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Viruses and amino acids in pandemics and epidemics

Vírus e aminoácidos em pandemias e epidemias

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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 (break-bone 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 virus multiplication. This protocol could perhaps be applied in cases of arboviruses infections.

Indexing terms: Arboviruses. Arginine. Lysine.

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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 arbovírus. 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 protocolo talvez possa ser aplicado nos casos de infecções por arbovírus.

Termos de indexação: Arbovírus. Arginina. Lisina.

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 H1N1influenza flu, also called swine flu. In 2019, the deadliest virus, SARS-CoV-2, emerged and spread around the world, causing fear, doubt and helplessness in the face of COVID-19 [1].

There have been other pandemics, but COVID-19 is unprecedented and has placed science in an immense race against time to develop therapies, medicines and vaccines whose results will only be seen in the long term. Further research is underway in several countries to identify new therapeutic targets in different viruses, both for antiviral therapy and to guide vaccine production [2,3].

In 2021, among these potential therapies, Melano and colleagues discussed balancing two amino acids, L-lysine and L-arginine, as a possible strategy against SARS-CoV-2 and H1N1 [1]. These enveloped viruses are dependent on amino acids for stages of entry into the host cell such as: binding, endocytosis or envelope fusion, internalization of the nucleocapsid with subsequent injection of the genetic material into the cell nucleus [1,4].

These same amino acids, L-lysine and L-arginine, have already been studied in other viruses and in the herpes virus family, positive results in signs and symptoms or in viral titers have been observed with arginine depletion. These viruses include cytomegalovirus, herpes simplex virus, roseovirus and herpes zoster virus [3, 5-8]

In some of these studies, arginine depletion alone was sufficient to disrup the viral cycle, while in others, lysine was added as a supplement and the results were enhanced due to its competitive antagonism with arginine [5, 9-11].

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 virus [2,12].

Arginine depletion is also being investigated in some tumor cases and this has already been discussed [13]. In 2023 Sindhu Rajashekar and co-workers, at the JSS Academy of Higher Education & Research, also discussed 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 [14] as well as viral control [11,13,15]. This highlights the importance of studying amino acids as a therapeutic proposition. What may be another antiviral alternative for some viruses does not seem to be properly explored for others viruses.

Pedrazini and co-workers 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 and may present as empty particles without genetic material, or as naked particles with structural defects in the capsid that expose the genetic material to enzymes from the host nucleus, such as DNases [11].

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 Poxviridae family [16].

Vaccinia virus, which causes cowpox and is used as a viral agent in smallpox vaccination, also belongs to the same family [17]. Interestingly, suppression of arginine showed positive results on vaccinia virus expression and virulence [12]. Given this context, arginine depletion could be investigated in the control of monkeypox virus which, like vaccinia virus, belong to the Poxviridae family.

In 2023 as far as other viruses are concerned, WHO data show that Brazil registered almost 3 million cases of dengue, and also in 2024, epidemiological surveys continue to show that, with the torrential summer rains, there is a new explosion of dengue cases in this country [18].

In 2024, the Brazilian Ministry of Health estimates that there will be more than 2 million cases of dengue. 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 [19].

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 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 pruritus. 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, decreased 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 severe dengue 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 [20].

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 four attenuated viruses in a single dose, prevented the disease in 79.6% of those vaccinated over two years. It protects both those who have 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 [21].

The Japanese Takeda laboratory currently supplies the Brazil's immunizer, Qdenga®. It has similar efficacy and is indicated for individuals aged 4-60. However, it is administered in 2 doses, three months apart. The second dose is essential for the vaccine to be fully effective. It 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 been proven to be highly effective against virologically confirmed cases of dengue and severe dengue in clinical trials involving 4 to16 year old patients living in endemic areas [22].

Unlike Dengvaxia®, the first vaccine available in Brazil and manufactured by the French laboratory Sanofi Pasteur, which is only recommended for people who already have the viral disease [23], Qdenga® can be administered to patients who have never manifested the disease, such as those who have already had the disease at some point [22], as well as the vaccine being tested by the Butantan Institute.

In 2019, an observation by Thomas & Yoon published 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" [24].

Antiviral therapies have been used against many viruses, but not yet against dengue. Stanford University (USA) and Pioneer Science, in collaboration with the DOR Institute for Research and Education (IDOR), have initiated preclinical testing of an antiviral drug against the dengue virus. Victor Gueddes, a 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, RNA viruses that belong to four families: Flaviviridae, Bunyaviridae, Reoviridae, and Togaviridae (ex: dengue, zika and chikungunya), with positive results in in vitro tests [25-27].

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 [11]. Similar to an antiviral, arginine depletion has also shown promising results in reducing hepatitis virus titers [28].

Analyzing what has been discussed above, the same antiviral used to treat viral hepatitis also shows positive results in arboviruses [26, 27]. It would also be interesting to observe whether arginine depletion, which is used against viral hepatitis [28], would result in interference with the virulence of arboviruses. This is a hypothesis that needs 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 [29]. Other

researchers are studying lysine as well. Its potential as an antiviral therapy is clear. Alone or in nanopolymer form, it would be an effective antiviral against a variety of viruses [30].

It is known that the nutritional characteristics of the host, that is, the types of food consumed or supplements used, can favor the persistence of infectious agents [7,8]. Studies on amino acids, all of which are present in food, concluded 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 [11,13,15].

Therefore, according to Melano et al. [1] and Pedrazini et al. [13,15], 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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Collaborators

MC Pedrazini, researcher responsible for the conceptualization, bibliographic review, writing proof and final version and, article submission. The author read and approved the final draft.

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