Ask-a-Biologist Vol 012 (Guest Miles Orchinik)

Stressed Out -

What is stress? We often know what stress feels like, but what is it and what causes it? We get a chance to learn about stress, the brain, and two very important areas in the brain, the hippocampus and hypothalamus. We also learn how the very vocal Bull Frog is helping biologist Miles Orchinik learn about stress and the brain. Listen to a ribbiting show...

Transcript

Dr. Biology: This is Ask-A-Biologist, a program about the living world, and I am Dr. Biology. Now imagine you're sitting in class. You have five minutes until the bell will ring and class will begin. Your heart, already beating fast, seems to be getting faster. Your breathing is rapid [sound of heavy breathing] and your hands are sweaty. Today is the day of the big test and you are STRESSED.

Stress, as we'll learn today, is a very common thing for humans and for all animals. Sometimes stress comes from things we would like to avoid, like tests, or speaking in public, or maybe when you're trying out for the soccer or volleyball team. Other times, stress comes from things we enjoy, like making the team, or when you're going out on that first date.

Our guest scientist today is Miles Orchinik, who is a professor in the School of Life Sciences at Arizona State University. Dr. Orchinik is a neurobiologist, or someone that studies how neurons in the brain work. We get a chance to talk to him about stress, and how a very vocal animal, the bullfrog, is helping us understand more about the brain and stress. Welcome to the show, Professor Orchinik.

Professor Miles Orchinik: Well hi, Dr. Biology, nice to be here.

Dr. Biology: At the beginning of the show I described some situations where stress is common. We're back in that schoolroom with the bell about to go and the big test. I'd like to start with a basic question: what is stress?

Miles: Well that's a very good basic question, but you know, we don't really have a good answer. You're right, you have pointed out that a lot of animals--in fact, all vertebrates, which means all fish, and amphibians, and reptiles, and birds, and mammals, including us--have an almost identical response to something we call stress, but we don't really know what stress is. So you know what stress is, everybody in the class knows what stress is, but the physiologists and the neuroscientists who work on stress don't know what it is.

We really don't know how to define it; so usually what we do is try and think of two things: something that causes us to feel stressful--we sometimes call that the stressor--and then we think of our bodies' response to this threatening situation, and we call that our stress response. That is what is really highly conserved among all vertebrates. So all

animals, whether it's a fish on a hook or a student taking an exam, will have the same sort of response in terms of the brain and endocrine system.

Dr. Biology: So what effect does stress have on the body? I mean, we know that it's good and sometimes it's bad. What's going on?

Miles: Well, so I guess that what you mean is, what effect does a stressor have on the body. OK, so when the brain perceives that there is a threat, certain brain cells, certain neurons, are activated, and those neurons start what we call a "hormonal cascade." So hormones are chemical messengers that are released into the bloodstream. In the case of a stress response, these neurons release a hormone which travels through the bloodstream to an endocrine gland we call the "adrenal gland." That sits on top of our kidneys; it's sort of at the back of our abdominal cavity. When they are activated, the cells in the adrenal gland release a well-known hormone called "cortisol." This is our primary stress hormone.

Cortisol is a steroid hormone. It is also called hydrocortisone. You may have seen some hydrocortisone in your medicine cabinet; your parents may have put it on a mosquito bite or another type of bug bite, because cortisol stops inflammatory responses, it stops the itching and the swelling. That's just one of the many things that cortisol does during a stress response, because almost all cells in the body can be targets for cortisol. So what I mean by that is that the cortisol that is circulating through a bloodstream when we have a stress response can act on any cells in the body that have receptors, and most of the cells in our body have some kind of receptors for cortisol.

That means that most of the cells in our body can respond when we are having a stress response, and this is really important, because when we get an activation of the stress response, when our life is being threatened or sometimes it may not actually be so threatening, like with a test--very few people have actually died from taking a test or not doing well on a test, but our brain thinks that we are facing a very serious threat, and so we activate many of these systems.

Dr. Biology: If we're talking about stress, and now we know a little bit how it works when you have the stressors, and the process of the activation, and this kind of tag-team of moving hormones down through the systems, and then it actually turns on and turns off particular hormones throughout the body, cortisol, say. A little stress obviously is good, because we need to know when we are under attack, or if we need to run, for example this fight-or-flight type of mechanism. So a little bit is good. But what happens when you get way too much stress?

Miles: Right, well most of the time nothing bad happens. I mean, I think that it's important to remember that most of the time the experience of stress or being exposed to stressors doesn't do anything all that bad to us. It may not feel that good at the time, but usually there are no lasting effects. It is not always the case. So the stress hormones, the cortisol, is a very, very powerful hormone. It is very powerful because it can change the way that genes are expressed in any cell, practically, in the body. Most cells that have receptors might have a change in the genes that are being expressed, which means a

change in the proteins that are being made, so this is a very powerful effect on the body.

Usually what we like to see in response to a stressor is a big response, so that we get a nice big release of cortisol, and then optimally, in the best case, cortisol levels come back down again very quickly. That is what we think is the most healthy response: a big response to a stressor, and then bring the cortisol levels right back down to normal, and that seems to protect us from some of the bad effects that might happen from stressors that were from chronic stressors.

Some of the things that we might see, if we have really bad stress or stress that goes on and on, as with people that are exposed to war sometimes see these things, you can have a stunting of growth; you can have your immune system, your ability to fight against infection, can be decreased; you can have mental problems. Older people might get cardiovascular disease, so heart disease, if there is too much stress that can't be controlled. So it is very important to terminate that response.

Dr. Biology: When you were talking about genes earlier, we often talk about genes and DNA, for example, on this show. Just as a reminder, the genetic material in the DNA, which is that blueprint of life, those are things that help tell the body what to make or not to make, or how to control certain things inside the body. So if stressors have this effect on them, it actually can tell whether the genes should be turned on or turned off? Does it actually have an effect on the DNA itself?

Miles: The stress hormone, the cortisol, doesn't have a direct effect on DNA, but when the cortisol binds to its receptor--receptors are proteins--that protein/hormone complex gets right into the cell nucleus and it binds to a specific region of the DNA, and that causes a change in the rate at which genes are expressed and proteins are synthesized.

Dr. Biology: So it can speed up or slow down how things are made.

Miles: Yeah, and we usually think of compounds increasing the rate, but with stress hormones there are very many genes that are turned off in response to stress hormones.

Dr. Biology: What I'd like to talk about next is the brain, because that's actually where we are getting this all started, the whole process. In particular, the hippocampus and the hypothalamus. These are two areas in the brain, the particular two areas of the brain that you study. Where are they located?

Miles: The hypothalamus tells you where it is located. The HYPO-thalamus is below the thalamus, so this is an area of the brain that we call diencephalon. It's a rather primitive brain region, and all vertebrates have a hypothalamus. The hippocampus is, first of all, you know what hippocampus means, right? Hippocampus means "seahorse." The hippocampus is really something that is developed in more advanced vertebrates. It's a brain structure that seems to be very important in learning and memory. There has been a tremendous amount of research in understanding the function of the hippocampus, for two reasons: one, because it plays such an important role in learning and memory; and two, because the hippocampus is so very important in stress responses.

Dr. Biology: Oh.

Miles: The hippocampus is probably the brain region that is most affected by stress hormones.

Dr. Biology: And the hypothalamus?

Miles: The hypothalamus is responsible for starting and stopping this endocrine cascade we talked about, that results in the release of cortisol. So the hypothalamus is very important in regulating our responses to stressors, and it is also involved in lots of very simple, primitive activities, like feeding, reproductive behavior, and thermal regulation. So the hypothalamus serves very simple, very basic types of behaviors that we see in all vertebrates, so that's another important area for stress responses.

Dr. Biology: So the hippocampus and the hypothalamus, they work together?

Miles: They do work together. There is a lot of interconnection between the hypothalamus and the hippocampus. Some people, in fact, refer to this endocrine cascade that we talked about as the "hippocampal hypothalamic pituitary adrenal axis."

Dr. Biology: Wow, now that's a mouthful! And in simple terms it means they all work together.

Miles: It does mean they all work together.

Dr. Biology: And actually, what's impressive, if you actually pull out a diagram of the brain and you look up the hypothalamus, one of the things that's interesting is, in a human it's about the size of an almond, which is pretty tiny, but there's a lot going on in there. The hippocampus, it looks to me that it comes in contact with the hypothalamus, but it seems to be a little bit larger.

Miles: The hippocampus is larger. The hippocampus is actually a beautiful brain region to work on, because it has a very distinct architecture, so the cells are put together in a very organized manner, and that has made it easy to study. So it is easy to tell what kinds of input there is, where the neurons are that provide input to the hippocampus, and it is easy to tell which neurons in the hippocampus talk to each other, and it is easy to tell the output from the hippocampus, and relatively easy to work with, if anything can be called easy to work with in a brain.

Dr. Biology: Well, we've been talking about stress, and the different types of stress. I do want to move on into some of your research that talks about the brain in particular. Before we move on I'd like to know, are there things we can do to control unwanted stress?

Miles: Well you know, all the things that your parents tell you to do--sleep well, eat well, exercise. I hate to say it, but these probably are things that are as effective as anything we know of. I was just preparing for a class I have this afternoon. We're talking about a paper about the hippocampus and the role that the hippocampus plays in learning and memory. This paper showed that during sleep, the hippocampus replays the

information that the animal is supposed to have learned that day. So we go through these experiences--in this case with rats, where a lot of the studies in neuroscience are done.

The hippocampus is very important in spatial memory--learning how the world is organized. As a rat learns about places in its environment, particular cells show activity in the hippocampus, and the animals learn the location of these places. When they go to sleep, the hippocampus replays the same patterns, and we think that what is happening then is, during sleep, the information then comes out of the hippocampus and goes to the cerebral cortex, which is where we are more likely to store long-term memories. The take-home message from this is, it is very important to sleep, because you are going to learn a lot better if you have a good sleep.

Dr. Biology: Wow! Now I didn't know that! That's pretty cool. Let's talk about the brain a little bit more. There's a common perception that once you are born, the number of brain neurons only decreases as you grow older. However, this turns out not to be true. Can you clue us in on what is really happening?

Miles: Well this is the area that we call the study of "adult neurogenesis." First of all, this field did not exist ten years ago, so for about 100 years we thought, on the basis of some very good information, that you were right, that we have all of the neurons that we are going to have by the time we are young, and then all that happens is that neurons die, that there are no more neurons for you. In the last ten years, maybe 15 years, though, neuroscientists have come to agree that there is a limited amount of production of new neurons in adult brains. We call this "adult neurogenesis, " the genesis of new neurons, birth of new neurons.

Interestingly, it only occurs in two places--in mammalian brains, at least--one is the hippocampus, and one is the olfactory vault. So you can imagine the amount of excitement that has been generated. Here we have the hippocampus, an area that we think is so important for learning and memory, and maybe the major target for stress hormones in the brain, and yet here is an area that does produce new neurons throughout life. And you know what? That process is very sensitive to stressors. So cortisol regulates the rate at which we produce new neurons in the hippocampus.

Dr. Biology: Wow. With all this talk of neurogenesis, maybe there's hope that as I grow older I'll be able to still stay sharp, or is there a change in the ability to regenerate cells as I get older?

Miles: Well, it looks like the rate of neurogenesis is going to decrease with age. So far we haven't been able to alter that, and I have to say, so far we don't really know what it means that we are producing new neurons. It sounds like it should be a good thing, and there are a lot of neuroscientists trying to figure out what, exactly, this adult neurogenesis does for us. It does seem to decline with aging, but you know what? This is just like, when we get old we still have to remember the things that our parents told us, because a good diet and exercise and sleep seem to be good for keeping up the rate of neurogenesis. We even know something about the molecules that are involved.

Dr. Biology: Let me ask you this--we're going to switch over. We talked about, at the beginning of the show, about a particular kind of animal, a very vocal animal. You have been working with bullfrogs, and you have been studying their brains, and you are also dealing with neurogenesis. I would like to know, what have you learned from these rather vocal animals?

Miles: They are vocal animals, indeed. I remember the first time I heard a bullfrog as an adult. I was not familiar with these frogs. I knew tree frogs and other little frogs, but I heard this sound, it sounded like a cow from Mars had landed in the swamp. So hopefully you can play some sounds of some bullfrogs.

Dr. Biology: Actually, we do. We have one. Matter of fact, let's just take a moment out now, and we'll listen to an adult bullfrog, and then we'll come right back.

Miles: OK.

[audio of adult bullfrog]

Dr. Biology: OK, so now that we got to listen to that amazing sound, so this is coming from a bullfrog. What have we learned?

Miles: OK, well we study bullfrogs because we are interested in understanding what stress does to the brain, and it's a very complicated process. So our approach, at least in part, is to use an animal that has a simpler brain and simpler behaviors. So this calling behavior we've heard [makes bullfrog sound]--well that was a bad one...

Dr. Biology: That was good, actually.

Miles: This calling behavior is one of the primary things that male bullfrogs do, and this call is intended to announce to other males that, "This is my territory. You let me have this space, " and to attract females. And so a lot of bullfrog behavior is centered around that simple activity. They feed, and they are very good at escaping predators--very hard to catch a bullfrog--but these are relatively simple behaviors compared to working with, say, a mammal like a rat.

So we looked at a simpler brain, these bullfrog brains. What we saw, in terms of adult neurogenesis, is that there is a lot more neurogenesis occurring in bullfrog brains than in the rat brains that people have done most of their studies on. In the bullfrog brain we see neurogenesis in an area we call the "medial pallium, " which is pretty much a hippocampus for a bullfrog, I think we can say that; but we also see neurogenesis in the hypothalamus.

What we think is that there is a change in the rate of neurogenesis that occurs in these frog brains, and it occurs seasonally, because the frogs' behavior changes from season to season. Seasons are very important in the life of a frog. So what we think is that there are new neurons produced on a seasonal basis that allow the bullfrog to engage in calling behavior and mating behavior. So that's one of the main hypotheses that we are testing, that in bullfrogs there is a simple role for adult neurogenesis, and that is to replenish these

special neurons that produce hormones that are involved in the simple, seasonal, reproductive-related behavior.

Dr. Biology: So frogs exhibit neurogenesis. Other animals?

Miles: Yes. Well, we now know that there is lifelong neurogenesis in every species that has been looked at.

Dr. Biology: Very impressive. So, birds and bees and...

Miles: Birds also have a very seasonal type of neurogenesis. We think it's related to the ability of some birds to relearn their song every year. Some birds get to be better singers on a seasonal basis, and a lot of birds sort of forget their song from year to year, and each year they relearn their song, and we think that the production of new neurons in the adult is involved in this relearning the song.

Dr. Biology: Hmm. By the way, how do you catch a bullfrog?

Miles: Well, you catch a bullfrog by getting the graduate students out there with the quickest hands. Bullfrogs, you know, in the West at least, are an invasive species. That means that someone introduced them here; they don't really belong here. But they are very successful here, and one reason is because they are very difficult to catch. We go out at night, because the best way to find a bullfrog is to listen for it, that very distinctive sound. We only hear that during the breeding season, and mostly you hear it at night. So we go out at night, we walk along the banks of a pond or we get out in our little inflatable raft, we use fisherman's dip nets or we catch them by hand, and it's not simple. Takes a lot of practice, but you have to get in there very quickly, before that bullfrog jumps away--boing!--and you hear the splash, and a bullfrog is gone. That's most of our encounters with the bullfrog, we hear the little "boink!" and a splash of the water and that bullfrog is gone.

Dr. Biology: Now, do you use a flashlight to see their eyes?

Miles: Oh yeah, this is sort of fun. We go out with headlamps. It looks kind of mysterious, especially when we have people probing along the banks of the ponds, and other people out in the inflatable rafts. Everybody has their headlights on, and you see these lights along the banks; and some of them are spiders, which takes a while to get used to. I didn't know that spiders had such bright, a lot of green eyes. But then we see these big bullfrog eyes, and that's how we see them. At night, listen for the calls and then locate them under the headlamps.

Dr. Biology: I can just imagine it looks like a science fiction scene out of some movie, with you going along with these headlamps on there, and seeing these bright green eyes, well they're the bright eyes of the bullfrogs. But in this case instead of an alien it's actually a bullfrog, which in this case IS an alien when you are talking about being invasive, which is a very important point because these frogs were introduced, which basically means they didn't belong there, they didn't start in that particular environment; and once they are introduced they often displace or make it very difficult for local

animals to survive. In some cases they actually eat the animals there, or they consume all the available resources and so the animals that typically would be there are no longer able to live there.

This is really important when you have a food web. If you start introducing these species that are so good at this, you can have devastating effects. For example, on the island of Guam there was a brown tree snake that got introduced, probably by some shipping that came in, and it eradicated every single bird species on the island. There are no birds on the island of Guam.

Miles: Yes, it's true, and there are a number of frog species that have been threatened because of the bullfrogs, and there are also some fish species that have been endangered, because these bullfrogs can take a lot of food in.

Dr. Biology: To finish up, Miles, I just would like to ask you what I typically ask every scientist that comes on here. There are three questions. The first one is, when did you know that you wanted to be a scientist or a biologist?

Miles: Well, I'll bet I give you one of the more unusual answers you get, because I was 35 years old before I started studying science. So I have an undergraduate degree in history and philosophy; and I was never particularly interested in science when I was younger. I just didn't like the way it was taught, I didn't like the way that science labs smelled, and it was only when I came to appreciate how powerful lab studies can be that I became interested.

So I was really interested in understanding behavior--that's why I studied history and philosophy, to understand human behavior--and I was interested in animal behavior, but what really interested me was when I took a course in physiology. In that course we got to understand something about how hormones work, those little signaling molecules that we've talked about, and how important they can be, interacting with brain cells to produce changes in behavior; and that really hooked me, and I have been fascinated with that topic ever since.

Dr. Biology: Actually, if you got into science when you were 35, I bet you had some interesting jobs along the way.

Miles: Oh, I've had some interesting jobs. I have had some less-than-interesting jobs. But let's see... one time I worked in an all-night factory, where we packaged fruit for gift baskets. Work started at 11:00 and continued all night, and that was not particularly good for our sleep rhythms. I also had a job working as a blood-gas technician in an intensive care nursery. This was actually one of the most satisfying jobs I've ever had, because we were on call to help the doctors determine how well these babies were doing, many of which were premature, born too early, others had heart problems. This was also a job that tended to go all night long, so it's not another one I would really recommend, but it was

very satisfying. I had jobs in the restaurant business, and I did a lot of outdoor work like painting and renovation work. So I've done a lot.

Dr. Biology: But you found your niche. Well, I'm going to take that away from you right now, and I'm going to ask you, if you were not a biologist, what would you be?

Miles: If I were not a biologist? Hmmm. Well, I think I would like to be a writer. I think I would like to be a writer. My wife is a writer, and I really appreciate the opportunity to be able to put down thoughts and have an audience for them, so I think I'd like to be a writer of some sort.

Dr. Biology: Fiction or non-fiction?

Miles: I think I would probably do non-fiction. I think if I could do anything, I'd be a columnist for the New York Times.

Dr. Biology: OK. What advice would you have for the--let's put it, for you--the "new to science" scientist, rather than just saying the young scientist, because here at 35, you're the perfect role model for shifting gears and going into a science career.

Miles: There's something to that, and I have often found that returning students, older students, do very well when they come to graduate school. I think one of the greatest things about science is, it's OK to make a mistake. If you're in business and you make a mistake, you have lost a lot of money and you have ruined a lot of things, probably. But in science we learn a lot from making mistakes. In fact, that's really how we make progress, is by disproving hypotheses. So we do experiments to determine whether our hypothesis is correct or incorrect, and it's a lot easier to determine when one is just not quite right, when we need to modify our hypothesis. So I think it is really important to enjoy the fact that it's OK to be wrong in science; you just need to keep plugging away.

And I think the other thing is, I would encourage everyone at all ages that are interested in science, not to become too specialized, to try and be able to appreciate your research questions in a larger context and stay open to the interesting things that other scientists and non-scientists are discovering.

Dr. Biology: Well Miles Miles, I want to thank you for visiting with us today.

Miles: It's my pleasure. Thank you, Dr. Biology, I appreciate your service to the community.

Dr. Biology: Well this is a very fun show, and every week or every couple of weeks I get to learn more and more from all the different biologists. You have been listening to Ask-A-Biologist, and my guest has been Professor Miles Miles from the ASU School of Life Sciences.

The Ask-A-Biologist podcast is produced on the campus of Arizona State University, and even though our program is not broadcast live, you can still send us your questions about

biology using our companion web site. The address is AskABiologist.asu.edu, or you can just Google the words "Ask A Biologist." I am Dr. Biology. That's it. [Frog noise] Yeah, yeah, we'll put those in there.

Miles: That was a better one.