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Review

Impact of the diet on net endogenous acid production and acid–base balance

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SUMMARY

Net acid production, which is composed of volatile acids (15,000 mEq/day) and metabolic acids (70–100 mEq/day) is relatively small compared to whole-body H^+ turnover (150,000 mEq/day). Metabolic acids are ingested from the diet or produced as intermediary or end products of endogenous metabolism. The three commonly reported sources of net acid production are the metabolism of sulphur amino acids, the metabolism or ingestion of organic acids, and the metabolism of phosphate esters or dietary phosphoproteins. Net base production occurs mainly as a result of absorption of organic anions from the diet. To maintain acid-base balance, ingested and endogenously produced acids are neutralized within the body by buffer systems or eliminated from the body through the respiratory (excretion of volatile acid in the form of CO_2) and urinary (excretion of fixed acids and remaining H^+) pathways. Because of the many reactions involved in the acid-base balance, the direct determination of acid production is complex and is usually estimated through direct or indirect measurements of acid excretion. However, indirect approaches, which assess the acid-forming potential of the ingested diet based on its composition, do not take all the acid-producing reactions into account. Direct measurements therefore seem more reliable. Nevertheless, acid excretion does not truly provide information on the way acidity is dealt with in the plasma and this measurement should be interpreted with caution when assessing acid-base imbalance.

1. Introduction

Maintenance of acid–base homeostasis is a vital function of living organisms. Many biochemical reactions of metabolism either produce or consume acids and bases and in usual physiological conditions, net endogenous acid production (NEAP) is modulated mainly by the diet. Since perturbations of the NEAP may have consequences on acid–base equilibrium, it is important to evaluate the mechanisms that control and maintain acid–base homeostasis and to predict how the NEAP may be affected by different diets. The acids in the body are classified as volatile acids (carbonic acid, H_2CO_3) and fixed acids, which are non-volatile acids ingested from the diet or produced within the body as intermediary or end products of metabolism. It is also important to distinguish between metabolisable acids (or bases), which are organic acids that can be consumed and transformed by endogenous metabolism, and non-metabolisable acids which consist mainly of inorganic acids and some organic acids, such as those that cannot be disposed of by metabolism and are excreted in the urine.[1] The combination of endogenous metabolism and dietary intake results in a net production of volatile and fixed acids. One major challenge to maintaining the acid–base balance is keeping the hydrogen ion (H^+) concentration at an appropriate level in body fluids.

2. Reactions and regulators of the acid-base balance

Overall, the whole-body H^+ turnover amounts to 150,000 mEq/day (1 Equivalent = 1 Eq = 1 mol/valency),[2,3] whereas net acid production amounts to only 15,000 mEq/day in the form of volatile carbonic acid[2,4] and 70 to 100 mEq/day in the form of non-volatile acids (fixed acids).[4]

2.1. Reactions producing and consuming H^+

The major source of hydrogen ions in the organism is the reversible reaction that involves the hydrolysis of cellular ATP and which occurs in the course of the metabolism of carbohydrates, lipids and proteins: $ATP^{4-} + H_2O \leftrightarrows ADP^{3-} + HPO_4^{2-} + H^+$. The complete oxidation of these carbon-containing fuels to CO_2 and H_2O leads to the daily formation of a large amount of

Abbreviations: NEAP, net endogenous acid production; AOH, organic acids; AO^-, organic anion; TA, titratable acid; NAE, net acid excretion; RNAE, renal net acid excretion; PRAL, potential renal acid load.

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volatile carbonic acid thanks to the equilibrium reaction: $CO_2 + H_2O \rightarrow H_2CO_3$. In addition, the carbohydrate, lipid and protein metabolic pathways involve the generation of H^+ and fixed acids as intermediary products (Table 1). Under steady conditions, because these acids are continuously produced and consumed, they do not accumulate in the body. However, when combustion processes are incomplete, these endogenously produced organic acids can accumulate and then participate in net acid production. More precisely, carbohydrates are degraded during glycolysis, which produces about 1300 mEq/day of H^+ and lactate, but the further metabolism of lactate, through complete oxidation to CO_2 and H_2O or gluconeogenesis in the liver, consumes an equivalent amount of H^+.[2,4] Similarly, the partial combustion of lipids through lipolysis and then ketogenesis produces ketoacids together with about 300 mEq/day of H^+ ions. However, the inverse reactions for synthesis of triglycerides from ketoacids or the complete oxidation of ketoacids to CO_2 consume identical amounts of H^+.[2,4] As for amino acids, their catabolism consists mainly in the conversion of their carbon skeleton to glucose or triglycerides, which globally consumes H^+, and in the synthesis of urea from their ammonium ion, which consumes HCO_3^- or produces H^+. Consequently, the metabolism of amino acids does not result in a net production of acid except for sulphur, cationic and anionic amino acids.[5]

Altogether, in a steady state, these reactions do not induce a net production of acid but participate in the large turnover of H^+ production and consumption. However, an imbalance between the reactions responsible for H^+ production and consumption, due for example to a loss of intermediary organic acids (loss of ketoacids during the ketonuria of diabetic acidosis) or to their local accumulation (accumulation of lactic acid in muscle during strenuous exercise), leads to an acute state of acidosis.

2.2. Potential additional sources of acid production

The oxidation of sulphur-containing amino acids from dietary proteins or endogenous tissue proteins during starvation results in the production of H^+ according to the reaction: $R{-}SH \rightarrow CO_2 + \text{urea} + 2\,H^+ + SO_4^{2-}$.[5,6] This production is reported to account for 25 to 70 mEq/day of H^+ production.[5,7] Depending on the composition of the diet and considering protein intakes of 100 g/day, the intake of sulphur-containing amino acids is about 3 g/day (FNB/IOM, AFSSA), which would lead to H^+ production of approximately 20 mEq/day. Along with sulphur-containing amino acids, cationic and anionic amino acids may be potential sources of acids and alkalis, respectively. Cationic amino acids (i.e. mainly arginine and lysine) contain an additional amino group, which is protonated at body pH, and their metabolism leads to the production of acid. Since these amino acids often come with an inorganic anion, Cl^-, acid is produced in the form of hydrochloric acid (HCl): $AA^+,Cl^- \rightarrow \text{urea} + CO_2 + HCl$. Conversely, anionic amino acids (glutamate, aspartate), which contain an additional carboxyl group, contribute to the production of alkali (or consumption of acid) when they are metabolized: $AA^-,Na^+ + H_2CO_3 \rightarrow NaHCO_3 + CO_2 + \text{urea}$. It should be noted that the metabolism of cationic and anionic amino acids will result in a net gain of acid or alkali only when they are balanced by an inorganic counter-ion (Cl^- or Na^+, for instance) as opposed to an organic counter-ion. The metabolism of phosphoesters and phosphoproteins is another source of acid: $R{-}PO_4 \rightarrow CO_2 + H_3PO_4$; $5\,H_3PO_4 + 9\,NaHCO_3 \rightarrow 4\,Na_2HPO_4 + NaH_2PO_4 + 9\,H_2CO_3$. Phosphates produced in these reactions will be excreted in the urine.[8,9] This acid production is reported to be of 5 mEq/day.[7]

Endogenous or dietary organic acids (AOH) are considered as potential acid sources since their metabolism involves the intermediate generation of organic anions (AO^-, which are relatively strong acids) together with the consumption of a base, usually bicarbonate (HCO_3^-): $AOH + HCO_3^- \rightarrow AO^- + CO_2 + H_2O$. However, organic anions do not usually accumulate in the body and their further metabolism regenerates HCO_3^-: $AO^- + H_2CO_3 \rightarrow CO_2 + H_2O + HCO_3^-$. As a result, the complete oxidation of organic acids does not contribute to acid production. Net acid production (or net alkali loss) occurs when organic anions are not completely metabolized and are lost in the urine, which can come about under two circumstances. First, under some particular conditions (e.g. ketonuria or strenuous exercise), the two reactions of production and combustion of organic anions are not concomitant or do not have matching rates, and organic anions (e.g. citric acid and lactic acid) may be excreted in the urine before being fully oxidized to CO_2. Second, some ingested organic acids cannot be fully metabolized in the body (e.g. uric, oxalic or hippuric acids) and their organic anions are formed as end products of metabolism with an equivalent consumption of HCO_3^- and retention of H^+. In both cases, HCO_3^- is not regenerated, which represents a loss of potential base.[6,9] The fate of ingested and endogenous organic acids and the consequences in terms of the acid-base balance are detailed in Table 2. The loss of bicarbonate due to the incomplete metabolism of organic acids is reported to be equivalent to an H^+ addition/retention of 40 mEq.[7]

The most important organic sources of alkalis in the diet are organic acids that are ingested in the form of salts of organic anions (e.g. citrate, malate and lactate). They lead to the production of HCO_3^- when they are oxidized in the course of the metabolism: $AO^- + H_2CO_3 \rightarrow CO_2 + H_2O + HCO_3^-$. Between 20 and 40 mEq of organic anions are likely to be absorbed daily,[3] but some of these anions are not metabolisable (e.g. tartrate) and are thus directly excreted in the urine without producing HCO_3^-.[3,9]

Inorganic acids and bases directly ingested through the diet also contribute to the addition of acids and bases to the body. However, their impact is not directly appreciable as it depends on their absorption by the gastro intestinal tract, which varies not only with the nature of the substance but also with the interaction with other exogenous and endogenous chemical substances.[9]

Table 1
Main reactions responsible for H^+ regeneration and consumption in the metabolism of carbohydrates, lipids and proteins.[a]

	H^+ regeneration	H^+ consumption
Carbohydrates	• Glycolysis glucose → lactate + H^+	• Regeneration of glucose from lactate lactate + H^+ → glucose • Complete oxidation of glucose lactate + H^+ → CO_2 + H_2O
	1300 mEq/d H^+[b]	1300 mEq/d H^+[b]
Lipids	• Lipolysis triglycerides → FA + H^+ • Oxidation of FA (ketogenesis) FA → ketone bodies + H^+	• Triglyceride synthesis FA + H^+ → triglycerides • FA synthesis ketone bodies + H^+ → FA
	300 mEq/d H^+[b]	300 mEq/d H^+[b]
Proteins and AA	• Urea synthesis NH_4^+ (from AA) → Urea + H^+	• Oxidation of carbon skeletons of AA ketoacids (from AA) + H^+ → gluc. or trig.
	• Overall catabolism of AA neutral AA → gluc. or trig. + Urea	
	cationic AA → gluc. or trig. + urea + H^+ sulfur AA → gluc. or trig. + urea + H_2SO_4	anionic AA + H^+ → gluc. or trig. + urea

FA, fatty acids; AA, amino acids; gluc., glucose; trig., triglyceride.
[a] The equations presented in the table are qualitative: they are not balanced and display only the molecules of interest as regards acid or base production.
[b] Indicate the amounts (mEq/d) of H^+ ions that are globally produced or consumed by the reactions.