“The Evolving View of Astrocytes” with Philip G. Haydon

Transcript of Cerebrum Podcast

Guest: Philip G. Haydon, Ph.D., is the Annetta and Gustav Grisard Professor and chair of the neuroscience department at Tufts University School of Medicine. He received his Ph.D. from the University of Leeds, UK. While a faculty member at Iowa State University in 1994, he performed a landmark study by demonstrating that astrocytes release chemical transmitters. In 2001, he joined the faculty of the University of Pennsylvania School of Medicine and, in 2008, moved to Tufts. For 25 years his research has addressed the roles played by glial cells. His recent focus is on the use of glial targets as therapeutic interventions for brain disorders. He has received the Alfred P. Sloan Scholarship, the McKnight Innovator Award, and the Jacob Javits Award from the National Institute of Neurological Disorders and Stroke.

Host: Bill Glovin serves as editor of *Cerebrum* and the *Cerebrum Anthology: Emerging Issues in Brain Science*. He is also executive editor of the Dana Press and *Brain in the News*. Prior to joining the Dana Foundation, Mr. Glovin was senior editor of *Rutgers Magazine* and editor of *Rutgers Focus*. He has served as managing editor of *New Jersey Success*, editor of *New Jersey Business* magazine, and as a staff writer at *The Record* newspaper in Hackensack, NJ. Mr. Glovin has won 20 writing awards from the Society of Professional Journalists of New Jersey and the Council for Advancement and Support of Education. He has a B.A. in Journalism from George Washington University.

Bill Glovin: Our guest on today's *Cerebrum* podcast is Phil Haydon, author of our October *Cerebrum* article, “The Evolving View of Astrocytes.” Dr. Haydon is the Grisard professor and chair of the neuroscience department at the Tufts University School of Medicine. He received his Ph.D. from the University of Leeds in the United Kingdom.

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Welcome, Dr. Haydon. Everyone seems to know about neurons. Can you explain the difference between a neuron, a glial cell, and an astrocyte?
By the way, I thought the description in the article, that likened glial cells to mortar that holds a house together, painted a great word picture.

Phil Haydon: That was super, yeah. We know neurons really, initially, from histology from the late 1800s, the type of stains that were used rarely stained the long projections of neurons. And then, during the 1900s, neurons were really focused upon

because they were electrically active, and we could record and stimulate. So, what scientists, what science can manipulate, they study.

The glial cells are electrically silent. So, they were essentially mute to all the stimulation methods possible. It wasn't till the late, till about the early 1990s, when Roger Tsien developed chemical indicators of biochemical signaling and then we saw that glial cells are active, although they speak a different language. Instead of electrical language, it's a chemical language.

And then, glial cells is a general term that's describing the non-neuronal cells in the brain, and there are several different types of glial cells. There's the astrocyte, that was originally named the astrocyte because it was thought to be star-like. Then, in addition to astrocytes, there are oligodendrocytes, microglia, and NG2-glia, and they all serve different functions.

Bill Glovin: How did you get interested in the topic?

Phil Haydon: So, my interest in glial cells, it started in the early '90s, and it was really just an experiment where we performed a controlled experiment and did not get the results we thought. We were measuring the release of chemical transmitters from neurons in a culture dish. And we removed the neurons and what we thought was an empty culture dish was releasing chemical transmitters.

So, we looked in the microscope and there were these glial cells. So, it was that "aha" moment, and we thought since they were so active, these may be of importance to the brain, and we switched gears and started studying glia.

Bill Glovin: Who first discovered glial cells and astrocytes?

Phil Haydon: So, the original discovery of glial cells was back to the classic histologists in the 1800s, like Golgi for example, and Santiago Ramón y Cajal. And I believe it was [Rudolph] Virchow, and I'm not pronouncing his name correctly, who named the astrocyte. Then it was really the histologists that did the early work, and they actually have some quite incredible insights.

For example, Cajal proposed in 1894 that astrocytes, as we now know them, could regulate sleep. And his idea was they extend their process in between the synaptic connection between neurons, that promotes sleep, and they retract it, and that promotes wakefulness. He had great insight from looking at static microscopy images, and today we know that astrocytes do regulate sleep.

Bill Glovin: What do astrocytes look like?

Phil Haydon: So, it really depends on the stains that you use. Now, with the more advanced stains, you find that an astrocyte is, where you can put a fluorescent protein through the whole of a cell, it's much like a very dense bush. If you can imagine, if I can put it in a two-dimensional structure, imagine it's like tiles on your

kitchen floor. One astrocyte, it has its own boundaries, and it touches the tips of the neighboring astrocyte, much like tiles touch one another.

But then if you think of that tile, it's extremely fine processes that allow the neuronal processes to invade through it. And there are so many processes of the astrocyte in the mouse hippocampus, a structure that's very important for learning and memory; one astrocyte contacts 140,000 synapses. It's quite an incredibly complex cell that has the potential to influence neuronal computation dramatically.

Bill Glovin: You mentioned microscopy. Is that the way that we image astrocytes, or do we use traditional microscopes?

Phil Haydon: So, through the history, again, it was static stains, but the big breakthrough came in the '90s, when technologies improved so that we have fluorescent indicators of biochemical events. So, for example, the calcium ion, when its levels changed, one of these indicators got brighter. And at that time, there were cameras that were sufficiently sensitive to see those changes.

Now we fast forward from 1990 to, you know, the 2000s, there are technologies called multi-cell ton microscopy, which allow you to actually look into the living cortex of a mouse. And you can see those same indicators in the living cells while an animal performs behavioral functions. So, you can actually essentially ask an animal for a form of behavior, you can record the electrical activity of a neuron, and at the same time the chemical activity of an astrocyte or glial cell.

Bill Glovin: Are we able to view a human being's glial cell or astrocyte yet?

Phil Haydon: So, we can't do it in vivo. You know, there's some ethical issues about imaging into human brains. But now what people are able to do, they're able to take ... you know there's this real advance in the last decade of being able to induce pluripotent stem cells from fibroblasts. And what they, would put these into a culture dish.

So, you can take a piece of skin from a human, put it in a culture dish, differentiate it into different cell types of the brain, including the astrocyte. And there you can now study the astrocyte behavior. And an interesting thing that one laboratory has done, they've even taken the human astrocytes and transplanted them into a mouse brain, to start to study the human astrocyte in a mouse environment.

Bill Glovin: Interesting. You mentioned synapse formation. And you write that astrocytes regulate synapse formation. Why is that important?

Phil Haydon: It's one of those million-dollar questions. An intriguing element of this is, in certain parts of the brain, you see neurons grow and come together, make contact one with one another. But they don't actually form their functional

synaptic connection until the astrocyte develops, which is slightly later, and then releases the factors. So, it's almost as if the astrocytes are the policemen that are regulating what those synapses do.

And so, on the other hand, they regulate your development. But then, during plasticity in the brain in the adult, they're also modulating how the synapses function.

Bill Glovin: Since glucose provides the brain with energy, can you explain the relationship between glucose and astrocytes?

Phil Haydon: So, you can consider the astrocyte as having two general compartments among these thousands of processes. One process extends and wraps around the vasculature in the brain, where it has transporters that take up glucose. In the astrocyte, that glucose is then used as an energy source, but it gives rise to another molecule called lactate, which can also be an energy source. And the astrocyte can deliver that lactate to the neurons.

Because the neurons don't make contact with the blood vessels, so the astrocyte acts as an intermediate. It takes glucose, takes a little bit of energy for itself, then passes along the residual energy supply molecule to the neuron, which demands a lot of energy to support its electrical activity.

Bill Glovin: Why are calcium waves important?

Phil Haydon: The importance of calcium waves goes up and down, in and out of fashion. What we're learning, in early days of studying ... you know you're always limited by your technology. And in the early days, we could stimulate calcium waves and we could see dramatic neuronal consequences. Now, as our imaging technologies are getting more exquisite and sensitive, we can see that the astrocyte has a range of calcium-signaling events.

For example, very local, next to synapses, just a portion of one of those branches has a calcium elevation. And you can look at another branch of the same astrocyte, and it has independent calcium elevations. So, if you now think again about dense bush, that dense bush has different regions that have independent activity.

But then sometimes, and we don't totally understand why that, then sometimes you get a synchronization across a large bush of astrocytes. And if we try and put it into a functional context, if you again, you think that bush is contacting 140,000 synapses, maybe the astrocyte's having just local control over one or two. But then, under the right context, when you get a big wave of calcium, it will coordinate the behavior of 140,000 synapses.

And one of the signals that people are looking at, that controls this, is called norepinephrine, which is a chemical transmitter that is released from neurons

when we wake up. So you can envision, as you wake up, you change the behavior of the astrocyte, how it influences the neuron.

Bill Glovin: Do astrocytes have a relationship to blood flow in the brain?

Phil Haydon: Yes, so, if we go back to structural relationship, because the astrocyte is a physical intermediate between neurons and the blood vessel, you ask yourself, "How is it with ... Neuronal activity demands energy. So how, when you have enhanced neuronal activity, do you get increased blood flow?" Which we know, from brain imaging studies, occurs.

So, the emerging picture is that the neuron stimulates a receptor on the astrocyte, that calls an astrocytic calcium signal that goes out to the blood vessel. Then that astrocyte causes a dilation of the blood vessel, to provide more blood flow, more glucose, and therefore more energy supply to that electrically-active neuron.

Bill Glovin: Can you talk generally about the impact of astrocytes on brain function?

Phil Haydon: So, in terms of a behavioral context, some of the sort of things that we're beginning to understand, is that wakefulness and sleep is one of the important regulatory roles for the astrocyte. For example, there's a chemical released from the astrocyte that's called adenosine, and we know adenosine tries to make us go to sleep.

When we wake up in the morning time, the astrocyte is measuring how long we've been awake, it's releasing adenosine, it's trying to make us go to sleep. And of course, many of us drink caffeine, which is an antagonist of the adenosine receptor. Or maybe when you drink your next cup of coffee, you can think to yourself, "I'm drinking an antagonist of my astrocyte, which is trying to put me to sleep."

Bill Glovin: Can you explain the controversy over D-serine as a glial transmitter?

Phil Haydon: Yes, so, I think, you know, in all ... In many cases in science, you have this pendulum that's swinging back and forth, and at some point, it will ultimately get to the correct position. And we have these periods where it's all the astrocyte, or all the neuron. There was really compelling early evidence showing D-serine released from the astrocyte, and that influencing the neuron. Then there's later evidence which has said, no, the D-serine comes from the neuron, not from the astrocyte.

And there's lots of very, you know, really good scientists on both sides of the sort of argument, and I actually think what's going to happen -- based on unpublished evidence I know is sitting in our laboratory -- is it's going to be a combination of the two. Actually, what we think is that there will be a certain amount of D-serine does come from the neuron, but there's one element is

regulated by the astrocyte. So at the end of the day, it's going to be, you know, the pendulum is going to fall somewhere between the two extremes.
And part of this is, again, technologies. When you first do an experiment, you have the technology of the day. As technology improves, you're able to refine what your understanding is and move closer to the ultimate truth of biology.

Bill Glovin: You write that we now know that astrocytes can signal neuronal degeneration in such disorders as ALS, Alzheimer's, and epilepsy, and that new drugs may someday be developed to target astrocytic pathways. Is there a timeline for this?

Phil Haydon: Well, yeah, so. Let me give you a ... I mean, there are drugs currently being developed. If we look historically through the drug development process, because we knew little about the glial biology, we didn't know enough about the proteins that are in glial cells to be able to develop drugs towards them. So we developed drugs towards neuronal proteins. And that was a very appropriate thing to do.

As we're learning more about the proteins in the astrocyte and their role, we are now starting to develop drugs towards that process. Interestingly, one of the major risk factors for Alzheimer's disease, which is an apolipoprotein called ApoE4, this is highly produced by the astrocyte. So with late-onset Alzheimer's disease, the astrocyte is coming, sort of to the center of focus, and there's now a lot of great enthusiasm to understand what this molecule does, how it causes Alzheimer's disease. And I would not be surprised to find a lot of drug development effort in that area, for example.

Bill Glovin: Is there anything that I've left out of importance, that you wanted to add?

Phil Haydon: I would say that we're still in the early days. We have a century of understanding neurons. We're now about 20 years into understanding glial cells. And we're starting to get a picture of what they do, but you know, it's much like a jigsaw puzzle with maybe 1,000 pieces, 10 have been put in place. And the next decade is going to be absolutely fascinating, to see the respective partnership between astrocytes and neurons, what the astrocytes do for neurons. So, I'd say stay tuned, and the next decade is going to be one heck of a lot of fun of understanding more about the brain and glial cells.

Bill Glovin: We will stay tuned. And thank you, Dr. Haydon, for your insights on astrocytes and glial cells. And to learn more about astrocytes, go to dana.org and link to October's *Cerebrum* article. Stay tuned for next month's podcast, which promises to be a fascinating discussion. Our topic: "The Mind of a Terrorist," with November *Cerebrum* author, Emile Bruneau at MIT.