Researcher discusses epigenetic transmission of stress and PTSD

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Cortisol, a stress hormone, is a key player in the subtle hormonal changes that have come to be associated with PTSD, and Dr. Rachel Yehuda, a neuroscientist and the director of the traumatic stress studies division at Mount Sinai School of Medicine in New York, has played a major role in advancing our scientific understanding of the role of cortisol in PTSD.

More recently, Dr. Yehuda also offered the PTSD scientific community a novel and intriguing idea: that the children of traumatized parents are at risk for similar problems due to changes that occurred in the biology of their parents, as a consequence of their trauma exposure. It is these epigenetic changes that are then transmitted to their children via a process called "intergenerational transmission."

Recently, I spoke with Dr. Yehuda about cortisol, intergenerational transmission of stress, and the future of PTSD treatment and research.

Dr. Jain: You played a key role in re-conceptualizing the neuro-endocrine basis for PTSD after it became apparent that individuals with PTSD consistently have low cortisol levels. Can you speak a little bit about how robust a finding this is and what this means for clinical settings? How can we use cortisol levels in the diagnosis of PTSD? Can we use it to

track if people are getting better?

Dr. Yehuda: The first published observation on cortisol in PTSD was in 1986 by John Mason and colleagues at Yale. The group was interested to see if tracking stress hormone levels in patients admitted to the psych unit would aid in determining when patients might be safely discharged, so they measured cortisol levels in a wide range of psychiatric patients. Generally, cortisol levels were higher for patients at admission and then were much lower at discharge, which is what one would expect if cortisol is a marker of stress. However there were two groups of patients, one being patients with post-traumatic stress disorder, for whom this did not appear to be the case. The authors were surprised to find that in fact PTSD patients showed significantly lower cortisol levels at admission and discharge compared to patients with other diagnoses. I joined Yale a year after that finding appeared in the literature. Like many others, I found it curious that cortisol levels would be low and thought for sure there had be some mistake, because we would expect, if anything, that cortisol levels would be high in a stress disorder, particularly one in which there was comorbidity of depression. So I attempted a replication with Mason and his colleagues, and of course, we were able to replicate the low cortisol findings in several studies in the early 90's.

What was so interesting, however, was how long it took the field to accept that the finding may reflect a reality. At the same time, and in the same patients, Mason and I observed elevated catecholamines. Neither Mason nor I had any trouble with the very first publication that catecholamine levels were higher in PTSD. No one thought to question the finding because it was something expected—that people who are aroused and under stress have high levels of catecholamines, like norepinephrine. Yet the cortisol data from the samples were difficult for people to believe. I guess when we hear something that makes sense to us, we do not need a lot of data. But we all questioned the low cortisol finding because it didn't make sense, and then we questioned the

methodology and so on. The reason the finding did not make sense, in the early 90s, was because the field of PTSD was new, and we didn't really understand PTSD yet. There were really no epidemiological studies until the early 90's, and even this very well accepted idea that PTSD only occurred in a subset of trauma survivors was not yet known. The prevailing concept was that PTSD always occurred following trauma exposure. But once there was a body of literature that showed that a lot of people are trauma exposed and only a smaller subset of those people get PTSD, the field could start speculating that perhaps low cortisol signals an abnormality that helps explain why recovery has not occurred. And when that happened, we began to ask what is cortisol's role in stress, anyway? In turns out that one of the things that cortisol does in response to stress is that it helps contain the catecholamine system—it helps bring down the high levels of adrenaline that are released during fight or flight. Since we all know that adrenaline and norepinephrine are responsible for memory formation and arousal, not having enough cortisol to completely bring down the sympathetic nervous system, at the time when it is very important for a person to calm down, may partially explain the formation of traumatic memory or generalized triggers.

The second part of your question is what does this mean in a clinical setting and how can we use cortisol levels in the diagnosis of PTSD? At this moment, we cannot use cortisol levels to aid in diagnoses. They are too variable, and although there is a mean difference between PTSD and other groups, in every study that has been performed to date, there are a lot of overlapping data. Furthermore, even the low cortisol levels in PTSD are well within the normal endocrinological range. The reason the low cortisol finding was important was that it led us down a trail of trying to understand why cortisol levels were low. Then it took us into the dynamics of the way that the hypothalamic–pituitary–adrenal (HPA) axis works and is regulated by the brain. Cortisol levels show natural variation during the day, and are affected by environmental perturbations. It is adaptive that cortisol levels vary , because cortisol

helps regulate many bodily functions when we are stressed, and when we are not stressed. What we have been doing for the last 25 years is studying the underlying dynamics of cortisol levels. We have examined circadian rhythm changes that may determine how the brain regulates the release of cortisol over a diurnal cycle. We have looked at cortisol metabolism, to try to understand how cortisol is broken down into its various metabolites in the brain, liver, and kidney. But most of our studies have involved the glucocorticoid receptor and all of the genes and proteins that are involved in regulating the activity and sensitivity of that receptor. These studies have begun to give us an understanding that there is something really different about the stress system in PTSD, or in specific subtypes of people with PTSD,, but it is not going to be cortisol levels per se that are going to be useful to a clinician.

Dr. Jain: So the picture is much more complicated than what may have been originally conceptualized?

Dr. Yehuda: When we say low cortisol levels, an endocrinologist would cringe. In PTSD, cortisol levels are not lower than normal range. They are significantly lower on average compared to persons without PTSD, but the levels themselves are not abnormal. The cortisol levels in PTSD do not suggest that the adrenal gland is broken in any way or not releasing cortisol, but rather, given the normal range of cortisol, which is large—between 20 to 90 micrograms per 24 hours of urine—the means we would get in PTSD were in the 40s. Whereas, a straight mean would be more like in the 50s and 60s. We are not talking about an endocrine problem. We are talking about a tendency to be at the lower end which is within normal variability. Why this was newsworthy, again, was that we were expecting that it would be higher in a stress disorder, because cortisol is associated with stress. I personally would not use cortisol levels, not even 24-hour urinary cortisol levels, as a diagnostic marker. I would want to know a lot more about how the glucocorticoid receptor

works. Is it more sensitive? What is the circadian rhythm like? What about cortisol metabolism? What about the genes that control cortisol and glucocorticoid functioning? So there is a potential to find biomarkers that relate to cortisol that may be clinically applicable—we have not given up on that idea at all. It's just important to understand what kind of neuroendocrine or molecular neuroendocrine information is most relevant.

Dr. Jain: But it is not as simplistic as doing a blood test to diagnose PTSD.

Dr. Yehuda: Would that it were!

Dr. Jain: I know! But you offer a very important clarification: the pattern in PTSD is of lowER cortisol levels, not low cortisol.

Dr. Yehuda: Somehow statistically lower became low, but the devil is in the detail.

Dr. Jain: Absolutely, and that is why it is so valuable to talk to people like yourself.

Dr. Yehuda: Furthermore, the effect size of cortisol differences is small, too. In the Boscarino study (1995), he reported that cortisol was lower in PTSD, but there was a very small effect size. So it is not a diagnostic test. It is just a clue, and we used it exactly as a clue to unravel a deeper mystery.

Dr. Jain: I totally see that. My next question is about the potential role of cortisol in the treatment of PTSD.

Maybe if you could speak about that a little bit. From a clinician point of view, that is really intriguing. It feels like immediate clinical applications might be on the horizon.

Dr. Yehuda: I see at least three or four ways that we could think about cortisol-based interventions. The first one might be prevention. That is the Zohar study, which is a study being conducted in Tel Hashomer hospital in Israel, headed by Dr. Joseph Zohar. When I first heard his idea of using cortisol in the ER to prevent PTSD, I have to admit I was skeptical, even though we are the ones that published that cortisol levels are lower in the immediate aftermath in persons who are more likely to develop PTSD. What Dr. Zohar said was, if that is true then we should be able to give cortisol during the "golden hours." But I was nervous. Why? Because I think that hormonal response is something that you want to be very careful about changing, because the body has a wisdom. That is my general view of the world, but he convinced me that if you give a single really high dose of glucocorticoids within a 4-hour window of a trauma, then the effect that that might have would be to recalibrate the HPA axis in a way that provides enough cortisol to quiet down the sympathetic nervous system in a very organic and permanent way. Also, Dr. Hagit Cohen's in Ben Gurion Medical School in Beer Sheva work with animal studies had shown that this might actually work to prevent PTSD if given during the "golden hours."

Dr. Jain: By "golden hours" you refer to that 4-hour window after the trauma?

Dr. Yehuda: We do not know what the window is. In our study we said 4 hours. I do not know if it is 8 hours or 12 hours! We do not know if it is 2 days! Ironically, when people give benzodiazepines in the acute

aftermath of a trauma, they are doing the opposite thing, as benzodiazepines lower cortisol levels. So even though in the short run, you may experience some relief, in the long run it just kicks the can down the road. Dr. Zohar's idea is that by intervening early you can set a pathway towards recovery.

There have been other studies like this. In fact, the first observation of this was by a physician in Germany named Dr. Gustav Schelling. He was treating septic shock and using hydrocortisone as a treatment for septic shock. What he noticed was that those who had received high levels of glucocorticoids, which not everyone did, had fewer complaints of traumatic memories from their traumatic experience of being critically ill. He searched for an explanation and finally did a randomized clinical trial. He concluded that there were beneficial effects of administering high doses of glucocorticoids in the early aftermath of a trauma. So prevention is certainly one potential avenue.

But there are people who have given glucocorticoids not during the "golden hours," but in a more sustained way over several weeks. They have also found potentially beneficial effects. We have just completed our study with Dr. Zohar and eagerly await the results. In this study we also measured biomarkers to see if treatment could be predicted.

Another way to effect changes in the HPA axis might actually be to block the glucocorticoid receptor. There is a trial that is ongoing now using a drug called mifepristone, which is a glucocorticoid receptor antagonist. You might know this drug by a different name. This study is being run by my colleague Dr. Julia Golier. You might know mifepristone as RU-486, or the abortion pill. RU-486 obviously has effects on the progesterone receptor, which is why it is an effective treatment to prevent pregnancy, but it also has effects on the glucocorticoid receptor. There is a trial that is ongoing now, ending August. The pilot study showed some benefit. What happens with that

treatment is that you can block the glucocorticoid receptor and really recalibrate the ratio of peripheral to central cortisol. The beauty of that treatment is again you give it once or you give it for a very short period of time, and you look for recalibration effects. People like to take medications that way as opposed to every single day.

Another way to think about glucocorticoid treatments is to use cortisol as an augmenter of psychotherapy. We have been doing some studies where you give moderate doses of cortisol or hydrocortisone about half an hour before an exposure based treatment. The rationale for that is that glucocorticoids facilitate new learning. They facilitate extinction, and it could be that administration of moderate doses of hydrocortisone could really set the stage for doing better in exposure therapies. We found that in case reports in a small trial we conducted. What we found was that there were fewer drop-outs out of prolonged exposure therapy if they were given hydrocortisone compared to placebo. If that continues, that is a big deal, because we know that a lot of patients drop out of these treatments prematurely. Anything that makes somebody just stay in treatment is probably good.

Dr. Jain: Moving on to the next question then. There is this whole issue regarding lower cortisol levels being a pre-traumatic trait, like, somebody already has this and then they are trauma exposed and have a higher chance of developing PTSD. What are the implications of this for screening and resiliency programs in clinical settings?

Dr. Yehuda: We have an artificial view of what "pre-trauma" means. Pre-trauma of the event that we happen to be thinking about now? Many of us don't consider enough what kind of early environmental events people

have experienced before they present for effects of the trauma that they are coping with now.

We know that many people in the military have had traumatic experiences prior to being in the military, yet we define their pre-trauma cortisol as being pre- combat, as opposed to before they ever experienced any adversity.

I think this is a tough nut to crack. In our studies, we found that lower cortisol levels were present in rape victims who had had a prior assault. They are more likely to develop PTSD, but was their cortisol level already low? Is that why it did not climb up higher than it could have?

I think that these are important issues. Now, there was a fascinating study that was published by Mirjam van Zuiden and her group in the Netherlands that basically took a thousand soldiers, before they went into combat, and looked at cortisol and glucocorticoids receptor measures and markers, as well as genes and epigenetic markers of the glucocorticoid receptor. They found that low cortisol and enhanced glucocorticoid receptor sensitivity were predictors of people that had PTSD a few months later.

Now, of course, we do not know if they also had prior trauma. We do not know that, but that was a very elegant demonstration.

It is exactly as you say, but it is hard to unpack these things. At least we are getting closer to understanding that not all the action occurs at the time of the trauma. That the stage might be set in advance, we are actually an accumulation of our experiences, and we hold biologic changes and then use them to respond differently to traumatic events as they emerge in our lives.

Dr. Jain: That is very true. I like that phrase—it is

setting the stage for subsequent trauma reactions. We have not figured out exactly how all those pieces come together.

Dr. Yehuda: There are a lot of people that are studying the effects of child abuse and early trauma even in the absence of PTSD. Their work is also supporting lower cortisol levels. It may be that low cortisol will impacts whether someone gets PTSD to a later trauma. The problem can be that when you study someone at one point in time and they have low cortisol but they don't have PTSD, that does not mean that they will not develop PTSD if exposed to a trauma in the future. We do not know whether low cortisol measures are markers or predictors of the future, but I would suspect that there is a genetic component as well as an early environmental component that would make these markers predictors. That is one of the difficulties in conducting such studies. The challenge of clinical research is that we are looking at a few points in time and trying to make decisions as if we were looking at stable phenotypes, when we know that there is an awful lot of change that occurs within individuals in terms of their mental state, not to mention the fact that people often have really complex lives with a lot of things going on. So, you might be resilient following the first three events, and then the fourth one occurs and then you develop PTSD. We do not really know how useful these measures are, but there is probably a way that we can do more longitudinal prospective studies to get a flavor of that. I know that those are studies that are ongoing in the VA system, which is really good.

Dr. Jain: That is great. Related to that and transitioning to this concept of this intergenerational transmission of stress: Your 2005 study with the women who were pregnant in the World Trade Center, it was fascinating to read that study. I thought that it was an elegant demonstration of this concept of intergenerational

transmission of stress. It would be great if you could talk a little bit about that study. One question that came to mind was a question about the pre-trauma cortisol level in the women. I wondered if that was measured, and did you gather data on their earlier experiences with trauma? That was just one particular question I had, but if you could just discuss the study in general, because I think it was really a fantastic contribution to the literature.

Dr. Yehuda: We did not have a lot of information on the women. In fact, this whole study was post-hoc in a sense that the study was designed for a completely different reason. It was to monitor pregnant women to make sure they gave birth to healthy babies. Everyone was really concerned about the level of environmental toxins after 9/11. Somebody from the environmental medicine group reached out to me because they noticed that a lot of women were really not doing very well emotionally and psychologically.

So by the time I was involved, some of the women had already given birth, but there had been a lot of information about what trimester they were in, about any pregnancy complications, exposure to toxins, etc. etc. So we added to that an evaluation of PTSD. Then when they came in for their 7 month to 1 year wellness baby evaluation, we were able to get salivary samples from the mother and the child. By then it did not surprise us to see that mothers with PTSD had lower cortisol levels than mothers without PTSD. But what did fascinate us was that in the mothers that had lower cortisol, the babies also had lower cortisol, but that this was a trimester dependent effect and that it seemed to split out in the second and third trimester in mothers who had been exposed in the middle of the second trimester or exposed in the third trimester.

When we had those findings, a lot of possibilities opened up in terms of how cortisol levels might be transmitted from parents to child or from mother to child. We were not the first people to make this observation.

There has been a literature that that has demonstrated that mothers who are exposed to under feeding before puberty have children and grandchildren that have metabolic problems. Since we knew that the women exposed to starvation during pregnancy also tend to give birth to children who were more prone to hypertension as adults, we knew that there was the possibility of in utero effects.

But what seemed to happen here was an example of glucocorticoid programming. In the middle of the second trimester of pregnancy, there is an enzyme that becomes expressed in the placenta. It is an enzyme that blocks the conversion of cortisol to its inactive metabolite, cortisone. The induction of this enzyme really helps protect the fetus from detrimental effects of maternal glucocorticoids, because the cortisol is broken down into its inactive metabolite, cortisone. The enzyme is called 11β-Hydroxysteroid dehydrogenase type 2. We had already been interested in studying this enzyme just because we were interested in cortisol metabolism. But it turns out that in mothers who are under stress, it is very possible that their enzyme levels and the amount of glucocorticoids they have could overwhelm the body's ability to metabolize cortisol into cortisone and affect the fetus. That was one idea that we had, that there might be a transmission based on offspring response in utero to maternal levels of stress hormones.

The message is straightforward: mothers who are stressed during pregnancy can program the stress response of their offspring, in utero, and the offspring accommodates somehow to the level of stress hormone. That has become a very important issue also in our intergenerational studies. It has become one viable mechanism through which mothers may "transmit" different vulnerabilities (or resilience) to their offspring. One does not need to have actual trauma experiences post-natally in order to have some of the neuroendocrine features associated with PTSD and PTSD risk. And this means that pregnancy is an important time with great social implications for our society. I do not

think that we think about pregnancy as the very important developmental event that it really is. Otherwise, we would be really taking much better care of traumatized pregnant women than we do.

Dr. Jain: Obstetrics care involves screening for gestational diabetes, congenital defects in the baby, and even screening for postpartum depression.

Dr. Yehuda: Yes, and we should screen for trauma, too.

Dr. Jain: Given how high the rates of trauma exposure are in the population, it is worthwhile screening for trauma in pregnant women.

Dr. Yehuda: Exactly.

Dr Jain: The other thing I wanted to ask about was early data indicating that exposure to trauma can impact the psychosocial functioning of second, maybe third generation offspring. I think there were some studies done with holocaust survivors. If you could speak a little bit to that, because obviously that has very widespread societal implications, too.

Dr. Yehuda: Yes, we have found that in the adult children of holocaust survivors, they are more vulnerable to psychopathology and this is true of offspring who have parents with psychiatric symptoms. In one study we were able to measure biological and epigenetic markers showing that there are effects on holocaust offspring, based on either maternal and in utero developmental factors, maternal exposure, or maternal and paternal

PTSD.

Dr. Jain: In general, what would you feel are the important questions for trauma scientists to answer in the next one to two decades? What would be top on your list to prioritize?

Dr. Yehuda: Many decades ago when the field first conceptualized the diagnosis of PTSD, our response was to emphasize the commonalities in trauma survivors regardless of what their exposures were. But I think it is important now to go back and see in a more clear way whether combat veterans are or are not different than other trauma survivors, or if interpersonal violence leaves a unique biological scar compared to a natural disaster, or whether age at traumatization matters or duration of trauma matters.

We basically have a threshold phenomenon where if you are over the threshold of what constitutes a trauma, you could be in the category depending on if you have the symptoms that are the symptoms of PTSD, but that is not very nuanced. In my experience, although there are similarities between trauma survivors in their mental health profile, there are also really important differences.

Some of the treatments that we have developed may really work better for some groups rather than others. For example, it seems like prolonged exposure is a fantastic treatment for interpersonal violence in women, and then the question becomes, is it as good for combat veterans? Have we studied this carefully enough? Should we be tailoring treatments based on trauma type and not just whether or not a threshold for trauma and symptoms has been met? We have to start customizing this.

The other thing that I think is really important is this idea that the

designation of PTSD is a static one, or that it is binary or not dynamic. We have to rethink that. Now that I have the perspective of having years in the field and seeing the same trauma survivors over a period of many years, even decades, I understand that the same person can at sometimes meet diagnostic criteria for PTSD while at other times, that person may not. Do we view the person as always at risk after s/he has recovered? Especially when you have recovered from something and you are asked about having had it in the past, your memory is not so good for how much you have suffered in the past when you are feeling good right now.

Sometimes, I have had the ability to actually do a diagnostic interview of someone, meet them 10 years later, ask them about their worst episode of PTSD, and if they are feeling fine today they won't remember how bad it was. What does that mean for biological studies, for biomarkers, and for risk? Just the idea of whether the categories are binary or not, I think is something that we really want to look at.

Finally, I think we have been paying a lot of attention to the psychological aspect of trauma and not enough to the physical illness part—the fact that people who are exposed to combat may die at an earlier age, make poor behavioral health choices, and are more prone to hypertension, metabolic syndrome, inflammatory illness, cardiovascular disease, and cancer. These cannot be coincidences, but may either be part of the trauma effects, or part of the PTSD effects. Why are we not more focused on the biomarkers that might help explain and reverse some of these illnesses? When will we start seeing PTSD and trauma exposure as the multisystem condition that it is and really try to integrate care plans that not only assess for nightmares, hyper vigilance, and concentration, but diet and exercise and hemoglobin A1c? These are markers for trauma survivors because they are at greater risk for all these issues, not to mention cognitive decline. What I would like to see is us incorporating a much more holistic approach to understanding the effect of trauma that does not divide the mind and the body into

different spheres and really focuses on wellness in a much more broad way.

Dr. Jain: So that integration between the physical and the mental, even in the way we treat them. Right now, it is separated out into mental health and physical health.

Dr. Yehuda: It does not make sense. Many veterans that come for care do not take such good care of themselves. It is not a priority for them. They do not maybe eat as well as they could or they have really disrupted sleep. I would like us to think about trauma as something that really does affect the whole body and our behavioral health choices. We should think broad, because those are the things that are really very important to ward off long-term diseases.

Dr. Jain: Yes, and enhance overall quality of life, too.

Dr. Yehuda: I think patients talk about what we (as healthcare professionals) want to talk about, and we lead the conversation in a symptom focused way. The symptoms of PTSD are impairing, don't get me wrong, I am just saying there is a greater range of problems than are contained in the PTSD diagnosis.

Dr. Jain: I could not agree with you more. I feel like it is in the air. We are on the verge of embracing it that way. We are just not quite there yet.

Dr. Yehuda: I completely agree with you, and I think that the reason for that is that as we do our research on a genome wide level, we identify that so many of the biomarker pathways that seem to be altered relate to

inflammatory immune functions. The pathways that are being identified in people with PTSD are not just those that associate with psychiatric symptoms, but really affect much more bodily functioning. I think that is also a lesson, just to close the loop on this that has been learned from the glucocorticoid story in PTSD. Cortisol is not just about mental health. There are glucocorticoid receptors in almost every cell in the body. Cortisol has a myriad of different functions in different target tissues, mostly in the metabolic systems promoting fuel and energy. It is silly to just think about cortisol's role in traumatic memory when cortisol is a ubiquitous hormone that has so many different roles.

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