Juan Pedro Bolaños: "We often think we have a God-given understanding of how to do certain things"

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Juan Pedro Bolaños is a biochemist and researcher in neuroscience specialised in neuroenergetics and metabolism. He is Professor of Biochemistry and Molecular Biology at the University of Salamanca. His research focusses on understanding the molecular mechanisms that regulate metabolism and redox homeostasis in cells of the central nervous system. Specifically, he studies the proteins and **signalling pathways responsible for adaptation of neuronal metabolism to the continuous, high energy demands and antioxidants imposed by neurotransmission**. He has received various awards throughout his scientific career, among which are the 2021 Castile and Leon Prize for Scientific and Technical Research and Innovation.

- **Your work has focussed on the study of cerebral metabolism. What's that got to do with cardiovascular disease?**

The regulation mechanisms of the metabolism are, to a large extent, common to all tissues. What is explored in the brain can also be extrapolated, but with its peculiarities because there are important differences. What interests me is cerebral metabolism and knowing how the brain adapts to the different situations we face every day.
It's understood that if we eat more fat, we are going to get fat and, if you do exercise, you lose weight. It seems we have everything well under control in terms of knowledge about how the metabolism regulates itself for the whole body, particularly in terms of adipose tissue. However, we know very little about how that directly affects the brain. What we intend to do is to attempt to understand what the adaptation mechanisms of neural cells are, I mean nerve cells, not just neurons. There are other cells called glial cells, for instance, astrocytes that have a unique morphological peculiarity, which is that they are the intersection between blood and the neuron. To explain this graphically, we could say that they are cells that hug onto the brain blood vessels, which is where they obtain nutrients, and on the other end of the same cell they are in direct functional, but not physical, contact with the synapsis.

And since **Cajal** we have known that the astrocytes must have, let's say, a bridging mission between the composition of blood and function of the neuron. But this was not studied because we didn't have the necessary technology.

The **astrocyte** is a type of neural cell that, as it does not have either synaptic or nerve activity, does not transmit impulses, but it does possess a very high metabolic dynamic, which means it can adapt itself metabolically, which in turn means that the biochemical reactions that take place in the cells can adapt on a large scale to very disparate conditions and survive. This does not happen in neurons, whose metabolism is a bit more rigid and more difficult to adapt.

And we don't know why. Currently, in my laboratory in Salamanca, we are trying to understand how, through the chemical composition of blood, astrocytes are capable of sensing changes in lifestyle, for instance, diet, exercise, etc. For many years, I have been working to decipher what the main pathways are that regulate the metabolism in astrocytes, in neurons, to establish their differences in order to achieve a better understanding of them. Over the years, this has led me to the conclusion that astrocytes are enormously plastic from a metabolic point of view.

This plasticity, the q**uality to change metabolic substrate and precursor of energetic fuel**, the quality they have to change from one to the other with hardly any apparent effects, does end up slightly altering the metabolic product.

The metabolism has a decomposition pathway of metabolites that is ultimately going to generate energy or produce other metabolic intermediaries which are released to the synapse, and which are used by neurons as, for instance, signals to regulate and modulate synaptic transmission, or even to obtain their own energy.

Without any doubt, these changes that simple astrocytes can undergo as a consequence of changes in lifestyle have an impact on neuronal activity.

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- **Could we say that astrocytes are a possible therapeutic pathway for neurocognitive decline?**

I don’t think we should lose sight of them.

- **Why are you so interested in cerebral metabolism and specifically in astrocytes?**

The truth is that sometimes you specialise in something by chance. I was in London doing my post-doc and we decided to cultivate the nervous system cells of a mouse, and we saw that it was easier to do it with astrocytes. Then I realised the potential of this line of research. At that time, I was studying the respiratory chain. We added a substance of nitric oxide, which is an important cardiovascular regulator, although we were more interested in nitric oxide as a regulator of mitochondria in the nervous system. **Working with neurons and astrocytes**, we added the same dose of nitric oxide, and we observed that the neurons died within minutes, whereas the astrocytes were happy. That also started to motivate me: I wanted to understand what differences exist between neuronal metabolism and that of astrocytes that allows them to adapt in such a different way.
Astrocytes adapt so well that, even with the respiratory chain blocked, without the cell’s main source of energy, the mitochondria survived.

- **Like a kind of supercell?**

That’s it, they are supercells. They are able to readapt their metabolism, obviously, changing other things, supplementing energy by obtaining it from different sources. That’s what **readaptation** is. That capacity to resist attracted my attention. I wanted to know what makes them so resistant. Maybe what we have to do is find out how we can add these resistance mechanisms to neurons and maybe prevent neurodegeneration that way. That was more or less the idea I had at that time, but it turned out not to be so easy.

- **Technology has advanced a lot since then.**

Now we can quite easily answer questions that were almost impossible back then. I’m still answering questions I asked myself at that time. It is true that the field of cerebral metabolism is slightly less advanced than, say, cancer cell metabolism or that of cardiomyocytes, due to the intrinsic difficulty involved in working with a biological material of great complexity, where different types of cells take different metabolic pathways.

- **Coming from a family of pharmacists, your path was clear.**

I was certain from an early age that I liked pharmacology, I liked research. My father was a **pharmacist**, and he had a clinical analysis laboratory, where I used to play. Instead of playing with chemistry set toys I had the real thing, made by my father, and I did all kinds of experiment. It was a daily thing for me. And my father always encouraged me. He challenged me to think: do this, and

why? he would say. My scientific vocation was unavoidable.

That's where it all began. I went to study a degree in Pharmacology at Salamanca and did my PhD under the supervision of José María Medina, the biochemistry professor who has just retired. I went to London for the post-doc; I was there for two years and worked very hard. At that time, we could say that metabolism was an area of research that was of no great interest to anyone and, least of all, that of the nervous system, which was what I liked. During those two years I published three original papers that are, curiously, the most cited of my scientific career.

On my return to Spain, I did the competitive entrance exam for a teaching position at the University of Salamanca and, after passing, I applied for my first National Plan project. That's when I created my group, without a penny to my name. I think it's good to have a work-life balance. It's true that before, research consumed you and it was much more difficult to devote yourself to research

- **And suddenly you found yourself up against something you had no training for: leading a group.**

Right. We often think we have a God-given understanding of how to do certain things. For instance, nowadays, for a National Plan project, you have to explain a series of things that are not just scientific. For instance, your approach to gender or how the data is going to be stored..., all of these aspects that we have no training for and don't know how to tackle. And the people who assess you are people like me, who don't have training in this field.

- **How has the profile of a researcher in Spain changed since those times?**

It's more or less the same. There are people who know they want to research, whereas others, when they realise what it takes to get a tenured position in an institution, in terms of time, effort and sacrifice, decide they are not willing to make that sacrifice. Let's say they are more practical. What I notice is that there are more and more practical people who prefer the pharmaceutical industry, etc. It's not because they don't want a career in research, but because they see the personal sacrifice as too great for what they will receive in return.

Science is very **demanding**. I think it's good to have a work-life balance and it is true that before, research consumed you and it was much more difficult to devote yourself to research. Before, it was normal to work at the weekend or keep going until 12 o'clock at night. And you don't see that anymore. Also, now, in some places you aren't allowed to work at the weekend.

Juan Pedro Bolaños gave the seminar "Peculiarities of brain energy metabolism" at CNIC at the invitation of Dr. Mercedes Ricote