Uncovering the Itch


And:

**The cells and circuitry for itch responses in mice.** Mishra SK, Hoon MA. Science. 2013 May 24; 340(6135):968-71

The pathways that mediate pain and itch are interconnected, and there has been uncertainty about whether they utilize distinct neuronal pathways. Agents that induce itch, for example the anti-malarial drug chloroquine, also activate capsaicin-sensitive neurons. Capsaicin is the chemical responsible for the burning sensation in chili peppers. Researchers are investigating whether the mechanisms for these two sensations differ at the cellular level. In the first study, Han et al., discovered that a population of neurons which express the receptor MrgprA3 (called *MrgprA3*+ neurons), located in the skin, respond specifically to chloroquine and other itch-inducing agents. When *MrgprA3*+ neurons were deleted in knockout mice, itch-associated behaviors (i.e. scratching) were significantly reduced, but pain-associated behaviors (i.e. facial wiping) were unchanged. Additionally, capsaicin caused scratching, but not wiping, in mice with *MrgprA3*+ neurons that lacked the TRPV1 ion channel, which mediates pain responses. These findings indicate that whether a stimulus causes a pain sensation or an itch sensation largely depends on the specific neuronal pathway that is being activated. In the second study, researchers Mishra and Hoon found that the molecule natriuretic polypeptide B (Nppb) plays a role in itch-associated responses in mice. Administration of Nppb induced scratching behavior in mice, while mice missing Nppb were rendered unresponsive to multiple itch-inducing agents, suggesting Nppb acts as a neurotransmitter for itch signaling. Based on their findings, the researchers hypothesize that Nppb acts as a secondary signal in response to itch. Taken together, the two studies suggest a potential itch pathway in which itch-inducing agents activate specific neurons that innervate the skin, the *MrgprA3*+ neurons, which then activate second level neurons leading to release of a neurotransmitter, Nppb, that mediates additional signaling in the spinal cord. Distinguishing pain and itch pathways is an important breakthrough because it may lead to the discovery of specific treatments for itch.

Opioid-Related Pharmaceutical Overdose Deaths Rise Dramatically


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In the past, fatal drug overdoses from illicit drugs such as heroin and cocaine were more common than overdoses from prescription medications. In recent years however, as death rates from drug overdoses have increased, pharmaceutical drugs have become a major contributor. These two articles focus on prescription opioid-related drug overdoses, and the role of other pharmaceutical agents that are subject to abuse, such as benzodiazepines. In the first study, researchers looked at the data trends from unintentional drug overdose death rates at ages 15-64 from 1999-2009. Overall, the
death rate across all ages increased by 400%. The increases were most concerning for the 15-24 year old age group, which increased by 600% overall. For example, deaths related to sedative hypnotics increased 5-fold in all persons aged 15-64, but increased 10-fold in persons aged 15-24. Males had higher death rates than females for all substances; the sex difference was less for pharmaceutical opioid and sedative hypnotics than for heroin, cocaine, and psychostimulants. The second study focused on pharmaceutical overdose deaths in 2010, and also demonstrated a predominant role of opioid analgesics in overdose deaths. The death rate related to pharmaceutical opioids was the highest among users of combinations of substances, particularly when opioids were taken in combination with benzodiazepines, antidepressants or antipsychotics. It is important to note that the non-opioid drugs that contribute to overdose deaths are drugs taken for mental health issues, a reminder of the challenges of treating pain susceptibility in the mental health population. The researchers suggest evaluation of tools, such as drug monitoring programs, as well as the need for better management of mental health and chronic pain disorders.

Newly Identified Mechanism for Bacterial Infection Pain


While bacterial infections can be quite painful, it isn’t clear why this is so. Most investigators have attributed this pain to proteins and other mediators released by our immune system. Using an animal model, scientists funded by the National Institute of Health studied the mechanisms by which *Staphylococcus aureus* (otherwise known as staph) infections trigger inflammatory pain. Following bacterial injection, scientists found that the time course of the pain associated with infection does not follow that of tissue swelling or immune activation, but instead parallels bacterial expansion or growth. They also noted that the immune response – the secretion of various factors by immune cells – does not appear to cause infection-induced pain. Instead, bacteria directly activate pain receptors by secreting a toxin called α-haemolysin (αHL) and molecules known as N-formylated peptides. Thus, their data suggest a novel pathway for bacterial infection-induced pain, whereby bacteria directly interact with and activate pain receptors to modify the immune response.

Pain in the Brain: A Brain Signature for Pain


There is substantial interest in understanding the central brain circuitry responsible for pain perception. One valuable tool for studying the brain in humans is functional magnetic resonance imaging (fMRI), which measures brain activity in specific regions by detecting associated changes in blood flow. Wager and colleagues conducted a series of fMRI studies using different subject groups to identify a neurological signature that is specific and sensitive to physical pain. They used fMRI to detect the brain’s response to painful heat and non-painful heat in normal subjects and evaluated the results with machine-based learning which permitted the identification of a distinctive response, or a pain signature, consistent across multiple individuals. In their first study, machine-learning analyses were used to identify the activity patterns measured by fMRI in specific brain regions associated with heat-induced pain and with non-painful warmth. These signatures were so distinct that they reliably discriminated painful heat and warmth. Subsequent studies that compared the pain signature associated with physical pain to that associated with social pain (in which subjects reported intense rejection due to a recent romantic breakup) revealed that they also were sufficiently distinctive to be predictive of the stimulus. In addition, they showed that administration of the analgesic agent Remifentanil reduced the strength of the physical pain signature response. This study demonstrates the ability to use fMRI to assess the pain response in healthy persons. The findings from these studies ultimately may help to provide more standardized, reproducible and less subjective measures of pain which could facilitate the development of more individualized and better treatments.
Endorphins May Play a Role in the Development of Chronic Pain


The μ-opioid receptor (MOR) is the main site of action for opioids, such as morphine, that relieve pain. Chronic use of opioids can produce tolerance (in which more drug is needed to get the same effect) and dependence (characterized by symptoms of withdrawal when the drug is stopped). Endorphins are natural opioids that are produced in humans and are released in response to pain as well as during certain activities such as exercise. Investigators have hypothesized that chronic opioid use may alter the endogenous opioid system so that it is constitutively activated. In this study, researchers tested whether chronic pain did, in fact, alter the endogenous opioid system. They found that tissue injury in mice produced constitutive activation of MORs that decreased pain sensitivity for months. An opioid blocker was used to prevent the activity of the endogenous opioids, which resulted in increased pain sensitivity and symptoms of withdrawal in mice. These findings indicate that chronic pain causes continuous activation of the endogenous opioid system which, while contributing to reduction in pain, may also contribute to dependence. These findings have important implications for understanding the development of chronic pain.

Brain Imaging and Machine Learning Identify Brain Changes in Chronic Low Back Pain Patients


Chronic low back pain (cLBP) is the leading cause of activity limitation in individuals over 45 years old with an estimated annual economic burden of $100-200 billion in the US. The origin of cLBP, however, is unknown for the majority of patients. Imaging studies had previously identified changes in brain structure and function in those with chronic pain but the results were inconsistent for cLBP. Here, researchers investigated the density of gray matter (GM) – the portion of the brain that contains most of the neuronal cell bodies – in un-medicated patients with cLBP and compared it to that of healthy controls. A machine-learning algorithm, in which a machine was trained to distinguish distributed patterns of changes in GM density, was utilized to distinguish cLBP patients from healthy controls. They found that, whereas total GM volume is similar, patients with cLBP display unique distributed patterns of GM density throughout the brain, particularly in areas associated with pain. Changes in areas of the brain less commonly associated with pain were detected as well. The researchers validated the use of GM density imaging and machine-learning to classify cLBP (76% accuracy). The results from this study advance the understanding of the brain’s role in cLBP and provide a tool to aid in identifying the disease.