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## Fight or Flight: Understanding Our Body's Response to Adrenaline

Dr. McDonough:

It's called the fight-or-flight response. Actually, it goes way back to caveman days when we were out there trying to catch the saber-toothed tiger, got a little adrenaline and we ran off and we were running for our lives, or we had a choice to fight.

Hi, I'm Dr. Brian McDonough. Welcome to Primary Care Today on ReachMD, and we're going to talk about the fight-or-flight response, the physiological effect on the body, what it means to our patients. And I'm really happy to have with me Dr. Partha Dutta. Dr. Dutta, thank you so much for joining us on the program. Tell me a little bit about your work and the entire fight-or-flight response and how it impacts white cells and also its impact on heart attack and that risk in people.

Dr. Dutta:

Yes, thank you very much for inviting me for this interview. The work is focused on understanding how our body responds and our immune system responds to adrenaline and to sympathetic activation, so what we actually found in our study was that there is a subset of leukocytes, or white blood cells, and they can produce catecholamines and mainly norepinephrine, and that's what causes fight or flight response. And as you know, the catecholamines are mainly produced by the sympathetic nervous system and also the adrenal glands, but what we found was a subset of leukocytes can also produce the catecholamines, and that was the most surprising part of the study. And besides that, we found that these catecholamines produced by leukocytes can actually activate the progenitors of leukocytes called myeloid cells, to say it correctly, because myeloid cells is a subset of leukocytes. And these myeloid cells are important for increasing atherosclerosis in diabetic patients, so that is the main finding of our paper.

Dr. McDonough:

You know, when I think about it as a clinician—and I'm sure you look at it this way as well—I think about how, okay, this was a really great physiologic response back when we were running from saber-toothed tigers and those things, but a lot of times I feel stressed during the day when I find out that we might be denied permission to perform a procedure or my patient can't get this or that, and then I get stressed out about it. I really have no way to relieve that stress, and I get frustrated, and I think we see that day after day in our lives. Is this a reaction that at one time was great for us that is becoming more and more problematic, and how do we deal with it?

Dr. Dutta:

Yes, exactly. So I think that it initially was beneficial for us because we could avoid danger using this response, but too much of this response of the chronic sympathetic activation is definitely not good for our health, and that has been shown by different studies even in myocardial infarction. Chronic sympathetic activation or sudden even sympathetic activation can cause myocardial infarction. And also, it's not known until now that it can also increase inflammation. So that's what we have shown, that this chronic sympathetic activation can actually trigger progenitor proliferation, progenitor myeloid cell proliferation, and they can differentiate into inflammatory myeloid cells, and these inflammatory myeloid cells can do a variety of bad things, including they can rupture plaques, they can increase insulin. We understand that they can even impair with healing of an organ. To some extent they are good—they can fight infection, of course—but too many of inflammatory myeloid cells is not definitely good.

Dr. McDonough:

What can we do about it? I mean, you've obviously made a great case for the problems associated with it and maybe why we run into trouble and we increase the risk of heart attack, but what can be done besides calming down? Is there anything physiologic, medications, those sorts of things, approaches we can take that you can look at?

Dr. Dutta:

The ideal will be to reduce activation of the sympathetic nervous system. So there are several ways that we can do that. One of them

will be regular exercise. Regular exercise, that's one way we can suppress sympathetic activation. The other way, as you said, that medication might also be other way of doing this. One of the findings of our paper is progenitors that I just mentioned, these myeloid progenitors, they express the beta 2 adrenergic receptor, and probably we have not tested that, of course, and we have some data. We have seen that in human, in even diabetic patients who are on nonselective beta blockers—for example, carvedilol that is specifically for both for beta 1 and beta 2, they have less inflammation compared to the patients who are only on selective beta 1 blockers, like metoprolol, so that might be one of the studies. I mean, even though we did not have many patients—we had, I think, 20 to 30 patients in each group—but this study was mainly mechanistic, so we have not done a lot of patient studies yet, but that might be one of the angles how we can reduce inflammation by suppressing sympathetic activation.

Dr. McDonough:

So you're looking at those sorts of things. Tell me a little bit about how you approach research and why you were interested in this. What was it that kind of got you excited about doing this research?

Dr. Dutta:

So the main reason that we did this research is to understand inflammation in diabetic patients, because it's well-known for several decades that diabetic patients have high inflammation; they have high white blood cell counts in their blood; they have higher TPRs; they have higher number of inflammatory monocytes and higher amount of inflammatory cytokines like chemokines and interleukin 1 beta—for example, that's one of the cytokines that has been shown to be involved in cardiovascular disease. So we wanted to understand the mechanisms by which these inflammatory cells are generated in diabetic patients, so that was the main reason why we did this project. And surprisingly, what we found was we were looking for source of catecholamines, and we found that the active sympathetic nervous system is the main source of catecholamines and probably they are producing high amounts of catecholamines in diabetic patients, but surprisingly, what we found was that actually in the spleen and also in the bone marrow, the major source of catecholamines is not the sympathetic nervous system but a subset of leukocytes, and that can produce catecholamines and that can trigger inflammatory cell generation.

Dr. McDonough:

That is interesting. So, you were more or less looking at the process, how it's working, what's going on.

By the way, you're listening to Primary Care Today on ReachMD. I'm your host, Dr. Brian McDonough. My guest is Dr. Partha Dutta. We're talking about his work looking at the fight-or-flight response and how it triggers white cells and increases heart attack risk in people with diabetes. When we think of white cells, obviously we think of white cells fighting infection, involved with infection. We look at white cells as being elevated when things are not going so well in the body, those sorts of things, and we also... You're right, when you see people with diabetes or stress, we see that reaction as well. I guess we've known this for years. We've looked at it for years. You're just looking at it a different way.

Dr. Dutta:

Yes, yes, we wanted to know how they are produced. It was already known that, as you said, already known that diabetic patients had higher levels of these white blood cells, inflammatory monocytes, but we wanted to know how they are actually produced, so that was the main aim of the study.

Dr. McDonough:

What do you see as the next step? Like, if you evolved beyond this, what would you be wanting to do?

Dr. Dutta:

There are leads, actually, that we have found, and one of them is these neuropeptide Y receptors, and they are mainly seen in the nervous system, but we found that the cells that express tyrosine hydroxylase, which is an enzyme in catecholamine production, also express neuropeptide Y receptor. So we don't know why they express that and if it has anything to do with higher inflammation, so that will be our next angle. We want to know if inhibiting neuropeptide Y would reduce inflammation in diabetic patients. Another angle will be to take it more comprehensively in diabetic patients, because as I said, we have done this in different mouse models and also we have some diabetic patient data. We did, like, 20 to 30 diabetic patients, but not a large cohort, so probably we need to do clinical trials to see if it is really true in diabetic patients, like that cohort.

Dr. McDonough:

When you look at research like this and you look at the work you're doing, as a primary care physician, we often see the end result. We see the work you've done in the lab, and it teaches us a little more, gives us an approach to treating patients. How much of a connection do you see? Do you ever get to really appreciate the contribution it makes to day-to-day care of patients?

Dr. Dutta:

Yes, yes, so that was my research, of course, has value. We are identifying a process, a mechanism, and then the next step will be to look in-depth; and as I said, that next step will also be to look if it can work in larger patient cohort, so definitely it has value, and particularly the kind of research is that we do nowadays where we look at how a patient can be benefitted from the research. For example, in this case, as I told you, that if we could develop a specific beta 2 blocker and if we can put diabetic patients on a beta 2 blocker, probably they will get benefit by reducing inflammation.

Dr. McDonough:

So, really, that's where you see the connection. You're looking at somebody with diabetes, and then you're trying to say, "Okay, what do we do as far as inflammation?" You bring up a good point. And I'm probably talking about, oh my gosh, 15 years or so ago I interviewed—and you may know him—a Dr. Dan Rader, who's at Penn, and Dr. Rader, all he did was talk about the role of inflammation in the heart and why we were at that time underestimating the role of inflammation. I think you're getting to the same thing. We don't always look at it, but my gosh, it is really important.

Dr. Dutta:

Yes, it is, actually. As you know, the main cause of mortality in diabetic patients is cardiovascular disease, like myocardial infarction and atherosclerosis. And there is a big trial where they showed that inflammation is one of the main culprits of plaque rupture and recurrent myocardial infarction in patients who already had myocardial infarction, so we need to understand better how these inflammatory cells are generated and how these patients have more inflammation; then only we'll be able to reduce inflammation.

Dr. McDonough:

I want to thank you. I really appreciate it. Dr. Partha Dutta, I want to thank you for joining us on Primary Care Today on ReachMD. I appreciate your time and also your insight. Thanks for taking the time to join us.

Dr. Dutta:

Thank you very much for your time and for this interview.

Dr. McDonough:

This is Dr. Brian McDonough. If you missed any of this discussion, please visit [ReachMD.com/PrimaryCareToday](https://ReachMD.com/PrimaryCareToday). You can download the podcast. You can learn more about the series. Thank you for listening and Being a Part of the Knowledge.