PHYSIOLOGICAL RESPONSES TO AMMONIA TOXICITY IN MAMMALS

by

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INTRODUCTION

Ammonia is known to be toxic to a wide variety of plants and animals. Reports of ammonia poisoning can be traced to 1872 when a technician was affected by ammonia inhalation from a mechanical refrigeration unit while attempting repairs in a refrigeration plant (21). Multiple individual burning accidents have occured due to leakage or sudden decompression of containers of liquid ammonia in crop fields (31). Experimental studies of ammonia toxicity *in vitro* have utilized rhododendron petals, red blood cells, intact plants (e.g., onion, peach trees, etc.) and mammals (from mice to men (50).

Urea as a supplement of protein extensively is used in modern cattle feeding. Death of animals under such feeding programs is not uncommon when urea is in quantities greater than the limit of their tolerance. It has been shown experimentally that tetanic convulsion and death may occur when NH_4+ rises to 14.8 ug/ml. This concentration occurs (within 18 minutes) following the adminstration of 310 gms of urea to a 1242 lb. Jersey steer (43).

If the endogenous ammonia production increases and/or the detoxification by the liver decreases there may be a manifestation of deleterious effects of ammonia without direct exposure. In fact, ammonia toxicity potentially is so pervasive that it may be adequately explained only by combined efforts of toxicologists, biochemists, pathologists, and physiologists. This report constitutes an attempt to define

the problem area, elaborate the current state of knowledge in this area and list few suggestions as to how this problem may be approached and solved.

LITERATURE REVIEW

A. Ammonia metabolism

Ammonia constantly is being formed in the body through the process of protein degradation and deamination. Under no circumstances is the accumulation of ammonia in the body desirable because ammonia is highly neurotoxic. In the hepatocytes of the liver ammonia is transformed into non-toxic urea by incorporating ammonia to form one molecule of urea (Fig. 1). When the rate of ammonia formation exceeds the rate of urea formation, ammonia may be incorporated with α-ketoglutarate to form glutamate (Fig. 2) which is nontoxic. Hushino et al. (19) confirmed that rumen ammonia is incorporated into glutamate in this fashion through a reaction catalized by glutamate dehydrogenaze of the rumen mucosa.

Weil-Malherbe (60) proposed that this reaction may inhibit the TCA cycle by removing α-ketoglutarate. McKhan and Tower (28) also studied the effects of ammonia on oxidative metabolism and found that addition of ammonia to cerebral cortex in vitro reduced oxygen uptake, doubled lactic acid formation, markedly increased glucose utilization, and resulted in a 30 to 40% decrease in oxygen uptake by mitochondria. Worcel and Erecinska (62) also found an inhibition of rat liver mitochondrea by the addition of ammonia.

Schenker and Mendelson (45) assayed brain glycogen and the three major sources of intracerebral energy--adenosine triphosphate, phosphocreatine and glucose--in rats given

FIGURE 1. Urea Cycle (Arginine-Ornithine Cycle).

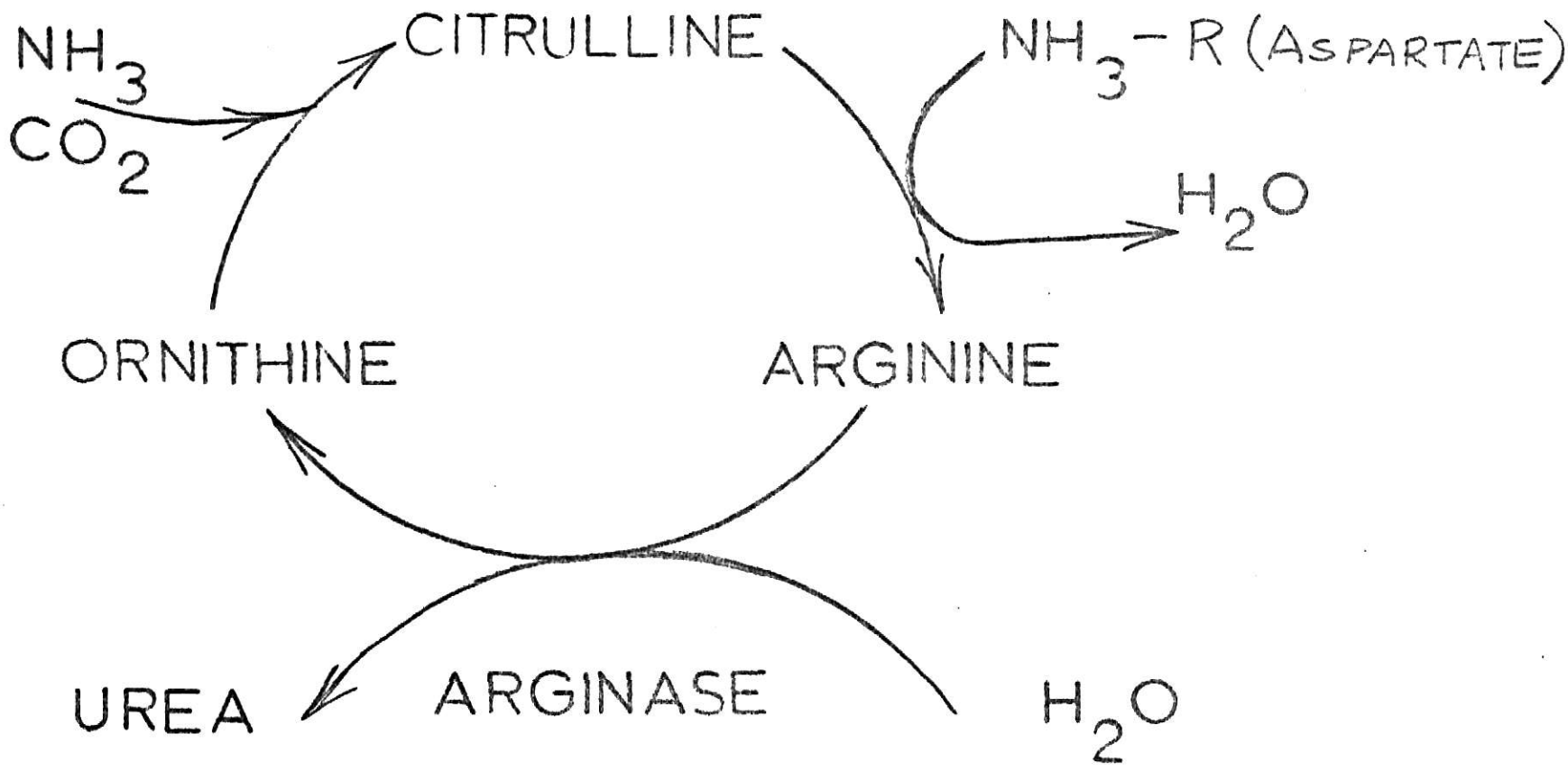

NH3
CO2
CITRULLINE
NH3 – R (ASPARTATE)
H2O
ORNITHINE
ARGININE
UREA
ARGINASE
H2O

FIGURE 2. Shunting of alpha-ketoglutarate from TCA cycle when ammonia is present in excessive amounts (52).

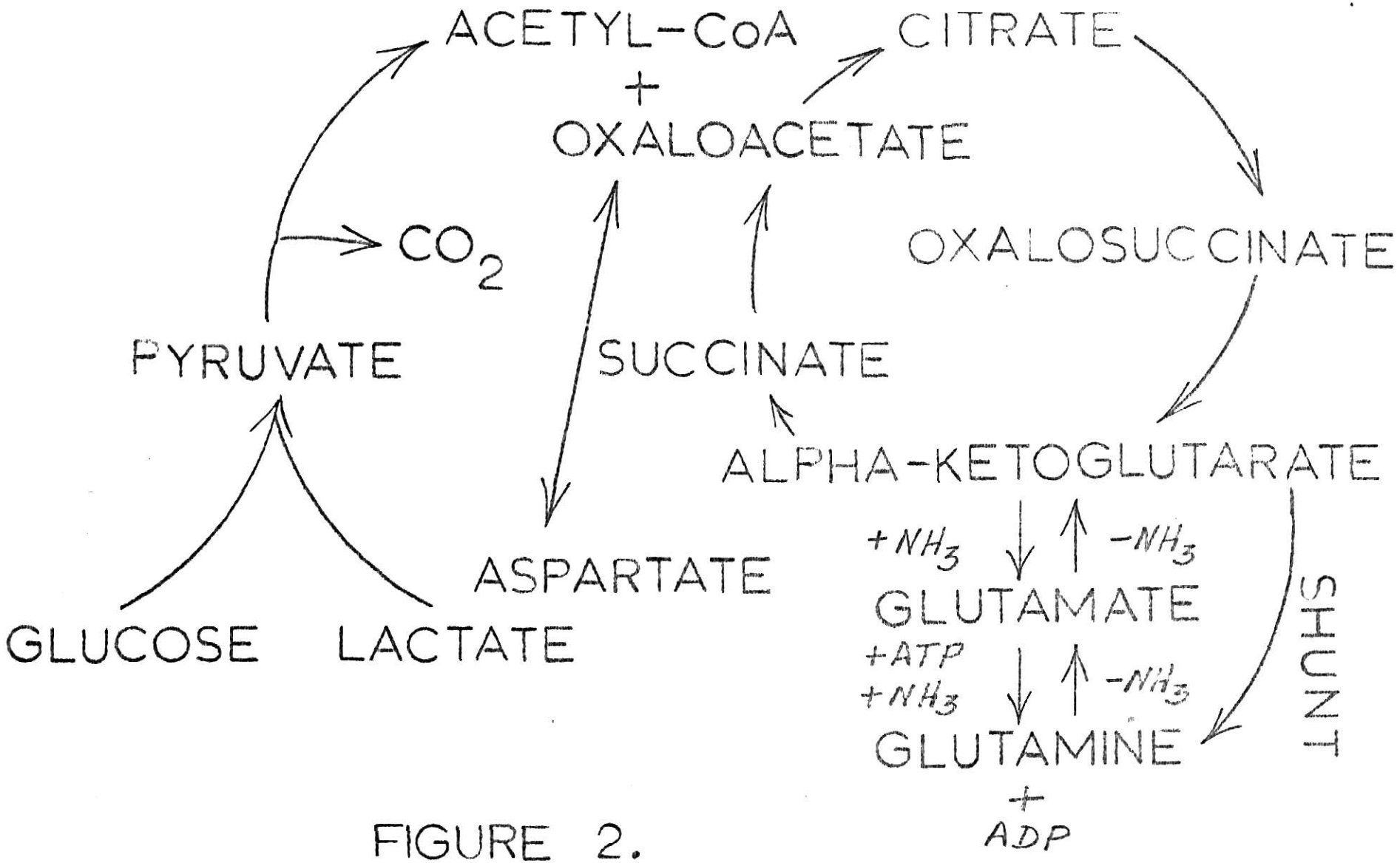

ACETYL-CoA
+
OXALOACETATE
CITRATE
OXALOSUCCINATE
CO_2
PYRUVATE
SUCCINATE
ALPHA-KETOGLUTARATE
$+NH_3$
$-NH_3$
GLUTAMATE
+ATP
$+NH_3$
$-NH_3$
GLUTAMINE
+
ADP
ASPARTATE
GLUCOSE
LACTATE
SYNTH

FIGURE 2.

ammonium acetate (dissolved in 0.9% sodium choride solution) intraperitonially at the dose of 60 mg/100 gm body weight. This treatment resulted in drowsiness in 5 minutes followed by coma lasting at least 30 minutes. Glucose, glycogen and ATP fell significantly in both brain base and brain cortex.

Handford (17) induced ammonia intoxication in dogs by intravenous injection of urease. This method afforded a unique preparation for the study of ammonia metabolism in vivo, since, within limits, self-perpetuation and cyclic release of ammonia were achieved through the action of this enzyme. NH_3 was released from urea and resynthesized to urea via the ornithine-arginine (urea) cycle in the liver. Measurements at 5, 30, and 60 minutes post-intoxication showed highly significant increases in plasma glutamine and ammonia levels but a decrease in blood urea nitrogen (BUN) (17). This indicates that glutamine synthesis plays a major role in the clearance of an overload of ammonia from the blood.

The first step of defense against ammonia toxicity is the synthesis of glutamate and then glutamine (Fig. 2). Glutamine synthetase and glutamate dehydrogenase are two enzymes involved in converting inorganic ammonia into organic compounds; from glutamate to glutamine and α-ketoglutarate (αKG) to glutamate, respectively. Warren (58) demonstrated that ammonia toxicity can be reduced to a great extent by the administration of glutamine synthetase inhibitors. Weil-Malherbe (60) studied

the removal of ammonia in brain slices in the presence of glucose plus either pyruvate or α-KG and was able to demonstrate in detail the ammonia binding mechanism. He observed that the disappearance of ammonia was correlated to glutamine formation.

Bessman and Evans (2) found that 40% of the arterial blood ammonia is taken up by muscle and that tissue ammonia concentration was higher than blood concentration. The rate of diffusion and distribution of ammonia varied from tissue to tissue with the concentration increase being equal for liver and brain but about double for muscle. Ammonia in muscle did not decrease after the blood concentration returned to normal, indicating an active mechanism of ammonia retention in the cell.

According to Rosado et al. (44) the sequence of events following the injection of an ammonia load appeared to be the following: initially, the ammonia is rapidly removed from the circulation by the muscle; then, glutamine synthesis takes place (mainly in the liver and brain); and, finally, urea synthesis takes place utilizing the ammonia gradually released from muscle and from the enzymatic hydrolysis of glutamine. It is likely that the capacity of muscle fixation and glutamine systhesis is saturated at the time acute toxicity occurs.

B. Ammonia toxicity and feeding of urea

For some time, scientists have believed that non-protein nitrogenous compounds could be utilized as protein supplements in ruminants but they did not know how much, in what form and how frequently those compounds should be fed for maximum benefit. Urea is this type of compound and is inexpensively

manufactured commercially from the atmospheric nitrogen.

In 1947, Osebald (34) reported the poisoning of a cow and her calf following the consumption of pure urea which had been spread in the field as a fertilizer. Since then, it has been hypothesized that toxicity of urea could be eliminated by feeding it in small quantities mixed with other feed. Davis and Roberts (7) fed urea mixed with concentrates to one group of cattle and drenched the other group with water solutions of urea. The group fed concentrates showed greater tolerance than the other group. Ataxia, dyspnea, and excessive frothy salivation were observed by Dinning et al. (8) in a 500 lb. steer after the administration of an urea solution containing more than 100 gms. of urea orally. Ataxia developed within 20 minutes when the blood ammonia level reached 2.5 mg% and symptoms of alkalosis--followed by death within 70 minutes--occurred at a level of approximately 4 mg%.

In a subsequent study, Dinning et al. (9) fed urea to steers at a dose of 6% of the dry matter but no clinical symptoms developed within 70 days and the animals appeared perfectly healthy. When no clinical symptoms developed within 70 days, these authors thought there might have been some internal lesions which were not severe or extensive enough to induce clinical symptoms. However, upon post-mortem examination no gross lesions or microscopic change could be seen in any organ.

Dinning et al. (9) proposed that an increased level of blood ammonia resulting from degradation of urea by the ruminal microflora might have caused an alkalosis which could

cause death. McDonald (27) previously had demonstrated the importance of ammonia production by microbial degradation of various sources of nitrogen and the absorption of ammonia from the rumen of anesthesized sheep. This later was confirmed by Davis and Roberts (7) who demonstrated a positive correlation between the level of blood ammonia and degree of toxicity in sheep and cattle. Lewis (24) concludes that there may be a hepatic ammonia threshold in ruminants and that ammonia produced by degradation of urea may not necessarily show up in the circulation depending upon hepatic efficiency of ammonia removal. This threshold level was not determined. As no significant ammonia toxicity was manifested in the sheep after Clark et al. (5) injected ammonia solutions, it was hypothesized by Hale and King (15) that the urea toxicity was due to the absorption of ammonium carbamate not to ammonia.

In their study Repp et al. (39) found that the dosage of ammonium carbonate in lambs correlated with blood ammonia level and that 1 mg% NH_4^+ in peripheral blood was the critical ammonia level. In these experiments, the toxic effect appeared within 30 to 45 minutes and death occurred in 90 to 120 minutes after administration of this nitrogenous compound. They (39) also speculated starvation could augment the susceptibility to NH_4+ toxicity. Becker (1) found varying degrees of toxicity in rabbits due to urea administration. He observed that the toxic effects in previously starved animals were more pronounced than in nonstarved ones. He concluded that ammonia toxicity by urea administration caused dehydration but the primary toxic effect was not shown.

In addition to the form of feed and mode of feeding, Repp et al. (39) found that fasted animals were more susceptible to ammonia toxicity than ad lib fed animals. Juhasz (20) did more elaborate work on this aspect of ammonia toxicity in which he measured pH and ammonia level in rumminal fluid, blood urea nitrogen and blood ammonia, blood cholesterol and blood sugar. He (20) found that urea and ammonia content doubled in ruminal fluid on 24 hours fasting and after 48 hours, the pH and ammonia level of rumen fluid increased further. Blood cholesterol increases were parallel to those of blood urea. Although no conclusions were drawn on these studies, Juhasz (20) was certain that total cholesterol and rumen ammonia production were correlated.

Roller (43) reported an initial 2.7% to 2.9% reduction in packed cell volume (PCV) in cattle after the administration of urea, but, five minutes later, a rise of 11.9% to 36.6% in PCV was observed. In all trials the PCV was found to be maximum when the pH approached maximum. He suggested that, since NH_4+ is irritating, the dilution of blood occurs initially due to a physiological response to reduce the intensity of irritation. He speculated that the increase of PCV in the later stage was due to redistribution of the fluid with ammonia into other tissues resulting in ascites and edema (3, 11, 18, 37, 41).

Frequent defecation and diarrhea were symptoms of ammonia toxicity in urea feeding reported by Roller (43). Coombe et al. (6) stated that with higher pH ruminal motility decreased with complete rumen stasis at pH 7.3. However, stasis did

not occur below pH 7.0. Cecal activity increased significantly with a higher frequency of contraction at abnormally high pH values which may explain the cause of more frequent defecation during ammonia toxicity.

C. Ammonia toxicity and pH

As the ionization of a compound depends on the pH of the solution, the severity of ammonia toxicity may be influenced by the pH of the tissue with which it interacts. Warren (56) observed that ammonia at a low tissue pH was less toxic than at a high pH. The proportion of total ammonia concentration ionized at a given pH is governed by the dissociation constant of the molecule, and the pKa varies with temperature and type of solution.

Since toxicity depends on the ammonia which enters the organism and thence the cell, it is of particular importance that the cell membranes are relatively impermeable to one form (ionized ammonia) whereas the other (unionized ammonia) passes tissue barriers with ease. Therefore, to be able to determine the degree of toxicity in an individual body system it is necessary to measure the percentage of ionized ammonia present. This calculation easily can be made by using the law of mass action (56) with appropriate pKa and pH values. For example:

$$\% \text{ ionized ammonia} = \frac{100}{1 + \text{antilog } (pH - pK)}$$

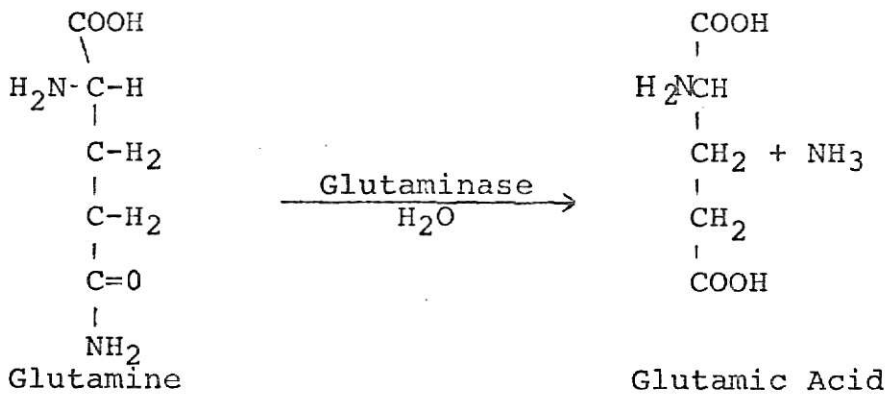
One reason for this indirect approach is that there is no established method for determining NH_4+ levels. The existing methods, which are mainly microdiffusion techniques, provide only the total concentration (NH_3 and NH_4+). However, the concentration of unionized ammonia in the blood of dogs recently has been measured from the quantity of ammonia gas given off by the lungs (10). These experimental findings (10) agree with those calculated from the above equation.

Since under normal conditions a pH gradient exists between intra- and extracellular fluids (56), the concentration of intra- and extracellular ionized ammonia also should be different. If the pH of the body tissues remains constant, an equilibrum is established by the movement of mostly unionized molecules. Where the pH gradient of intra- and extracellular fluid is disturbed by the alteration of pH in either one or both sides of the barrier (cell membrane) a redistribution will take place. On the basis of the principle of mass action the following equation can be formulated and the intra- and extracellular concentration of ammonia calculated.

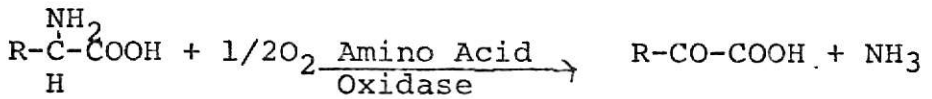
$$\frac{\text{Concentration (Intracellular)}}{\text{Concentration (Extracellular)}} = \frac{1 + 10\ (\text{pKa} - \text{pH intra})}{1 + 10\ (\text{pKa} - \text{pH extra})}$$

Renal ammonia excretion and its role in acid-base balance also is important. Walker (55) was able to demonstrate that ammonia formation takes place in the distal tubules and collection tubule. Nash and Benedict (30) showed that the renal tubular cells form ammonia from a precursor in the renal

arterial blood and secrete it into tubular fluid. It was later found by Van Slyke et al.(54) that about two thirds of the ammonia formed in the kidney is produced by deamination of glutamine (Equation 1) and one third by oxidative deamination of amino acids (Equation 2).



DEAMINATION OF GLUTAMINE - - - - - - - - - - - - - (1)



OXIDATIVE DEAMINATION OF AMINO ACID - - - - - - - -(2)

The NH_3^+ formed enters the tubular fluid, where it combines with H^+ from the tubular cells to form NH_4^+. The NH_4^+ then replaces Na^+ in the tubular fluid and the Na^+ is reabsorbed by the H^+ - Na^+ exchange mechanism and reenters the plasma as $Na^+HCO_3^-$. The NH_4^+ is excreted in the urine as NH_4Cl (Fig. 3).

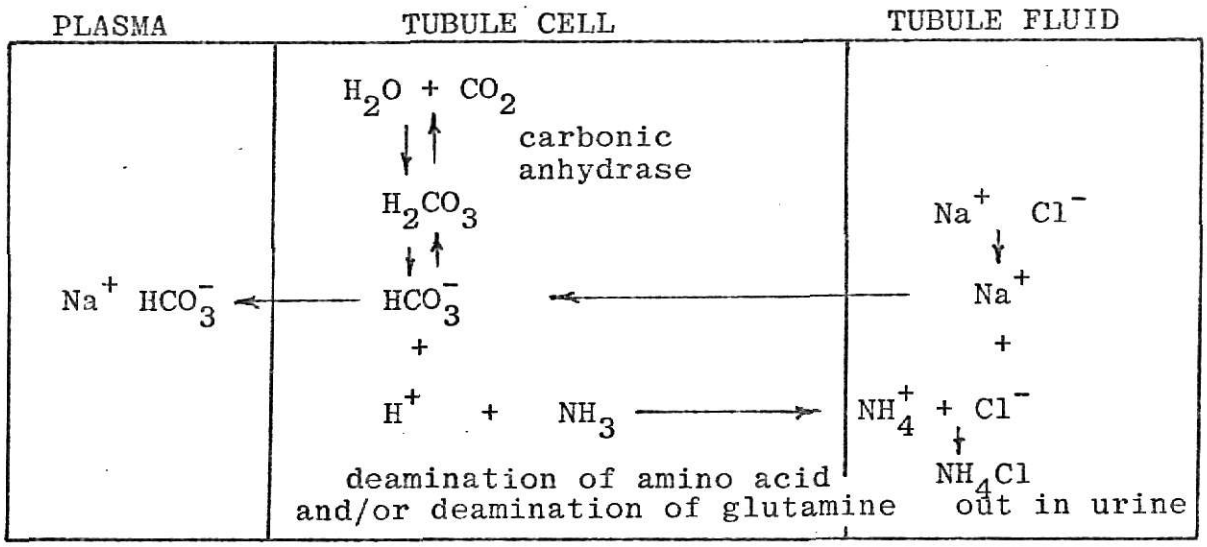


Fig. 3

Orloff and Berliner (32) found that the ammonia excretion in the renal tubule is not active but passive. In later studies Orloff et al. (33) established that ammonium salts exert a direct renal tubular effect characterized by inhibition of sodium reabsorption. Orloff et al. (33) also induced increased endogenous production by the renal tubular cells by infusing precursor amino acids with no interference with sodium transport. They concluded that an increase in the concentration of the ammonium ion (NH_4^+) in the peritubular circulation probably interfered with sodium reabsorption.

Gilman and Brazeau (13) found urine to become alkakine after administration of a sulfonamide drug acetazoleamide (Diamox). This indicated that the H^+ - Na^+ exchange mechanism had been inactivated and that NH_4^+ excretion in the urine had dropped markedly. In such a condition, however, ammonia continued to be produced in the kidney. Therefore, in light of the work by Orloff et al. (33) and Gilman and Brazeau (13),

it can be hypothesized that ammonia toxicity might have a similar action to acetazolamide thereby causing electrolytic imbalance. As this possibility was not mentioned in either of the two articles, further studies on this point might help to elaborate other aspects of ammonia toxicity.

Since ammonia is strongly alkaline in nature, it is obvious to think of alkalosis accompanying ammonia toxicity. In contrast to this Roller (43) found blood pH to initially rise to 7.16 but to decline after 20 minutes, reaching a pH of 7.3 after forty minutes. He found a consistant acidosis prior to death after administering urea solutions directly into the rumen of Jersy steers at a dose of about 2gm/kg body weight. He concluded that cellular destruction and accumulation of metabolic acids might have led to acidosis.

Read and his coworkers (38) found that a diuretic, chlorothiazide, caused potassium depletion which altered the acid-base balance and disturbed the intra- and extracellular equilibrium of hydrogen ion concentration. It is known that potassium depletion in mammals results in an intracellular acidosis accompanied by extracellular alkalosis, a situation that should maximally enhance passage of ammonia into cells. Even when diuretics are not employed, hypokalemia may be associated with this syndrome (48). Sherlock (49) found that patients showing signs of potassium depletion often improve after treatment with potassium salts. This may indicate that potassium deficiency <u>per se</u> is a pathogenic factor in the impending hepatic coma syndrome.

D. Neuromuscular responses to ammonia toxicity

As early as 1893, Hahn et al. (15) performed experiments by making a connection between the portal vein and hepatic vein (Eck-fistula) thus bypassing the liver. They found that these dogs appeared to undergo a severe derailment of central nervous system function when fed meat. The blood ammonia levels were considerably increased in these "meat intoxicated" dogs and it was concluded that high blood ammonia level might be the cause of the observed nervous symptoms.

Parnas (35) measured the blood ammonia from the radial vein of an exercised arm and found this to be higher than in blood from the resting arm. This indicates that the contraction of skeletal muscle may have caused the formation of ammonia. Other work (12, 14, 17) demonstrated that many nervous symptoms were related to increased levels of blood ammonia which leads to the assumption that the nervous tissue is directly influenced by ammonia. It also has been assumed (10) that nervous symptoms or comma induced by ammonium salts injected intravenously were more severe when anemia, hypokalemia or alkalosis also was present. Egense (10), however, believes that the toxic action of ammonia on nervous tissue is direct although the actual mechanism of this toxicity has not been fully elucidated.

Schwartz et al. (47) reported that peripheral blood ammoia concentration increased by about two-fold following muscular exercise. Feinberg and Alma (12) found that injected L-epinephrine increased the cardiac effort (heart rate times blood pressure) and resulted in increased ammonia production.

Ulshafer (13) injected ammonium carbonate intravenously into rats at levels sufficient to produce convulsion. He found consistant diminution of acetylcholine levels in experimental rats relative to control animals and proposed that ammonia deprived the brain of acetylcholine at the synapses thus producing a "biochemical decerebration." Metzger (29) later confirmed this proposal by decmonstrating increased acetylcholinesterase activity in ammonia poisoning.

Richter and Dawson (40) were able to demonstrate that the brain level of ammonia incrases during excitation and decreases during anesthetization. St. Omer (52) in his doctorate work on the effects of four structurally unrelated chlorinated hydrocarbons (lindane, dieldrin, heptachlor and D.D.T.) also confirmed that many neurotoxic agents increase brain ammonia levels. He was able to creat seizures in rats and cockerels following intravenous injections of these compounds. Lindane was found to be the most toxic and its degree of toxicity was directly related to the brain ammonia levels.

Detrimental effects of ammonia also depend on its physical form and the tissue exposed. Since ammonia is strongly alkaline it combines with tissue to form albuminate; and with natural fats to form soaps (36). It gelatinizes tissue to form soluble compounds and by so doing may produce painful destruction of tissue (36).

E. Ammonia toxcity and the respiratory system

The lungs, liver and kidney all play a role in the removal of ammonia from the body. Robin et al. (42) measured a significant amount of ammonia in the expired air after the intravenous injection of ammonium acetate in dogs. They also measured the partial pressure of ammonia in alveolar air and noted similarities between NH_3 and CO_2 and concluded that, as with CO_2, the study of NH_3 removal by mammalian lung may prove to be a useful approach for further investigation of gas exchange.

Handford (17) demonstrated a mechanical obstruction of the trachea during ammonia intoxication and, in spite of tracheal intubation, 15 dogs died. The mucous secretion became so extensive that air passages were filled with ropey mucous causing complete mechanical obstruction and death due to asphyxiation. Pulmonary edema also was observed in those dogs. Earlier, Handford (17) and Koenig and Koenig (22) had been able to produce acute pulmonary edema in rats by injecting ammonium salts, Guinea pigs and cats responded like rats; but rabbits did not develop any significant pulmonary edema (22).

Weil-Malherbe (61) has reported an increase in respiratory rate in ammonia toxicity due to the ammonia induced depression of high energy phosphate concentration with a consequent stimulation of glycolysis and respiration. Contrary to this, Mayan and Merilan (26) found that exposure to 50 ppm and 100 ppm ammonia for 2.5 to 3 hours significantly decreased respiration rate 34.0% and 32.3%, respectively, in experimental compared to control rabbits.

The frequent exposure of industrial workers to ammonia fumes for long periods of time has led to the generally accepted impression that when the ammonia concentration is not sufficient to cause acute damage, chronic damage need not be anticipated. Weatherby (59) investigated this by exposing male guinea pigs to an atomospheric concentration of 170 ppm of ammonia for periods of 6 hours per day, 5 days per week for 12 weeks. No significant evidence of chronic ammonia intoxication developed within 12 weeks. However, an exposure for 18 weeks resulted in relatively mild, though definite, changes in the spleen, kidneys, suprarenal glands and liver. The changes were most severe in the spleen; least in liver. Heart, lungs, stomach and small intestines showed no consistent changes suggestive of chronic intoxication.

F. Ammonia toxicity and liver disease

Bessman and Evans (2) found an elevated blood ammonia in heart failure. To explain this relationship, the authors postulated that the chronic passive congestion associated with heart failure probably prevented the liver from removing endogenous ammonia from the portal system.

Rosado et al. (44) investigated the relative importance of the liver and other tissues in the removal of ammonia from the animals. They injected ammonium carbonate into the portal vein and after two minutes, only 10-15% of the amount injected remained in the extracellular space for the rest had been removed from the circulation by the liver. On the other hand, the uptake by muscle, liver, and brain was 75%, 2.5% and 0.5% respectively. Liver and brain ammonia levels returned to

normal within 10 minutes. The conclusion of the authors (44) was that liver removes and muscle retains ammonia from blood in order to combat acute ammonia toxicity.

Stahl (51) observed that the high ammonia level in blood during liver disease appears to be due to damage of hepatocytes and to the existance of shunts between the portal system and the hepatic vein. He (51) also found electroencephalographic changes were related to different blood ammonia patterns in patients with liver cirrhosis and concluded that these changes could be used in the diagnosis of this condition.

G. Ammonia toxicity and hypoxia and temperature

Warren and Schenker (57) observed no difference in the LD_{50} level of rats at oxygen concentations of 15% and 21% following injection with ammonium chloride. The toxicity, however, was augmented at 13% oxygen and appeared to be inversely related to the percentage of oxygen. Further, rats, comatose at 7% oxygen, became normal in about two minutes when oxygen of the chamber was increased to 21% although there was no change of ammonia levels in the brain. The ammonia toxicity resulting from ammonium carbonate injection was 1.76 times greater at 11% oxygen than at 21% oxygen.

Koylov (23) demonstrated that ammonia toxicity was enhanced in rabbits housed in a chamber heated to 50°C for 1-2 hours. He found that blood ammonia concentration increased when the body temperature increased and concluded that ammonia toxicity could be reduced by application of cold packs to the body. Schenker and Warren (46) injected ammonium chloride

intravenously into mice who were then subjected to hypothermia and hyperthermia. Since ammonia toxicity was more severe at high temperatures than at low temperatures, the authors (46) inferred that during hypothermia there is a decreased cerebral blood flow and a decreased metabolic activity of brain tissue. During hypothermia there appeared to be less demand for oxygen by the brain tissue and a reduced influx of ammonia into the brain and the animals were protected against ammonia toxicity. One year later, Zuidema et al. (63) confirmed these findings.

DISCUSSION

The use of cages in the raising or storage of pets and laboratory animals is a widely accepted practice. Infrequent cleaning of these cages may result in potential health hazards from ammonia toxicity to the caged animals as well as to their attendents. Ammonia production by the microbial degradation of urea by urease positive bacteria is a major source of contamination in animal rooms. The ammonia gas thus produced is inhaled constantly by the caged animal, and occasionally by the attendant.

As viewed by Lewis et al. (25), there exists a hepatic ammonia threshold that, if exceeded, may result in ammonia toxicity. If some pathological condition of the animal decreases this hepatic threshold, the deleterious effect of ammonia may take place in environments containing a reduced level of ammonia. There are many known and unknown etiologies for hepatitis and liver necrosis and any condition of this sort may reduce the hepatic ammonia threshold.

Ammonia produced in animal quarters cannot be filtered efficiently. Therefore, emphasis should be given to the prevention of ammonia formation or the scrubbing of the room air. As has been mentioned elsewhere in this report, ammonia in the animal quarters is formed by the degradation of urea (excreted as waste product in the urine) by the urease positive bacteria. Inhibition of the growth of urease positive bacteria through chemical sterilization should prevent an increase in the ammonia levels in these rooms.

The LCt_{50} for mice has been established to be 2750 ppm (confidence interval 2250-3290) for one hour exposure; whereas exposure 440 ppm for 2 hours daily for 14 days did not cause death (4). Chickens and turkeys seem to have a lower tolerance to ammonia for at 200 ppm they exhibit clinical signs of conjunctivitis and the egg production is reduced. Bats appear to be very resistant to ammonia for caves occupied by bats often are found to contain 1800 ppm of ammonia. On the other hand, the LCt_{50} in New Zealand White rabbits, Golden hamster, mice and chinchillas are not significantly different (4).

Even though this LCt_{50} of ammonia appears to be relatively high, it can cause discomfort by its characteristic odor and irritation effect (expecially in the eyes) at much lower concentrations. Further, it is customary to assume that the toxic effect of a substance is of importance only when the animal shows some clinical signs or symptoms and this may not always be true. Even if not detected clinically, a substance may have manifested some biochemical dysfunction intracellularly. Elaborate studies of ammonia toxicity at the intracellular level also may be necessary to explain the true mechanisms of its toxic effects.

SUMMARY

A review of available literature was made to provide a basis for more detailed experimental work on "ammonia toxicity."

Ammonia in the form of solid, liquid and gas can cause deleterious effects to normal physiology of mammals. Extensive studies have shown little or no toxic response following feeding of urea to ruminants as a protein supplement. Urea poisoning, when it occurs, appears to be ammonia toxicity. If the rate of detoxification is rapid, no noticeable toxicity of ammonia will take place; hence "ammonia toxicity" refers primarily to acute toxicity. Few cases of chronic ammonia toxicity have been reported. Toxicity can result either from an increased production of ammonia or by a decrease in its removal by the animals liver. Therefore, ammonia toxicity and liver disease generally are associated and often related. Little work has been done on the toxicity of ammonia in the gaseous form. An experimental protocol for this type of study has been outlined.

Ammonia also is neurotoxic and the central nervous system directly involved in "ammonia toxicity". The actual mode of action has not yet been established although the following steps obviously are involved: increased acetylcholinesterase activity produces "biochemical decerebration"; ammonia inhibits oxidative decarboxylation; and, mitochondrial oxygen uptake decreases.

Dyspnea, due to excessive ropy mucous secretion, causes mechanical obstruction of the trachea and death by asphyxiation. Ammonia upsets the acid-base balance of the body. Several workers reported occurance of acidosis prior to death.

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PHYSIOLOGICAL RESPONSES TO AMMONIA TOXICITY IN MAMMALS

by

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AN ABSTRACT OF A MASTER'S REPORT

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ABSTRACT

Ammonia as a solid, gas or liquid causes many deleterious effects to mammals as well as lower animals and plants. Animals may be subjected to ammonia toxicity by the inhalation of gaseous ammonia as well as ingestion of excess quantities of urea. Muscle contraction appears to cause degradation of protein and deamination of amino acids resulting in release of endogenous ammonia. This ammonia is either reaminated and protein is resynthesized or it is transported to the liver to be transformed into urea and excreted through the kidneys. The normal ammonia level in man is 10-20 ug/100 ml blood. The blood ammonia level varies with species and with the metabolic condition of the individual. The urea cycle is an efficient mechanism for detoxifying of ammonia and is directly influenced by the condition of the liver. Therefore, a patient with liver disease may display ammonia toxicity symptoms without being exposed to ammonia from an exterior source.

Acute pulmonary edema, ropy secretion in the trachea, muscular twitches, recumbancy and tetanic convulsions all are associated with ammonia toxicity. Increased production of metabolic acid and or release of metabolic acids due to cellular destruction may lead to acidosis prior to death. Ammonia toxicity appears to be very much dependent on blood pH.