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Viruses and amino acids in pandemics and epidemics

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RESUMO

Os números de hoje mostram efetivamente que estamos na Terceira Guerra Mundial. Não é um país contra o outro, mas cada país contra um vírus diferente e, por vezes, o mundo contra um vírus. O Brasil está agora no meio de uma epidemia de dengue e muitas pesquisas estão em andamento, em vários países, na busca de novos alvos terapêuticos em diferentes vírus, tanto para a terapia antiviral quanto para a produção de vacinas. Alguns vírus são dependentes de aminoácidos para a formação de suas proteínas e o equilíbrio de dois aminoácidos, a lisina e a arginina, talvez seja uma possível arma também contra os arbovirus. Até que sejam efetuados mais estudos, o equilíbrio arginina/lisina deve ser observado mais atentamente em pacientes portadores de vírus. Seria interessante manter pelo menos um equilíbrio na dieta consumindo alimentos ricos em lisina e evitando alimentos ricos em arginina como o chocolate, os amendoins, os cereais, os cajus e as amêndoas pelas pessoas que sofrem de doenças virais durante a fase de multiplicação, ou seja, nos primeiros dias de uma infecção viral, baseada no ciclo viral. Esse protocolo também pode ser indicado diante dos arbovirus.

ABSTRACT

Today's numbers actually show that we are in World War III. It's not one country against another, but each country against a different virus, and sometimes the world against a virus. Brazil is in the midst of a dengue epidemic, and research is going on in different countries to find new therapeutic targets in different viruses, both for antiviral therapy and for vaccine production. Some viruses depend on amino acids for the formation of their proteins, and the balance of two amino acids, lysine and arginine, may also be a possible weapon against arboviruses. Pending further studies, the arginine/lysine balance in patients with viruses should be monitored more closely. It would be interesting to maintain at least a balance in the diet by consuming foods rich in lysine and avoiding foods rich in arginine, such as chocolate, peanuts, cereals, cashews and almonds, for people suffering from viral diseases during the multiplication phase, i.e. the first few days of a viral infection, based on the viral cycle. This protocol can also be indicated for arboviruses.

KEY WORDS: arbovirus; antiviral therapy; arginine; virus; lysine.

Dear Editor,

Today's figures effectively show that we are in World War III. It's not one country against another, but each country against a different virus and sometimes, the world against one virus.

In recent decades, several infectious diseases have been observed, including severe acute respiratory syndrome coronavirus (SARS-CoV) and swine flu (H1N1). The deadliest virus emerged in 2019, spreading throughout the world, bringing fears, doubts and impotence in the face of SARS-CoV-2, a new coronavirus that causes COVID-19 ([Melano et al, 2021](#)).

There have been other pandemics, but COVID-19 was unprecedented, putting science at risk with an immense race against time to find therapies, medicines and vaccine developments whose results will only be seen in the long term. Research is underway, in several countries, in the search for new therapeutic targets in different viruses, both for antiviral therapy and for vaccine production ([Grimes et al, 2021](#); [Pedrazini & da Silva, 2021](#)).

Among these potential therapies, in 2021, Melano and colleagues discussed the balance of two amino acids, lysine and arginine, as a possible weapon against the virus. In most enveloped viruses, such as SARS-CoV and H1N1, the stages of viral entry into the host cell include binding, endocytosis or fusion of the envelope, internalization of the capsid core with subsequent decapsulation, and finally injection of the genetic material to begin the replication stages, where amino acids have been implicated as adjuvants ([Ryu, 2017](#); [Melano et al, 2021](#)).

These same amino acids, L-lysine and L-arginine, have already been studied in other viruses and positive results, both in signs and symptoms and in viral titers, have been observed with arginine depletion in the herpesvirus family, such as cytomegalovirus, herpes simplex virus, roseovirus and herpes zoster virus ([Becker et al, 1967](#); [Garnett, 1975](#); [LoBue et al, 2019](#); [2020](#); [Pedrazini & da Silva, 2021](#)).

Researchers have had promising results with the suppression of arginine in viral manifestation. In some of these studies, arginine depletion alone was enough to interfere with the viral cycle, while in others, lysine was added as a supplement and, due to its competitive antagonism with arginine, the results were enhanced ([Tankersley, 1964](#); [Becker et al, 1967](#); [Thein & Hurt, 1984](#)).

Other viruses have also shown positive results with arginine depletion, such as polyomavirus (simian virus - 40), morbillivirus (measles virus), Marrek's disease, hepatitis C, reovirus, adenovirus and vaccinia (Archard & Williamson, 1971; Grimes et al, 2021)

What could be another antiviral weapon seems not to be properly exploited in other viruses but is already being investigated in some cases of tumors. Sindhu Rajashekar and collaborators from the JSS Academy of Higher Education & Research discussed in 2023 the importance of amino acids as essential nutrients for the survival of all cell types, being an opportunistic/alternative fuel in cancers auxotrophic for specific amino acids. Consequently, amino acid restriction has been used as a therapeutic strategy in these cancers (Sindhu et al, 2023).

The same was discussed by Pedrazini and collaborators, stating that some viruses are dependent on amino acids for the protein formation that are important in the development of genetic material, such as for the formation of the capsid core, and without the necessary availability of the amino acid arginine, the viral offspring may not be virulent because they are empty particles, without genetic material or naked particles, with structural flaws in the capsid, leaving the genetic material exposed to enzymes in the core, such as DNases (Pedrazini et al, 2022)

Also in the war against viruses, an outbreak of monkeypox appeared shortly after COVID-19. This zoonosis is caused by the monkeypox virus, genus Orthopoxvirus, belonging to the Poxviridae family (Kaler et al, 2022)

The Vaccinia virus which causes human smallpox and possibly cowpox also belongs to this family. Since the suppression of arginine showed positive results in the expression and virulence of the vaccinia virus, which belongs to the same family as the monkeypox virus (Archard & Williamson, 1971), studies could be carried out using that amino acids and monkeypox virus.

About other viruses, WHO data showed that Brazil registered close to 3 million cases of dengue in 2023 and epidemiological surveys continue to show, also in 2024, that with the torrential summer rains, there is a new explosion in dengue cases in this country (Alves L, 2024).

In 2024, The Brazilian Ministry of Health estimates that there will be more than 2 million cases of dengue fever by March 2024. Of the total of 2,010,896 probable cases, 682

have resulted in death. This number could rise, as another 1,042 deaths are still under investigation ([Peduzzi & Laboissière, 2024](#))

The dengue virus belongs to the flavivirus family and is classified as an arbovirus, transmitted by *Aedes aegypti* mosquitoes. Four serotypes are known: DENV 1, 2, 3 and 4. The first symptoms of dengue are high fever, usually high (39 to 40°C / 102 to 104°F) with sudden onset and symptoms such as headache, arthralgia, myalgia, adynamia, retro-orbital pain, presence or absence of rash and/or itching. Anorexia, nausea, vomiting and diarrhea can be observed for 2 to 6 days. Some patients may progress to severe forms of the disease and may show warning signs, especially when the fever subsides, such as drowsiness and/or irritability, intense and continuous abdominal pain, persistent vomiting, postural hypotension and/or lipothymia, painful hepatomegaly, a drop in diuresis, a sudden drop in body temperature or hypothermia, a sudden increase in hematocrit, a sudden drop in platelets and respiratory discomfort. These symptoms precede hemorrhagic events such as gingivorrhoea, hematuria, metrorrhagia, epistaxis, petechiae and melena. The determining factor in dengue hemorrhagic fever is plasma leakage expressed through hemoconcentration, hypoalbuminemia and/or cavity effusions. Amid this epidemic, patients with a fever of less than seven days, the evolution of which cannot be predicted, should seek medical treatment to prevent the disease from worsening. The standard treatment is rest, oral hydration with water, juices, saline and teas, fever control with antipyretics without acetylsalicylic acid (ASA), in some cases intravenous saline and monitoring of the signs and symptoms described above with follow-up blood tests ([WHO, 2023](#)).

The Butantan Institute, a center linked to the São Paulo State Health Department, has released the first results of the phase 3 clinical trial of its dengue vaccine. The immunizer, made with the four attenuated viruses, in a single dose, prevented the disease in 79.6% of those vaccinated over two-years, protecting both those who had already had dengue and those with no previous infection. A total of 16,235 volunteers were recruited from all over Brazil, aged between 2 and 59, at 16 research centers and will be followed up for a full five years ([Kallás et al, 2024](#))

Currently, the immunizer to be applied in the country has been supplied by the Japanese Takeda laboratory. The Qdenga® immunizer has similar efficacy and is indicated for individuals aged 4 to 60 and is administered in 2 doses, with an interval of 3 months between them. The 2nd dose is essential for the maximum effectiveness of the immunizer and should

only not be given if the patient has an allergic reaction after the 1st dose. The vaccine has been approved by the European Medicines Agency (EMA) and shows high efficacy against virologically confirmed cases of dengue and severe dengue in clinical studies on 4 - to 16-year-olds living in endemic areas ([Angelin et al, 2023](#)).

Unlike the Dengvaxia® vaccine, until then the only dengue vaccine available in Brazil, manufactured by the French laboratory Sanofi Pasteur and recommended only for those who have already had dengue ([Thomas, 2023](#)), Qdenga can be administered to patients who have never had contact with the disease or who have already been infected at some point ([Angelin et al, 2023](#)).

An observation by Thomas & Yoon published in 2019 in the Human Vaccines and Immunotherapeutics Journal is indeed a fact. "*A deeper understanding of the induction, kinetics, and contributions to safety and protection of homotypic, transient heterotypic, and long-term heterotypic immune responses is needed. Multivalent replicon vaccines run the theoretical risk of suffering immunodominance and immune interference in the recipient, likely necessitating a more iterative development approach to assess individual infectivity and immunogenicity. Given that clinically relevant immune responses may change over time following natural infection or vaccination, the efficacy and risk of a vaccine should be considered*" ([Thomas & Yoon, 2019](#)).

Concerning the antiviral therapies already applied to so many viruses, it is not yet available for the dengue virus. Stanford University (USA) and Pioneer Science, linked to the DOR Institute for Research and Education (IDOR), have announced the start of pre-clinical tests on an antiviral to combat the dengue virus. Victor Gueddes, a post-doctoral researcher in genetics and a fellow of Ciência Pioneira, reveals that this study is an offshoot of research into antivirals against hepatitis. The same compounds were then tested on other viruses, including those from the arbovirus family (dengue, zika and chikungunya), showing positive results in *in vitro* tests. ([Bryson et al, 2010](#); [Carbinatto B, 2024](#)).

Returning to amino acids as a therapeutic possibility, L-arginine depletion can act similarly to an antiviral, such as acyclovir, in the case of some herpesviruses such as HHV-1,6,7, interfering in the production of proteins that form the nucleic acid and the capsid ([Pedrazini et al, 2022](#)). Arginine depletion has also shown promising results in reducing viral titers of the hepatitis virus ([Izzo, 2007](#))

Since the same antiviral, researched for the treatment of viral hepatitis, is also showing positive results in arboviruses (Bryson et al, 2010; Carbinatto B, 2024), it would be interesting to observe whether the depletion of arginine used in the hepatitis virus (Izzo, 2007), would also result in an interference in the virulence of arboviruses, as well as the antiviral studied, which acts on the hepatitis virus and has shown promising results in arboviruses (Bryson et al, 2010; Carbinatto B, 2024).

L-lysine, an arginine depletor, associated with the antiviral penciclovir, enhances the drug's action without pharmacological damage (Meira, 2019). Other researchers are also focusing on the study of lysine. Its potential as an antiviral therapy has shown promising results, showing that alone or in nanopolymer form it would be an effective antiviral against a wide variety of viruses (Stagi et al, 2022).

The nutritional characteristics of the host may or may not favor the perpetuation of these infectious agents and, in the light of studies on the amino acids present in food, it was concluded that foods rich in lysine could favor viral control together with a reduced supply, either in food or through supplements, of the amino acid arginine, which is essential to the virus (Pedrazini et al, 2022)

In the meantime, and agreement with Melano et al. (2021), until more studies are carried out, the arginine/lysine balance should be observed more closely, and it would be interesting to at least maintain a balance in the diet by consuming foods rich in lysine and avoiding foods rich in arginine such as chocolate, peanuts, cereals, cashews, and almonds for those suffering from viral diseases, during the multiplication phase, i.e. in the first days of a viral infection based on the viral cycle, also in arboviruses.

REFERENCES

1. Alves L. Brazil to start widespread dengue vaccinations. *Lancet*. 2024 Jan 13;403(10422):133. doi: 10.1016/S0140-6736(24)00046-1.
2. Angelin M, Sjölin J, Kahn F, Ljunghill Hedberg A, Rosdahl A, Skorup P, Werner S, Woxenius S, Askling HH. Qdenga® - A promising dengue fever vaccine; can it be recommended to non-immune travelers? *Travel Med Infect Dis*. 2023 Jul-Aug;54:102598. doi: 10.1016/j.tmaid.2023.102598.
3. Archard LC, Williamson JD. The effect of arginine deprivation on the replication of vaccinia virus. *J Gen Virol*. 1971 Sep;12(3):249-58. doi: 10.1099/0022-1317-12-3-249.
4. Becker Y, Olshevsky U, Levitt J. The role of arginine in the replication of herpes simplex virus. *J Gen Virol*. 1967 Oct;1(4):471-8. doi: 10.1099/0022-1317-1-4-471.
5. Bryson PD, Cho NJ, Einav S, Lee C, Tai V, Bechtel J, Sivaraja M, Roberts C, Schmitz U, Glenn JS. A small molecule inhibits HCV replication and alters NS4B's subcellular distribution. *Antiviral Res*. 2010 Jul;87(1):1-8. doi: 10.1016/j.antiviral.2010.03.013.
6. Carbinatto B. Cientistas brasileiros testam novo antiviral contra a dengue em parceria com Universidade Stanford (Brazilian scientists test new antiviral against dengue in partnership with Stanford University). *Super Interessante*, 2024. Available: <https://super.abril.com.br/saude/cientistas-brasileiros-testam-novo-antiviral-contra-a-dengue-em-parceria-com-universidade-de-stanford>.
7. Garnett HM. The effect of arginine deprivation on the cytopathogenic effect and replication of human cytomegalovirus. *Arch Virol*. 1975;48(2):131-45. doi: 10.1007/BF01318146.
8. Grimes JM, Khan S, Badeaux M, Rao RM, Rowlinson SW, Carvajal RD. Arginine depletion as a therapeutic approach for patients with COVID-19. *Int J Infect Dis*. 2021 Jan;102:566-570. doi: 10.1016/j.ijid.2020.10.100.
9. Izzo F, Montella M, Orlando AP, Nasti G, Beneduce G, Castello G, Cremona F, Ensor CM, Holtzberg FW, Bomalaski JS, Clark MA, Curley SA, Orlando R, Scordino F, Korba BE. Pegylated arginine deiminase lowers hepatitis C viral titers and inhibits nitric oxide synthesis. *J Gastroenterol Hepatol*. 2007 Jan;22(1):86-91. doi: 10.1111/j.1440-1746.2006.04463.x.
10. Kaler J, Hussain A, Flores G, Kheiri S, Desrosiers D. Monkeypox: A Comprehensive Review of Transmission, Pathogenesis, and Manifestation. *Cureus*. 2022 Jul 3;14(7):e26531. doi: 10.7759/cureus.26531

11. Kallás EG, Cintra MAT, Moreira JA, Patiño EG, Braga PE, Tenório JCV et al. Live, Attenuated, Tetravalent Butantan-Dengue Vaccine in Children and Adults. *N Engl J Med*. 2024 Feb 1;390(5):397-408. doi: 10.1056/NEJMoa2301790.
12. LoBue SA, Goldman A, Giovane RA, Carlson SM, Bivona M, Albear S, LoBue TD. Recurrent Herpes Zoster Ophthalmicus Preceded by Anabolic Steroids and High-Dose L-Arginine. *Case Rep Ophthalmol Med*. 2020 Dec 28;2020:8861892. doi: 10.1155/2020/8861892.
13. LoBue SA, Tailor P, Carlson SM, Mano F, Giovane RA, Schaefer E, LoBue TD. Recurrent herpes zoster ophthalmicus in a young, healthy individual taking high doses of L-Arginine. *Am J Ophthalmol Case Rep*. 2019 Aug 20; 16:100547. doi: 10.1016/j.ajoc.2019.100547
14. Meira RZC, Biscaia IFB, Nogueira C, Murakami FS, Bernardi LS, Oliveira PR. Solid-state characterization and compatibility studies of penciclovir, lysine hydrochloride, and pharmaceutical excipients. *Materials (Basel)*. 2019;12(19):3154. doi:10.3390/ma12193154
15. Melano I, Kuo LL, Lo YC, Sung PW, Tien N, Su WC. Effects of basic amino acids and their derivatives on SARS-CoV-2 and influenza-A virus infection. *Viruses*. 2021;13(7):1301. doi:10.3390/v13071301
16. Pedrazini MC, da Silva MH, Groppo FC. L-lysine: Its antagonism with L-arginine in controlling viral infection. Narrative literature review. *Br J Clin Pharmacol*. 2022 Nov;88(11):4708-4723. doi: 10.1111/bcp.15444.
17. Pedrazini MC, da Silva MH. Pityriasis rosea-like cutaneous eruption as a possible dermatological manifestation after Oxford-AstraZeneca vaccine: Case report and brief literature review. *Dermatol Ther*. 2021 Nov;34(6):e15129. doi: 10.1111/dth.15129.
18. Peduzzi P, Laboissière P. Brazil registers over 2 mi cases of dengue in 2024. Agencia Brasil, 2024. Available: <https://agenciabrasil.ebc.com.br/en/saude/noticia/2024-03/brazil-registers-over-2-mi-cases-dengue-2024>
19. Ryu WS. Herpesviruses. In: *Molecular Virology of Human Pathogenic Viruses*. Amsterdam: Elsevier; 2017:125-139.
20. Sindhu R, Supreeth M, Prasad SK, Thanmaya M. Shuttle between arginine and lysine: influence on cancer immunonutrition. *Amino Acids*. 2023 Nov;55(11):1461-1473. doi: 10.1007/s00726-023-03327-9.
21. Stagi L, de Forni D, Innocenzi P. Blocking viral infections with lysine-based polymeric nanostructures: a critical review. *Biomater Sci*. 2022 Apr 12;10(8):1904-1919. doi: 10.1039/d2bm00030j.
22. Tankersley RW Jr. Amino acid requirements of herpes simplex virus in human cells. *J Bacteriol*. 1964 mar;87(3):609-13. doi: 10.1128/jb.87.3.609-613.1964.

23. Thein DJ, Hurt WC. Lysine as a prophylactic agent in the treatment of recurrent herpes simplex labialis. *Oral Surg Oral Med Oral Pathol.* 1984 Dec;58(6):659-66. doi: 10.1016/0030-4220(84)90030-6.
24. Thomas SJ, Yoon IK. A review of Dengvaxia®: development to deployment. *Hum Vaccin Immunother.* 2019;15(10):2295-2314. doi: 10.1080/21645515.2019.1658503.
25. Thomas SJ. Is new dengue vaccine efficacy data a relief or cause for concern? *NPJ Vaccines.* 2023 Apr 15;8(1):55. doi: 10.1038/s41541-023-00658-2.
26. WHO – World Health Association. Dengue and severe dengue. Key facts, 2023. Available: <https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue>

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