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This is the podcast for the journal Neuropsychopharmacology, I’m Cynthia Graber.

Recently, Nicole Petersen, assistant professor in the department of psychiatry and behavioral sciences at UCLA, was invited to be a part of a panel submission on neuroendocrinology, or the study of hormones that affect the brain, at the meeting of the American College of Neuropsychopharmacology. She was then invited to be on a second neuroendocrinology panel. And though she knew she couldn’t do both, she was excited by the thought that a field she hadn’t seen well addressed at an ACNP meeting was getting more attention. But then both panels were rejected.

NP: I know that you can't win them all in science and you have to get good at taking rejection. But I really thought it was a mistake. I think neuroendocrinology deserves to be front and center especially right now because of the FDA approval of zuranalone. So that's the true story behind my commentary.

Her commentary is a new paper in the journal Neuropsychopharmacology, called “Spotlighting SHAPERS: sex hormones associated with psychological and endocrine roles.” Dr. Petersen, you start the paper describing an unnamed signaling molecule that can affect the physical structure of the brain and that seems to be related to a wide number of psychological and neurological conditions, and then you reveal that this is estradiol. Why did you start this way?

NP: I used 17beta estradiol as an example because almost everyone has heard of estrogen. And I think because it is such a common part of our colloquial dialogue about human bodies, I think people have an assumption that it must be something that we mostly understand. Like, we know pretty well how estrogen works in the body, including the brain. And I think we have sort of a stunning lack of knowledge that I think the average person does not realize how little information we have about it.

The point you make in the paper is that estrogen isn’t the only one, there are quite a number of substances that affect the brain in ways that we just don’t understand. What problem have you run into in talking about these neuroactive substances?

NP: I find it difficult to talk about the hormones that I'm trying to talk about because there isn't a discrete category. So steroids are a huge category of molecules. Neuroactive steroids are a smaller category of molecules.

But neurosteroids can do many different things. And the corticosteroids and sex steroids, they certainly interact with one another, but they seem to have sort of more or less distinct functions.

So there are sex steroids that have actions on the brain, and some of those actions seem very clearly tied to psychological and emotional processes, and other sex steroids don't. But there isn't that I know of a clear delineation between those sex steroids that have a psychological effect on the brain and the ones that seem only involved in reproduction. So like luteinizing hormone, follicle stimulating hormone, they definitely act on the brain, but mostly in in brain regions that are linked to reproductive functions like ovulation. That's not to say that they will never be linked to any kind of psychological processes, just that, as far as I know, they haven't been yet. By comparison, estradiol, progesterone, testosterone, DHEA seem to have very dramatic effects on psychological processes, including but not limited to emotion and affect.

So what did you end up coming up with as a name?

NP: I settled on SHAPERs, which stands for sex hormones associated with psychological and endocrine roles.

You started off our conversation by saying that this is a particularly timely moment to discuss SHAPERs because of a big breakthrough – the drug zuranalone. It’s the first FDA approved oral treatment for postpartum depression. How does it work and how does this add to the body of knowledge about SHAPERs?

NP: Oh, that's a tough one. I can tell you what's in it. I don't think anyone can actually tell you how it works.

Zuranalone is an allopregnanolone molecule that I believe has some kind of proprietary thing attached to it that makes it more bioavailable. It's believed to be a positive allosteric modulator at the GABAA receptor. But how does that relieve depression? To me that's like one of the big juicy questions about neuroscience. Why would positively allosteric modulating the GABAA receptor alleviate any kind of depression? Is it specific to postpartum depression? The company, at the time that they applied for FDA approval, they tried to get an indication for major depression as well, which FDA denied. So it gives the impression that there may be something qualitatively different about postpartum depression and major depression. But that is definitely an open question that hasn't been settled.

So many unanswered questions. So how has the field been changing – what have we been learning about how SHAPERs affect mood and mood disorders?

NP: If you had asked me that a few years ago, I would've had to say, well, we know that they're correlated with mood symptoms, but do they cause problems with mood? Well, correlation implies causation, but it doesn't determine it. And I think now for the first time, we can say there is a causal role. SHAPERS, estrogen and progesterone, specifically in some individuals produce very negative mood symptoms, life threatening mood symptoms in some cases. And tthat was not - until recently it was just a correlation. It was speculative. But in these tightly controlled studies, we can show for the first time that causal role.

Some of these tightly controlled studies you’re referencing block endogenous hormone signaling and then use medications to add back controlled amounts of each type of hormone to determine how they affect mood. You also write about neuroimaging studies. Let’s focus on the neuroimaging now, what have these revealed?

NP: So I am the most excited about the neuroimaging studies. And neuroimaging studies are showing that these SHAPER hormones, especially estradiol and progesterone are the two that have been studied the most carefully, they seem to have really quite substantial effects on brain structure.

I think most people kind of imagine if you're taking a static brain image, a structural brain image, we imagine that that brain image, the cortical thicknesses and the subcortical volumes are going to be relatively static.

But it turns out that in individuals who are having a menstrual cycle, that's definitely not true. The brain is constantly changing. I mean, even these things that we imagine to be static, like cortical thickness and subcortical volumes, are constantly changing as the menstrual cycle changes. And then you get even more dramatic changes when you look at something like functional connectivity, which we know to be flexible and responsive to what's going on in the environment around you.

So in the paper, you point out that it’s important to be studying SHAPERS in men, too.

NP: Yes. I think this is a huge missed opportunity that there's been a growing movement to understand how estrogens and progesterone and hormonal contraceptives affect the brain. And I don't in any way want to imply that I think the job is done and we figured it out, but we have some momentum now finally. We're getting there, some really good work is going on.

But when you think about the sort of like classically male hormones like testosterone, the same work has not been done. And there's really no reason to believe that estrogens and progestins are unique and that testosterone isn't having this kind of impact on the brain. I think it's a huge missed opportunity that we haven't done those studies yet.

You bring up the importance of not silo’ing this research. What do you suggest?

NP: One really important way to encourage enthusiasm is commitment and support from professional organizations like the ACNP and Society of Biological Psychiatry. If there were more panels and invited speakers focusing on these topics, I think that could really spread engagement. And funding agencies, they play a really outsized role in what we learn about the human body. So if they invest in neuroendocrinology projects, then I personally think it'll be a high return on investment. And I think the case of zuranalone is a good example of just that.

This is the podcast for the journal Neuropsychopharmacology. To read the article discussed in the podcast, go to [www.nature.com/npp](http://www.nature.com/npp). I’m Cynthia Graber