The Chronic(les) of Pain Research
Pain in the Brain – Part II

MYSTERY NARRATOR: (0:00)
Previously, on Pain in the Brain…

(Gra Hovedvei)

DR. ALLAN BASBAUM: (00:03)
…The bane of pain is plainly in the brain. It's a *percept*. That's the most important thing. It's not a stimulus; it's a complex perception.

RYAN: (00:11)
I learned about 4 types of pain: neuropathic, migraine, inflammatory, and cancer. What was really interesting was to hear how these can all morph from acute pain, which is helpful, to chronic, debilitating situations.

DR. ISHMAIL ABDUS-SABOOR: (00:28)
Chronic pain is pain that outlasts the healing period – it's months, you know, years after. So, there's no more injury or damage, but you're still in pain.

KYANNA: (00:39)
I had no idea how to function in the world, living in pain every single day.

DR. BASBAUM: (00:44)
The problem with pain, as opposed to most diseases – you can't see it.

MARILYN: (00:48)
There are so many types of pain and they are all complicated…but, what can we *do* about pain?

(CTOR tag)

MARILYN: (01:11)
Hi, I'm Marilyn —

RYAN: (01:12)
— And I'm Ryan.

MARILYN: (01:14)
Welcome to part 2 of the Pain in the Brain series! We will be sharing insights from our experts again, Dr. Allan Basbaum, here at UCSF, and Dr. Ishmail Abdus-Saboor, at the University of Pennsylvania, both of whom you just heard in the recap.

RYAN: (01:30)
In this episode, we'll be talking about how standard and newer treatments for pain work; how the placebo effect can sometimes actually relieve pain and why that makes discovering new drugs

more complicated; and how our guests' cutting-edge animal research can lead to new drug development.

(Taoudella)

MARILYN: (01:56)
I'm sure episode 1 got you thinking about the last time you were in pain. What did you do? Did you grab an ibuprofen pill from the medicine cabinet?

RYAN: (02:05)
Yeah, I always keep some Advil handy just in case, but never really gave it a second thought. Why do we even need pain? Can't we just find some miracle drug that makes all pain go away?

DR. BASBAUM: (02:16)
The *last* thing you want to do is eliminate all experience of pain. There are individuals, uh, who have congenital insensitivity to pain: they *never* experience pain. That's a disastrous condition. Uh, it turns out many of them have a loss of function of, of a channel, so-called $Na_V1.7$ channel. It's a voltage-gated sodium channel that is normally involved in conduction of information. We know those channels are necessary to conduct information by nerves. If they're missing this one channel, they never experience pain. These individuals were described originally in a Pakistani family of kids who, who would cut themselves and jump off bridges to break a leg.

Uh, it sounds great, but it's terrible. Because acute pain is a warning signal, tells you something's wrong. If you have an $Na_V1.7$ loss-of-function mutation, and then get appendicitis, you'd never know it and you would die. Uh, so the question is, can you develop a drug that will target that, but not shut everything off and control pain?

MARILYN: (03:21)
So, the short answer to your question is: No. We actually need pain as an indicator to keep us safe. But of course, sometimes, we feel *too* much pain even when we know there is no immediate harm. In this episode, we're going to learn all about some treatment options for different types of pain, how they can be improved, and what we can look forward to in the realm of pain research as scientists identify new, better ways to treat pain.

(Color Country)

MARILYN: (03:53)
Because pain is a percept, there are many ways to treat it: some people use psychotherapy or hypnosis, while other times pain is treated by turning off certain neurons with drugs. These drugs may act on many different parts of the nervous system, or reduce the inflammation associated with pain.

DR. BASBAUM: (04:11)
So there's many different ways to treat pain. It's kind of like, if you think of depression, the data's pretty clear that antidepressants are very effective in many patients. Um, psychotherapy is very effective and apparently equally effective, but drugs work a lot faster.

MARILYN: (04:29)
However, one thing to keep in mind is that not all types of injuries respond to drugs the same way.

RYAN: (04:35)
That makes sense. In the last episode, we learned about the main categories of pain: inflammatory pain, which comes from the immune response to tissue injury, neuropathic pain, which results from damage to the nerves themselves, cancer pain, and migraine.

MARILYN: (04:49)
That's right. We're going to talk about different treatments for these types of pain, some of which you might be familiar with, and some of which are brand new. Let's start with the classic treatments for inflammatory pain:

DR. BASBAUM: (05:02)
And that is actually usually responsive to ibuprofen-type drugs—anti-inflammatory drugs—and opiates can work on that.

RYAN: (05:10)
Yeah that was one of the types of pain we talked about in the last episode — tissue injury and inflammatory pain, like when you sprain an ankle. So how do drugs like ibuprofen work?

DR. BASBAUM: (05:20)
How aspirin works, how ibuprofen works, very straightforward. You know, it blocks an enzyme when you have a sore elbow, and that's how you get relief.

MARILYN: (05:30)
The enzyme that Dr. Basbaum is referring to is a protein in your body called cyclooxygenase. Aspirin and ibuprofen inhibit this enzyme from producing the molecules that lead to swelling and pain.

RYAN: (05:41)
Oh okay, then the injured site will not be inflamed.

MARILYN: (05:44)
Right. And that's why aspirin and ibuprofen are known as NSAIDs: Non-Steroidal Anti-Inflammatory Drugs. You may also know these as Motrin, Advil and Aleve.

RYAN: (05:56)
Ah, I never knew how those drugs worked. But all these medicines are over-the-counter, so I imagine they have their limits. What happens if you have surgery or a really big injury?

MARILYN: (06:06)
Then you'll be given a long-relied-upon pain treatment medicine — an opioid. For example, one of the most commonly prescribed pain medications is morphine, which is a natural opioid.

RYAN: (06:18)
Yeah, aren't opioids found in poppy seeds? How do they actually work?

MARILYN: (06:23)
Yeah, the poppy plant has been cultivated for its effects of its resin for over five thousand years. Extracts from the plant, and synthetic versions of opioids developed in the past two centuries, decrease pain by dampening the transmissions of pain signals from your nerves to your brain. While these drugs can be highly effective, they come with unwanted side effects, as our guests can explain. First, Dr. Abdus-Saboor:

DR. ABDUS-SABOOR: (06:48)
So, so for sure – if you look in the pain field, you know, we're still using centuries-old medications to treat pain, like opioids. They've been around for thousands of years and we know they're really good at acute pain; for chronic pain, the jury is still out. But as you know, opioids have lots of unwanted side effects and abuse potential. So, we have a really dire need to move away from opioids to find other ways to treat chronic pain.

RYAN: (07:20)
What types of side effects are there for morphine?

DR. BASBAUM: (07:22)
Uh, morphine is a great drug, but it has *unbelievable* side effects: constipation, can cause dependence, and in a certain dose, it'll shut off your respiration and it'll kill you.

RYAN: (07:34)
Oh man, that sounds pretty serious. But why do these side effects occur?

MARILYN: (07:39)
Dr. Basbaum has a good story about that. He was giving a lecture one day to the public ….

DR. BASBAUM: (07:45)
And a gentleman put his hand up and said, "I think, I think I have a dumb question," but I said, "there's no dumb questions – what is it?" And he said, "how does the ibuprofen know where to go?" I said, "That's brilliant. The ibuprofen has no idea where to go."

And now you know why you have side effects, and this is the problem with most, almost all drugs, whether it's opiates or in any drug you take, doesn't know where to go. Uh, and it's what we call *therapeutic window*. Can you find a dose that will give you a great effect if it's pain relief (if that's what you want) and less side effects?

RYAN: (08:22)
Just to make sure I have this right — the drugs we currently use to treat tissue injury and inflammatory pain work pretty well — BUT — they also are pretty non-specific, in that they can have lots of side effects?

MARILYN: (08:33)
Yeah, that's a good way to think about it. And these side effects result because of the same part of our biology that the drug uses to prevent pain, can be found elsewhere in the body. That's why aspirin can be used to thin your blood, because that enzyme, cyclooxygenase, that it targets, also produces proteins for your blood cells. And that's why opioids can get you high: opioid receptors are found in the pain pathway and in the "pleasure" parts of your brain.

RYAN: (09:00)
Got it. But what about other types of pain we talked about in the last episode? Neuropathic pain, which is caused by direct injury to the nervous system, seemed to be a lot different. Can we treat that with NSAIDs and opioids?

DR. BASBAUM: (09:11)
Opiates are not effective, ibuprofen is not effective, NSAIDs are not effective. So neuropathic pains, the first line therapy are called the gabapentinoids. It's an anti-convulsant.

MARILYN: (09:24)
Anti-convulsants are most commonly used to treat epilepsy. Epilepsy, like chronic pain, results from an over-activation of the nervous system. Dr. Basbaum went on to explain how effective the gabapentinoid treatment is:

DR. BASBAUM: (09:38)
Unfortunately, the numbers say that *maybe* it's 30% effective in 30% of patients, maybe up to 50% effective, but that means that most patients are not helped.

RYAN: (09:52)
Those numbers aren't great. Is there anything else doctors can do to help these patients?

MARILYN: (09:58)
Dr. Basbaum listed a bunch of treatment options, like antidepressants or stimulators in the spinal cord, but unfortunately those don't always work either, and when they do relieve neuropathic pain, it's not yet clear how.

RYAN: (10:12)
Seems like the pain field could do with some new discoveries…. Which reminds me, didn't you say in the last episode that another type of pain, migraine, has a new treatment?

MARILYN: (10:21)
Yeah! That was one of two great examples our guests mentioned for how recent research into pain biology has been yielding some promising new treatments. Here's Dr. Abdus-Saboor talking about pain research and its benefits:

DR. ABDUS-SABOOR: (10:35)
A really nice example is in the case of long-term facial pain in the form of migraine. Migraine headache is a chronic pain disorder. Um, and the field has, now in the market, arguably the best migraine drugs ever developed, blocking this neural peptide called CGRP.

MARILYN: (10:57)
In the last episode, we talked a little bit about CGRP, or “calcitonin gene-related peptide.”

RYAN: (11:04)
Oh yeah, I learned in the last episode that CGRP is an inflammatory molecule. It causes blood vessels to dilate, or get wider. When there’s too much CGRP around, the blood vessels over your brain can dilate and push on your nerves, causing you to get a migraine.

MARILYN: (11:19)
Right, but it’s also important to know that CGRP has receptors inside the brain, too. Those aren’t the ones we want to target when treating migraine.

RYAN: (11:29)
So how can we get rid of all the extra CGRP around the blood vessels, without affecting the other functions of CGRP?

DR. BASBAUM: (11:36)
And the approach to treatment, the new revolutionary approach, is antibodies against CGRP that basically scavenge all the CGRP. The beauty of it is that the antibodies are big. They can't get into the brain so that they don't block CGRP at some other site in the brain.

MARILYN: (11:52)
Okay, let’s break this down: the antibodies attach to CGRP, then the immune system removes the antibody… along with the bound CGRP. Importantly, because of their large size, antibodies can’t get into the brain, which means they’ll only bind the pesky CGRP that’s associated with blood vessels, which cause migraine.

RYAN: (12:14)
So, because the antibodies don’t go into the brain, there are less side effects. That’s really cool! So, no more migraines for anyone, right?

MARILYN: (12:22)
Well, not so fast…

DR. BASBAUM: (12:25)
They *are* effective, they are not gonna work for everybody. What is exciting about it is that they're not only effective in blocking a migraine, which can ruin a person, um, but it does seem to be somewhat prophylactic. It can reduce the – some people have 15 migraines a month. Um, there’s really nothing that a patient can take to *prevent* getting lots of migraines. So, is it perfect? No, nothing's perfect, but it's, it's gonna make a difference.

RYAN: (12:54)
Being able to prevent migraines before they even start sounds awesome to me — go science!

(Color Country)

MARILYN: (13:07)
Dr. Basbaum offered another recent example of science like this impacting treatment options – this time for people with osteoarthritis, which is loss of the cushioning cartilage within joints:

DR. BASBAUM: (13:18)
On the horizon for, uh, inflammatory pain, particularly osteoarthritis—and I expect this will be approved within a year, a year and a half—are antibodies to nerve growth factor. Now, nerve growth factor, as you probably know, is an essential factor – protein – during development. But in the adult, it turns out NGF is one of the products released in the setting of inflammation and it actually causes pain. It's a pain producing molecule.

Antibodies to NGF seem to be— well, the data is looking pretty good. There've been several phase three trials now in osteoarthritis—can be dramatically effective, reducing pain by more than 50% compared to placebo. That's – could be one of the biggest replacements for opiates, uh, in patients with osteoarthritis because that's what many patients turn to, uh, when nothing is effective.

RYAN: (14:14)
So, the extra NGF in these patient's joints will be broken down instead of causing pain? It sounds like the antibodies to CGRP for migraine, except now we're targeting NGFs instead.

MARILYN: (14:25)
Sure does. And osteoarthritis may just be the start. Clinical trials for antibodies to NGF to treat other types of pain conditions have also begun. But, of course, we'll have to wait to see how effective and safe these actually are, especially compared to placebo. A placebo is something that is known to *not* have any therapeutic effect, like a sugar pill. As we'll soon learn, this comparison is really important….

(Taoudella)

RYAN: (15:03)
Why is it so important to compare the efficacy of new pain drugs to a placebo treatment?

MARILYN: (15:08)
We asked Dr. Basbaum this very question, and he had a really interesting answer that shed some light on the biological basis of pain perception.

DR. BASBAUM: (15:16)
Placebos are very effective. That's one of the other problems in coming up with new drugs is, placebos work, right? And your drug better, your treatment better be better than a placebo.

RYAN: (15:26)
So, placebos act as a control group to compare the active drugs to. But Dr. Basbaum just said they worked — why's that? Aren't they *not* supposed to do anything?

DR. BASBAUM: (15:37)
Um, if I come up to a human who you're treating and nothing's worked. And I say, “look, you know, I just heard about this new drug. I'm really excited about it. I've heard from my colleagues. It really is showing dramatic effects. I'd like to try it. Uh, really, I think we have a good opportunity.” I am adding a *huge* placebo component to that. I'm saying I have confidence; I think there's a good thing. The patient becomes a believer. That's going to help, all right? And if I give them just placebo alone, that will work in a large number of patients, and it'll last for a while, eventually stop working. Placebos work. Okay?

Then there's something called the “no-cebo”, alright? If I, now you're my patient. I say, “Look, you know, I've been working with you for so long. We've tried everything, nothing. Somebody told me about this stuff, to be honest, I don't think it's going to do you any good, but what the hell? We don't know what to do. So, so here give it a try. I'm not very confident, but come back in a month, we'll see what happens.” Same drug, different message. I can make your pain worse with my drug by giving you the wrong message. So, this is what I mean, there's a powerful cognitive component to the experience of pain.

RYAN: (16:47)
You mean how hopeful you feel about the drug or treatment you’re getting can actually affect how well it works?

MARILYN: (16:53)
To quote Dr. Basbaum from our previous episode, “the Bane of Pain is plainly in the Brain”. It’s our brain that ultimately encodes the signals from our experience and tells us what we’re feeling is pain. That’s why your emotional outlook on the treatment affects how well it “works”.

RYAN: (17:11)
So, for those new drugs we talked about earlier – the antibody treatments for migraine and osteoarthritis — it must have been really important to present all the patients in the trials with the drug, or the placebo, in exactly the same way.

MARILYN: (17:25)
Yeah, Dr. Basbaum talked about how a large positive response from a placebo can make it really hard to know if a drug is working.

DR. BASBAUM: (17:32)
And because placebos work, you do a trial of, maybe a phase two trial, maybe a hundred people against placebo and you just may get bad luck. And then you get a 50% placebo response. All of a sudden drug failed, company says, [*whistles*] “that's it, we're not studying this anymore.” They're not going to put another 10 million or a hundred million dollars into it, yet the drug might actually have been okay.

RYAN: (17:56)
Okay, the placebo effect certainly seems like a big complicating factor in drug discovery. But can we leverage placebos, or at least use them to understand biology?

DR. BASBAUM: (18:08)
We know quite a bit about the biology of the placebo. Placebo analgesia is actually blocked by Naloxone, the opiate antagonist. Okay? And therefore, it engages pain circuits. Naloxone kicks the drug off the opioid receptor.

RYAN: (18:23)
I see, so placebos interact with the same pathways that opioids do to relieve pain. That's why it can be so hard to find a drug that is actually *more effective* than a placebo.

MARILYN: (18:31)
Right – significantly changing the way that someone is thinking about their situation can make a big difference for pain. One way to do this is to trick someone by giving them a fake pill, but there are also non-drug forms of therapy that leverage the cognitive aspect of pain.

There is actually a push to implement this in the clinic by supplementing medications with cognitive behavioral therapy. For example, at UCSF's pain management center, psychologists work with chronic pain patients to develop coping skills and resilience, which can be very effective at reducing pain.

RYAN: (19:05)
Just to be clear, we're not saying that therapy is the cure to chronic pain, or that therapy is a kind of placebo. Our goal is to introduce you, the listener, to the types of treatments that exist and are being developed.

MARILYN: (19:17)
While we mostly focus on drug treatments in this episode, we did want to acknowledge that therapy and alternative treatments exist and are effective for some patients. We released an episode all about homeopathy and complementary alternative medicine back in September—we'll link it in the show notes if you want to check it out.

RYAN: (19:35)
Getting back to *placebos*… how do they compare to alternative treatments for pain?

DR. BASBAUM: (19:41)
So the jury is still out, uh, and placebos are a barrier, but we can talk about things like acupuncture, um, a variety of other things. I happen to think that acupuncture is an exotic placebo. Um, other people disagree completely with me. Uh, it, I, I'm absolutely a hundred percent certain that it doesn't matter where you put the needles. When they've done studies where they use different, uh, uh, points on the Meridia, it doesn't really make a difference. I certainly don't see it as anything beyond a placebo. And there's always a med student in the audience who has been a former acupuncturist and they give me a hard time and I'm used to it.

RYAN: (20:23)
Dr. Basbaum isn't necessarily excluding considering non-drug therapies as methods of relief: as he even said: placebos often work, but the effects will just wear off over time. At the end of the day, we still need to find new ways to treat pain.

MARILYN: (20:39)
And we'll get into that by talking about the state of the pain research field. But first, let's recap what we've learned so far.

RYAN: (20:46)
All right, well, we learned how anti-inflammatory drugs work for inflammatory and tissue pain, but how those same drugs don't work for neuropathic pain. Instead, neuropathic pain is often treated with drugs like gabapentinoids. We also talked about some pretty cool new, targeted treatments for specific types of pain. Both of them use antibodies: CGRP antibodies for migraine and NGF antibodies for osteoarthritis.

MARILYN: (21:13)
Also, there are a ton of drugs for acute pain, but not as many good options if you have a chronic condition: you don't want to be popping pills with potential side effects for your whole life. Plus, for new drugs, your brain's natural optimism makes it hard to prove that they're more effective than a fake pill.

(Taoudella)

RYAN: (21:42)
It sounds like there are so many barriers to treating and studying pain. I don't want to be a downer, but how do we expect to do that when we don't even have a very reliable way of measuring pain?

MARILYN: (21:53)
Right, it's definitely a huge problem. But, you know, we've spent all this time so far talking about pain in *humans.* We need to start talking about animal models.

RYAN: (22:03)
Yeah, because we don't just start testing on humans right? [*muahaha*]

MARILYN: (22:08)
Both of our guests today use mice in their research.

DR. BASBAUM: (22:11)
The reason why we use mice is because of the ability to generate transgenic models. I'm interested in the genes that code for proteins that are relevant and we can, as you know, generate mice in which a gene is deleted and understand whether that gene works. Well, it's very difficult to do that in anything but a mouse.

RYAN: (22:31)
I understand studying the genetics of pain, but, well, they're mice, right? How useful is that to understanding human pain genetics?

MARILYN: (22:39)

Yeah, that's a really important question in scientific research. You definitely want to keep that in mind when you read pop science articles. Discoveries in animals don't necessarily translate to human medicine. Otherwise, we'd probably have cures for cancer and Alzheimer's Disease by now, right? But human and mouse genomes are actually 85% identical – as mammals, we share a lot of the same genes. So, as a result,

DR. ABDUS-SABOOR: (23:03)
So, we use mice as a model system, uh, for a number of reasons. Their neurocircuits are wired in a very similar fashion as to you and I, same genes, same receptors, et cetera. So, they're awesome models and the tools available to manipulate neurocircuits are incredible.

Throughout this process we've identified inbred mouse lines that have abnormal pain responses. So, we've uncovered behaviors or phenotypes that hadn't been previously reported. We found a strain that's pain hyposensitive, so it responds to painful stimuli as if they were touch. So, it doesn't really care about mechanical pain. And we found another strain that's hypersensitive to pain. So even really soft at baseline, no injury or infection, they respond to every touch as if it was painful.

MARILYN: (23:56)
In the last episode, we talked a little about how pain is influenced by both nature and nurture. For the latter, it's the external environment…

RYAN: (24:05)
Like how you'll respond to a new medication based on how your doctor introduces it to you…

MARILYN: (24:10)
Right, and the nature side, well, that's genetics.

RYAN: (24:14)
Like those people missing the $Na_V1.7$ gene that Dr. Basbaum told us about earlier in the episode. They don't feel pain at all.

MARILYN: (24:21)
So, what Dr. Abdus-Saboor is describing here is that different lab mouse strains actually react to noxious stimuli differently. It's not necessarily as dramatic as *not* feeling pain at all, but certain strains are more sensitive while others are less.

RYAN: (24:36)
And that's just like people, right? I mean, everyone has different pain thresholds, so maybe we could understand why that happens if we understood the underlying genetics of these mouse strains. Could that eventually help us personalize treatments for patients?

MARILYN: (24:49)
Yeah! So, using genetics to create mouse lines lays the foundation of research – we can almost replicate human conditions in these mice. For example, we can create mouse lines that actually

reflect human traits of being more or less sensitive to pain. But then, what's the next step in research?

Well, we'd need a way to quantify how much pain these animals are in during experiments, to test whether certain genes are involved in pain perception. In the next section, we'll talk about measuring pain through behaviors and brain imaging.

(Color Country)

DR. ABDUS-SABOOR: (25:30)
A fundamental question is, how do you know an animal is even in pain? And that's a starting point for any, like, basic science discoveries. And to make a long story short, the status quo or the more commonly used assays in our field to measure, to determine if an animal is experiencing pain or relief from pain are rather crude and heavily biased.

So, what essentially is performed is that you have a mouse or rat on a raised platform and you apply a sensory stimulus to its paw or toe. And if the animal responds, you just say yes and you sort of record their response frequency. Um, but animals will move their paw to something innocuous versus noxious. So just saying yes or no, the animal did something, it doesn't inform you about its sensory experience, you have to bias yourself and what you think that stimulus is measuring. And then a lot of the stimuli we use in the field, there's no consensus on what they're measuring.

MARILYN: (26:34)
So, we don't know if the animal is moving in pain or just because. That's where a lot of the bias comes in, which can make studying pain and developing treatments all the more difficult. But, with a computer-based *automated* pain scale, everyone can be sure that what they are seeing is consistent.

DR. ABDUS-SABOOR: (26:52)
One of the major projects we have ongoing in the lab is to develop more objective automated tools to measure the mouse's sensory experience. So, we combine, we use highspeed video imaging to record mouse behaviors to get sub-second ethograms of their behavioral responses to innocuous versus noxious stimuli. And it turns out there are, you know, 10 or 15 different behavioral signatures that really define an animal's sensory experience in pain or not in pain.

RYAN: (27:27)
What's an ethogram?

MARILYN: (27:28)
It's a list of all the behaviors that a species can do. So, for mice, it would be things like burrowing, scratching, and moving their paw when they're in pain.

DR. ABDUS-SABOOR: (28:37)
So for example, we know the paw dynamics of the stimulated paw are quite important and really help us define that sensory experience. So, for example, just like you and I, if you withdrew your

paw, your hand from a hot stove, you're going to retract it quickly and shake it and you may look at it and attend to it and do all these defensive-like behaviors. Animals do a lot of those as well. And the nature of the response, how fast they withdraw it, how high they lift it when they withdraw. All these things inform the mouse's sensory state.

So, we use machine and deep learning algorithms or programs to automatically find the paw through thousands of frames of high-speed video imaging and we measure the paw dynamics. So, what you get in the end is what we're calling an automated mouse pain scale.

RYAN: (28:34)
Okay, so with this automated "pain scale", it doesn't even matter that mice can't verbalize how they're feeling. Now, researchers can precisely measure their behavior and reactions to stimuli. That's pretty cool!

MARILYN: (28:46)
Yeah! And Dr. Abdus-Saboor has been using techniques like this to look at all different types of pain. One of the studies in his lab really caught our attention:

DR. ABDUS-SABOOR: (28:56)
So again, we're using mice, then the question becomes how do you know a mouse has tooth ache? [*Interviewer: Yeah*] So we had to start again by establishing the behaviors. So, we can do a surgical manipulation to induce tooth injury in a mouse. And then we came up with three different behavior readouts to determine the state. One is just looking at the animal's facial features and we can see grimacing and squinting, changes in their, what they do with their ears, their cheeks, their nose, all these things. They have a "pain face" that we can read out. And we can apply sensory stimuli to the animals like orofacial area and look at how they respond. Animals that have tooth pain have heightened responses.

And we also built this apparatus where the animal has to expose their face to an open environment. And mice are inquisitive, so if you give them the ability to stick their heads out of an apparatus, they will. [*Interviewer: Mhm.*] When they stick their heads out, we stimulate their facial area. Mice that have tooth pain, they have less of an incentive or motivation to expose their faces because they know they're going to get poked and it hurts. So that's another readout we have to study tooth pain.

RYAN: (30:16)
It sounds like Dr. Abdus-Saboor's behavior tracking can figure out if a mouse's tooth hurts without bringing it to the dentist!

MARILYN: (30:24)
Right! So, first, he's interested in whether the mice are in pain. But second, he is also interested in where that pain is represented within the mouse's brain.

DR. ABDUS-SABOOR: (30:34)
So now that we have these behavioral readouts, we're using that to start to get at, "Okay, what are the sensory neuron types that are driving pain?" We want to begin to record brain activity as an

animal has tooth pain, and maybe we see heightened activity in certain pain-relevant brain areas that could describe this very common clinical phenomenon. Why is tooth pain the worst pain of all – ever? It could just be heightened representations in the brain. So, these are ongoing questions in the lab for sure.

MARILYN: (31:10)
To record brain activity, Dr. Abdus-Saboor's lab uses brain imaging techniques, where you can actually see which cells in the brain are active at any given time. As you'll soon see, this technique is used in many labs that work on pain…

(Country Color)

RYAN: (31:35)
In our last episode, Dr Basbaum *also* emphasized how important brain activity is. This is actually one of his research focuses — measuring brain cell activities associated with pain.

DR. BASBAUM: (31:47)
Um, well, my lab is very eclectic. I spent, uh, years working on spinal cord organization, which we still do, and how information is processed from, from the periphery, from an injury site, for example, and how that information is transmitted to the brain. But I never, I never really studied, until very recently, what's happening in the brain, where pain is actually processed.

RYAN: (32:11)
One of the primary goals here would be to find a pain biomarker, right? Some kind of brain activity signature that could be observed across all patients and correlate with the level of pain they felt. And then researchers could use that biomarker to better study and treat pain conditions?

MARILYN: (32:26)
Eventually, yes. For now, though, Dr. Basbaum – and Dr. Abdus-Saboor – will focus on understanding what parts of the brain are important for the pain experience in general.

DR. BASBAUM: (32:37)
I don't think we're going to find a pain biomarker, but I'm interested in the circuits in the brain that are necessary for the experience of the emotional component or the sensory discriminative component with a view that then I can use that endpoint to perhaps screen drugs.

MARILYN: (32:55)
To record brain activity, Dr. Basbaum's lab uses a technology called calcium imaging. So, neurons communicate using electricity and calcium plays a huge role in this. The calcium levels inside of neurons spike way higher than usual when a neuron fires. How do you get that to *literally* light up the cell so that we scientists can see it under our microscopes? You add a calcium indicator, a molecule that lights up when calcium levels are high, into the cells we want to measure from.

RYAN: (33:23)

Woah, so then whenever one cell talks to another cell in your brain, you can literally watch this in real time?

MARILYN: (33:31)
Yup!

RYAN: (33:32)
How are we able to find these active brain cells in a mouse?

DR. BASBAUM: (33:35)
And every time a neuron fires, you see a calcium flash, camera picks it up, the computer monitors it; the animal's running around, behaving. We can monitor behavior at the same time, correlate activity…We don't just record from random populations. We can say, "I only want to record from a subtype of those inhibitory interneurons that I know are screwed up in an animal with epilepsy or an animal with a certain chronic pain condition." Um, when an animal learns to avoid a particular stimulus, does a certain population of cells turn on.

RYAN: (34:07)
These experiments are really exciting! It's kind of mind-boggling that we can watch, in real time, the neurons that are active as the mouse is behaving a certain way.

MARILYN: (34:16)
And eventually, we can map out where pain is processed and figure out how to target those areas for treatment. If we jump back to tooth pain, Dr Abdus-Saboor is doing exactly that, in collaboration with another UPenn professor, Dr Greg Corder.

DR. ABDUS-SABOOR: (34:31)
And Greg, in his postdoctoral studies, had shown with a series of imaging and really intricate genetic mouse tools that there's a population in the amygdala of the brain that controls the unpleasant response of pain. And we've been doing experiments alongside the Corder lab where we're activating these neurons.

It allows us to essentially play back bad memories, to reactivate neurons in the brain that were once activated during this painful stimulation.

MARILYN: (35:09)
So, they're basically playing inception with the animal – playing back memories by stimulating the area of the brain that holds these memories. And while they're doing that, they're using the automated pain scale to match what the animals are doing with what areas are active.

DR. ABDUS-SABOOR: (35:24)
What does this sensory experience feel like to an animal? To turn on this unpleasant circuitry or manipulate it in the brain while doing peripheral stimulation? Unclear. We're interested in further expanding that. We want to begin looking in other brain areas besides the amygdala, like the central amygdala right next door, the parabrachial nucleus, paraventricular thalamus.

And again, we're doing some of this with our friends and collaborators in the field. And we want to combine our peripheral stimulation with using fiber photometry and calcium imaging or even miniature microscopes to record as the animal is experiencing pain driven by peripheral input, which brain areas are controlling the animals' behavioral responses, all in real time. And again, this is like basic science, understanding how the periphery and the brain are connected to drive these pain signatures.

MARILYN: (36:27)
Dr Abdus-Saboor is using brain imaging techniques to look at neurons in the amygdala that are important for the pain experience, and he's using the automated pain scale, to look at how pain behavior changes when you turn off and on the amygdala cells.

RYAN: (36:46)
So, they'll play back these bad memories and the mouse will react as if it's in pain? That's a really powerful experiment! I wonder if there's a way to use this technique to study the *absence* of pain, too. That seems like an important part of the puzzle, right? To know what the brain looks like when there's no pain at all?

MARILYN: (37:04)
So funny that you mention that! Dr Basbaum's lab is using calcium imaging to answer exactly that: by studying the effects of anesthetics on the brain.

DR. BASBAUM: (37:14)
See, the point is that we know that anesthetics, quote, shut off the brain, so you can do surgery and things. Uh, they block pain, they cause amnesia, and they produce unconsciousness.

RYAN: (37:25)
You know, that makes sense. You'd never want a surgeon to operate on a patient who could feel what was happening.

MARILYN: (37:32)
Exactly. But no one knows how anesthetics work to make surgeries pain-free. Do they work by shutting off activity in the brain to prevent the pain experience?

DR. BASBAUM: (37:42)
And we know globally how they work, using fMRI or PET. But we are now looking and we have been able to demonstrate in certain areas of the brain, that one particular anesthetic will shut off all activity. Of course the animal is still alive, so the other areas are still functioning.

But another anesthetic will actually turn *on* the cells in certain areas. Uh, and so we're, we're getting a handle on how they work. And there were so-called stages of anesthesia where the first stage was pain-free. Then there was amnesia where you could be talking to the patient and they won't remember anything. Then they were unconscious. Okay? We think that it may be possible now, taking advantage of stages, to identify different neural circuits that are contributing to the pain state, the loss of pain state, the amnestic state and then the unconscious state.

Um, so this is a whole new area and we have several people in the lab studying this, it's really exciting stuff. We monitor their behavior, their running, their respiration, variety of other activities. And then correlate that point with the activity patterns, which neurons are most susceptible, how do they recover, uh, over what time course? Turns out that, depending on the anesthetic, neurons recover very differently. We're very excited about that.

MARILYN: (39:03)
In essence, identifying the cells that respond to anesthetics may let us know which cells turn on and off pain perception while you're awake. Imagine being able to target those neurons that process the pain itself without affecting aspects of normal functioning.

RYAN: (39:19)
Sounds like you could bypass nasty side effects that you get from conventional drugs like morphine!

MARILYN: (39:24)
Yeah, that's kind of the "holy grail" of understanding and treating pain, right? As Dr. Basbaum explains it:

DR. BASBAUM: (39:31)
Can I come up with a drug that will prevent that and influence those cells? So, I'm actually finally getting to the place where pain is processed. I don't know *the* area.

RYAN: (39:39)
Based on our guests' research, it sounds like scientists are still trying to find drugs that can target the specific cells associated with pain.

MARILYN: (39:47)
Dr. Abdus-Saboor summarizes primary ways in which pain research can help us develop better drugs.

DR. ABDUS-SABOOR: (39:54)
But another approach is we need to find whole new systems to block pain. And that's really going to start by identifying new genes through some of the basic science we're doing: identifying new receptors, new ion channels that control reduced or heightened pain susceptibility and being able to show that we can block these receptors, these peptides, these channels, and really turn off pain.

RYAN: (40:21)
I see, so the future of drugs that relieve pain can be thought of in two ways: First, we want to make our current treatments better, more focused and secondly, we need to find new places in our body that are associated with pain and then try to block those.

MARILYN: (40:36)
Best of luck to the researchers! We're counting on them.

(Di Breun)

MARILYN: (40:55)
In this episode, we discussed the ways in which older drugs, like opioids, and newer drugs, like CGRP antibodies, work to combat pain.

RYAN: (41:04)
We also learned why it's important to compare new, developing drugs to placebos.

MARILYN: (41:09)
Many of the existing drug treatments are not precise, so people may experience unpleasant side effects.

RYAN: (41:16)
That's why we have researchers like Dr. Abdus-Saboor and Dr. Basbaum going back to the basic science. First, we need to find good mouse models, and then find ways to objectively measure pain in these animals. In this episode, we discussed two ways that they do this: automatic behavior tracking and brain imaging.

MARILYN: (41:34)
Once research has identified the parts of the nervous system controlling pain perception, then we can move on to our main goal, which was noted by the audience member Dr. Basbaum referred to. He asked, "how does ibuprofen know where to go?" — it doesn't! Sometimes, taking drugs is like throwing darts blindfolded. They can go anywhere in the body – sometimes they hit the target you want them to, and sometimes they don't. But, if you throw the right amount of darts, you'll hit enough of the targets and relieve pain.

RYAN: (42:05)
Research is trying to help us take off the blindfolds, so we know exactly where we're aiming those darts!

MARILYN: (42:11)
Hopefully, in this episode, we were able to help you understand the drugs people take for pain and reveal a glimpse of how pain research is conducted.

(Slow Toe)

MARILYN: (42:28)
This episode was written and produced by Cindy Liu, Nancy Cai, Ryan Morrie, and me, Marilyn Steyert. We also had help from the rest of the team at Carry the One Radio.

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RYAN: (42:51)

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