the WINNOWER

REDDIT

Science AMA Series: This is Dr. Cheryl Stucky and Francie Moehring. We do research on touch and pain, including the mechanisms underlying the role of chronic pain in skin diseases, and we're here today to talk about it. AMA!

ELIFE_AMA R/SCIENCE

Hi Reddit

About us:

Dr. Cheryl Stucky: Hi! I am a Marvin Wagner Endowed Professor in the department of Cell Biology, Neurobiology and Anatomy, and the Neuroscience Doctoral Program Director, at the Medical College of Wisconsin. I am broadly interested in understanding touch and pain mechanisms.

I have run a research laboratory for about 18 years at the Medical College of Wisconsin, where we use rodent models to study the mechanism of pain in diseases such as sickle cell disease, Fabry disease, arthritis and postsurgical pain. My lab also focuses on understanding how we sense touch, and we recently found out that our skin plays a large role in this. Building upon this knowledge, we are now investigating what role damaged skin plays in chronic pain conditions. The ultimate goal of our research is to identify new targets for which topical drugs can be developed in order to treat these pain conditions and avoid the negative side effects of many current treatments that are already out there.

Francie Moehring: I am the senior graduate student in Cheryl's laboratory. Many skin disorders such as dermatitis and psoriasis share a common hallmark: increased sensitivity or even pain to touch or normally unpainful stimuli. My project in the Stucky lab focuses on laying the foundation for understanding dysfunctional signaling processes during these disorders to potentially reveal new drug targets for topical treatments that directly target the site of pain. In order to study these processes, we are trying to understand how our skin, and the specific cells that form it, can interact with neurons and nerves within the skin that are typically involved in sensing mechanical stimuli from the environment.

We're here to answer questions about a recent paper we published in the journal eLife (https://doi.org/10.7554/eLife.31684?utm_source=reddit&utm_medium=forum&utm_campaign=AMAFeb18; plain-language summary: https://doi.org/10.7554/eLife.31684.002?utm_source=reddit&utm_medium=forum&utm_campaign=AMAFeb18) – where we studied how our skin communicates with the nervous system – or queries related to our research more broadly. Please note that we are unable to provide any medical advice, as this goes beyond the scope of our research. We'll start answering questions at 1pm EST. AMA!

CORRESPONDENCE:

DATE RECEIVED:
February 13, 2018

DOI:

How can some pain that occurs due to a stress or anxiety response feel so real?

Booyacaja

Hi, thank you for joining us. Pain due to stress and anxiety is in fact real. Pain is defined as an unpleasant sensory and **emotional** experience associated with actual or potential tissue damage. The emotional and cognitive aspect of how an individual perceives pain is a very large part of what makes

10.15200/winn.151844.43467

ARCHIVED:
February 12, 2018

CITATION:
eLife_AMA , r/Science , Science AMA Series: This is Dr. Cheryl Stucky and Francie Moehring. We do research on touch and pain, including the mechanisms underlying the role of chronic pain in skin diseases, and we're here today to talk about it. AMA!, *The Winnower* 5:e151844.43467 , 2018 , DOI: 10.15200/winn.151844.43467

the pain be so distressful. With chronic pain in particular, there are often many other distressful conditions that affect a person, such as fear and worries, anxiety, stress, lack of sleep. All of these factors worsen the distressfulness of a painful event. Sometimes chronic pain occurs without an obvious physical cause, but it is nonetheless real, and these cognitive factors enhance the feelings of pain.

I am currently looking at topical Cannabinoids for dermatological conditions (for a research paper). Have you any thoughts or anecdotal evidence regarding this possible therapeutic avenue? Thanks!

geithman

I think this is a great idea and have been wondering about it as well. Cannabinoid (CB) receptors are present on human skin cells, and a endogenous (made within the body) CB receptor ligand called anandamide blocks keratinocyte differentiation. Also, the type 1 CB receptor in keratinocytes has been found to modulate (dampen down) allergic contact dermatitis, which is associated with pain. Long ago, our lab found effects of a cannabinoid agonist (CB1 receptor) in our skin-nerve recordings, meaning that the action potential firing from the nerves in our skin was changed by the cannabinoid receptor activator. Cannabinoids are very lipophilic (fat loving) and so they will likely get from the skin into the circulation (transdermally) very easily.

I suffer (mildly) from Eczema, usually on my hands. It's nothing serious, easily treated with topical steroid creams and ointments. However sometimes it itches like mad, other times I don't notice it unless I'm brushing my fingers against each other and I can feel the dry skin against normal patches of skin

What is the mechanism that drives the itching? Why isn't it just painful (such as when the skin actually splits?) And why is it so inconsistent?

Sorbicol

Hi, this is a very interesting question. Our lab currently does not currently investigate itch signaling pathways, however, multiple neuronal pathways responsible for producing the sensation of itch have recently been identified such as the histamine-independent (i.e. atopic dermatitis) and histamine dependent pathways (caused by allergies or infections). Itch and pain are thought to be different, because we can clearly differentiate the two sensations, however itch is also inversely related to pain, as itch can be decreased by scratching (a painful stimulus). The field hypothesized and recent evidence shows that there is some overlap between pain sensing nerves and itch sensing nerves and that is potentially why scratching can decrease the itch we feel. One possibility why you do not always notice your eczema until you brush against the affected skin might be that once you touch the affected areas, the receptors found within your skin become irritated and this then in turn sends signals through nerve fibers in the skin to the spinal cord and then up to the Cerebral cortex in your brain. An area of the brain that has been shown to be involved in our itch sensation is the amygdala, which is involved with the experience of emotions.

How does neuropathic dermatitis begin? Why do some people get it? Is it psychosomatic itching?

samisJane

Neuropathic dermatitis is a skin condition that begins with an itch, anywhere on the body. The itch can be so intense that the individual itches the patch so frequently that the scratching can damage the skin. It can be so annoying that it wakes a person from a sound sleep. What causes it. First, why do some

people get it? The individual often has a history of eczema (atopic dermatitis), psoriasis or contact dermatitis. This means they are more susceptible to getting neuropathic dermatitis, perhaps because of their specific genetic background. Second, what triggers a specific attack can include a nerve injury (peripheral nerve in the hand, arm, leg) such as that from a surgery, including plastic surgery to the skin, a bug bite (which induces infection, elevates the immune system), traffic exhaust or allergens in the environment, tight clothing made of scratchy fabric like wool, and stress or emotional trauma. More research is greatly needed for this challenging and life impacting disorder. Neuropathic dermatitis (which has identifiable causes in the skin, environment) is not the same thing as psychosomatic itching, which is also very real, but is instead driven from the brain and cognitive processing and descending control (anxiety might cause this). A common example of mild psychosomatic itch is if a person just thinks about getting a mosquito bite, it can cause the person to itch their skin. If a person sits in a talk where the person is discussing itch mechanisms, this can cause the listener to start itching their skin. A few years ago, there was a fascinating article in The New Yorker magazine that described a patient who had such severe psychosomatic itch in her scalp skin, that during the night she itched incessantly, first through her hair, then through her skin, then through the scull, and finally into the brain tissue.

Would skin transplants be effective in treating or curing chronic pain?

LameJames1618

This is an interesting question, but I don't think this is likely. I'm not aware of there being reports of less pain in the "recipient" site of a skin graft. We don't know enough yet about the roles of skin cells/keratinocytes in persistent or chronic pain and more research needs to be done in this area. Importantly, chronic pain is also caused and maintained by altered neuronal circuits in the brainstem and spinal cord.

Hello! I'm not sure if this is entirely related to your fields of study, but I was wondering if your research touched on the pain associated with pressure in patients with fibromyalgia?

StonedPhysicist

Good question. Our research does not focus on fibromyalgia, a chronic disorder that is characterized by widespread musculoskeletal pain, fatigue and very sensitive, tender points in specific body areas. Fibromyalgia affects more women than men and people that have fibromyalgia often have also been diagnosed with another disorder such as arthritis, depression or anxiety. The causes of fibromyalgia are currently debated and of high interest for the pain field. One current hypothesis is that there is a malfunction in how the brain and spinal cord process pain and touch signals that come from the nerves in the skin and muscles. Another possibility is that there may be overactive nerves or support cells in muscle. At this point, much more research needs to be done to clearly define the causes of fibromyalgia and discover ways to best treat this devastating disorder.

Francie Moehring, in your studies of skin disorders, have you seen any increase in pain or sensitivity or lack thereof in patients with alopecia? Without the hair follicles in those areas, is there a lack of sensitivity or *more* due to the body compensating for it's crazy immune system? (I'm a 27yr old male with alopecia universalis)

SwoleMedic1

Hi, thank you very much for joining us and asking this question. Alopecia is a partial or complete absence of hair from areas of the body where it normally grows, for example "baldness." We honestly

have not investigated alopecia in our models yet, however the current understanding is that alopecia is considered a chronic inflammatory disease. It is thought to be caused by an autoimmune disorder when the body's own immune system attacks certain hair follicles. Since it is an inflammatory disorder, I believe that most patients experience increased pain instead of a decrease in pain. Interestingly, in several of our mouse strains, we notice that alopecia (spots of hair missing on the back) is common. We do not know why this occurs. It might be itch that causes the animal to scratch, which removes the hair. It might be excessive grooming by the mouse, perhaps caused by anxiety or it might be due to excessive "barbering" or grooming by another mouse. We think this would be an interesting research project to test some of these mice to see whether they have increased or decreased sensitivity to touch or pain stimuli. Another interesting recent finding is that a lab at the NIH showed that hair follicles are enwrapped by pain-sensing neurons. We do not know how these pain receptors "change" after the hair is lost, but this would be another very interesting research study to do.

I have chronic pain due to ulnar neuritis and just generally crap tendons. I've been through years of PT.

I never really let my doctors know how chronic and severe the pain is because I don't want to be prescribed opioids. I also seem to have low sensitivity to ibuprofin and other over the counter pain relief.

What's the time to market estimate on non-opioids that are more efficacious as either OTC or prescription pills?

Any general tips for pain management?

PelagianEmpiricist

Hi, thank you very much for joining us today. A lot of basic science research is focused on developing non-opioid based treatment options for cases like you. Drug development and then testing (clinical trials) is a long term process, which typically can take 7-8 years before the drug makes it to the market. We are not physicians so we cannot advise you on what is the appropriate treatment for your specific chronic pain, thus we would advise you to talk to your physician about the best possible treatment route for your specifically. As every case is different, your physician should tailor the pain management specifically to you, and there are a lot of non-opioid pain relievers out there (eg. Neurontin or Gabapentin) that can help, especially with nerve pain.

Why is it so difficult to find the cause of urticaria?

shem73

Urticaria (hives) is a vascular reaction of the skin marked by the transient appearance of a rash (with smooth and elevated wheal), which often cause severe itch. It is the most common causes of skin inflammation, where up to 20% of the population will at least experience it once in their lives. Most of the time this is caused by an allergic reaction to food, medicine or other irritants (such as makeup, soaps, perfumes or lotions). Thus, there are a wide variety of environmental factors that could lead to urticaria. Most clinicians diagnose urticaria via examination of the clinical picture and patient history. Additionally, skin tests or radioallergosorbent assay tests (RAST) can be performed to test for food allergy, some antibiotics, or insect sting hypersensitivity. Because pollen and other inhalants are hard to avoid as triggers on a daily basis they are often not tested, unless a severe allergy might be causing the symptoms. Additionally, physical challenge tests for suspected stimuli such as heat, pressure, or cold can be performed. In addition to the factors listed above that can cause urticarial, infections such as hepatitis or chickenpox can also cause hives. Therefore, there are multiple tests out there that help determine the cause of urticaria, however there are also lots of reasons that could cause it, therefore

making a diagnosis sometimes challenging.

Have you seen any cases in the mice where they were impermeable to pain?

And serious, did you have trouble causing pain to the mice at first? And if so, how long did it take to let's say, not care as much?

Thank you!

ldru4

Our institute has very strict rules and regulations about pain studies in animals, and these rules are governed by a national organization in the United States called the Institutional Animal Care and Use Committee (IACUC) which is overseen by the NIH Office of Laboratory Animal Welfare (OLAW). The mice are freely able to escape from a potentially painful stimulus when we test them in behavioral tests. For any injections or surgeries, we use appropriate anesthesia and pain medications. Our laboratory members take the welfare of the animals very seriously.

Have you seen any cases in the mice where they were impermeable to pain?

And serious, did you have trouble causing pain to the mice at first? And if so, how long did it take to let's say, not care as much?

Thank you!

ldru4

Good question. We have not with our models. However, other researchers have discovered the mechanisms that cause a condition called Congenital Insensitivity to Pain (CIP). While there are several reasons for this, one is that the ion channels (sodium channels) that lead to the nerve signal (action potential) in pain receptors have a mutation defect in them that causes the pain receptor not to signal to the spinal cord and brain, even though the painful stimulus is present. Another different reason that some people have Congenital Insensitivity to Pain is that when the nervous system is developing before we are born, the pain-sensing neurons need to access a molecule called Nerve Growth Factor (NGF) that guides the neuron terminals to go to the right places in the skin as well as to survive to adulthood. The nerve endings have specific receptors to receive the NGF signal. In some CIP patients, there is a mutation defect in the NGF receptor so that the nerve ending cannot detect the signal, even though it is present. This causes the pain receptors to die. So these patients grow up without most of their pain receptors. Patients with CIP (from either cause) can't sense painful stimuli, but they can sense touch and skin stroke and where their feet are on the ground (proprioception), which is essential for walking properly.