2014 IPRCC Advances in Pain Research
Basic to Clinical

**Human Fibroblast-derived Neurons: a New Model for Pain**


Research into the physiology and molecular basis of pain using animal models has yielded a wealth of information about the basic mechanisms of pain. Little of that research unfortunately, has translated into clinically useful therapies. Conducting basic science research with human cells might help overcome this problem, but human nerve cells are difficult to obtain. Previous studies have shown that applying a series of transcription factors, molecules that regulate gene expression, to human stem cells allowed those cells to become neurons in a dish. Collecting human stem cells however, is also difficult. Researchers from Harvard University and Boston Children’s Hospital have developed a method to bypass these problems. Using easily obtained human skin fibroblasts they were able to generate neurons that are functionally similar to and mimic the diversity of human pain signaling neurons, called nociceptor neurons. Scientists first generated nociceptor neurons from mice by treating mouse skin fibroblasts with a cocktail of lineage-determining transcription factors. They showed that these fibroblast-derived neurons recapitulate many of the markers and functional hallmarks of pain signaling neurons directly cultured from mice, and even presented a similar variety of cell types. They were then able to transform human fibroblasts in a similar way and found that these reprogramed neurons behaved in a similar manner to human pain signaling neurons. To explore the potential for human neurons as models of disease, fibroblasts also were taken from patients with familial dysautonomia (FD), a condition in which patients have difficulty sensing pain. Previous studies of FD have shown that a protein called IBKAP is made incorrectly in pain sensing neurons of FD patients, but that their fibroblasts have both the normal and abnormal protein. It was not known which form of the protein would be made in the fibroblast derived neurons of the FD patients. Analyzing these reprogrammed cells has shown that only the improperly-made IBKAP is present and results in abnormalities in the neurons that might account for the sensory changes in these patients. The nociceptor neurons from FD patients are less numerous, do not have as many branches, and do not function as well as those neurons from healthy controls. The disease process alters their fibroblast derived pain-sensing neurons. This technological advance has great potential as a disease model and represents the potential to study “pain in a dish” using human cells from healthy individuals and those with pain conditions, to better understand pain mechanisms. The ability to reprogram cells directly from patients with pain will help us better understand individual variability in pain risk factors and aid the development of new treatments for pain.

**MMG22 produces extremely potent relief from bone cancer pain in mice**


Opioids have long been the gold standard for pain treatment in bone cancer patients. Less than half of patients however, report adequate pain reduction from opioids, highlighting a need for new and improved pain treatments. Recent animal studies have demonstrated that glutamate receptor (mGluR5) antagonists, molecules that work by blocking a specific glutamate receptor, when given with opioids, suppress the tolerance and dependence on opioids, while enhancing their pain relieving effects. This study investigated the analgesic effects of a drug called MMG22, which is made by binding an opioid agonist, a molecule that works by activating a specific opioid receptor, to an mGluR5 antagonist. The results showed that MMG22 produced extremely potent pain relief relative to morphine alone. It was also much more effective in relieving pain than when both molecules were given, but delivered separately. The researchers hypothesize that the greater order of magnitude of
the combined drug over that of the two separate drugs may be its physical linkage to a third receptor (NMDA) known to be involved in increasing pain levels. Furthermore, the drug notably was not associated with any evidence of tolerance, toxicity, or other adverse effects that occur with opioid therapy. In fact, the drug’s potency increased during tumor growth. This allowed researchers to administer lower doses to mice over the course of tumor growth while still achieving the same levels of pain relief. At present, it is not clear how MMG22 produces its powerful pain relieving effects. Future studies are likely to test the viability of MMG22 in humans while also investigating how the drug works. This research is a valuable first step towards developing improved pharmacological pain relief for bone cancer patients.

**Activation of Cannabinoid Receptor 2 reverses chemotherapy-induced neuropathic pain**

**Chronic Cannabinoid Receptor 2 Activation Reverses Paclitaxel Neuropathy Without Tolerance or Cannabinoid Receptor 1-Dependent Withdrawal.** Deng L1, Guindon J2, Cornett BL3, Makriyannis A4, Mackie K5, Hohmann AG6. *Biol Psychiatry.* 2014 Apr 25. pii: S0006-3223(14)00274-1

Chemotherapy used to treat some forms of cancer can cause neuropathic pain, which may be severe enough to limit the therapeautic dosing needed to treat the cancer. Neuropathic pain is nerve pain that is often characterized as burning or stabbing and is often resistant to treatment with currently available drugs. Molecules that bind to cannabinoid receptors may offer relief without side effects of currently used analgesics. Tetrahydrocannabinol or THC, the active ingredient in marijuana, has been used to successfully reduce neuropathic pain from chemotherapy drugs such as paclitaxel. The use of THC however, is limited due to its psychotropic effects (i.e., feelings of being ‘high’) and tolerance development. THC activates two types of cannabinoid receptors, CB1 and CB2. While CB1 activation evokes unwanted psychotropic effects, CB2 activation has anti-nociceptive (pain-reducing) properties. In this study, researchers examined properties of a drug, AM1710 that preferentially activates CB2 over CB1 to determine its therapeutic potential for neuropathic pain. In mouse models, hypersensitivities (allodynia) to cold and mechanical stress are proxy measures of neuropathic pain. Mice with only CB1 receptors (CB2 Knock Out), only CB2 receptors (CB1 Knock Out), or both receptors (normal, Wild Type) were treated with paclitaxel to produce allodynia. The researchers found that one dose or repeated doses of AM1710 decreased paclitaxel-induced allodynia in wild-type and CB1 Knock out mice, but not in mice lacking the CB2 receptor, indicating that AM1710 acts on the CB2 receptor to suppress pain. This was further tested using a CB2 blocker which reversed the pain-relieving properties of AM1710. Furthermore, while THC caused symptoms of withdrawal (i.e., paw tremor), AM1710 did not. This study demonstrates that drugs such as AM1710 have therapeutic potential for treating chemotherapy-induced neuropathic pain without psychotropic side effects and tolerance.

**Disparities**

**Automatic/subconscious bias contributes to racial disparities in pain perception and response**


While pain care may be considered inadequate for a large percentage of the population, there are subgroups that are particularly vulnerable to disparities in pain care. Racial disparities in clinical pain treatment are well-documented and underscore the need to identify factors that contribute to differences in care, treatment and outcomes. Provider bias has been studied and demonstrated to contribute to racial disparities in pain care and treatment. Research results vary however. It can be difficult to test bias in an experimental research setting because study participants may be aware of the study purpose and deliberately alter their response to reduce presentation of conscious prejudices. In this study, researchers utilized a method called ‘racial priming’ to distinguish implicit (subconscious) bias from explicit (conscious) bias. A photo of a black or white male was shown to participants (student volunteers) for an instant (milliseconds) -
evoking an implicit or automatic response, or for several seconds - evoking an explicit or deliberate response. The effect of patient race is presumed to be below conscious regulation in the implicit prime condition and influenced by deliberate motivation in the explicit prime condition. Participants then were presented with a case study of a male’s pain state and circumstance followed by questions that probed the participants’ perception and responsiveness to the patient’s pain. Results from the study showed that participants were less responsive and perceptive to the patient’s pain when presented with the African-American photo than the European-American photo in the implicit (automatic) test, but more responsive and perceptive to the patient’s pain when presented with the African-American photo than the European-American photo in the explicit (deliberate) test. The differential response in the explicit v. implicit tests was more significant for European American participants than for African-American participants. This study supports previous research that shows people are less perceptive and responsive to pain in African-Americans. It also demonstrates that automatic, rather than deliberate reactions are primarily associated with racial bias in pain perception and response. Future studies should employ both implicit and explicit measures when testing racial biases in clinical settings to ensure more consistent results.

Racial differences in opioid prescribing for Veteran’s pain


Many factors, including prescribing practices, contribute to racial differences in pain management and outcomes. Studies show that black patients are less likely than white patients to receive opioid medications for chronic non-cancer pain. In this study, researchers examined whether racial differences in opioid prescribing were observed in the Veterans Administration healthcare system. The study utilized a large national sample of black and white veterans with varying levels of pain intensity. In the age range of 65 and younger, blacks were less likely than whites to receive opioid prescriptions for moderate or severe levels of pain. These differences occurred regardless of the medical history of the patient. It is interesting to note that when pain ratings were zero, blacks were more likely than whites to be prescribed opioids. The differential opioid prescribing is consistent with existing literature in the field. While the researchers did not determine factors that account for these differences, they discussed possible contributors. Based on previous studies, racial stereotypes of perceiving blacks as riskier patients for misuse potential, provider empathy for patients of their own race, and the perception that blacks experience less pain than whites, might all contribute. Patient preferences also might play a role. For example, studies have shown that blacks are more likely to have concerns with taking opioid medication for fear of addiction or side effects. The authors note that their findings of differences in prescribing rates do not provide evidence related to quality of care or outcomes of care, and as such, should be considered differences rather than disparities in care. Differences in pain care based on race should be carefully considered when developing treatment strategies, to ensure that inequities are eliminated.

Pain Mechanisms

Delta opioid receptors may be a pharmacological target for relieving injury-induced hypersensitivity to light touch

Opioids have been associated with pain relief, but it now seems that the opioid system broadly regulates the mechanosensory system – that is, it regulates the neurons that relay painful stimulation of the skin and neurons that relay the sensation of touch. The body’s mechanosensory system allows us to feel both harmless and noxious mechanical stimulation of the skin – perceived respectively, as touch and pain. Dysfunction in this system can cause light touch to be perceived as painful. Such touch-evoked pain, also called mechanical allodynia, is a common and distressing symptom of damage to the nervous system itself. There are distinct types of neurons that relay harmless signals and noxious stimuli from the skin to the spinal cord as part of the pain processing pathway. Scientists have not had a clear understanding of the expression patterns of opioid receptors across these different types of neurons. Opioids that are commonly used to treat pain, such as morphine and oxycodone preferentially target a specific receptor, the mu opioid receptor. Other opioids can act through different types of opioid receptors, including the delta opioid receptor (DOR). In this study, the researchers discovered that whereas the two subtypes of neurons express opioid receptors, they have unique expression patterns of receptors that link them to their function. They show specifically, that mechanosensory regulation is mediated by the delta opioid receptor (DOR) subtype, which is primarily expressed by neurons that relay touch sensation. These data give insight into the mechanism by which opioids regulate sensation from the skin and suggest that specifically targeting the DOR with appropriately designed analgesics may help relieve touch-evoked neuropathic pain.

New Biomarker Discovered for Pain Relief in Animals


A biochemical signal or “biomarker” for ongoing pain relief has yet to be identified, but would be helpful in testing the potential effectiveness of novel analgesic drugs. Pain is a subjective experience, which includes sensory, cognitive, and affective dimensions, making it difficult to assess new drugs in preclinical settings. The affective dimension is that unpleasant feeling that motivates an organism to avoid painful situations and can be quantified by analyzing a specific behavior in which an animal selects or avoids a certain environment depending on whether or not it has pain. The nucleus accumbens (NAc), along with other brain regions, influences such motivation and is driven by the neurotransmitter dopamine, which facilitates the behavior associated with pain relief. Using microdialysis in the brains of rat models of ongoing neuropathic pain and post-surgical pain, researchers measured the neurotransmitter dopamine in the NAc during the behavioral test. When clinically effective pain relievers were administered, the rats’ behavior indicated a reduction of ongoing pain and levels of dopamine in the NAc went up. However, when ineffective pain relievers were administered, the rats’ behavior did not indicate a reduction of pain and NAC dopamine levels were unchanged. In other words, dopamine levels in the NAc correspond with the alleviation of pain. For these two pain conditions, the clinical efficacy of the drugs tested reflected the dopamine levels and pain behaviors in both animal models. These findings suggest that NAc dopamine may be a biomarker for relief of ongoing pain. In the future, it may be possible to test the efficacy of novel analgesic drugs in different pain conditions simply by quantifying dopamine in the NAc. This represents a scientific advance in the assessment of pain relief in animal studies.
Serotonin from the Central Nervous System Modulates Pain in the Periphery


The perception of pain depends on complex neural circuitry. A set of neuronal membrane receptors known as TRPV1, or transient receptor potential vanilloid 1 are known to play a crucial role in signaling pain through peripheral nervous system pathways. The contribution of TRPV1 receptors in the pain circuits of the central nervous system however, is less clear. To learn more, researchers used a model of nerve injury in mice and subsequently found that TRPV1 receptors in the trigeminal subnucleus caudalis (Vc), a specific portion of the central nervous system, had become hypersensitive in that they were now responsive to painful stimuli. This indicates a role for central nervous system TRPV1 in processing pain signals. Furthermore, peripheral TRPV1 receptors in an adjacent skin region, not directly affected by the nerve injury, also became hypersensitive, suggesting that information regarding the injury was sent to neighboring skin regions through central circuits. The team then investigated the mechanism of this communication to neighboring regions. They found that nerve fibers throughout the Vc that secrete the neurotransmitter serotonin, including those associated with the injured and uninjured neighboring region became more active after the nerve injury. Deactivating those serotonin projections reversed hypersensitivity in both regions. This finding indicates that serotonin fibers in the Vc are necessary for nerve injury-induced hypersensitivity in both the injured and the neighboring region. The investigators went on to show that the effect of serotonin is mediated by a specific type of serotonin receptor known as 5-HT3A receptor. This novel finding indicates a mechanism for the modulation of chronic pain through serotonin signaling and will inform the development of pain treatment strategies that target the serotonergic circuitry.

MicroRNAs Activate Pain Sensitive Neurons


Pain signaling is a complex process. In each pain-sensing cell, multiple proteins interact with each other and with external factors for the cell to be activated and to transmit the pain signal to the brain. In addition, pain-sensing cells can change their properties when an animal is injured to become more sensitive to stimuli such as heat and pressure. Researchers found that microRNA may represent a whole new class of pain mediators that function through an unconventional role in the pain signaling system. MicroRNAs are small pieces of RNA that can act either within a cell or with receptors on the surface of a cell to alter its activity. This study found that a specific miRNA, called let-7b, can interact with the toll-like receptor-7 (TLR7) on the surface of pain sensing neurons to directly activate and excite the neurons. This activation is incredibly rapid and robust suggesting a mechanism that may be used to induce pain quickly. In addition, let-7b is found in clusters of pain sensing neurons called dorsal root ganglia (DRG). When these neurons are activated by a painful stimulus they can release let-7b to the extracellular space and then through a selective functional interaction of TLR7 and a receptor called TRPA1 may enhance the function of neighboring neurons. Under normal circumstances, this could be a useful adaptation to make neurons temporarily more sensitive to noxious stimuli and help an animal to avoid serious harm. If let-7b is present when it is not needed, it could make cells unnecessarily sensitive to stimuli that should not be painful. It could therefore be a potential target for the treatment of chronic pain conditions.
The discovery that let-7b functions as a pain mediator shows that new analgesic targets may be discovered in some very surprising places.

### Risk Factors & Causes

**Altered brain activity in IBS patients associated with exposure to adverse early life events**


Irritable bowel syndrome (IBS) is the most common functional pain disorder, affecting 10 to 15 percent of U.S. adults. Scientists have identified various factors that make people more vulnerable to developing stress-sensitive disorders such as IBS. These vulnerability factors include both sex and early adverse life (EAL) events, such as loss or chronic illness of a parent, discordant relationships between parents, or various types of abuse. In this study, the researchers worked with a group of individuals with IBS in an effort to identify disease- and sex-based differences in brain activity. The researchers used brain imaging techniques to analyze activity in brain networks relevant to pain, such as those associated with cognitive control, attention, emotion, and perception. They found that in both male and female IBS patients, a history of EALs was associated with altered brain network activity relevant to anxiety and abnormal sensorimotor integration. Male patients also exhibited alterations in the cerebellar network, which is involved in fear, movement, and visual-motor learning. These abnormal patterns were not seen in healthy controls with a history of EALs, suggesting an important interaction between EALs and other factors involved in IBS pathophysiology.

![Graphic representation of some brain regions imaged in this study. Image credit: Arpana Gupta](image)

### Treatment of Complex Regional Pain Syndrome (CRPS) in Children Normalizes Brain Activity


A Resting State Network (RSN) is a collection of interconnected brain regions that are active concurrently while a person is not performing a goal-directed task. The networks can be identified with non-invasive brain imaging techniques. Within a given brain, there are many RSN’s called components, which usually comprise brain regions with similar functions during active tasks. They are often altered in chronic brain-related disease states and may change in response to drugs and other therapies. This study investigated RSN components in children with a chronic pain condition called Complex Regional Pain Syndrome (CRPS), which typically presents with persistent and intense pain on localized regions of the body following a major or even very minor injury. The study investigated whether pediatric CRPS alters RSN components and whether treatment of CRPS can normalize those altered components. Relative to healthy controls, pediatric CRPS patients showed widespread alteration of the brain’s resting state activity during pain. In addition, treatment of the CRPS condition resulted in normalization of brain activity in the altered components, producing patterns more consistent with healthy controls. These findings demonstrate that RSN components can be used to...
assess altered brain function in the pain state and as a result of treatment. In the future, analysis of RSN components may be used to predict severity of the disease and to implement appropriate treatment strategies.

**Surveillance & Human Trials**

**A more consistent measure of Americans suffering from persistent pain.**

Prevalence of Persistent Pain in the U.S. Adult Population: New Data From the 2010 National Health Interview Survey
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To effectively meet the needs of managing a health condition at the population level, it is imperative to know how many people are affected. The lack of data on overall prevalence and on subpopulations who are at greater risk is notable for chronic pain. The reported prevalence for constant or frequent pain in the US population varies from as low as 11% to as high as about 47%. These vastly differing numbers are due in part to the inconsistent criteria for defining chronic pain. It is important to have a “precise and consistent” measure of the unmet burden of chronic pain to develop effective treatment strategies and to track their progress. This study suggests that measuring “persistent pain” defined as self-reported pain “every day” or “most days” for the past 3 months is a useful measure. Using these criteria, the authors added a quality of life supplement to the 2010 National Health Inventory Survey (NHIS), which queried about 35,000 households. The research team found that approximately 19% of American adults suffer from persistent pain, with differences across subgroups. Many more older adults than younger adults reported persistent pain. Women are slightly more likely than men to report persistent pain. Race, education, and health indices, especially anxiety, depression, and fatigue influence the rate of reporting. The prevalence of persistent pain is related to, but not equivalent to that found in other studies in which somewhat different measures were used to assess chronic pain and disability. The prevalence estimates in all studies however, highlight the enormous public health issue of pain.

**Cognitive Behavioral Therapy for Children with Functional Abdominal Pain May Enhance Long-term Benefits of Treatment for Both Patients and Parents**

Twelve-month follow-up of cognitive behavioral therapy for children with functional abdominal pain.

Functional abdominal pain (FAP), or recurrent abdominal pain with no discernible medical cause, is a common issue for children. In addition to decreased quality of life, children with FAP are at greater risk for developing chronic pain conditions in adulthood. With any treatment plan it is important to consider long-term maintenance of benefits. This is especially important in pediatrics where well-meaning parents can hinder a child’s ability to develop coping mechanisms by promoting illness behaviors rather than encouraging wellness. Researchers provided a group of parent-child pairs with three sessions of cognitive behavioral therapy and social learning strategies to manage FAP symptoms in addition to their regular treatments. Follow-up testing, twelve months after the sessions, revealed that children who had received this training were better able to cope with their symptoms. In addition, their parents learned to help them manage their symptoms and keep a more positive attitude. This promising result suggests that a series of brief psychological interventions, incorporated into a patient’s regular treatment plan, could yield long-lasting benefits for children suffering from abdominal pain as well as their parents.
Cognitive-behavioral therapy may improve symptoms for chronic pain patients


Most people with chronic pain also have poor sleep quality, with insomnia being the most common type of sleep disturbance associated with chronic pain. Prior research has demonstrated that poor sleep increases both the risks and consequences of chronic pain, including impaired immune function and emotion regulation, and increased sensitivity to pain. Interventions that target sleep in patients with chronic pain may produce improvements in pain symptoms, and may be an important treatment strategy given that chronic pain is often difficult to treat pharmacologically. In this article, the authors reviewed data from six randomized controlled trials examining cognitive-behavioral therapy (CBT) for insomnia and/or pain in patients with comorbid insomnia and chronic pain. The data suggest that CBT improved sleep, as well as pain-related functional outcomes such as pain interference and disability. The authors argue for expanding on these findings with larger-scale clinical trial research, as well as more comprehensive pain assessments with longer-term follow-up. Such research would clarify the value of hybrid CBT approaches, in which patients are treated for both insomnia and pain, and may also reveal whether, over a longer timeframe, CBT produces improvements in pain severity.

Tools/Instruments

**Illuminating Pain Pathways**


Recent studies using optogenetics have provided valuable insight into the mechanisms of pain transmission. This technology is one in which light sensitive proteins, called opsins, are introduced into a living animal’s neurons. Light can then be used to control neuronal activity through stimulation of the opsins. This tool has provided a great deal of information about how activated neurons behave. In the past however, it has relied on genetically modifying animals, a time consuming and expensive process needed to express the opsins in neurons. In this study researchers used a novel and clinically relevant method to deliver the opsins to neurons. They engineered a virus that targets nerves to carry the opsins to pain signaling neurons in the spinal cord of normal mice and those with neuropathic pain. The virus, carrying either Chr2, a blue light-sensitive protein that stimulates neural activity, or NpHR, a yellow light-sensitive protein that inhibits neural activity was injected into the paw and carried by nerves to the spinal cord neurons. When mice that express Chr2 were exposed to blue light, they exhibited pain behaviors including paw licking and flinching. When exposed to a low level of blue light, they did not show any pain behaviors, but were sensitive to touch and temperature that were not normally painful. They also learned to avoid the pain inducing blue light. When mice expressing NpHR were exposed to yellow light, they were desensitized to normally painful stimuli. Illumination with yellow light also prevented animals from becoming more sensitive to painful stimuli after nerve damage. This study represents an important advance in optogenetics, because it shows that using viruses to introduce opsins is a clinically tested and viable alternative to genetic modification. Although there are many hurdles to using this technique in humans, it likely
will prove invaluable for basic research. This development of faster and cheaper optogenetics, when combined with genetically manipulated animals, will allow scientists to target very specific types of neurons and study neural pain pathways in unprecedented detail.

**Powerful Microscopy Suggests Unique Activation Properties of TRPV1**


TRPV1 is an ion channel which is expressed in heat and pain sensitive neurons. These neurons react to a variety of different stimuli, and are important for the hypersensitivity to touch and temperature that is seen with inflammation. In this study, researchers mixed purified TRPV1 channels with capsaicin or resiniferotoxin, compounds known to activate the channel. They then used single-particle electron cryomicroscopy, a powerful magnifying system, to visualize the channel and determine the effects of these compounds on the channel structure. Each compound binds a different region of the TRPV1 protein and changes the conformation in a unique way. The unique binding sites show that TRPV1 channels have an “upper” and “lower” gate that are each selectively opened by different compounds. This independent regulation suggests an answer to the question of how TRPV1 can have unique reactions to different compounds, and be more sensitive when inflammatory factors are present.

**Use of Services, Treatments & Interventions**

**Recommendation to Reduce Systemic Barriers to Effective Cancer Pain Management**


The management of pain medication regimens by cancer patients and their caregivers in their home environments is complex. Proper outpatient treatment often requires multiple physicians, medications, dosing regimens, family caregivers, and reimbursement schemes. In this study, investigators qualitatively analyzed audio-taped pain management discussions between patients, family caregivers, and nurses about a recently completed 10-week medication program. Patients reported a variety of barriers to access to their medications, prescription errors, miscommunication between doctors and caregivers, and a lack of coordination among clinical, reimbursement, and regulatory systems. These problems increased the likelihood of safety problems, treatment delays, and dosing errors by caregivers. The findings highlight the difficulties inherent to the nation’s current system for the treatment of pain. As a result, the authors recommend that future healthcare reforms improve access to medications, promote safe use of those medications, and reduce unnecessary burdens placed on patients and caregivers.