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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 único vírus e suas mutações. O Brasil está agora no meio de uma nova epidemia, a de dengue causada por um arbovírus. 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 L-lisina e a L-arginina, talvez seja uma possível terapia também contra os arbovirus. Até que sejam realizados novos estudos, o equilíbrio arginina/lisina deve ser observado mais atentamente em pacientes portadores de vírus. Seria interessante, nestes pacientes, manter pelo menos um equilíbrio na dieta com o consumo de alimentos ricos em lisina e o controle na ingestão de alimentos ricos em arginina como o chocolate, o amendoim, os cereais, o caju e as castanhas em geral, nos primeiros dias da infecção viral, fase de maior de multiplicação do vírus. Esse protocololo talvez possa ser aplicado nos casos de infeccões por arbovírus.

ABSTRACT

Today's numbers effectively show that we are in World War III. It is not one country against another, but each country against a different virus and, sometimes, the world against a single virus and its mutations. Brazil is now in the midst of a new epidemic, dengue fever caused by an arbovirus. Much research is underway, in several countries, in the search for new therapeutic targets in different viruses, both for antiviral therapy and for vaccine production. Some viruses are dependent on amino acids for the formation of their proteins and the balance of two amino acids, L-lysine and L-arginine, may also be a possible therapy against arboviruses. Until new studies are carried out, the arginine/lysine balance should be observed more closely in patients with viruses. It would be interesting, in these patients, to maintain at least a balance in the diet with the consumption of foods rich in lysine and control the intake of foods rich in arginine such as chocolate, peanuts, cereals, cashews and nuts in general, in first days of the viral infection, the phase of greatest multiplication of the virus. This protocol could perhaps be applied in cases of arbovirus infections.

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

Dear Editor,

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

In recent decades, several infectious diseases have been observed, including severe acute respiratory syndrome (SARS-CoV) and swine flu (H1N1). The most deadly virus emerged in 2019, SARS-CoV-2, spreading around the world, bringing fear, doubts and helplessness in the face of COVID-19 (Melano et al, 2021).

There have been other pandemics, but COVID-19 was unprecedented, putting science in an immense race against time to find therapies, medicines and the development of vaccines whose results will only be seen in the long term. Other research is still ongoing, in several countries, in the search for new therapeutic targets in different viruses, both for antiviral therapy and to guide the production of vaccines (Grimes et al, 2021; Pedrazini & da Silva, 2021).

Among these potential therapies, in 2021, Melano and colleagues discussed the balance of two amino acids, L-lysine and L-arginine, as a possible strategy against SARS-CoV-2 and H1N1 (Melano et al, 2021), enveloped viruses whose host cell entry stages include: binding, endocytosis or fusion of the envelope, internalization of the nucleocapsid with subsequent injection of the genetic material into the cell nucleus, where the amino acid-dependent stages of replication will begin (Ryu, 2017; Melano et al, 2021).

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

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, Pedrazini et al, 2022).

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 may be another antiviral alternative for some viruses does not seem to be properly explored for others. However, arginine depletion is already being investigated in some cases of tumors. Sindhu Rajashekar and coworkers at 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, as well as a nutrient for tumor cells in cancers that are auxotrophic for certain amino acids. Consequently, amino acid restriction has been used as a therapeutic strategy in these cancers (Sindhu et al, 2023). Viruses depend on cells and cells depend on amino acids.

Pedrazini and coworkers discussed that some viruses also depend on amino acids for the formation of their proteins, which are important for the development of the viral genetic material and for the formation of the capsid. In theory, amino acids are present in the host cell, which the virus uses as a factory for new viruses. In the absence of good availability of the amino acid arginine, the newly produced viruses may not be virulent, presenting themselves as empty particles, without genetic material, or as naked particles, with structural defects in the capsid, defects that leave the genetic material exposed to enzymes from the host nucleus, such as DNases (Pedrazini et al, 2022).

Returning to the topic of epidemics, in the fight against viruses, an outbreak of monkeypox occurred shortly after COVID-19. This zoonosis is caused by a virus of the genus Orthopoxvirus, belonging to the family Poxviridae (Kaler et al, 2022).

Vaccinia virus, which causes human smallpox and possibly cowpox, also belongs to this family. Interestingly, suppression of arginine showed positive results on vaccinia virus expression and virulence (Archard & Williamson, 1971). Given this context, arginine depletion could be investigated in the control of monkeypox virus.

As for other viruses, WHO data show that Brazil registered nearly 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 of 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 2,010,896 probable cases, 682 have resulted in death. This number could increase, as another 1,042 deaths are still under investigation (Peduzzi & Laboissière, 2024).

Dengue virus belongs to the flavivirus family and is classified as an arbovirus transmitted by the Aedes aegypti mosquito. Four serotypes are known: DENV 1, 2, 3 and 4.

The first symptoms of dengue are high fever, usually high (39 to 40ºC / 102 to 104ºF) 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 may be observed for 2 to 6 days. Some patients may progress to more severe forms of the disease and may exhibit warning signs, especially as the fever subsides, such as drowsiness and/or irritability, severe and persistent abdominal pain, persistent vomiting, postural hypotension and/or lipothymia, painful hepatomegaly, a decrease in diuresis, a sudden decrease in body temperature or hypothermia, a sudden increase in hematocrit, a sudden decrease in platelets, and respiratory distress. These symptoms precede hemorrhagic events such as gingivorrhea, hematuria, metrorrhagia, epistaxis, petechiae, and melena. The defining factor in dengue hemorrhagic fever is plasma leakage, expressed as hemoconcentration, hypoalbuminemia and/or cavitary effusions. In the midst of this epidemic, patients with a fever of less than seven days whose course cannot be predicted should seek medical treatment to prevent worsening of the disease. The standard of care 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 affiliated with the São Paulo State Health Department, has released the first results of the Phase 3 clinical trial of its dengue vaccine. The vaccine, 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 between the ages of 2 and 59 were recruited from all over Brazil at 16 research centers and will be followed for a full five years (Kallás et al, 2024).

Currently, the immunizer to be used in the country is supplied by the Japanese Takeda laboratory. Qdenga® immunizer has similar efficacy and is indicated for individuals between the ages of 4 and 60 years and is administered in 2 doses with an interval of 3 months between them. The second dose is essential for maximum efficacy of the vaccine and should only be omitted if the patient has an allergic reaction to the first dose. The vaccine has been approved by the European Medicines Agency (EMA) and has shown high efficacy against virologically confirmed cases of dengue and severe dengue in clinical trials in 4-16 year olds living in endemic areas (Angelin et al, 2023).

Unlike Dengvaxia®, the only dengue vaccine available in Brazil at the time, which is manufactured by the French laboratory Sanofi Pasteur and is recommended only for people who have already had dengue (Thomas, 2023), Qdenga® can be administered to patients who have never been exposed to the disease or who have 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).

While antiviral therapies have been used against many viruses, they have not yet been used against dengue. Stanford University (USA) and Pioneer Science, associated with the DOR Institute for Research and Education (IDOR), announced the start of preclinical testing of an antiviral drug against the dengue virus. Victor Gueddes, postdoctoral researcher in genetics and fellow at Ciência Pioneira, reveals that this study is an offshoot of research into antivirals against hepatitis. The same compounds of these antivirals were then tested on other viruses, including those of the arbovirus family (dengue, zika and chikungunya), with 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 in a similar way to an antiviral agent. Acyclovir, used in the case of some herpesviruses such as HHV-1,6,7, interferes with the production of proteins that form the nucleic acid strand and the capsid, thereby reducing signs and symptoms in patients. Arginine depletion through dietary control and/or the use of its antagonistic competitor, L-lysine, also showed improvement in the signs and symptoms of HHV-1,6,7 carriers (Pedrazini et al, 2022). Similar to an antiviral, arginine depletion has also shown promising results in reducing hepatitis virus titers (Izzo, 2007).

Analyzing what has been discussed above, the same antiviral used to treat viral hepatitis also shows positive results in arboviruses (Bryson et al, 2010; Carbinatto B, 2024). It would

also be interesting to observe whether arginine depletion, which is used against viral hepatitis (Izzo, 2007), would result in interference with the virulence of arboviruses. A hypothesis to be studied.

L-lysine, an arginine depleter, is being studied as an antiviral therapy. It has been associated with the antiviral drug penciclovir, enhancing the drug's effects without causing pharmacological damage (Meira, 2019). Other researchers are also focused on studying 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 variety of viruses (Stagi et al, 2022).

It is known that the nutritional characteristics of the host, that is, the types of foods consumed or supplements used, can favor the persistence of infectious agents (Lobue et al, 2019; 2020). Studies on amino acids, all of which are present in food, conclude that foods rich in lysine may favor viral control, along with a reduction in the intake of foods rich in arginine, an essential amino acid for many viruses (Pedrazini et al, 2022).

Therefore, according to Melano et al. (2021), pending further studies, it is necessary to pay more attention to the arginine/lysine balance, and it is interesting to maintain a diet rich in lysine and with reduced consumption of foods rich in arginine (chocolate, peanuts, cereals, cashews and almonds) in people suffering from viral diseases, especially in the initial phase of infection when viral replication is greater. This approach could also be used in the face of epidemic outbreaks such as dengue.

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