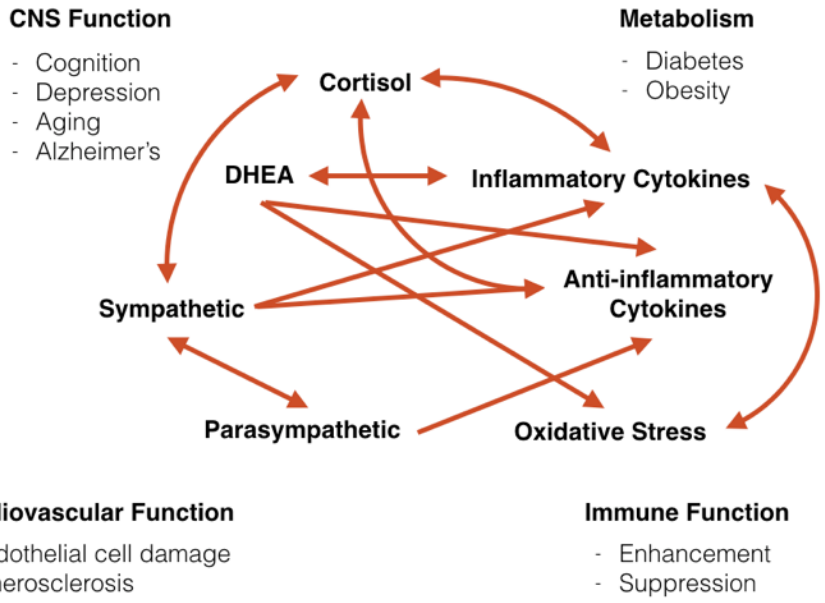
HPA-D: HPA Basic Physiology – Part 1

Hey, everyone, in this presentation we're going to talk about the basic physiology of the HPA, hypothalamic–pituitary–adrenal, axis. To understand HPA axis dysfunction, you need to understand the stress response and its components. As I mentioned in the introduction, it's literally impossible to successfully treat a patient with chronic disease without addressing stress-related dysfunction. A greater understanding of the mechanisms that govern the stress response will make your diagnoses more accurate and your treatments more effective.

Hans Selye coined the term stress, and he defined it as a nonspecific response of the body to a demand made upon it. The prominent psychologist Richard Lazarus defined stress as any event in which environmental demands, internal demands, or both tax or exceed the adaptive resources of an individual. And then another commonly accepted definition of stress is a threat, real or implied, to the psychological or physiological integrity of an individual.

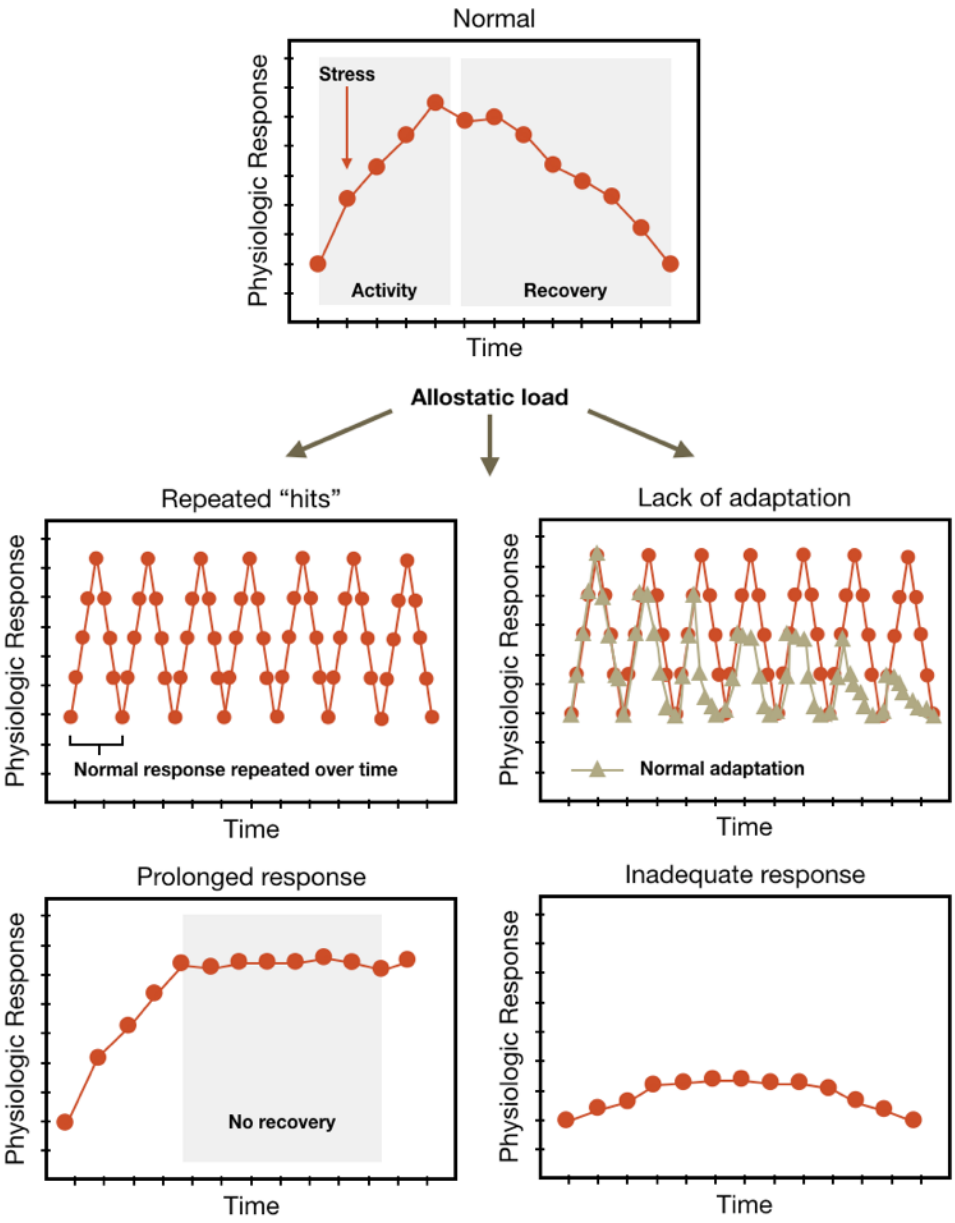
A crucial concept to understand is that the systems that react to stress, the autonomic nervous system and the adrenocortical system, are important protectors of the body in the short run, but the continual activation of these systems can cause damage and accelerate disease over long periods of time. Put another way, that which is protective in the short term is often damaging in the long term. Protection and damage are opposite and to some extent unavoidable extremes of the release of adrenal hormones during stress, and this is the reason that stress is such a significant cause of disease in the modern world, where stress response mechanisms that were designed to be active only for brief and distinct periods of time are continually active, albeit at a lower level.

Allostasis: Maintaining stability through change



Adapted from: McEwan BS. Karatsoreos LN. Sleep Med Clin. 2015 Mar;10(1):1-10

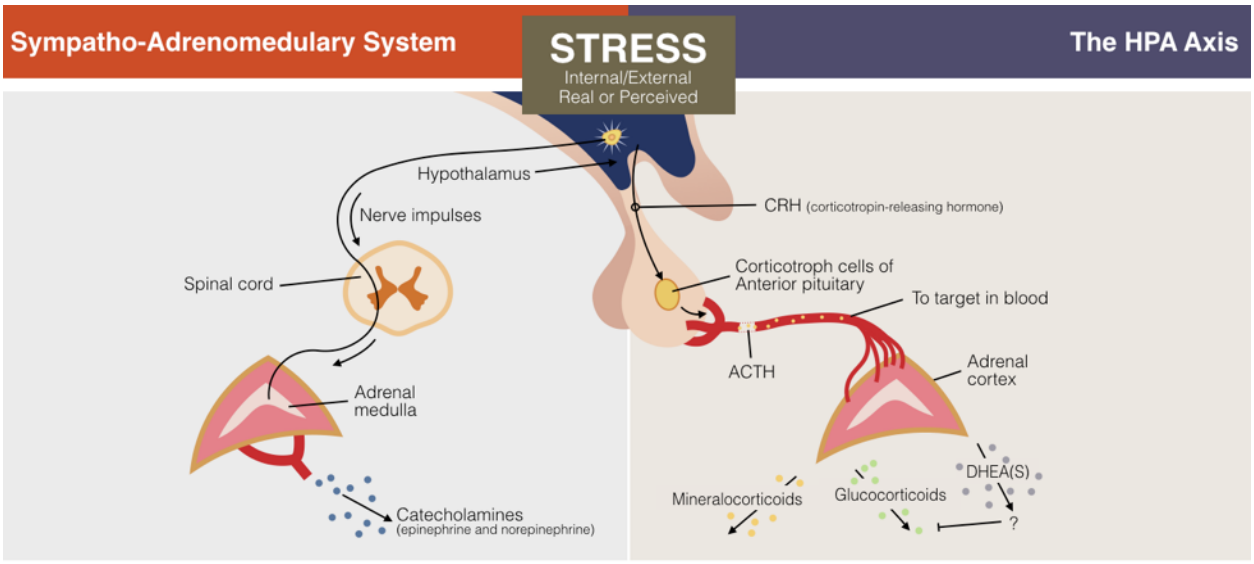
Allostasis is a term that refers to the process of adaptation to acute stress. It was coined by Sterling and Ayer in a 1988 paper. Another way to think of allostasis is maintaining stability through change. The factors that mediate allostasis are interconnected, as you can see here on this slide, which means that too much or too little of each mediator can disturb the entire network, leading to dysfunction and disease. So just to give you an example, a relationship between inflammatory cytokines and glucocorticoids like cortisol is complex and bidirectional. Pro-inflammatory cytokines stimulate the production of cortisol, but on the other hand, cortisol suppresses inflammatory cytokine production. The sympathetic nervous system, which is involved in the fight-or-flight reaction, which I'm sure you've heard of and experienced like all of us have, that reaction increases pro-inflammatory cytokines, whereas the parasympathetic nervous system response, rest and digest, decreases inflammatory cytokines. We need both of these systems, and the relative balance between these systems is what's really important. When cytokine production exceeds the anti-inflammatory capacity of cortisol, we end up with chronic inflammation, which of course is at the root of most modern disease. But on the other hand, when cortisol suppresses inflammatory cytokines too much, then we have a weakened immune response, and we can see this in increased capacity to get colds and flus and possibly even things like cancer.



Allostatic load is the wear and tear produced by imbalances in the mediators of allostasis. So examples of allostatic load would be things like hypertension, atherosclerosis, and diabetes, as well as stress-induced remodeling in the parts of the brain that support memory, executive function, and mood. So to put this in simpler terms, allostatic load refers to the price that the body pays for being forced to adapt to adverse psychosocial or physical situations, and it represents either the presence of too much stress or the inefficient operation of the stress hormone response system, which must be turned on and then turned off again after the stressful situation is over. We're going to talk about allostatic load in more detail later in the unit, but for now I just wanted to give you a little bit of an introduction here. As you can see, the figures on the slide depict at the top a normal

stress response, where there's a stressor and the activity of the system goes up, and then there's a recovery period when the activity drops. And with allostatic load, there are some different possibilities. There are repeated hits on the system with a normal response, where you see an increase and then a decrease, an increase and a decrease, and that's a normal response repeated over time, but in a pathological situation where the person loses the capacity to adapt, as you can see in the diagram, the activation is blunted over time, and the individual's less and less able to mount an adequate response to stress. Then we have a prolonged response to stress, where the patient is under continual stress, and the system gets activated and then it just stays activated over time, but for some people, that can progress into an inadequate response where they're just really unable to mount a stress response at all. So these are just some of the presentations that can manifest with allostatic load.

People often get confused between allostasis and allostatic load, so let's just briefly review the difference. Allostasis refers to all of the processes that are involved in maintaining stability in the face of ever-changing conditions and in response to stressors. Allostatic load refers to the particular state in which the normal allostatic processes have worn out, failed to disengage or shut off. And this, in turn, leads to a failure of the organism to adapt. Today, the concepts of allostasis and allostatic load are commonly used, more commonly than previous concepts like homeostasis, to represent the dynamic and complex effects of stress on human physiology.

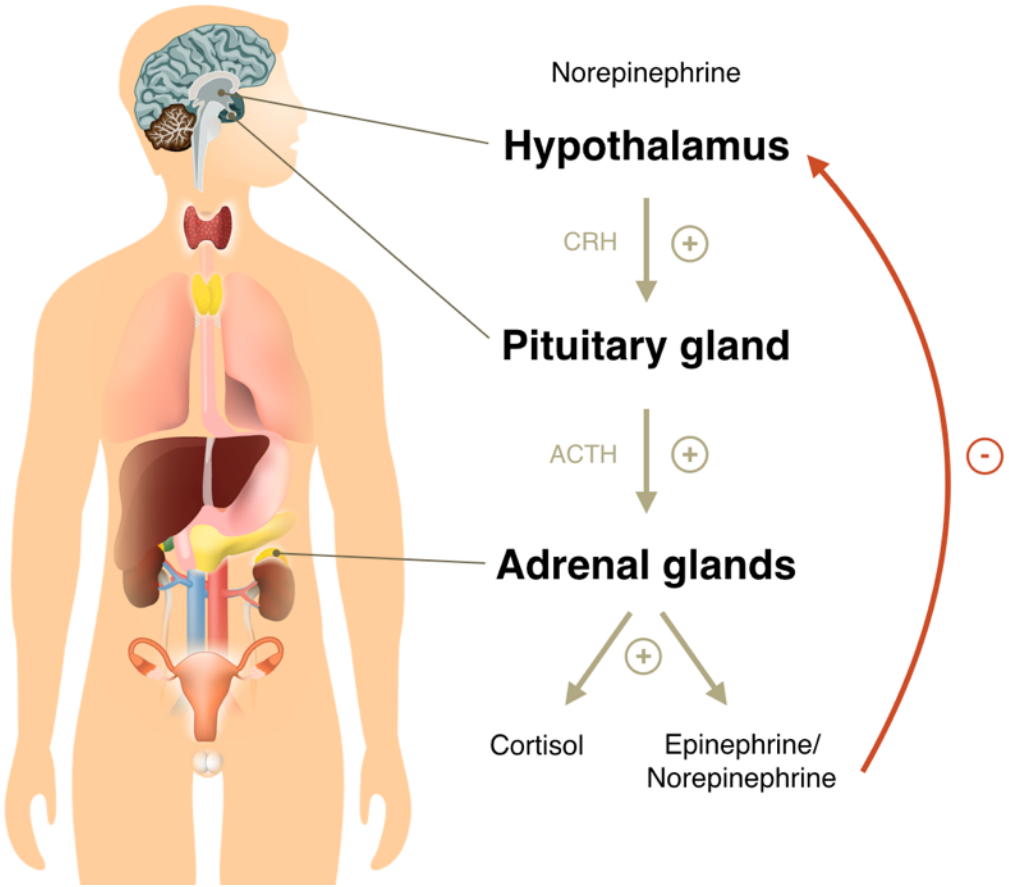


Short-term Stress Response	Long-term Stress Response	
Increased heart rate	Retention of sodium and water by kidneys	↑ Gluconeogenesis
Increased blood pressure		↓ Insulin Sensitivity
Liver converts glycogen to glucose and release glucose to blood	Increased blood volume and blood pressure	↓GH ↓T3
Dilation of bronchioles		↓ Immune/Inflammatory Response
Changes in blood flow patterns leading to increased alertness, decreased digestive system activity, and reduced urine output		↑ Fat & Protein Mobilization
Increased metabolic rate		

Adapted from: Guilliams, T. The Role of Stress and the HPA Axis in Chronic Disease Management., p.23

Okay, let's talk a little bit more about what happens when we experience stress. Stress triggers the hypothalamus, which then activates two distinct pathways of the stress response. The sympathoadrenal medullary system, or SAS, is part of the sympathetic nervous system, and it's responsible for the immediate fight-or-flight response that allows the brain to respond quickly to a threat. It's mediated by catecholamines like norepinephrine, a.k.a. noradrenaline, and epinephrine, a.k.a. adrenaline, and these are transmitted via nerves, so it's relatively instantaneous, and that's what allows the stress response to happen almost immediately. The HPA axis, on the other hand, is responsible for the intermediate to longer term stress response. Unlike the SAS, the effects take hours rather than moments to manifest because it's primarily mediated by hormones like cortisol, which have to travel through the bloodstream. So when the hypothalamus is triggered by a stressor, corticotropin-releasing hormone, or CRH, which is also known as corticotropin-releasing factor, or CRF, and another hormone named argenine vasopressin, or AVP, which is also known as antidiuretic hormone, or ADH, are released, and these travel down the pituitary and provoke the production of ACTH, and they also activate noradrenergic neurons from the locus coeruleus norepinephrine, or LCNE system, in the brain. Noradrenergic neurons and the LCNE system are responsible for the immediate fight-or-flight response, and they create, as I said, an almost instantaneous hypervigilant arousal state to allow the brain to respond really quickly to a threat. So if you hear somebody drop a book and you have that startle response, that's the system that we're talking about.

Stress activates noradrenergic neurons from the locus coeruleus norepinephrine, or LCNE system, in the brain, and again, this is why that response is relatively immediate. The LCNE system is the nucleus of norepinephrine-containing neurons, and it's located in the brainstem, the pons, and this is the system that creates that classic adrenaline response to stress that we experience just moments after the stress begins. It's increased heart rate, blood pressure, alertness, increased metabolic rate, all the things that go into preparing us for fight or flight. Any dysfunction of the LCNE would be thought to play a role in both hyperarousal states, like ADHD and PTSD, and then hypoarousal states, like narcolepsy and sleep disorders.



Once norepinephrine is released from the brainstem, it acts on the hypothalamus, which releases corticotropoid-releasing hormone, CRH, and argenine vasopressin, or AVP. CRH and AVP then trigger the release of adrenocorticotropic-releasing hormone, ACTH, from the posterior pituitary. ACTH then travels through the bloodstream, which again is why the response takes longer in this case, and then acts on the adrenal glands, which produce the stress hormones, including cortisol. ACTH also partially stimulates the production of DHEA to act as a counter-regulatory hormone and buffer the effects of cortisol. Minimal corticoids like aldosterone are also at least partly controlled by ACTH action on the adrenal cortex.