

# [CHAPTER 25]

## The Liver and the Gut

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### 25.1 INTRODUCTION

Throughout this book we have seen that the Stewart formulation can be used to help understand the mechanisms of acid-base equilibrium during health and disease. Of course the physicochemical principles discussed in this book cannot establish mechanism; they can only point toward one possible solution. However, the solution they point to appears to be very robust even if experimental proof is lacking. Further study is needed in this area, particularly as it relates to the role of the liver and GI tract in regulating acid-base balance. Because these organs handle both strong and weak ions, they have important roles to play in maintaining acid-base homeostasis. Given the well-documented consequences of disease in these organs for acid-base disorders, it is important that we attempt to understand their roles. Like much of this book, the formulations proposed here and the explanations for observations that have been made are somewhat speculative given the absence of direct experimental evidence. Where possible experimental evidence is cited; but often it is lacking and further work is required.

### 25.2 NORMAL PHYSIOLOGY: THE GI TRACT

Like the kidney, the GI tract handles strong ions and thus plays an important role in determining the [SID]. Unlike the kidney, the GI tract is responsible for adsorbing dietary cations and anions as well as weak acids. The role of diet and the role of the GI tract in controlling acid-base balance are under-appreciated and poorly studied, especially in humans.

Along its length, the GI tract handles strong ions quite differently. In the stomach,  $\text{Cl}^-$  is pumped out of the plasma by the parietal cells and into the lumen reducing the [SID] of the gastric juice and thus reducing the pH. On the plasma side, [SID] is increased by the loss of  $\text{Cl}^-$  and the pH is increased producing the so-called “alkaline tide” which occurs at the beginning of a meal when gastric acid secretion is maximal [1]. In the duodenum  $\text{Cl}^-$  is reabsorbed and the plasma pH is restored. Normally, only slight changes in plasma pH are evident because  $\text{Cl}^-$  is returned to the circulation almost as soon as it is being removed. However, if gastric secretions

are removed from the patient, either by suction catheter or vomiting,  $\text{Cl}^-$  will be progressively lost and the [SID] will steadily increase. It is important to note that, under the Stewart formulation, it is the  $\text{Cl}^-$  loss not the  $\text{H}^+$  that is the determinant of plasma pH. Although  $\text{H}^+$  is "lost" as  $\text{HCl}$ , it is also lost with every molecule of water removed from the body. When  $\text{Cl}^-$  (a strong anion) is lost without loss of a strong cation the [SID] is increased and therefore the plasma  $\text{H}^+$  concentration is decreased. When  $\text{H}^+$  is "lost" as water ( $\text{HOH}$ ) rather than  $\text{HCl}$ , there is no change in the [SID] and hence no change in the plasma  $\text{H}^+$  concentration.

In contrast to the stomach, the pancreas secretes fluid into the small intestine that has a [SID] much higher than plasma and is very low in  $\text{Cl}^-$ . Thus, the plasma perfusing the pancreas has its [SID] decreased, a phenomenon that peaks about an hour after a meal and helps counteract the alkaline tide. If large amounts of pancreatic fluid are lost, for example from surgical drainage, an acidosis will result as a consequence of the decreased plasma [SID]. In the large intestine, fluid also has a high [SID] because most of the  $\text{Cl}^-$  has been removed in the small intestine and the remaining electrolytes are mostly  $\text{Na}^+$  and  $\text{K}^+$ . The body normally reabsorbs much of the water and electrolytes from this fluid but when severe diarrhea exists, large amounts of cations can be lost. If this loss is persistent, the plasma [SID] will decrease and acidosis will result.

Finally, whether the GI tract is capable of regulating strong ion uptake in a compensatory fashion has not been well studied. In one study, 10 anesthetized dogs received 1 mg/kg of *Escherichia coli* endotoxin. Total metabolic acid flux across the gut, liver and kidneys (comparing arterial to venous) was calculated using the standard base excess formula and the [SID] method while  $\text{PCO}_2$  was maintained by controlled mechanical ventilation [2]. Mean arterial pH decreased from 7.34 to 7.22 with acute endotoxemia. Although transvisceral pH gradients revealed net acid release, the source of this was purely respiratory ( $\text{CO}_2$ ). During early endotoxemia, the gut significantly increased metabolic acid uptake ( $36.60 \pm 6.60$  mmol/h,  $p < 0.05$ ) while a much smaller increase by the kidney was not statistically significant [2]. Thus, during early endotoxemia in the dog, the gut is a major site of metabolic acid removal. However, the full capacity of this organ to affect acid-base balance is unknown.

### 25.3 DIET

Obviously the GI tract is also the place where substances containing strong and weak ions are absorbed into the body. As any food label at the grocery store will attest, most of the foods we consume are rich in strong ions, particularly  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$ ; but also  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ , and host of "trace elements". To the extent that our food comes from plants and animals who also have a need to regulate acid-base balance, it should come as no surprise that much of our food resembles, particularly that derived from animals, our own chemical make-up. Meat for example contains large amounts of  $\text{K}^+$  and  $\text{Cl}^-$ , and also weak acids like phosphate and proteins. Thus the [SID] of our food is usually positive, sometimes markedly so. However, we as humans, also have a tendency to add inorganic material to our food, especially  $\text{NaCl}$ . Predictably, just as saline lowers the plasma [SID] when it is infused into our veins, salt lowers the SID of food.

This is usually of little consequence to us because our kidneys are so efficient at maintaining our plasma [SID] primarily through excretion of  $\text{Cl}^-$ . However, dietary [SID] has been manipulated in animals to change plasma pH. For example, the prevention of milk fever in dairy cows involves manipulation of the so-called dietary cation-anion balance (essentially [SID]). About 27% of dairy farms in US feed dairy cows a diet with a negative SID to induce a mild metabolic acidosis which has proved effective in reducing subclinical hypocalcemia [3]. Similar results have been reported in sheep [4].

## 25.4 LIVER-KIDNEY INTERACTION

In order to alter the [SID], the body must affect a change in the relative concentrations of strong cations and strong anions. Although the kidney is the primary organ that affects this change, the kidney can only excrete a very small amount of strong ion into the urine each minute and several minutes to hours are therefore required to impact significantly on the [SID]. The handling of strong ions by the kidney is extremely important because every  $\text{Cl}^-$  ion which is filtered but not reabsorbed decreases the [SID]. Since the typical human diet contains plenty of  $\text{Cl}^-$ , there is usually sufficient  $\text{Cl}^-$  available for this to be the primary regulating mechanism. This is particularly apparent, when we consider that renal  $\text{Na}^+$  and  $\text{K}^+$  handling are influenced by other priorities (e.g. intravascular volume and plasma  $\text{K}^+$  homeostasis). Accordingly, "acid handling" by the kidney is generally mediated through  $\text{Cl}^-$  balance. How the kidney handles  $\text{Cl}^-$  is obviously very important (see chapter 24). Traditional approaches to this problem have focused on  $\text{H}^+$  excretion and emphasized the importance of  $\text{NH}_3$  and its add-on cation  $\text{NH}_4^+$ . However, the kidney does not excrete  $\text{H}^+$  any more as  $\text{NH}_4^+$  than it does as  $\text{H}_2\text{O}$ . Thus, an alternative view of the purpose of renal ammoniogenesis is to allow the excretion of  $\text{Cl}^-$  without  $\text{Na}^+$  or  $\text{K}^+$ . This is achieved by supplying a weak cation ( $\text{NH}_4^+$ ) to excrete with  $\text{Cl}^-$ .

In this view  $\text{NH}_4^+$  is important to systemic acid-base balance not because of its carriage of  $\text{H}^+$  or because of its direct action in the plasma (normal plasma  $\text{NH}_4^+$  concentration is  $< 0.01$  mEq/L), but because of its "co-excretion" with  $\text{Cl}^-$ . Of course  $\text{NH}_4^+$  is not only produced in the kidney. Hepatic ammoniogenesis (and also glutaminogenesis) is important for systemic acid-base balance and, as expected, it is tightly controlled by mechanisms sensitive to plasma pH [5]. Indeed this reinterpretation of the role of  $\text{NH}_4^+$  in acid-base balance is supported by the evidence that hepatic glutaminogenesis is stimulated by acidosis [6]. Nitrogen metabolism by the liver can result in either urea, glutamine or  $\text{NH}_4^+$ . Normally, the liver does not release more than a very small amount  $\text{NH}_4^+$  but rather incorporates this nitrogen into either urea or glutamine. Hepatocytes have enzymes to enable them to produce either of these end-products and both allow for the regulation for plasma  $[\text{NH}_4^+]$  at suitably low levels. However, the production of urea or glutamine has significantly different effects at the level of the kidney. This is because glutamine is used by the kidney to generate  $\text{NH}_4^+$  and facilitate the excretion of  $\text{Cl}^-$ . Thus, the production of glutamine can be seen as having an alkalinizing effect on plasma pH because of the way in which the kidney utilizes it.

Further support for this scenario comes from the discovery of an anatomical organiza-

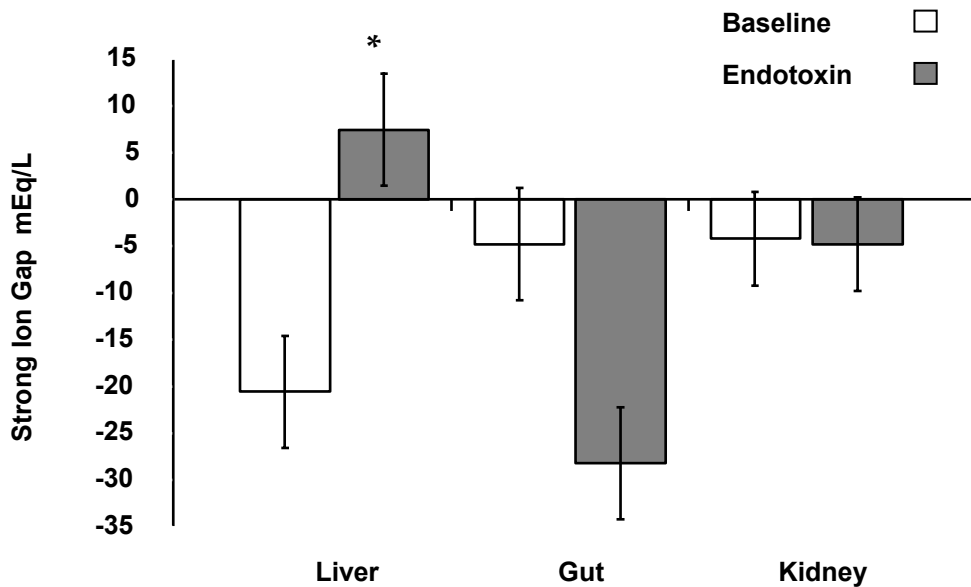
tion of hepatocytes according to their enzymatic content [7]. Hepatocytes with a propensity to produce urea are positioned closer to the portal venule and thus have the first chance at the  $\text{NH}_4^+$  delivered. However, acidosis inhibits ureagenesis and under these conditions more  $\text{NH}_4^+$  is available for the downstream hepatocytes which are predisposed to produce glutamine. Thus the leftover  $\text{NH}_4^+$  is "packaged" as glutamine for export to the kidney where it is used to facilitate  $\text{Cl}^-$  excretion and hence increases the [SID]. However, against this interpretation is evidence that the liver does not contribute to the regulation of acid-base equilibrium by controlling the rate of ureagenesis in response to changes in plasma acidity [8]. In a recent study, rates of ureagenesis were measured in eight healthy volunteers during control, chronic metabolic acidosis (induced by oral  $\text{CaCl}_2$ ), and recovery as well as during bicarbonate infusion (200 mmol over 240 min). Rates of ureagenesis were correlated negatively with plasma pH during adaptation to metabolic acidosis as well as during the chronic, steady-state phase. Thus ureagenesis, an acidifying process, increased rather than decreased in metabolic acidosis. During bicarbonate infusion, rates of ureagenesis decreased significantly. The authors conclude that ureagenesis has no discernible homeostatic effect on acid-base equilibrium [8].

## 25.5 THE LIVER AND [SIG]

The liver appears to play an important direct role in the handling of various ions which influence acid-base balance. In 10 anesthetized dogs measurements were obtained across various organs (liver, gut, kidney, lung) at baseline and 30-45 min after the intravenous infusion of endotoxin [9]. The total unmeasured anion flux across the liver was calculated from the SIG. At baseline, the liver removed unmeasured anions ([SIG]) from the circulation (-0.34 mEq/min). With early endotoxemia, however, the liver switched to the release of anions (0.12 mEq/min;  $P = 0.0046$ ) (Figure 25.1) [9]. Anion flux across the lung and kidney was unchanged. Overall, the net change from control to endotoxemic conditions was 4.2 mEq/hr. In a 20 kg animal this corresponds to an increase in [SIG] by about 0.35 mEq/L each hour. Assuming a normal pH at baseline and a constant  $\text{PCO}_2$ , this would correspond to a decrease in pH of about 0.01 per hour. Thus, the liver, which removes anions at baseline, switched to release anions during early endotoxemia and may be a major site of [SIG] generation during early sepsis.

## 25.6 THE LIVER AND $[\text{A}_{\text{TOT}}]$

Of course the liver may also influence acid-base balance by influencing  $[\text{A}_{\text{TOT}}]$ . The weak acids, are mostly proteins (predominantly albumin) and thus, hepatic synthetic function is a major determinant of  $[\text{A}_{\text{TOT}}]$ . The identification of  $[\text{A}_{\text{TOT}}]$  as the third independent acid-base variable has lead some authors to suggest that a third "kind" of acid-base disorder exists [10-12]. Thus, along with respiratory and metabolic, we would also have acidosis and alkalosis due to abnormalities in  $[\text{A}_{\text{TOT}}]$ . However, neither mathematical nor chemical independence necessarily imply physiological independence. Although the loss of weak acid ( $[\text{A}_{\text{TOT}}]$ ) from the plasma space is an alkalinizing process, there is no evidence that the body regulates  $[\text{A}_{\text{TOT}}]$  to



**Figure 25.1** Shown are the mean SIG fluxes (venous [SIG] – arterial [SIG]) across various organs before and after administration of intravenous endotoxin for 10 animals. Error bars are standard error; \*P = 0.0046. Adapted from Kellum et al. [9].

maintain acid-base balance. Furthermore, there is no evidence that we as clinicians should treat hypoalbuminemia as an acid-base disorder.

Critically ill patients frequently have hypoalbuminemia and as such their  $[A_{TOT}]$  is reduced. However, these patients are not often alkalemic because their  $[SID]$  is also reduced [13]. When these patients have a normal pH and a normal SBE and  $HCO_3^-$  concentration, it would seem most appropriate to consider this to be physiologic compensation for a decreased  $[A_{TOT}]$  [14] rather than classifying this condition as a complex acid-base disorder with a mixed metabolic acidosis/hypoalbuminemic alkalosis. Thus, it seems far more likely that this “disorder” is in fact the normal physiologic response to a decreased  $[A_{TOT}]$ . Experimental support for this view comes from recent studies of the Nagase strain of rat under conditions of respiratory acidosis [15]. Nagase is a genetic variant of the Sprague-Dawley rat which is analbuminemic. At baseline standard acid-base parameters (pH, bicarbonate, base excess and plasma lactate concentrations) were not significantly different between Nagase rats and normal animals. However, values for  $[SID_A]$  were much lower in Nagase rats, along with the reduced total weak acid concentration and resultant reduction in buffer base. Despite this fact, Nagase rats didn't reveal increased susceptibility to hypercapnia and acidosis-induced hypotension when compared to normoalbuminemic rats [15]. Importantly, the presence of a lower  $[SID_A]$  in the Nagase rats, despite a similar base excess, is consistent with a reduction in the “set-point” for  $[SID]$  to maintain acid-base equilibrium in the face of a reduced weak acid content. These results suggest that rather than a second primary acid-base disorder lowering the  $[SID]$  is a normal compensatory mechanism.

<b>Normal [SIG]</b>	
RTA: Urine [SID] ( $[\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-] > 0$ )	Non-Renal: Urine [SID] $< 0$
Distal (Type I): Urine pH $> 5.5$	Gastrointestinal: diarrhea; small bowel/pancreatic drainage
Proximal (Type II): Urine pH $< 5.5$ ; low serum $[\text{K}^+]$	Iatrogenic: parenteral nutrition; saline; anion exchange resins
Aldosteron Deficiency (Type IV): Urine pH $< 5.5$ ; high serum $[\text{K}^+]$	
<b>Increased [SIG]</b>	
Anions Identified	Anions not fully characterized
Lactate, Ketones, Salicylate, Methanol, Ethylene Glycol, Paraldehyde, Isoniazid	Renal Failure, Sepsis, Liver Failure

**Table 25.1.** Differential Diagnosis for Metabolic Acidosis (decreased [SID]). RTA: Renal Tubular Acidosis.

Thus, the normal physiologic response to hypoalbuminemia would appear to be to lower the [SID]. Notably, in this same study, Nagase rats had significantly higher [SIG], even at baseline, compared to normal rats. This finding could represent anionic proteins produced in place of albumin or it might represent a greater stress response in the Nagase animals, potentially leading to a worse outcome [16]. The finding that SBE was virtually identical between Nagase and wild-type animals favors the first explanation as there was no evidence of increased acidosis in the Nagase animals.

Finally, since changes in  $[\text{A}_{\text{TOT}}]$  generally occur slowly, the development of alkalemia would require the kidney to continue to excrete  $\text{Cl}^-$  despite an evolving alkalosis. Most experts would consider such a scenario to be renal-mediated hypochloremic metabolic alkalosis, the treatment for which would include fluids and/or chloride depending on the clinical conditions. Stewart's designation of a "normal" [SID] of  $\sim 40$  mEq/L was based on a "normal"  $\text{CO}_2$  and  $[\text{A}_{\text{TOT}}]$ . The "normal" [SID] for a patient with an albumin of 2 g/dl would be much lower (e.g.  $\sim 32$  mEq/L).

## 25.7 PATHOPHYSIOLOGIC MECHANISMS

A decrease in [SID] resulting in acidosis may be brought about by the generation of organic anions (e.g. lactate, ketones) the loss of cations (e.g. diarrhea), the mishandling of ions (e.g. renal tubular acidosis) or the addition of exogenous anions (e.g. iatrogenic acidosis, poisonings). By contrast metabolic alkaloses occur as a result of an inappropriately large [SID], although the [SID] need not be greater than the "normal" 40-42 mEq/L. This may be brought about by the loss of anions in excess of cations (e.g. vomiting, diuretics), or rarely by administration of strong cations in excess of strong anions (e.g. transfusion of large volumes of banked blood). Tables 25.1 and 25.2 provide a means of differentiating the various causes of metabolic acidosis