Episode 31 – Sandra Encalada: Linking traffic jams in the brain to neurodegenerative disease

Drew (00:03):

Greetings listeners. And thank you for joining me for this edition of Science Changing Life. If you were expecting PreSCRIPPSion Sound, then never fear. The content is just the same. We've simply had a slight name change. If you are familiar with Scripps Research, the institute's motto is *Science Changing Life* to really encapsulate the impact that the research has on the wider world and the motivations that drive our scientists. So we thought we should continue that sentiment here and align the podcast name as well. Administration aside, today we take a journey along our brain cells to explore the transport network inside neurons and its critical role in health and disease. I'm joined by neuroscientist, Sandra Encalada, who investigates how this transport system breaks down and why it may be involved in neurodegeneration. But before we get there, let's find out how some pivotal moments in Ecuador set Sandra on the path that eventually led her to a fascination with tiny biological machines.

Sandra (01:02):

I think my interest in science started around the time I was maybe probably 13, you know, somewhere in my early teens, I was in Ecuador. You know, I'm from Ecuador originally. And I was born in a household of four girls. I was the first of four and you know, my mother's a, an amazing homemaker. She took full care of us, but, uh, my father was a social scientist who I remember at dinner would talk to us a lot about things in life and, and about choosing what do we like and, and our interest. And so one of the things that I remember he emphasized, how is how quantitative skills are so important in that if we studied mathematics, for example, or quantitative skills or the physical world, we would always have a stronghold on understanding reality, basically, right? And I remember that kind of striking me as, as a very important, you know, lesson.

Sandra (01:52):

And I developed this very strong interest in physics initially. And so in Ecuador back then, we had to sort of choose directions early on in high school. Even then there were different paths that you could choose with regards to the classes that you took. And I took a lot of physics and math classes, you know, I just really got enamored with that, but I gotta say in a society where physics and math are not encouraged of girls, I had a pivotal interaction with a women scientist who was actually working with my father in environment. She had been a, a radio astronomer in Puerto Rico at the Arecibo, um, radio telescope. And my father arranged for me to, to talk to her and have lunch with her. And I was 13 then, and it was really great. It was just the two of us. And she basically showed me a face of a woman who could do physics and this really impacted me. And so from then on, I was sort of determined that I wanted to do that. And a few years after that, I was able to make it to the us. And I was studying my undergrad at Earlham College and I was a physics major. So I think my scientific interest started early, but it, you know, was role models. That really was important for me, that one role model anyway.

Drew (03:08):

Yeah. Those inspiring mentors are so important. And I'm curious, how do you see the scientific landscape sort of in Ecuador compared to say the US or other countries?

Sandra (03:18):

Yeah. You know, I think that Ecuador has done a lot lately, you know, in the, in the year, since I left, which was gosh, over 30 years ago, but it's difficult there with regards to resources, availability for

research, right? Education is available, you know, to most people, but regarding science and research, it's hard to find resources for that. They have a lot of priorities that are more applied toward direct, pragmatic needs and requirements that the country has. And so for conservation biology, for example, and so forth. So, you know, the aspect of research that I do now, it's a little bit harder to find. And for example, education is very good. I think at the level up to undergrad, there are not that many graduate programs there. Right. So to be able to do research one is sort of forced to reach out outside of Ecuador to get our either masters or, um, doctorate degrees.

Drew (04:14):

Sure. Yeah. It's always difficult to decide where to allocate those resources. And so with your sort of growing interest then in, in physics, was that your way in then to neuroscience?

Sandra (04:24):

I started as an undergrad major in physics, like I said, as an, in, at Earlham College, but I, when I was there around my third year, I had some extra hours to fill in my schedule. And so I decided to take biology because I was curious about what all the fuss was about because a lot of people like about a third of students, there were biology majors. And so I thought, well, I have some time and I'm just gonna take, you know, this cell biology class that they were offering, that was a lower level class. And one of the labs coincided with the visit from an alumni, an alumnus, a scientist who had graduated from her alum, you know, years ago, but she had now her own lab and came back to visit and she was studying the microtubule cytoskeleton.

Sandra (05:06):

And so I didn't know what this was at that time. And as part of the lab, she did a demonstration where she simply put some slides under a fluorescent microscope. And I peeked in and, you know, I never forget what I saw that day. So I saw this cell with an array of fluorescently labeled filaments. And these were these microtubules right, these long, uh, polymers that were lit up all concentrically coming from the middle of the cell, reaching out over the periphery of this round cell. And the cell was actually dividing. So it was just this fantastic image of these filaments. And ever since then, I just got so interested and hooked on this microtubules that I decided, you know, I love physics, but I really wanna find out what these things do, what these microtubules do. So I switched for my PhD. I actually studied the role of the cytoskeleton on cell division in early embryogenesis. And I started to investigate the role of these tiny molecular machines that translocate on these filaments, this microtubules, and these are called molecular motors and some of these move sort of like in a bipedal manner. So they walk along these microtubule tracks and they take things components of the cell from one place to another place in the cell.

Drew (06:24):

Wow. Really cool. And I think it's amazing you had that visual epiphany, and I think a lot of people have this perception of the cell of just like a lot of empty space, but it's amazing that there's all these, like you said, all these different tracks and kind of so much cargo is sort of moved from one place to another. It's just a fascinating coordination going on.

Sandra (06:45):

Indeed. It's just a very busy, it’s super crowded. The environment inside the cell actually is really remarkable how anything can move at all, really given how crowded it is, you know, in any, any cell

really. And so it is fascinating indeed to see, and to be able to understand and sometimes visualize as we do in our lab, how well this movement occurs. And sometimes when it's not so understood how the movement doesn't occur very well. And this, it turns out is associated with disease, especially if it happens in this very specialized neurons, uh, cells that are called neurons that are really important for brain function. Right.

Drew (07:26):

Right. And so that is the focus of your lab. And when we talk about neurons and this kind of trafficking, what are we talking about? What is actually being trafficked? What is being moved from one sort of, is it from one end to the cell to another? Or is it different places in the cell?

Sandra (07:42):

Yeah, so, you know, neurons are very distinctive type of cells because unlike many others and most other cells, uh, they're very polarized, right? So the main sort of central part of the cell is called the cell body. And, but there's all these projections that emanate from that central cell body that can get very, very long and they make so that the cell becomes very asymmetric, right? Unlike, for example, a blood cell, which is very round or oval, and maintains all these components, very close to where the components are made and biosynthesis, right. But neurons being so highly asymmetric, they shoot out these very long projections called axons that sometimes can measure in our human bodies, for example, over a meter long, like one example of one of these, uh, very long axons is the one that radiates from the back of your spine or the way to the tip of your toes.

Sandra (08:43):

That's a single axon that is over a meter in length. And so things in that axon, for example, are made in the back of your spine. That's where the, the mothership is, the soma, is what it's called or cell body, right. But you need to take things all the way from meter and length to the tip of your toe. So you can sustain the, the health and the life of that axon and that, that neuron, right. And of course that process is almost solely responsible by this machines that I mentioned to you. These little nano machines are called molecular motors, that translocate along these filaments, the microtubules that I was talking about earlier, and, you know, the cargo that we're talking about principally about 99% of what the neuron needs for its survival is made in that main cell body that's in the back of the spine.

Sandra (09:34):

So you need to take those things like, for example, mitochondria, to promote cell growth, to promote energy, to provide energy to all these long distance axons, is made in the cell body. But you need to take those very long organelles all the way down to the tips in order to maintain, like I said, the health of neuron, to transmit information back from, for example, mechanical sensation at the tip of your toes, to sense pain, to sense temperature all the way back to the cell body. So that that connection gets made back in turn to the brain. And so transport as we call it of these cargos by these molecular motors is absolutely essential. And you can imagine, you know, what happens if this gets disrupted, right, is sort of like having water running through a hose, but somehow you constrict the hose at, at a certain point, but water tries to keep running. You'll have this big bulge made as water tries to run through that. And so this, this is a traffic jam, right? And we call them traffic jams when it happens in the brain, those traffic jams are directly linked and associated with neurodegeneration. And so they're very big consequences for dysfunction and this process of transport that, you know, our lab has been very busy studying.

Drew (10:58):

Wow. So how is it that these traffic jams happen? How does that transport breakdown?

Sandra (11:03):

I can tell you that one of the consequences, and we can start with that first, is that things get piled up at different regions along this long axonal fiber, all right, along this projection. And when things get clogged up or plugged up along the axon, you start forming these swellings that occur all along the axon that are similar to like beads on a string. And along those areas that are swollen, you can, if you take a knife and cut through them and look through the microscope, what you see is that things have gotten stuck and things that you find in there are all kinds of cargo that the cell has tried to move from the soma to the tip, but that has not been able to get through. Right? So mitochondria is there, there are a number of filaments themselves that get stuck. There, many proteins that are really required at the tip that we call the synapse, right?

Sandra (12:02):

That are critical components for transmission of information, between neurons, right, critical for memory formation and so forth. Those have gotten stuck on those traffic jams, right? And so there are many reasons how people think that those traffic jams occur, but one of the ways that it can occur, if you disrupt somehow the molecular machinery that carries those there. So for example, there's tiny little motors that carry them. If you have mutations in those, you disrupt directly the cargo movement. And this is one way that you can obtain those incidentally. When you look at the population of humans, there's certain percentage of humans that have mutations in those tiny molecular motors, and they have symptoms and pathologies that are neuropathic, right? So they are completely consistent. They occur in the nerves, especially in the very long nerves, like the peripheral nerves of the, like the one that I was telling you about - the sciatic nerve - as well as some of the, the extremities in, in the upper extremities, right? The ones that come to the tip of your hands and those peripheral neuropathies as they're called, they have distinctive traffic jams in their long axons, right? So this is one way to disrupt the proper flow of things in axons and to create those traffic jams down.

Drew (13:26):

Got it. So would you say that the longer the nerve is the more vulnerable it might be to having these traffic jams?

Sandra (13:34):

Yeah. This is a very, very, uh, astute, uh, comment that you have Drew, because I think it is. I think the longer, the distance that these motors have to travel and that the cargo has to travel, the more probability, the more opportunities that there are for things to go wrong. And this is why we think that when people have mutations in molecular motors, you know, the more prominent signs of disease occur in the longest nerves in the body.

Drew (14:04):

Got it. So it's kind of like an analogy would be more likely to sort of have a crash and traffic jam the longer you are on a, a journey.

Sandra (14:11):

Right, exactly. Right. Yep. Very,

Drew (14:14):

So in that case, is it better in general for trafficking to happen faster in the neuron?

Sandra (14:20):

You know, this is a really interesting question, you would think so, right? You would think that promoting the trafficking of components would be a good thing, right? So if you have a mutation where you impair transport, then somehow accelerating that transport would do things better. However, it turns out we've learned through a lot of investigations at the sub-cellular level that promoting transport might not be so beneficial necessarily, right. It's a tricky business of balancing, right. There's a balancing act between having too much and having too little. Yeah. Because it turns out if you target and make a motor faster or better at taking things that motor is not a specialist for just one kind of cargo, but you might be disrupting the movement or accelerating the movement of many things that shouldn't be taken too fast to the synapse. Okay. And so it's a very tricky thing to think about changing the parameters and making things faster is not as intuitive as one would would think, right. While transport impairment is bad, accelerating transport might not be the greatest way to go about fixing that.

Drew (15:33):

Sure. Yeah. We're always tempted to correct something, but you know, that overcorrection can be just as bad.

Sandra (15:39):

Right.

Drew (15:39):

Our ability to learn and remember things is highly dependent on this constant transport of cargo along neurons to send signals from one brain cell to another requires a whole symphony of molecular machinery. And the instructions for making these machines are often made at one end the cell body, and must travel all the way to the other end to begin construction.

Sandra (16:00):

Broadly speaking, I think the movement of all these signals, right, that you need to transfer from one part of the cell is neuron to the other. For example, all these signaling components organelles. And it turns out also messenger ribonucleic acids, like RNAs, which are the precursors or templates in which you build proteins and make proteins, right? Those all need to be transported. You need to move these molecules to the tips of neurons, because there it is very, this factors are very critical. For example, to start making proteins right there at the tips of neurons that are required, and that are very, very important to maintain synaptic activity. Right. And what haptic activity is, is this information exchange that occurs between neurons, usually at the tips and that exchanges signals that mediate the storage of information and, and that help with memory consolidation in the brain.

Drew (16:56):

And so when we talk then about different neurodegenerative diseases, it seems like some of them are quite specific, you know, in the case of Parkinson's disease, we have a degeneration of dopamine neurons. So aside from just the length of the neuron, do these jams sort of occur in specific sets of neurons?

Sandra (17:19):

Yes. You know, there's some indication in, in the vast literature that there's what we call neuron vulnerability to the formation of traffic jams in neurons, in the brain, right. It is not really well understood how we can get certain neurons to form the sort of swellings that occur versus others that don't have the propensity. We don't understand very well yet at all, I would say, how some neurons have that ability versus others. And so there's some affinity between neurons, like you mentioned, and vulnerability, and there's also vulnerability within the neuron itself. It seems like the axon seems to be much more able to get the traffic jams than the rest of the neuron itself in those swellings, by the way, contain also aggregates inside of them, of these proteins that tend to aggregate and misfold in disease, which are yeah, you know, very characteristic of neurodegeneration.

Drew (18:23):

Right? Yeah. That's what we hear about. So can you have neurodegenerative disease without the presence of these traffic jams?

Sandra (18:33):

Ah, great question Drew. Yeah. You know, I think with the traffic jams themselves, I think are a manifestation of perhaps something else, right. That goes on in brains of, of people that are affected with neurodegeneration. Right. But one of the consequences, potential consequences of traffic jams is the accumulation of this proteins that I alluded to earlier that tend to misfold and start sticking to themselves, right, to each other, this sort of aggregates, protein aggregates. And the protein aggregates when they do this and they accumulate specifically in the axon, contribute to this traffic jams perhaps as a secondary effect. Okay. And so to get to your question of, you know, would you get near generation without traffic jams? You know, it is possible. However, it is also a very clear observation that very early in disease, the presence of these aggregates inside axon is, is, is almost virtually a hundred percent observed in brains of any neurodegenerative disease as well. Right. So whether they occur directly as a result of traffic, like trafficking defects, that is not super clear, but when they're formed and they're formed, they're formed almost always in neurodegeneration. Right. So it's an observation that occurs in virtually every neurodegenerative disease.

Drew (20:08):

Got it. So it could be a cause, but could also be a consequence of, uh, something else happening in the pathology.

Sandra (20:14):

Yes, indeed.

Drew (20:16):

So it seemed like your lab had identified some mutations that could increase the propensity for these traffic jams to happen. And that could be a clear genetic reasoning for neurodegenerative disease. So what do you think about that interplay with sort of environmental triggers? Because it seems like, you know, lifestyle factors now are being linked with neurodegenerative disease and, you know, things like exercise could contribute to brain health. We've got, you know, things like diabetes that co-occur with neurodegenerative disease. So how do you think these environmental triggers could influence traffic jams?

Sandra (20:51):

Huh. You know, that's something that it's, I, I think has received very little attention, you know, with regards to research the environmental effects and how that could influence traffic jams. I think that it's unclear how that would be with regards to maybe lifestyle, lifestyle choices and so forth. But I think with regards to the environment, there's many, many environmental confounding factors that have been identified. I think that contribute to the progression or the initiation and progression of many of the diseases. You know, Parkinson's disease is a really good example. There's a lot of influence of epidemiological evidence that strongly supports the exposure of environmental pollutants, for example, yeah. To like heavy metals, pesticides, solvents, detergents, and other industrial byproducts are highly associated with the development of, of Parkinson's disease and a few other neurological disorders actually. Right.

Drew (21:49):

Yeah.

Sandra (21:50):

So this toxins are known to cross the blood brain barrier, right. So they're able to infiltrate the brain and the consequences to the health of the, of the cells and the brain are pretty consequential once they, once they do that. Right. So heavy metals are very particularly toxic. The, for instance, of, of these trace elements, right. Of, for example, heavy copper, zinc, aluminum, they, they're actually known to accelerate the rate at which these aggregates form inside neurons. Right. And these aggregates are some of the aggregates that could clog, for example, this transport that we were talking about that needs to occur in the axon. Right?

Drew (22:31):

Sure. And speaking of actually these kinds of outside substances, I suppose, do you know how certain addictive drugs might affect the transport of these different components along our neurons and then even hallucinogenic drugs that might remodel the way we learn?

Sandra (22:49):

That's so interesting. You know, I gotta say, I don't know too much about that. It's a fascinating topic to me because, you know, I think is very clear that obviously those substances remodel pathways, you know, and many of them are temporary, but I think some other are longer lasting. And so the effects of some of these substances, like hallucinogens and so forth, I mean, obviously they're clearly modulating the abilities of neurons to communicate. Right. I think that there's no question about that, how they do that. And specifically with respect this particular process that our lab studies, you know, this transport, I don't know how they would be doing it. I would be surprised to be honest if they didn't, but you know, I don't know that that process has been studied, you know, it'd be fascinating to do it.

Drew (23:40):

Yeah, sure. Yeah. Possible grant in the future.

Sandra (23:44):

Yeah. Right. Sure. There would be a lot of students that might volunteer for this.

Drew (23:50):

Yeah. It's certainly getting more popular. Definitely. So has your lab or other labs identified possible molecules that could help with breaking down these traffic jams and potentially reduce the burden of different neurodegenerative diseases?

Sandra (24:05):

Yes. So, you know, my lab is very interested in this and finding compounds that we could develop into therapeutics. As you know, there's not really very good treatments for these diseases at all. So we are actually actively pursuing this to both identifying characterize compounds. And at Scripps has been really great because this is a, a perfect place to do this. Right. We've paired up with chemical biologists and chemists here at Scripps that are actively trying to identify compounds that do various things, right? So we're working alongside the laboratory of Kelly hear at Scripps who has identified a number of small molecules that regulate degradation of proteins in cells. Right. And one of those proteins that we think are being degraded by the treatment of specifically neurons with these compounds are these proteins that are very sticky. That form aggregates that are really either, we think that are at the center of producing toxicity, neurodegenerative diseases.

Sandra (25:04):

And we have modeled this in cells and in mouse brains as well. And these compounds that I mentioned that the Kelly lab has identified when you treat cells that have these bulges, when you treat them early enough before they're forming these aggregates, they very efficiently inhibit the formation of these aggregates. Right. Right. And we are treating them at later and later time points after these aggregates are formed. And we're finding that in some occasions, they actually might be inhibiting the formation afterwards. So they might be promoting the degradation of already formed aggregates, which would be really important actually. Right. For thinking about using them for treatment, not just as prophylactics, but for treatment once these aggregates have formed already in the brains of patients. Right. And one of the things that we're really excited about is that at least in cellular, within this context of cells in a dish, once these molecules inhibit the formation of these aggregates, they completely restore neurological function of those neurons. And so that, to us, the extent of the robustness of that, of that data that we're finding is making us very excited about moving forward now.

Drew (26:21):

Wow. Yeah. It's a tantalizing idea to be able to not just stop these plaques in the brain from forming in the first place, but also reverse them. And the incidences of these diseases is pretty high now. So it would be a, a massive impact if you, uh, if you could achieve that.

Sandra (26:38):

Yeah. We're right now in a, pretty much in the pandemic of Alzheimer's disease with, you know, one in nine Americans, age 65 or older being stricken with Alzheimer's. So this is a pretty high incidence indeed, yeah.

Drew (26:51):

Yeah. Much needed work. So when you're not in the lab navigating your way down neurons, what are some of your other hobbies and passions outside of the lab?

Sandra (27:01):

Yeah, no, you know, with the last few years I have a five year old, so I've spent a lot of time with her and, and it's actually pretty good because I have to completely switch my brain from, from science to doing a very, very different type of, kind of thinking, which is really great actually, and welcome, but you know, I also, I like to swim a lot and uh, I've gotten very slowly back to swimming in the ocean here in San Diego. Oh, you know, we are fortunate here to have, um, the ocean that is pretty available pretty much year round with good wetsuit. Um, of course, because the water's pretty cold, in the winter at least, but I've also, you know, taken up piano lately. You know, I, I actually was trained classically from the time I was like seven years old, but in Ecuador when I had my piano, of course I could play it there, but you know, for the last 30 years or so I haven't actually owned one until very recently. And uh, so now I've taken up teaching myself how to improvise in piano, which I find is very difficult for classically trained pianists so I'm definitely exercising some brain plasticity.

Drew (28:07):

Yeah. Remodeling there.

Sandra (28:09):

Yeah. Yeah.

Drew (28:12):

Cool. All right. Well maybe I'll just end with my final roundup question. So if you could give somebody your one piece of advice or golden piece of wisdom, you know, in the realm of work, career progression, life health, self-improvement, honestly, anything, what do you think it would be and why?

Sandra (28:29):

Yeah, one of the, I think skills that has been really key for me to, to develop and, and like I said, science in life has been to observe to, to develop the, the power of observation of your subject right. Of your organism as I call it. And what I mean by organism is the subject of your study, right? Uh, in doing science, we all have a focus and you know, in our cases studying the movement of these organelles inside neurons, right. But all this interesting approaches that we're using nowadays are very fancy. You know, this genomics, proteomics sort of big “omics” approaches as well as all these new techniques in microscopy that we use and all that. Those are serving science very well. But the what, what I think we, we can serve very well from is to really observe intently our, our, our organism, because this allows us to be able to understand things at a level that we might miss.

Sandra (29:29):

If we get really enamored with, you know, there's, there's very, very sort of provocative and sexy approaches that we're using that detaches us a little bit sometimes from knowing our subject very well. Right. I remember that I learned this from, from an ecologist, right. Because ecologists know how to do this observation really, really well. And she told me, you know, if you observe carefully your organism, you will understand things and you would get a gut feeling for what is the process that you are observing that is second to none other feeling that you will get. Okay. So I think this advice, I, I think I've been able to put in practice for our science and for certain parts of my life as well. So, you know, I would say really observe and, and develop that skill.

Drew (30:21):

A great note to end on there, that the scientific method begins by making even the most basic observations of the world around you. A big thank you to Sandra for joining me and showing us the potential power of correcting this neuronal trafficking for treating or reversing neurodegeneration. In the show notes you can find more links to Sandra's work as well as other recent Scripps Research content. Remember to hit that five star rating if you like this podcast and stay tuned for more upcoming episodes. So until we meet again, thank you for listening, stay curious and farewell.