



Allostatic Load and Medical Illness 2

Written Video Transcript

Really it all boils down to that. PTSD is very complex. And the more I learn about this disorder it seems like almost any psychobiological system that you look at you're and folks with PTSD they're different in some ways. [00:00.20.00] And one might ask—and that's not true of all psychiatric disorders. Some of our psychiatric disorders such as panic disorders seem to be relatively simple. Certain important systems are affected, other systems seem to be normal. But in PTSD almost it seems like every system that we at least can measure at this point in time seems to show some [00:00.40.00] abnormalities with the PTSD folks as compared to the non PTSD folks. Why should that be? Well my belief about why that should is that is that PTSD involves many if not all of the neurobiological and psychological mechanisms that have evolved for coping, adaptation and survival [00:01.00.00] of the species. Because the kinds of models that I use to understand PTSD are basically about coping and adaptation. And I do think that PTSD is an abnormality that uses the neurobiological hardware and software that has evolved in order to help us survive as a species. And [00:01.20.00] that would explain because in order for survival you need to you know use everything that you've got, or most of it. And I think that's one of the reasons why we see so many different abnormalities. And to just very quickly—I'm not going to go over this in any great detail but just to kind of sort of look at the left hand side over here. Just to identify, point out some [00:01.40.00] of the psychobiological systems where there seems to be some fairly solid research—some more solid than others—showing abnormalities among people with PTSD as compared to those without. So, certainly the adrenergic nervous system particularly in terms of hyperreactivity. And I'll have a lot to say about that before we're done. Certainly the hypothalamic [00:02.00.00] pituitary adrenal cortical system, the classic stress system as defined by (Hans Selye) in the mid 20th century, a very important system. Another system which I think is very important particularly from a medical perspective is the opioid system. And there is some data, it's not great, but it again it's consistent [00:02.20.00] that there seems to be some changes in PTSD folks compared to those without. This is (corticotropin) releasing factor, elevated levels. Again that's part of the HPA system. This is a very important area, hasn't received anywhere near the attention that it deserves that people with PTSD have a [00:02.40.00] neurological, neurobiological, psychobiological system that is on a hair trigger level. It responds very rapidly with little or no provocation at times. And we have some very important neurological models, sensitization kindling models that have been looked at in terms of [00:03.00.00] seizure disorders in [3:02] they've been looked at in terms of recurrent psychotic disorders. I think they're also relevant for PTSD. And we could be spending a lot of time on that but we'll just go over that very quickly. Some of the other systems where the data is less compelling but very, very intriguing. [00:03.20.00] Certainly the, the (glutamatergic) system, the MMDA receptor which is the mechanism through which learning takes place. I also think that disassociation, an important symptom in PTSD, is



mediated through this system. The (serotonirgic) system, here we have a very interesting situation—because I'm not going to talk about serotonin today [00:03.40.00] so, let me take a second or two—that even though there's been very, very little research on serotonin mechanisms in PTSD some work on serotonin and the stress response—not a lot but the two drugs that have received FDA approval—one Zoloft and the other— [00:04.00.00] well, (Certraline) and the other Proxipene or Paxil which is going to get its FDA approval any minute—these two drugs, the first two drugs with FDA approval in PTSD they both work on (serotonigic) mechanisms. Thyroid systems seems to be abnormal. We will, we will be talking about thyroid function. [00:04.20.00] So, when we're talking about PTSD I think that the psychobiological system that has to be the context, the frame of reference for all this, is the stress system. And the stress system as I've defined it here coordinates the generalized stress response whenever a stress of any kind [00:04.40.00] exceeds a threshold. And the main components, the two major components of the stress system, that have been well researched with regard to PTSD, one is the HPA system, the (cortatrophic) releasing hormone and the (locus cirilius) which activates the adrenergic system, the arousal system. [00:05.00.00] And we'll be getting into this. And then there's all kinds of downstream affects cascading as a result of abnormalities in the stress system. Another very important—where this definition is somewhat deficient but it's deficient because there just isn't any data in PTSD of course is the third [00:05.20.00] major, major pillar of the stress response is of course the immunological system. And that has obvious implications for medical illness. And we'll get on to that in a minute. So, let's—here's a picture of some of the key brain systems involved in the stress system. [00:05.40.00] The (locus seillius) which contains the majority of the adrenergic neurons that activates the sympathetic nervous system downstream and all kinds of brain mechanisms upstream. The hippocampus, which is an important site for learning and fear conditioning, as well as the (imigula) which is emotional [00:06.00.00] conditioning. So, all of this stuff is very much important in PTSD and we know that. The other important piece of these stress response of course if the HPA system. H for hypothalamus, P for pituitary and A for the adrenal gland. And we'll be talking about this system quite a bit. [00:06.20.00] Again, just to remind you all this is inside the brain. Again the (locus serillius), the beauty of the stress response, of the key players, is that they have neuronal connections to all parts of the brain. So that the (locus serillius) has all kinds of upstream cortical connections, (hippocampal, imigula, hypothalamic), [00:06.40.00] etc. and downstream connections as well. A very important mechanism. And here's just one other picture. Again I'm just trying establish a context here. And actually this is the ignition switch, (corditropic) releasing hormone. Because CRH or CRF which I prefer to use, [00:07.00.00] number one has the downstream HPA system. But notice the HPA system is off to one side. Because the other thing that a lot of folks don't appreciate about CRF is it also functions as a neurotransmitter. And there's a lot of very interesting work suggesting it is the final common pathway to activate the (adrenergic) system, the fight, flight or freeze [00:07.20.00] (cannon bard) system. So, if you want to turn on the human stress response you want to turn on CRF, CRH which is why a finding that I'll talk about later that people with PTSD has shown consistently elevated CRF levels in the cerebro-spinal fluid and elevated CRF function, this is quite consistent [00:07.40.00] with a hypothesis suggesting that this, the whole



stress system, is excessively active in PTSD with all kinds of downstream consequences. And some of these downstream consequences we can understand in terms of a specific brain structures, whether it's the (mesocortical, mesolimbic) [00:08.00.00] systems, the (amygdala hippocampus), etc., or in terms of the different neuromodulators, neurotransmitters, serotonin [8:07] GABA, etc. And all of this is affecting the target tissues. And it's the target tissues where medical illness is going to be detected. Okay, let's unpack this a little bit. [00:08.20.00] Well, this is the HPA system. I've talked about that several times. But everything is interconnected is really what the bottom line of the last slide was. So that CRH is also going to affect the thyroid system directly affecting (somatostatin) which will inhibit thyroid stimulating hormone [00:08.40.00] and effects on T3 which is the most active peripheral thyroid hormone. Also it will inhibit growth hormone and all of the downstream effects from [8:51] so the growth system is inhibited. Paradoxically, the thyroid system although inhibited, TSH is elevated T3. [00:09.00.00] So, hyperthyroidism is something you'd be looking for in PTSD. So, to summarize the HPA abnormalities, increased CRF, important finding. This is a controversial finding. Earlier studies with vets and postmenopausal Holocaust survivors suggest that the (glucocorticoid) [00:09.20.00] receptor system is super sensitive in PTSD. This has been used to explain a number of findings in PTSD. And we'll get into allostasis in the second part of my talk here. But this is a controversial finding because it appears that this may not be as true for premenopausal women. So, this is [00:09.40.00] a finding that we are revisiting. Again, cortisol levels, previous data again with chronic veterans of PTSD suggested that cortisol levels were low in PTSD. That may not be written in cement. The lower cortisol levels [00:10.00.00] can increase at times. We need to try to understand that. One way to understand that, and I'll mention it now because I think it's important to try to make some sense out of this complicated data, is I think when we think about abnormalities and PTSD we have to think about both tonic abnormalities—the system at rest is changed in some important ways. [00:10.20.00] But there are also phasic abnormalities because the hallmark of PTSD is hyperreactivity. And it's those phasic responses that seem to be responsible for some of the very important pathology. So, what may appear superficially to be paradoxical that you may have a tonic system that is at a lower level of function you may have a reactive [00:10.40.00] phasic system that is hyperreactive. But I think that unless you understand and think in terms of both the tonic and phasic consequences of PTSD it's very hard to understand anything that we really [10:52]. I think that's true for psychological facts, phenomenon as well, but that's way beyond—and I think gender differences. Most of the research has been done in males, [00:11.00.00] we're starting to catch up with women. But there's some things about the biology of females that may be affecting CRF system, GR. Women, both estrogen and progesterone are likely to make glucocorticoid receptors less sensitive. [00:11.20.00] So, I think some of the sexual differences, some of the sexual dimorphism may be very real, may not be an artifact of a particular researcher's findings. Now, if you think about this what does (cortisol) do for a living? Well it really suppresses immunological [00:11.40.00] responses, inflammatory responses so that if indeed the low cortisol that has been found in veteran's studies is a real persistent finding then one would expect that there would be lower cortisol levels and higher immunological functioning. [00:12.00.00] On the other hand since there's increased—



but the (gluco corticoids) are immunosuppressive so that we might expect they'll be—CRF, here's the paradox. Low (cortisol) levels might suggest excessive immunological [00:12.20.00] activity. High CRF would suggest just the opposite. So that we might see problems in terms of a failure to turn off the immunological system such as autoimmune disorders which are more common in females, hypersensitivity in terms of allergies, etc, etc. We'll get into some of this later on [00:12.40.00] just so you can begin to appreciate how these different findings are related to one another. But if indeed we have high (gluco corticoid) receptor sensitivity we might actually see a system in which there's excessive HPA activity. My belief is that we do have—what PTSD is, [00:13.00.00] forgetting all of this stuff, is that essentially we have a HPA system that is functioning at a much higher level. So, in that way I think that PTSD is much like chronic stress. So that is my hypothesis, that PTSD is like chronic stress is a disorder in which there is excessive HPA activity and so one is going to see immunosuppression [00:13.20.00] rather than the opposite. Other kinds of medical complications and you can read these. Well, we expect cardiovascular problems, irritable bowel, hyperthyroidism, reproductive problems, sleep disorders, eating disorders. And we'll get into some of this later on. [00:13.40.00] Now, here is a study that's very interesting because what this shows is that the response, the stress response in different people who have been traumatized may be different depending on whether or not you have PTSD. In this case this is an experiment by Christine (Hime) and her colleagues at Emory University [00:14.00.00] where people, where women who had been sexually abused as children were given a dose of ACTH which—I'm sorry were given a dose of CRF, (corticotrophic) releasing hormone which produces ACTH. And these are the normal women. The women were never, never abused and have no [00:14.20.00] PTSD or depression. And this is what their ACTH response looks like. These are depressed women with and without abuse. And the depressed women almost all of them also have PTSD. And what you can see is a blunted response. So, the women with PTSD and depression have a blunted response [00:14.40.00] to CRF. These are the women with sexual abuse and no PTSD or depression. So that what you see is knowing that someone has been sexually abused doesn't tell you what you need to know psychobiologically. And I think it's important. A lot of our research we look at abused, non-abused. Well, the situation is [00:15.00.00] much more complicated than that. And this is kind of a fine grained way of looking at this that we need to do more of this. If we move to the (adrenergic) system the hyperreactivity that we see in the sympathetic nervous system, people with PTSD [00:15.20.00] had excessive cardiovascular responses. Their blood pressure goes up, their pulse rate goes up. They also have elevated blood pressures and pulse rates at a resting stage, excessive startle response, disrupted sleep. People with PTSD are in a state of not just increased arousal but I think most importantly for medical issues [00:15.40.00] hyperreactivity. And as a result of this hyperreactivity there are other downstream effects. Once you push something, something happens in return. So there's down regulation of some of the (adrenergic) receptors. And this which I think is going to be a very important area, and we'll talk about this later, is neuropeptide Y. [00:16.00.00] Neuropeptide Y is a neuropeptide. It lives in the same neurons as norepinephrine. It's released with norepinephrine. At low doses it enhances the response but at higher doses it basically reduces the response to adrenaline, norepinephrine, etc. [00:16.20.00] More



importantly, neuropeptide Y, as I'll show later, clinically has anti anxiety affects. It's an anxiogenic. So, neuropeptide Y reduces anxiety and neuropeptide Y antagonizes CRF. So, here we have something in the body that will antagonize [00:16.40.00] CRF. And in point of fact it may be that the elevated CRF may be partly due to the fact that the neuropeptide Y is reduced. You know, I don't know which came first the chicken or the egg. But we have is a situation here is excessive HPA activity and a reduced capacity [00:17.00.00] to neutralize it, to normalize it in people with PTSD. I think that has important consequences. It also suggests treatment approaches. So, here are some of the kinds of consequences that you might expect in a person with PTSD who has excessive adrenergic activity and more importantly excessive adrenergic [00:17.20.00] hyperreactivity. And most of the important cardiovascular diseases are on this list, atherosclerosis, hypertension, cardiac arrhythmias, damaged myocardium etc. And there—and some of reasons this hyperreactivity is going to increase coronary vascular tone, it's going to produce shearing [00:17.40.00] forces within the coronary arteries which could lead to a clot formation and platelet aggregation. So, just understand the path of physiology of PTSD just in the adrenergic domain makes you begin to really wonder, worry about, about these kinds of cardiac consequences. [00:18.00.00] The opioid system, a system has been poorly studied, erratically studied. Opioids antagonize adrenergic activity. And we have shown there's data suggest that people with PTSD have lower opioid activity which would suggest more pain syndromes, which we do see clinically, whether it's general pain, [00:18.20.00] pelvic pain, abdominal pain, headaches. On the other hand when they are stressed people with PTSD can produce more opioids. An animal phenomenon called stress induced analgesia which is why when people are in very stressful situations they may be able to deal with and survive certain kinds of painful situations [00:18.40.00] that when the stress is gone are very, very dysregulated. We've talked a little bit about elevated thyroid levels and there is data showing the people with PTSD have elevated thyroid levels and possible hyperthyroidism.

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