence for this is that following continuous common carotid infusion of nitrogen label from [^{15}N] ammonia, the label rapidly appears principally in the amino group of glutamate and in both glutamine nitrogens (37, 148). Labeled carbon appears in glutamine within 1 min of a large L-[U^{14}C] glutamate infusion intracisternally (18), indicating a rapid turnover in a small active glutamate pool in the astrocyte rather than in a whole brain glutamate compartment (Fig. 4). Glutamine appears to act as a principal intermediary of two-way ammonia-nitrogen exchange across the BBB (1,2, 39, 49, 53) in the regulation of brain ammonia. A direct loss, < 3% of the total brain NH_3 free base, occurs at rest (31, 125). The extent of this loss or gain during exercise, however, is unknown.

In associated reactions, glutamate may also undergo oxidative decarboxylation by glutamate decarboxylase (GAD) to form GABA (65, 66, 130). Glutamate and GABA, respectively, have defined excitatory and inhibitory actions as neurotransmitters, while glutamine has no known neurotransmitter action (86).

Regional differences in the capacity for ammonia removal (buffering) have been demonstrated for brain tissue. Butterworth et al. (25) have suggested that the cerebral cortex (CC) has only a limited capacity to remove blood-borne ammonia by the formation of glutamine compared with the brainstem. This is due to a moderate decrease of glutamine synthetase (GS) activity in the CC accompanying hyperammonia. Thus, ammonia concentration may become regionally elevated in a manner which could be disruptive to coordinated activity. As an example, inhibitory postsynaptic transmission (IPSPs) in the brain is directly and negatively affected by hyperammonemia (76, 95, 121, 123). The resultant disinhibition in regulatory control is almost certainly associated with

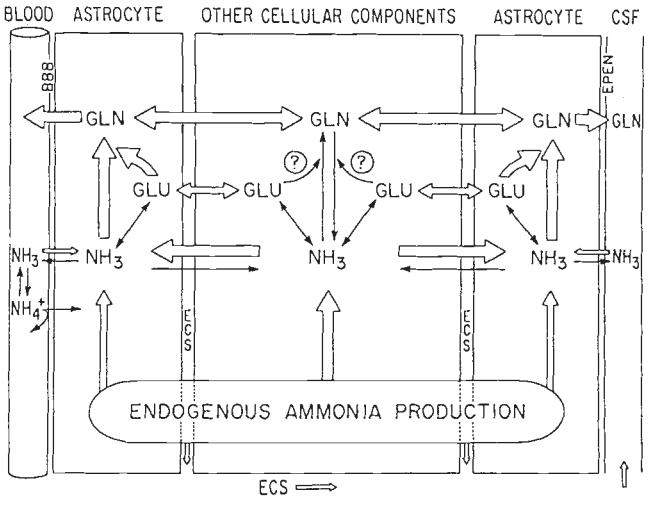

Fig. 4 Compartmentation of ammonia metabolism in rat brain. Arrow thickness indicates the relative importance of various pathways [from Cooper and Plum (34), Fig. 1, with permission].

developing clinical symptoms of ammonia toxicity in humans. Neurological symptoms ascribed to ammonia toxicity include abnormal locomotor behavior (74), altered sleep pattern (12), and modification of neuromuscular coordination (52).

Ammonia from Protein Catabolism During Exercise – Its Influence on CNS Toxicity

Exercise exerts several important effects on protein metabolism which may be relevant to CNS toxicity. Firstly, it stimulates catabolism of amino acids in muscle (principally BCAAs) and contributes to elevated blood ammonia (90); secondly, the hyperammonemia accompanying exercise increases the permeability of the BBB to NAA relative to other amino acids (26, 48, 97, 138); thirdly, the circulating BCAA fraction of the NAA group is reduced relative to the AAA fraction, which are neurotransmitter precursors, probably due to enhanced BCAA uptake by active skeletal muscle (2, 20, 28, 113). Thus, the AAAs (Phe, TYR, and TRP) are positioned more favorably for uptake across the BBB (79, 80, 81).

Skeletal muscle has a well-developed capacity for amino acid catabolism, particularly the BCAAs (LEU, ISOLEU,VAL) (90). The necessary enzymes for degradation of BCAAs are found principally in skeletal muscle (103). Exercise also increases the activity of a principal enzyme (BC 2-oxo acid dehydrogenase) which continues the degradation of BCAAs, after an initial transamination, to glucogenic and ketogenic residues (165).

Enhanced uptake of the neurotransmitter precursors (PHE, TYR, and TRP) may contribute to a neurotransmitter imbalance within the CNS (3, 79, 80, 81). Romanowski and Grabiec (128) were first to report an exercise-induced increase in brain serotonin (for which TRP is the precursor) and were also probably the first to speculate on its potential role in mediating CENTRAL FATIGUE. Several subsequent studies have supported this theory, reporting an exercise-induced decrease in the ratio of BCAA/AAA in blood, or an increase in the brain uptake of AAA and brain

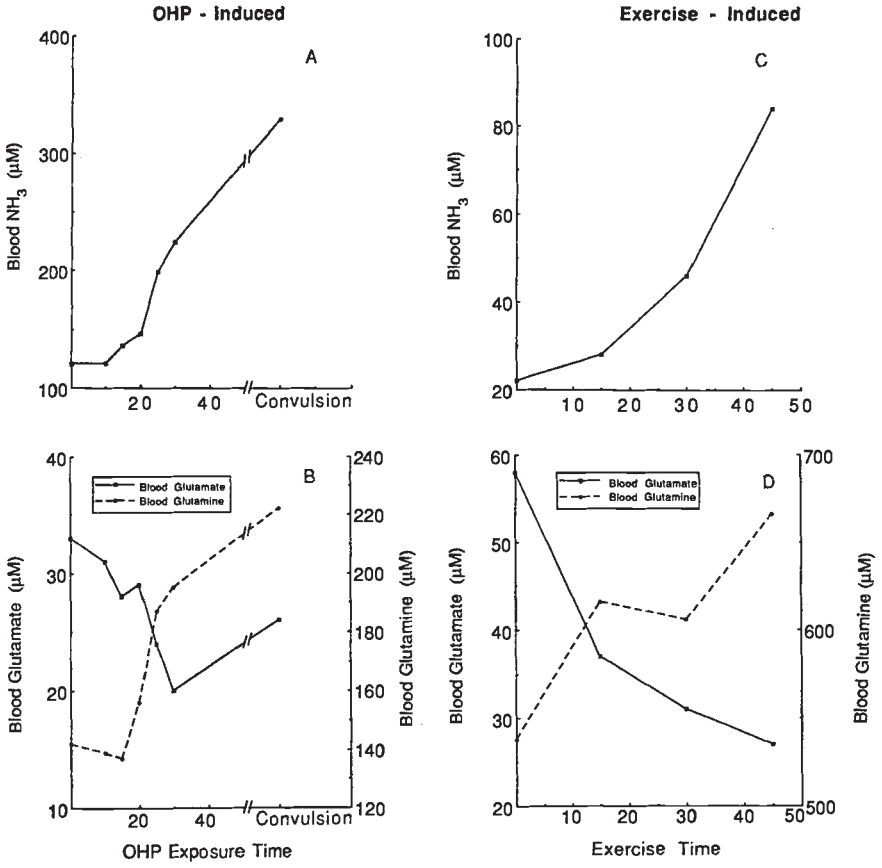

Fig. 5 Corresponding changes in blood ammonia, glutamate, and glutamine induced by high pressure oxygen (OHP) leading to convulsion (5A, 5B) and by exercise-induced hyperammonemia (5C, 5D). Quantitative differences may be accounted for by species differences [data from Singh and Banister (142) (Fig. 5A, 5B) and Eriksson et al. (42) (Fig. 5C, 5D), with permission].

serotonin concentration (2, 20, 28, 29, 113). Elevated brain serotonin resulting from exercise could trigger such fatigue-related symptoms as lethargy, appetite suppression, and sleep disorders (23, 126). A recent report, however, seems to challenge these ideas, indicating that TRP ingestion prior to exercise, which would potentially increase brain serotonin synthesis, enhanced treadmill running endurance by almost 50% (140). Increased serotonin concentration was postulated to decrease sensitivity to pain, thus allowing intense exercise to continue significantly longer.

Chronic elevation of brain NE and serotonin (23), both of which are synthesized from AAA precursors, has also been reported in response to endurance training. A potentially negative aspect of the above exercise-induced AAA response is that endogenous brain ammonia could be significantly increased by enhanced deamination of brain catecholamines and serotonin. Augmented catecholamine turnover with no change in the whole brain catecholamine pool size has been clearly demonstrated in rats during OHP exposure leading to brain hyperammonemia, using an α-methyl-p-tyrosine block of catecholamine synthesis (9).

In spite of the above negative effects, the hyperammonemia of exercise may also induce a balancing set of reactions important for brain homeostasis which partially restores the glutamate carbon and nitrogen pool. Active CO_2 fixation in the astrocyte (cells in the brain which bridge between capillaries and neurons) is stimulated by ammonia (19, 164) and replenishes the carbon skeleton for GLU and GLN synthesis. Glutamate-nitrogen may also be replenished in the astrocyte by amino acid uptake from the blood, principally from BCAAs (45), in addition to active uptake of GLU, ASP, and GABA (65, 66). By contributing to replenishment of the astrocyte GLU pool (32), BCAA uptake by the brain, which continues in spite of a reduced plasma BCAA/AAA ratio, is viewed by some investigators as occupying a pivotal role in the glutamate-glutamine cycle of the brain (34). During exercise the absolute plasma concentration of BCAAs actually rises, and is two to three times higher than AAAs (2, 20, 113). Although the ratio of BCAA/AAA declines steadily throughout endurance exercise, it seems to remain above 2.0 (20, 113). The importance of continued BCAA uptake by the brain is illustrated by the reported effect that restoration of the "normal" brain BCAA/AAA ratio (by BCAA infusion) has upon reducing ammonia-induced toxicity in hyperammonemic animals (48) and possibly in humans with liver disease (127, 129).

Although disputed (96, 97), it has been proposed that the uptake of BCAAs relative to AAAs is facilitated by a concomitant GLN efflux of ammonia-nitrogen from the brain (26, 79, 80, 81, 127). Glutamine is reportedly uniquely synthesized *in situ* in brain microvessel epithelium and astrocytes by enhanced glutamine synthetase activity (26, 50, 82, 108, 112). Ammonia-induced disruption of the fine structure of the astrocyte-microvessel anatomical site of the BBB (36, 109, 111, 163) may also increase its permeability to NAAs, as noted above.

Comparison of the Ammonia - Glutamine System in Blood and Brain: An Extrapolation to Exercise

Evidence for a developing ammonia toxicity in the brain directly attributable or secondary to EIH is singularly lacking in the literature. Only one paper seems to have

Table 3 Concentration of ammonia, glutamate, and glutamine in blood and brain produced by exercise, in disease states, or at the onset of coma or convulsion by other toxic stimuli. Original sources are indicated by reference numbers in the table

	Blood			Brain			
	NH_3	GLU (μM)	GLN	NH_3	GLU ($\mu mol \cdot g^{-1}$)	GLN	Selected references
Human							
Sub max. 80% max	84	27	666				42
Exh. ex 97%	210	163	524				84
Exh. ex. 100%	240						6
Exh. ex. (run)	130		700				5
Exh. ex. (cycle)	90						35
Exh. ex. (handgrip)	174						145
Pathological states (with neurological symptoms)	62–1490						76
Liver disease	62–264						91
Rat							
Ex.	530			2.94			113
Exh. ex.	350						104
Exh. ex.	540						100
Ex. 2-h run		147	594				28
NH_4C1 infusion				0.44	2.0	5.57	159
				1.00		5.00	159
OHP (convulsion)	452	32	256	1.13	5.1	3.82	7, 9, 142, 143, 144
CO_2 breathing		61	75.4				75
PCA	400			Cortex: 0.5		15	25
	400			Brainstem: 0.4		6.5	25
PCA (coma)	1500			Cortex: 4.5		15	25
	1500			Brainstem: 3.0		14.5	25
Lindane (convulsion)				1.25		6.25	114
Telkodrin				2.5		7.0	59

Some data are extrapolated from graphs. PCA=portacaval anastamosis; Ex.=exercise; Exh. ex.=exhaustive exercise.

addressed this topic, almost incidently, during the study of exercise-induced stimulation of neutral amino acid transport into the brain (113). It is evident, however, that OHP exposure of the rat produces a corresponding pattern of elevation in blood ammonia and glutamine, and a concomitant reduction in blood glutamate as has also been observed during intense fatiguing exercise in humans (Fig. 5) (42, 142).

Several papers have described similar changes in these metabolites both in blood (human and animal) and brain (animal) during the course of developing hyperammonemia induced by different stimuli, including exercise (Table 3). Some data could not be included as they were reported as ΔNH_3, not as absolute values (e. g., 38). This is in spite of species differences and variability of analytical techniques introduced in the various reports (see table for cited references). The similarity in order of magnitude of the final ammonia concentration *in extremis,* i. e., either at exhaustion or convulsion, produced by exercise or a variety of other toxic stimuli in blood and brain, respectively, is compelling. It may indicate that an upper limit of tolerable organ hyperammonemia exists in the whole brain or in some critical brain compartment, above which signs of CNS dysfunction become apparent.

Fig. 6 shows that the pattern of change of ammonia, glutamate, and glutamine concentration is similar in both blood and brain during the course of animal exposure to OHP at 5.5 ATA leading to convulsion. GABA and glutamate decrease while concomitantly brain ammonia and glutamine increase (142).

Metabolic Effects of Ammonia

Details of the metabolic effects of ammonia have been reviewed previously (34, 87, 105). A summary is presented in Table 4. It seems the multiple secondary effects of exercise hyperammonemia may be traced first to an energy deficit in the periphery enhancing ammonia production by the PNC and BCAA catabolism which leads more importantly and finally to a depletion of ATP in critical regions of the brain.

The reported effect of ammonia on specific enzyme-mediated reactions and associated metabolic pathways suggests that ammonia may alter the rate of energy production and subsequent availability of ATP. An ammonia concentration of 1–3 $\mu mol \cdot g^{-1}$ in the brain depletes ATP and elevates ADP and AMP, particularly in the brainstem (33, 53, 67). Brain ammonia attains these values in several hyperammoneic conditions (Table 3).

The reduction in oxidative metabolism through the Krebs' cycle and electron transport chain may not be matched by increased glycolysis induced by hyperammonomia, although conflicting observations limit precise interpretation of the role played by ammonia in intermediary metabolism.

Theoretically, the diversion of glucose carbon to glutamine synthesis through CO_2 fixation induced by hyperammonemia in the major detoxification process in the brain may also represent a loss of 28 of 38 equivalents of ATP potentially available from glucose oxidation (30). CO_2 fixa-

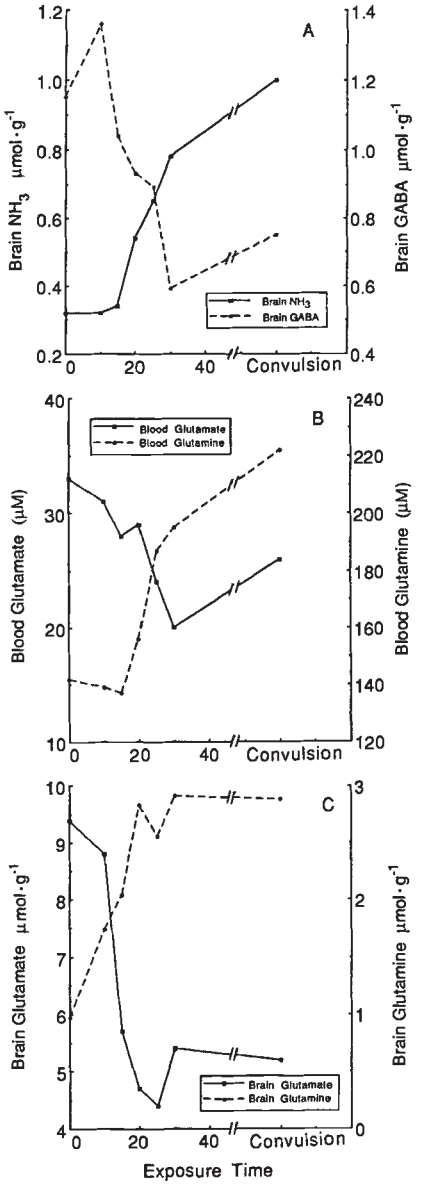

Fig. 6 Changes in blood and brain metabolites observed during OHP exposure leading to convulsions in rats. Glutamine was measured as combined glutamine and asparagine [from Singh and Banister (142), with permission].

tion, which replenishes the brain's carbon pool, is also an energy-requiring process (19, 116, 134). Carbon drain on the BBB astrocyte pool may be replenished in the astrocyte by the anaplerotic reactions described above, by neuronally derived amino acids, or NAA uptake as described earlier.

Indirect evidence supporting such a simplifying concept of energy depletion stems from prominent astrocytic changes induced by hyperammonemia, including enlargement and mitochondrial proliferation (27, 56, 57, 109, 180). Significant changes in neuronal astrocyte fine structure may reflect the intense metabolic activity needed to sustain glutamine synthesis and brain ammonia homeostasis. This may be analogous to the fine structure disruption observed in the periphery leading to proliferation of skeletal and cardiac muscle mitochondria following their initial disruption in response to exhaustive exercise (11, 54, 58, 85, 89).

Table 4 Mechanisms of hyperammonemic disruption of biochemical pathways and energy metabolism. Original references are cited. ↑ indicates an increase in activity, ↓ indicates a decrease in activity, → indicates no change in activity, ↓ ? indicates a possible inhibition or depletion

Process or Reaction	Action	Reference
Adenylate cyclase (rat brain, liver & fat)	↑	107, 174
Adenylate cyclase (liver & fat)	↓	174
Glutamate decarboxylase	↓	132, 149
Glutamate dehydrogenase	↑	110, 133
Isocitrate dehydrogenase	↓	16, 83
MAO (brain)	↓	132, 148
Na-K-ATPase (brain)	↓	132, 149
PFK	↑	94, 150
Pyruvate carboxylation	↓	99
Tissue ATP	↓?	47, 69
BBB permeability to NAA, BCAA	↑	79, 80, 81, 97
Blood glucose, lactate, FFA, ketone bodies	↑	17, 22, 122, 141, 160
Carbamoyl phosphate synthesis (liver)	↑	146
Cerebral respiration	↓	99, 166
Electron transport chain	↓?	71
Energy charge ratio	→	69
Glycogen stores (skeletal muscle, heart, liver, brain)	↓	122, 174
Glycolysis	↑	99
Lac/Pyr, NADH/NAD ratios	↑	53, 70, 71
Malate-aspartate shuttle	↓	34, 70
PCr (brain)	↓	69, 98, 135
Protein synthesis (brain and liver)	↓	40, 139, 168

Integration of the EIH Effects in the Periphery and CNS

Fig. 7 summarizes the overall ammonia flux and interorgan relationships proposed to result from EIH.

Ammonia arises directly from skeletal muscle activity under exercise stress. Peripheral fatigue may be influenced by the *in situ* production of ammonia in skeletal muscle and its stimulating, but perhaps wasteful effect upon glycolytic flux, local lactic acid production, and substrate depletion. Proposed causal relationships between ammonia, lactate, and fatigue are disputed, however, and remain equivocal (78, 156, 172). It is certain, however, that muscle activity during exercise contributes in a significant manner to hyperammonemia, and that the blood compartment absorbs and distributes an increasing ammonia load to other metabolic sites including the liver and brain. During sustained, extremely exhausting exercise, the detoxification capacity of peripheral organs may become saturated and blood NH_3 rises. The brain thus becomes exposed to the toxicity of excess ammonia.

Endogenous sources of brain ammonia include (i) neurotransmitter deamination, (ii) oxidative deamination of GLN and GLU in nerve endings and astrocytes, respectively, and (iii) the brain PNC, some or all of which may be stimulated by exercise.

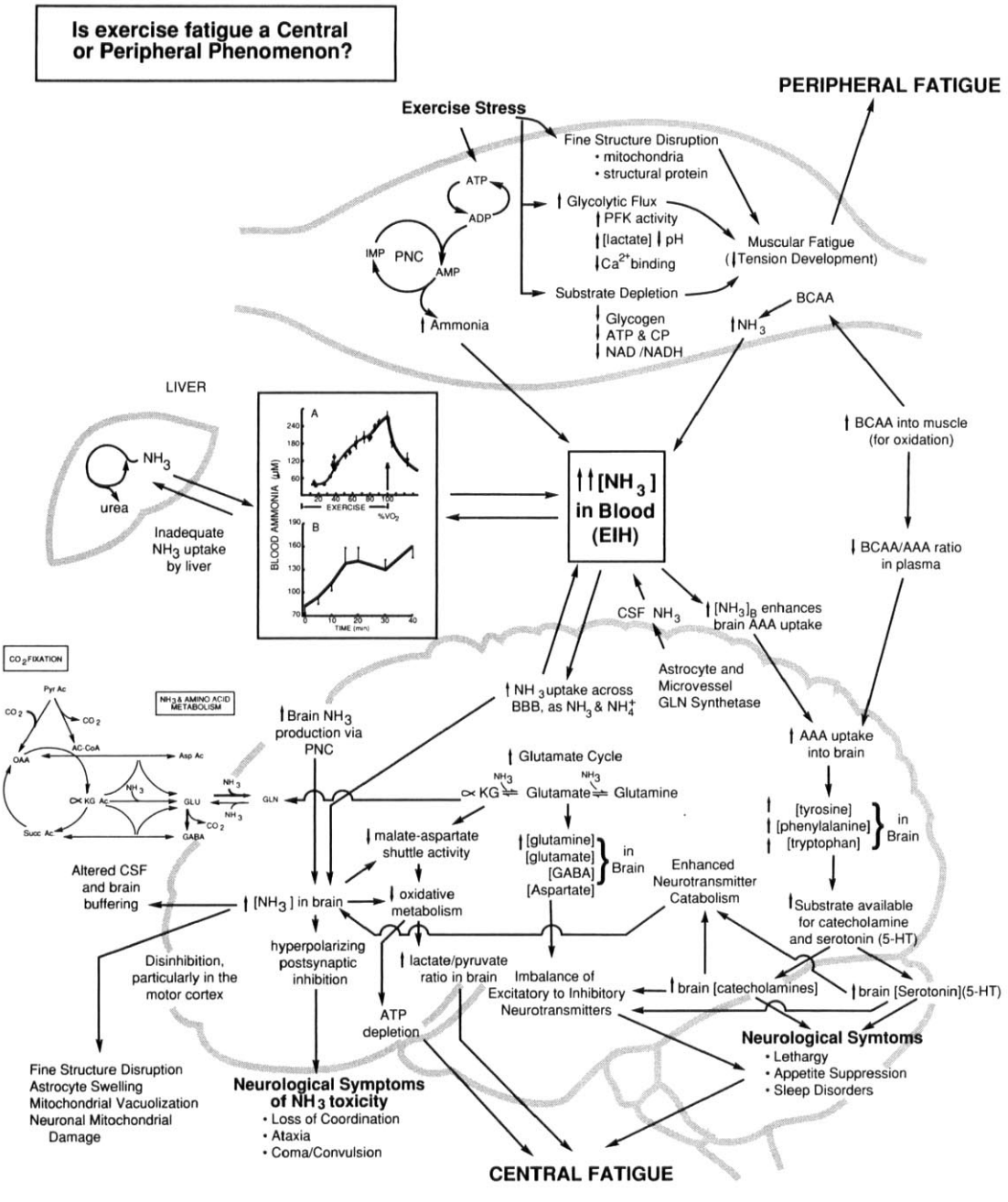

Fig. 7 Pathways of ammonia production and detoxification during exercise-induced hyperammonemia. Postulated mechanisms contributing to PERIPHERAL and CENTRAL EXERCISE FATIGUE. Abbreviations used are described previously [figures incorporated in the diagram are modified from: Banister et al. (6), (Fig. 2), Graham et al. (55), (Fig. 1), Weyne et al. (173), (Fig. 5), with permission].

Enhanced brain ammonia may interfere with the concentration of key metabolites of the tightly linked tricarboxylic acid cycle and malate-asparate shuttle transporting reduced equivalents from the cytosol to the respiratory chain in mitochondria. There may be disruptive hyperammonemic effects on: (i) metabolism and ATP availability in critical regions of the brain, (ii) astrocyte and neuronal fine structural disruption, (iii) an increase in the lactate/pyruvate ratio, and (iv) brain pH.

Although the chronic hyperammonemia of chemical toxicity and disease is manifest in the well-defined neurological disturbances discussed earlier, symptoms of neurological dysfunction induced by acute and even chronic exercise-induced hyperammonemia may present more subtly due to the relative transient nature of the stimulus producing them. Nevertheless, they may be identified and associated with performance decrement during *exercise extremis*. Dramatic illustration of this is the loss of coordination (ataxia; collapse) during intensive endurance exercise under compounding, alien, environmental conditions, e. g., in the heat or at altitude

(Fig. 2). The onset of heat stroke for example is heralded by conflicting CNS-associated symptoms, e. g., a bounding or thready pulse, by agression or apathy, by a dry red skin, or by profuse sweating. Overall there is loss of motor coordination and finally stupor and coma (178). The observed symptoms may be first interpreted as indicative of PERIPHERAL FATIGUE in which there is no accompanying loss of coordination, or lucidity of thought, or behavior, but only developing muscle weakness and an awareness of strained breathing, heart sounds, sweating, and an unwillingness to continue. Under more strenuous and alien environmental conditions, the toxic CNS effects of serious hyperammonemia become increasingly obvious so that *in extremis* CENTRAL FATIGUE is dominant in which motor control, coherent thought, and even consciousness are lost.

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