Journal of Theoretical Biology 392 (2016) 35–47

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Impulsive mathematical modeling of ascorbic acid metabolism in healthy subjects

Mostafa Bachar [a,*], Jochen G. Raimann [b], Peter Kotanko [b,c]

[a] Department of Mathematics, College of Sciences, King Saud University, Riyadh, Saudi Arabia
[b] Renal Research Institute, 4th Floor, 315 East 62th Street, New York, NY 10065, United States
[c] Icahn School of Medicine at Mount Sinai, 1428 Madison Avenue, New York, NY 10029, United States

HIGHLIGHTS

- We have developed a mathematical model allowing the prediction of ascorbic acid dynamics at different states of vitamin C intake.
- In addition to intestinal uptake, distribution and dynamics in the extracellular volume and the tissue, we have also included a novel approach to quantify the glomerular excretion of ascorbic acid.
- We also analyzed the global asymptotic stability of acid kinetics model in healthy subjects.

ARTICLE INFO

Article history:
Received 14 February 2015
Received in revised form
8 November 2015
Accepted 26 November 2015
Available online 24 December 2015

Keywords:
Ascorbic acid deficiency
Ascorbic acid metabolism in human
Bio-availability
Fixed point theory
Global stability
Impulsive ordinary differential equation

ABSTRACT

In this work, we develop an impulsive mathematical model of Vitamin C (ascorbic acid) metabolism in healthy subjects for daily intake over a long period of time. The model includes the dynamics of ascorbic acid plasma concentration, the ascorbic acid absorption in the intestines and a novel approach to quantify the glomerular excretion of ascorbic acid. We investigate qualitative and quantitative dynamics. We show the existence and uniqueness of the global asymptotic stability of the periodic solution. We also perform a numerical simulation for the entire time period based on published data reporting parameters reflecting ascorbic acid metabolism at different oral doses of ascorbic acid.

1. Introduction

The first reports of the occurrence of scurvy were published early in the 18th century and described observations in soldiers of the Austrian army (Kramer, 1736). Despite the fact that the disease was well-known and occurred often in sailors at sea for long periods of time, the exact causes and pathophysiology were unclear. The disease remained somewhat mysterious until the British naval surgeon James Lind hypothesized that the lack of variety in the diets of sailors (mainly consisting of carbohydrate-rich potatoes) may play a role. Lind conducted experiments with sailors showing symptoms of scurvy aiming to find a cure for the detrimental disease. Notably, Lind's experiment is nowadays considered to be the first randomized placebo-controlled trial in medical history. The naval surgeon compared the disease severity after allocating affected sailors in a randomized fashion to different diet groups. The diet of these groups differed substantially in composition and included items rich in Vitamin C (lemons, oranges, and others available), a molecule also referred to as ascorbic acid (AA), in the “intervention” groups and a regular diet (mainly comprising potatoes) in the “control” group. As a result of his studies, Lind was able to conclude that the addition of specific food items (namely the AA-rich items) to the notoriously monotonous diet at sea, prevented sailors from the incidence of scurvy and brought improvement to those already affected. Lind's report is the first piece of evidence on the importance of AA-rich food in health and disease (Lind, 1753).

In recent years the characteristics and functions of AA have been investigated in much detail. In all its functions AA basically acts as an electron donor and is consequently present in either a reduced or an oxidized form. Reported functions range from carnitine synthesis to

* Corresponding author.
E-mail address: mbachar@ksu.edu.sa (M. Bachar).

http://dx.doi.org/10.1016/j.jtbi.2015.11.030
0022-5193/

the production of tyrosine and catecholamines and also includes antihistaminic effects. It has been also proposed that AA is an antioxidant and a free-radical scavenger and thus protects metabolically active cells from oxidative stress (Raimann et al., 2013). It also acts as a cofactor for numerous other enzymatic reactions.

While most mammals are able to synthesize AA from glucose, humans and other primates are not able to synthesize AA because of the lack of the enzyme *L*-gulono-γ-lactone oxidase. This enzyme is required for the last step in the synthesis of AA (Nishikimi and Yagi, 1991). As a consequence humans need to absorb AA from their diet.

Recommendations on daily intake have been published based on retrospective and prospective data and it is known that the needed amounts are dependent on many factors such as body composition, comorbidities, age and lifestyle (Levine et al., 1999). Notably, in healthy subjects it is impossible to overdose AA because of the ability to excrete excess AA. However, a long-standing excessive intake of AA associates with the occurrence of (calcium-oxalate containing) kidney stones (Thomas et al., 2013).

In those with reduced excretory capabilities, the situation is more complicated: While beneficial effects of AA administration on anemia management in chronic kidney disease have been reported (Tarng, 2006; Deved et al., 2009), calcium-oxalate deposition is of great concern for the community. The circulating levels of AA and the oxidized end-products are substantially higher in the absence of renal excretion and the molecules are more likely to convert to oxalate if present in higher concentrations. Oxalate, if present in high levels, may crystallize and precipitate, causing deposition in various tissues (including retina, vessel walls and myocardium) (Raimann et al., 2013). Despite reports of AA deficiency in dialysis patients, even resulting in symptoms of scurvy and an increased incidence of periodontitis, the nephrology community practices a restrictive approach to AA supplementation due to this concern (Raimann et al., 2013; Levine et al., 2001; Tarng, 2006; Deved et al., 2009; Sirover et al., 2015).

In concert, this emphasizes the need for a mathematical model allowing to determine optimal AA intake (and supplementation) not only for the general population but also for those with chronic kidney disease and those receiving dialysis. A model for the general population was proposed by Graumlich et al. (1997) based on data acquired in a prospective study (Levine et al., 1996), which first depleted subjects from AA and then resupplemented them in gradually increasing dose steps (each lasting until steady state was reached for at least 7 days) until unphysiologically high doses were reached (Levine et al., 1996). However, for patients suffering from chronic kidney disease, particularly those on dialysis, the model requires additional considerations and is not included in the current model.

In this work, we propose and develop an impulsive ordinary differential equation (IODE) model in Section 2 to simulate, based on the approach proposed by Graumlich and colleagues, the dynamics of AA in the intestines, extracellular fluid, tissue and the urine. In Section 3, we study the existence and the global asymptotic stability of the periodic solutions according to regular drug intake, and we perform a numerical simulation for long-term treatment fit based on existing data from the literature reporting AA metabolism during the use of large doses of oral AA. Finally, clinical interpretations are offered in Section 4.

2. Model development

Humans cannot produce AA and need to absorb it from the diet in order to maintain appropriate levels in the body. AA is consumed and metabolized and excess AA is excreted by the kidneys. The following presents the details and rationale of each of these steps.

2.1. Transmembranous transport of ascorbic acid (AA)

Generally AA is transported by specific transporters in the gastrointestinal tract, called the “sodium-coupled Vitamin C transporters” (SVCTs) which are encoded by the SLC23 gene family. The human SLC23 family encodes two different transporters, SVCT1 and SVCT2. The oxidized form of AA (dehydroascorbic acid; DHAA) can, in addition to the uptake using SVCT1, also be taken up by facilitated diffusion via members of the GLUT family (GLUT2 and GLUT8) (Corpe et al., 2013). SVCT1 and SVCT2 are examples of a secondary active transport because they couple AA uptake to the concentration gradient of sodium ion across the plasma membrane that is maintained by $Na^+/\ K^+$-ATPase. Both SVCT1 and SVCT2 transport AA with high affinity and the expression of these transporters in the cell membrane is mainly dependent on the intracellular AA concentration (Hornig, 1975).

SVCT1 has high affinity for AA and considering the relationship as a Michaelis–Menten like function, the concentration at which the rate $K_{M_{SVCT1}}$ of the process is half of the theoretical maximum transport rate is 20–100 μmol L^{-1} (Takanaga et al., 2004; Wang et al., 1999; Tsukaguchi et al., 1999; Wang et al., 2000).

SVCT2 is widely distributed to deliver AA into cells. The highest expression of SVCT2 is in adrenal gland, brain, lung and bone tissue, however this transporter is found in muscle, lymphoid organs and reticuloendothelial cells, and platelets. It is of note that a large amount of the whole-body AA content is found in skeletal muscle where it protects cells from oxidative stress and sustains enzyme activities required for carnitine biosynthesis. Therefore, AA is transported at a high rate into the muscle cells and stored in substantial amounts of 3–4 mg per 100 g tissue weight (Hornig, 1975).

2.2. Absorption of ascorbic acid (AA) in the gastrointestinal tract

As mentioned above SVCT1 transporters are AA responsible for the absorption of AA in the gastrointestinal tract and facilitates the transport across the apical membrane of enterocytes. Uptake of AA and DHAA takes place along the entire length of the human small intestine with the highest activity in the distal ileum. Notably, the DHAA uptake is higher in jejunal segments. The ratios of AA versus DHAA uptake are 3.3 in the duodenum and jejunum but increase to 4.8, 7.2 and 30 in ileum segments I_1, I_2 and I_3. According to the literature (Malo and Wilson, 2000), the intestinal AA transport is saturable, with an Michaelis–Menten constant $K_{M_{AA}}$ of 267 ± 33 molL^{-1}, and for DHAA, $K_{M_{DHAA}}$ of 805 ± 108 molL^{-1}. The kinetics have been described as Michaelis–Menten-like dynamics but are currently not sufficiently studied to be expressed as actual Michaelis–Menten kinetics. This would require further experimental research to characterize the transport more accurately. In line with previous approaches including the model by Graumlich et al. (1997), we considered the uptake dynamic as a saturable process of the magnitude of AA ingested following this outlined Michealis–Menten like kinetic. Furthermore the bio-availability of synthetic and “natural” forms of AA are assumed to differ very little (Corpe et al., 2013; Levine et al., 2001), which may be seen in contrast to claims made by several manufacturers. In addition, it is known that the intestinal absorption of AA can be modified by other nutrients. For example it was speculated that the high content of quercetin and other flavonoids in red grape juice may account for the observation that drinking this juice decreases absorption of AA into the body when AA is administered orally to human subjects (Bates et al., 2004). The actual uptake of AA in the