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Understanding the Cellular Basis for Altered Cognition in Schizophrenia

Ashley Baker:
You're listening to *NeuroFrontiers* on ReachMD. I'm psychiatric nurse practitioner Ashley Baker, and I'm speaking with Dr. Samuel Dienel, who's a student in the Medical Scientist Training Program at the University of Pittsburgh. Today, we'll be discussing his research on the prefrontal cortical patterns of molecular alterations in somatostatin neurons in schizophrenia.

Dr. Dienel, welcome to the program.

Dr. Dienel:
Thank you so much, Ashley. It's great to be here.

Ashley Baker:
So to start us off, Dr. Dienel, can you explain your study and the significance of somatostatin messenger RNA levels in the dorsolateral prefrontal cortex in individuals with schizophrenia?

Dr. Dienel:
Yeah, absolutely. So this work was conducted in the lab of Dr. David Lewis at the University of Pittsburgh. And our lab is interested in understanding schizophrenia, and specifically, we're interested in understanding why people who have schizophrenia have cognitive dysfunction. And when you think about schizophrenia, you usually think about what we call the positive symptoms. These are the hallucinations and the delusions. But the cognitive deficits in people who have schizophrenia are actually some of the best predictors of long-term functional outcome. So our hope is that by better understanding the cellular basis for altered cognition in schizophrenia, we can better treat it, and by better treating it, we can improve the functional outcome in this patient population.

And we primarily study schizophrenia through postmortem studies, and this resource allows us to study the organ in which the disease process is taking place in the brain. And because we're interested in cognition, we largely focus on understanding the alterations to the prefrontal cortex, which is sort of a keynote in how certain cognitive functions are executed.

And so in this study, what we wanted to do was we wanted to look at a particular group of GABA neurons. This group of GABA neurons expresses somatostatin. And we were really interested in this group of neurons because it seems that they have really important roles in attention and controlling different aspects of working memory, which is impaired in schizophrenia, so we wanted to better understand what's going on with these neurons. And in order to do that, we wanted to look across different areas of the prefrontal cortex because different somatostatin neurons are present in these different layers, and we wanted to look across diagnoses. So we wanted to ask is this specific to schizophrenia, or are these differences also seen in people who are diagnosed with other psychiatric disorders like major depression and bipolar disorder?

Ashley Baker:
So what were the specific methods that you used in this study?

Dr. Dienel:
Our study used two main methods. The first method was quantitative polymerase chain reaction, or qPCR, and that allows us to reliably index levels of mRNA in postmortem tissue from people who have schizophrenia and comparing it to people who don't have schizophrenia, and it gives us a really sensitive assay for determining differences between those two groups. We combined this with a method called laser-capture microdissection, where we can use small lasers to dissect out the different layers of the prefrontal cortex, and by doing so, we could capture these different groups of somatostatin neurons. And then the other method we used was called

fluorescence in situ hybridization, or FISH. And this method allows us to fluorescently label somatostatin mRNA, which also gives us a separate way of indexing the differences in mRNA levels between people who have schizophrenia and people who don't.

Ashley Baker:
With that background in mind, let's zero in on the results. What were the key findings?

Dr. Dienel:
So what we found was we looked in two different layers or laminar zones of the prefrontal cortex. So we looked at the most superficial layer—so this is the layer that's closest to the outside of the brain—because that's where there's one group of these somatostatin neurons, and then we also looked in the superficial white matter. So this is a little bit deeper down, and there's a totally separate group of somatostatin neurons present in that zone. And what we found was that in people who have schizophrenia, levels of somatostatin mRNA were lower in both of these zones, suggesting that at least the two different populations in these two laminar zones were affected in schizophrenia. And one thing that was interesting was we found that this deficit was present by using both quantitative PCR and FISH, and so we had kind of methodological replicability for that finding.

And in addition, what we found was that the deficits in somatostatin mRNA in these two laminar zones in schizophrenia were only partially shared by people who have major depression. So in major depression, SST was lower in the superficial zone but not in the white matter. And in bipolar, there was actually no significant difference that we could see in somatostatin mRNA in either the superficial or deep zones.

So what that suggested to us was that there was some specificity to the patterns of how somatostatin was altered across the prefrontal cortex that was specific to schizophrenia and partially seen in major depression and not seen in bipolar disorder, which was a little counterintuitive to us.

Ashley Baker:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm psychiatric nurse practitioner Ashley Baker, and I'm speaking with Dr. Samuel Dienel about his research on the prefrontal cortical patterns of molecular alterations in somatostatin neurons in schizophrenia.

I know that we just spoke a little bit about the differences among individuals with schizophrenia, bipolar disorder, and major depressive disorder, but was there anything additional that you found that would be important for our audience to know?

Dr. Dienel:
One of the key goals of our research efforts are to better understand how these alterations in the prefrontal cortex affect cognition. And one of the downsides of using postmortem tissue is that we don't have reliable indices of cognitive function in the individuals whose brains we are studying.

So we wanted to take advantage of proxy measures of cognition, and one proxy measure, although very imperfect, is educational attainment. And educational attainment is, again, certainly imperfect and influenced by many other factors, but one thing that's at least supportive is that people who have schizophrenia consistent with the clinical literature have—and was true in our cohort—lower levels of educational attainment relative to psychiatrically unaffected individuals and relative to individuals who have major depression or bipolar disorder. So at least in the relatively smaller samples that we're looking at through postmortem studies, we find what is found in the population at large. And I think for people who have schizophrenia, the lower levels of educational attainment that they're not able to reach ultimately is reflective of the disease process and how cognition impairs the ability to continue to rise to what might otherwise be higher levels of educational attainment.

And in addition to finding the diagnoses differences just in educational attainment, what we found was that the deficits in somatostatin mRNA were associated with educational attainment in individuals with schizophrenia, and this association wasn't seen in people who have major depression or bipolar disorder, and so at least one interpretation of it among many is that the alterations that are seen in somatostatin neurons are associated with this proxy measure of cognition, educational attainment. And if these alterations are present early in the disease process, then that might influence the ability for people who go on to develop the disease to continue climbing the educational ladder.

Ashley Baker:
And how might these results impact clinical practice and the treatment of patients with schizophrenia?

Dr. Dienel:
So just kind of coming back to our initial surprise at the difference between being so stark between schizophrenia and bipolar disorder, one really interesting thing that this highlights is how the cognitive dysfunction in schizophrenia really is a feature of schizophrenia that is

not seen in other features like psychosis, things like that. In terms of treatment and in terms of better understanding how we might target these neurons, one approach that I'm particularly excited about is especially the somatostatin neurons that are in the superficial layers, which seem to have an outsized role in cognition, and, at least in our study, where it was specifically where the deficits were associated with educational attainment are sensitive to the effects of inputs from other brain regions, especially acetylcholine release from different brain regions onto those neurons. And so one potentially attractive therapeutic target is to augment the function of the somatostatin neurons by increasing their sensitivity to acetylcholine signaling, which might improve the cognitive function in the disorder and ultimately, ideally improve the functional outcomes for people who are diagnosed with the disorder.

Ashley Baker:
So, Dr. Dienel, anything else that you would like our audience to leave with today regarding your research, regarding schizophrenia treatment, maybe future investigations?

Dr. Dienel:
Yeah. I guess one thing I just wanted to note was that this study and the work that we do in the lab is really only possible through brain tissue donation, and it's an extremely challenging time for loved ones. And even in the midst of that pain, they are willing and recognize the importance of trying to understand these brain disorders more thoroughly, and so they make this very gracious gift of their loved one's brain tissue for these purposes, and we're extremely indebted to that.

Ashley Baker:
Well, as those final thoughts bring us to the end of today's program, I want to thank my guest, Dr. Samuel Dienel, for joining me to share the key findings from his research on schizophrenia. Dr. Dienel, it was wonderful speaking with you today.

Dr. Dienel:
Thank you so much for the invitation, and I really appreciate your time. Thank you.

Ashley Baker:
For ReachMD, I'm Ashley Baker. To access this and other episodes in our series, visit *NeuroFrontiers* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.