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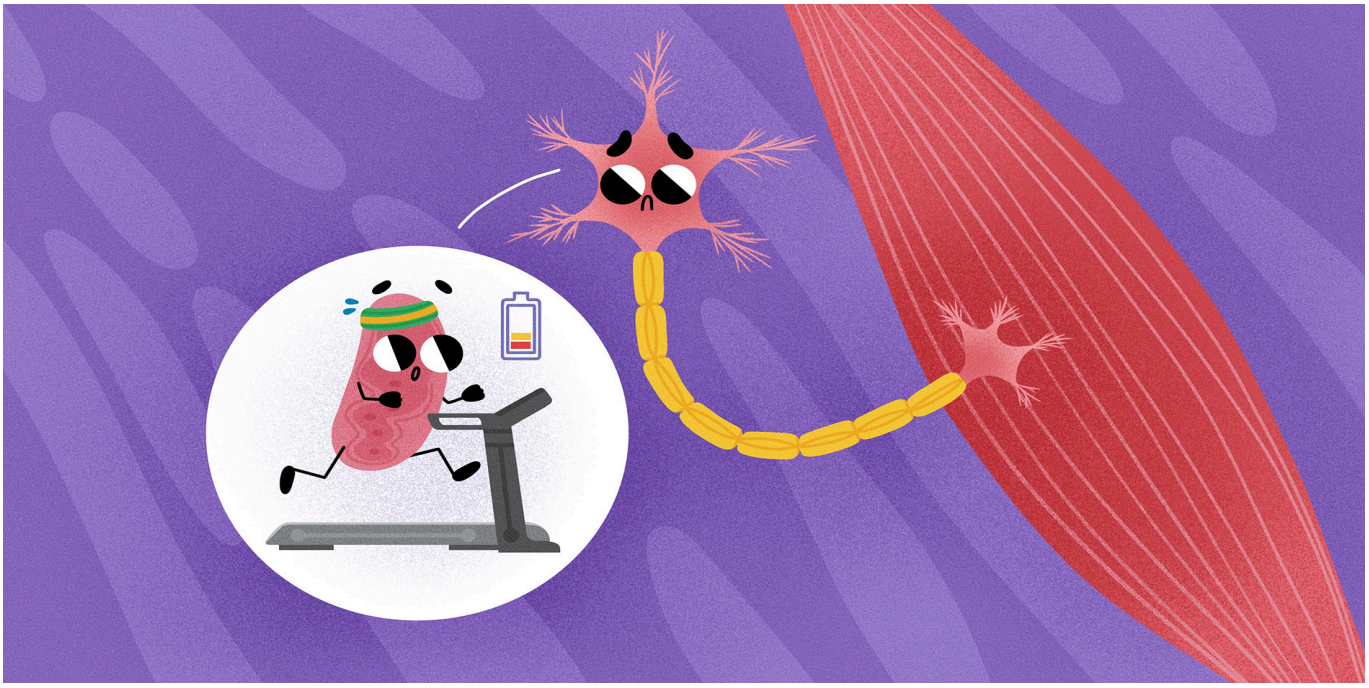

AMYOTROPHIC LATERAL SCLEROSIS: WHEN NERVE CELLS RUN OUT OF POWER

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YOUNG REVIEWERS:

ARITRO
AGE: 14

CLAUDIO
AGE: 15

Amyotrophic lateral sclerosis (ALS) is a serious disease of the nervous system, in which the brain and spinal cord cannot communicate properly with the muscles to coordinate the body's movements. Consequently, the muscles gradually stop working and things like walking, eating, breathing, and speaking become more and more difficult. Many aspects of ALS remain a mystery, but we know that cells called neurons run out of energy in ALS patients, resulting in the loss of communication with muscles. This happens due to defects in mitochondria—the tiny structures within our cells that produce energy. Researchers have been working hard to discover how to keep mitochondria healthy, avoid the death of nerve cells, and ultimately restore the communication between neurons and muscles.

WHAT IS AMYOTROPHIC LATERAL SCLEROSIS?

NEURONS

Cells of the nervous system that communicate with each other and link the brain and spinal cord to all organs in the body. Motor neurons control movement.

The brain and spinal cord control every little thing we do, such as thinking, moving, feeling, and learning. They even control things we are not aware of, such as heartbeat, breathing, and digestion. But they cannot do everything alone! The brain and spinal cord are connected to each organ and muscle by cells called **neurons** (Figure 1A).

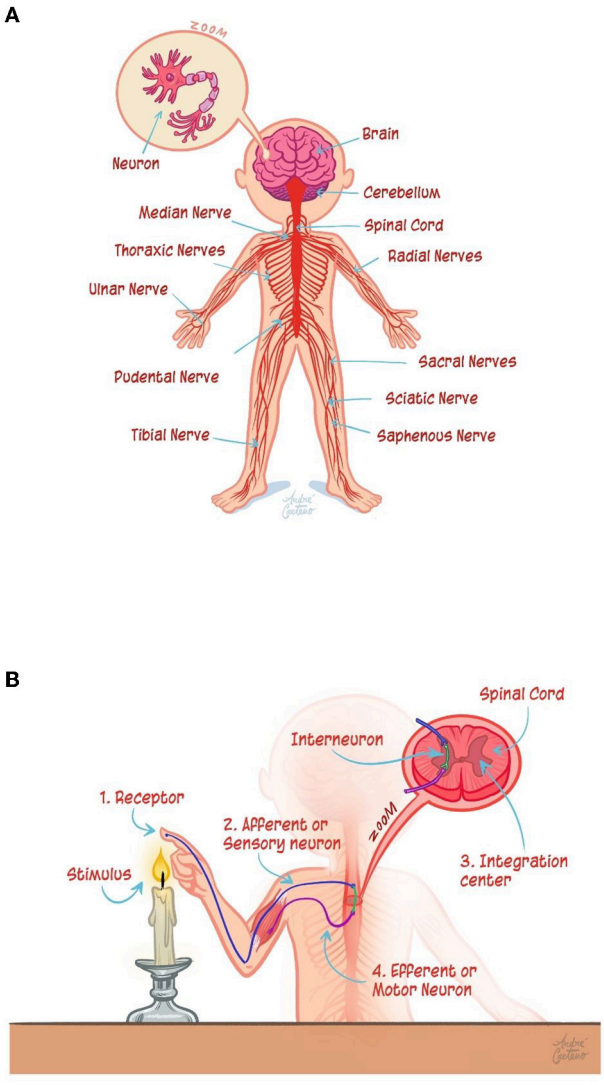

Figure 1

(A) The brain and spinal cord control the body with the help of neurons, which make up the many nerves that connect to all the body's organs. **(B)** When you touch something hot, the sensory neurons in your skin send a message of pain to the spinal cord. As a result, through the motor neurons, the spinal cord immediately tells the muscles of the arm to contract, removing your hand from the heat. When this precise coordination is not working properly, as happens in ALS, the malfunctioning motor neurons may be unable to send information to the muscles, and the muscles gradually stop working.

The human body contains billions of neurons, which work every second of our lives. Neurons communicate with each other inside the brain, and they also communicate with the various parts of the body, controlling all body functions. For example, when you touch a hot surface, the heat sensors in your skin communicate with neurons that send a message of pain to your spinal cord, which immediately returns a message back to contract the muscles in your arm so that you

pull away (Figure 1B). The neurons responsible for muscle contraction are called motor neurons, and they control every movement of the body.

In **neurodegenerative diseases**, some neurons do not work properly. This is what happens in amyotrophic lateral sclerosis (ALS), a disease in which the motor neurons get sick and can no longer effectively communicate with the muscles. Consequently, the muscles in the entire body gradually stop working. Because ALS evolves rapidly, within a few months ALS patients develop difficulties walking, eating, breathing, and speaking (Figure 2). Thus, ALS is a devastating disease and patients need a lot of support, both from other people and from mechanical devices like wheelchairs. ALS is generally diagnosed in people aged 54–69, and it affects 4–8 people out of 100,000 [1].

NEURO-DEGENERATIVE DISEASES

Diseases caused by the loss of structure or function of neurons that affect many of your body's activities—balance, movement, talking, breathing and heart function, for example.

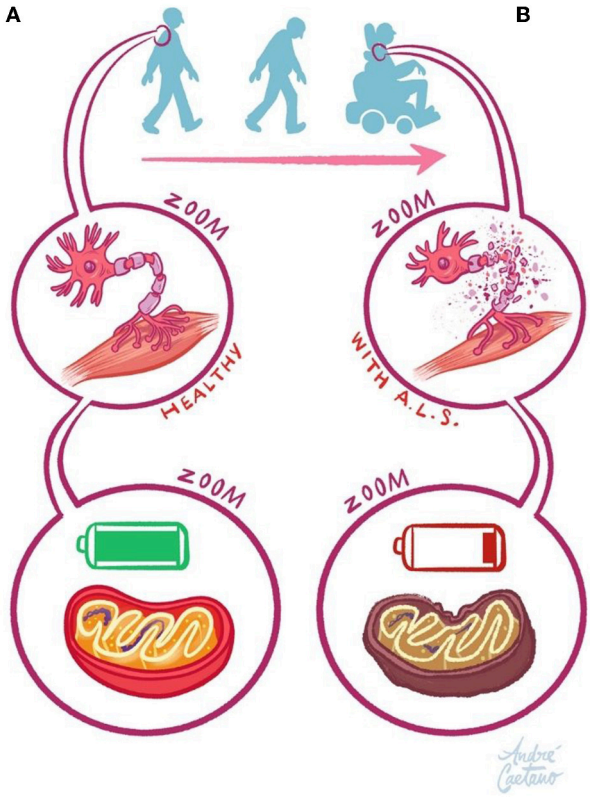

Figure 2

(A) Like all cells, neurons need energy to work properly. This energy is provided by the mitochondria—the cells' batteries. Since neurons are constantly working, they rely on a precise and continuous supply of energy. As such, neurons contain numerous mitochondria. **(B)** However, if something interferes with the function of mitochondria, energy production is affected and neurons "run out of power." When this happens, the communication between motor neurons and muscle cells fails, resulting in ALS.

WHY DO NEURONS FAIL TO COMMUNICATE WITH MUSCLES?

Just like every cell of the body, neurons need energy to work. Think of neurons as your mobile phone—if your phone runs out of power, you can no longer communicate with your friends. That is what happens to the motor neurons of ALS patients—they run out of energy

and become unable to communicate with their respective muscles (Figure 2).

MITOCHONDRIA

Cellular components responsible for energy production.

The power needed by neurons (and all other cells) comes from cell parts called **mitochondria**, which function as cellular batteries. Different types of cells contain different numbers of mitochondria, depending on how much energy they need—the more energy a cell needs, the more mitochondria it will have. Since neurons are constantly working, they have a lot of mitochondria. Did you know that the brain consumes 20% of the body's energy? Because neurons need so much energy to perform their important functions, small defects in energy production can lead to neuron death, which can cause the development of neurodegenerative diseases. Beyond decreased energy production, studies in ALS patients discovered that the mitochondria of their motor neurons may have other problems, too [2].

WHAT IS OXIDATIVE STRESS?

OXIDATION

Reaction of an element with oxygen.

REACTIVE OXYGEN SPECIES (ROS)

Highly reactive molecules produced by cells that steal electrons from other molecules, damaging them.

OXIDATIVE STRESS

Imbalance between ROS and antioxidants in the body, which can lead to cell damage.

Oxidation is a natural process that happens when something is in contact with oxygen, such as when you cut an apple and leave it in contact with the air for hours (Figure 3A). Something similar occurs inside our cells when cellular components are in contact with **reactive oxygen species (ROS)**. ROS are molecules that steal electrons from other molecules. In normal conditions, ROS are important for controlling critical cellular processes. But when excessive amounts of ROS are produced and our cells cannot cope with them, ROS start to damage essential cellular components, including mitochondria. This is called **oxidative stress**, and it can kill cells (Figures 3B, C).

When mitochondria are not working properly, neurons become more susceptible to damage from oxidative stress, and the neurons can no longer perform their functions. High levels of oxidative stress in the motor neurons of ALS patients lead to mitochondrial damage that prevents neurons from communicating with muscles [2, 3].

WHAT CAUSES ALS AND HOW CAN WE TREAT IT?

The brain and neurons are extremely complex, and we still do not know exactly what causes ALS or how to treat it. We know that 10% of ALS patients inherit the disease from their parents (called familial ALS), while in the remaining 90% of cases there is no clear origin (called sporadic ALS) [4]. Both familial and sporadic ALS are associated with mutations in more than 50 genes [5]. Certain behaviors, including smoking, being overweight, lack of physical activity, and exposure to pesticides or heavy metals, have been identified as risk factors for ALS—but we still do not understand the exact role of these factors in causing the disease [6].

Figure 3

(A) If you cut an apple and leave it in the air, the oxygen causes it to turn yellow and shriveled, and it eventually becomes brown and dried. This process is called oxidation. **(B, C)** A similar process occurs when the inner components of our cells interact with reactive oxygen species (ROS) or free radicals, molecules that try to steal electrons from other molecules. If the cell cannot neutralize ROS, a condition called oxidative stress results, which can cause cell damage and even death. This is believed to be how the loss of motor neurons occurs in ALS.

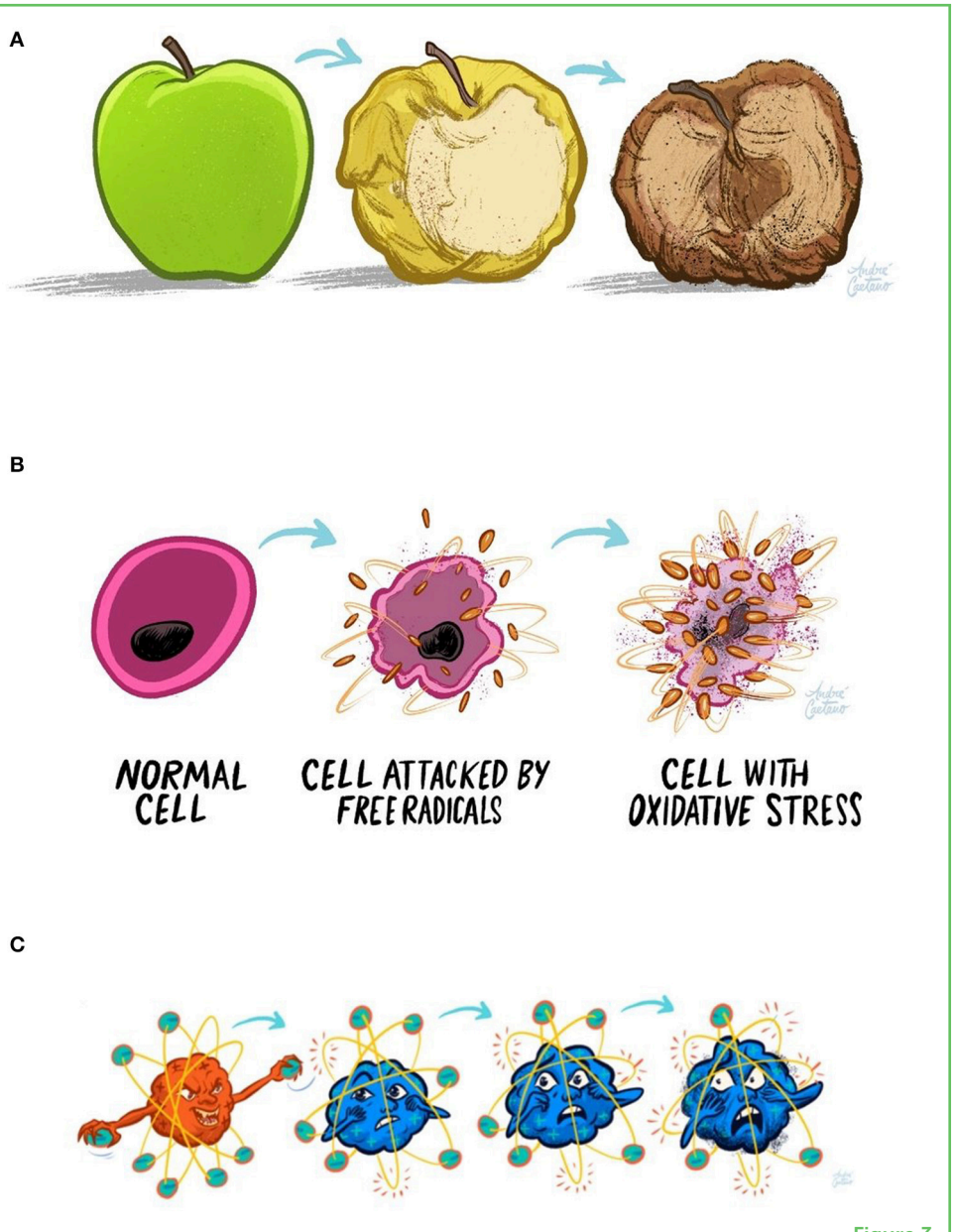

Figure 3

ALS remains incurable and the therapies that are available only help with symptoms [7]. But scientists have been exploring possible treatment ideas, including the use of substances called **antioxidants**, which can decrease ROS levels and reduce oxidative stress in motor neurons. These antioxidants may keep mitochondria healthy, keep motor neurons alive, and restore communication between motor neurons and muscles. Researchers worldwide are seeking to unravel the mechanisms behind ALS to better understand how this disease progresses. This knowledge could lead to the identification of **biomarkers** (indicators of the disease that can be measured, for example, molecules that could be detected by blood tests) that would allow us to diagnose ALS earlier. Research could also help us develop potential drugs to treat the disease. As each case of ALS has its own

ANTIOXIDANTS

Molecules that decrease oxidative stress by donating electrons to other molecules.

BIOMARKER

Biological indicator of a biological state.

characteristics, it might be necessary to customize treatments for each individual. Until we have a successful treatment for ALS, we will continue to work hard to discover ways to help ALS patients and their families.

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YOUNG REVIEWERS

ARITRO, AGE: 14

Hello! I am an exuberant violist and enjoy playing with the local youth orchestra. Summer gives me the opportunity to play tennis with friends and go on long kayaking trips with my family. I love traveling and will be going to Austria to tour and play music with my orchestra in summer!

CLAUDIO, AGE: 15

I love science and physics, as well as learning about computer programming. I also love basketball. Go Celtics!

AUTHORS

MARTA QUATORZE

I am a biologist with a master's degree in cellular and molecular biology. After two years studying how the brain regulates metabolism, I realized that what I really enjoyed was taking science outside the laboratory and communicating with the public. I monitored experimental scientific activities for primary school students, and I worked on a European project that aimed to promote health literacy in rural areas. Currently, I am working at the Science Communication Office of the Center for Neuroscience and Cell Biology (CNC) of the University of Coimbra, working every day to engage society in science.

FILOMENA SILVA

I am a biochemist with a Ph.D. in healthy science and technology, and currently the chief scientific officer at a company called MitoTAG. From May 2018 to April 2021, I was the principal investigator of a project called "Development of Novel Mitochondria-Targeted Antioxidants for Improving SOD1-Familial Amyotrophic Lateral Sclerosis Phenotype" in the Mitochondrial Toxicology and Experimental Therapeutics (MitoXT) group at the Center for Neuroscience and Cell Biology (CNC) of the University of Coimbra. In that project, I explored the role of mitochondria and oxidative stress mechanisms in the progression of ALS, and found new mitochondria-targeted antioxidants that can contribute to the treatment of this neurodegenerative disease.

ANA I. DUARTE

I am a biologist with a Ph.D. in cell biology. I am curious about what makes neurons and heart cells work well when they are healthy and why diseases like type 2 diabetes, hypertension, obesity, or cardiac or neurodegenerative diseases affect their function. I also try to understand how gender affects those cells and if innovative compounds can help diseased neurons and cardiac cells to recover. I enjoy participating in science-awareness activities—they help me focus on what matters: science with social impact, from the people to the people. I also enjoy understanding things and trying to make "complicated" science into "simple" science.

JOÃO CARDOSO

I am a Ph.D. student in science communication, currently working at the Science Communication Office of the Center for Neuroscience and Cell Biology (CNC) of the University of Coimbra, where I amin charge of the institution's communication with the public. I have also been involved in several public engagement and outreach initiatives, and I have a strong interest in developing innovative strategies to communicate about health sciences and raise awareness of diseases. In my Ph.D. project, I am exploring the historical and cultural connection between Portugal and Japan, to develop multimedia materials to promote health literacy in both countries.

CAROLINA CAETANO

I am a biologist with a master's degree in cellular and molecular biology, working in science communication. Currently, I work as a press officer at the Science Communication Office at the Center for Neuroscience and Cell Biology (CNC) of the University of Coimbra. I am responsible for producing press releases that present science to society in an understandable way, and that bring the community and scientists together. I also manage social networks and produce audiovisual content on scientific topics. In addition, I have been involved in science communication projects at CNC, which involve schools, associations, art, and theater. My interest in engaging the public with science is still growing, as is my feeling of responsibility to communicate science in an honest and inclusive way.

JOÃO RAMALHO-SANTOS

I am a biologist with a Ph.D. in cell biology. Basically, I try to understand how the cells of the body work, why we get sick when they do not work, and what we can do to keep them happy and healthy. I often use comics and cartoons to explain these

things, because I really like comics (and movies and TV series), and I think they can make complicated science easier to understand.

PAULO J. OLIVEIRA

I am a biochemist with a Ph.D. in cell biology. I coordinate a research laboratory at the Center for Neuroscience and Cell Biology of the University of Coimbra, with the fancy name of Mitochondrial Toxicology and Experimental Therapeutics (MitoXT for short). I work with mitochondria—cell components that produce most of the energy we need to live. I believe that a problem with mitochondria exists in every human disease and that we should treat mitochondria to treat the condition. I even believe that a giant mitochondrion exists in the center of the Universe, but no one takes me seriously.

SARA VARELA AMARAL

I am a biochemist with a Ph.D. in science communication. At the moment, I coordinate the Science Communication Office at Center for Neuroscience and Cell Biology of the University of Coimbra. I have been involved in several projects that aim to promote clear communication between scientists and various audiences, and to promote education about the biomedical field. These national and international projects involve a strong interaction with schools, public-engagement initiatives, art and science projects, fundraising projects, and impact-evaluation studies—all aimed to increase scientific literacy, which could contribute to a truly scientific culture and citizenship. *sara.amaral@cnc.uc.pt