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STUDIES EXPLORE NEW APPROACHES TO TREATING PAIN

Research includes drug and non-drug interventions

Washington — Scientists are discovering promising approaches to treating pain, one of the most common and debilitating neurological complaints, according to research released today at Neuroscience 2011, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. Studies show that "mirror box therapy" can help reduce arthritis-related pain, and that a new opioid-like drug may be able to relieve acute pain without the euphoric effects that can lead to dependency. Additional research also identifies the possible neurobiological source of common side effects of morphine.

Specifically, today's new findings show that:

- Two of morphine's most common side effects, itch and headache, may be due to the drug's activation of immune cells in the membrane surrounding the brain and spinal cord (Julie Wieseler, PhD, abstract 178.12, see summary attached).
- A visual feedback technique called mirror box therapy can help alleviate hand pain in patients with arthritis (Laura Case, abstract 72.03, see summary attached).
- In an animal study, a novel drug relieves acute pain without the dangerous side effects associated with opioid painkillers such as morphine (Stephen Harrison, PhD, abstract 178.10, see summary attached).

Other recent findings discussed show:

- A gene therapy treatment reduced pain in 10 people in a Phase I clinical trial that tested for treatment safety (David Fink, MD, see attached speaker's summary).
- A naturally occurring protein that supports the survival and growth of neurons in the brain and spinal cord may be a potential therapeutic intervention to prevent chronic pain following spinal cord injuries, according to animal research (Ching-Yi Lin, PhD, see attached speaker's summary).

"Pain is one of the most intransigent and difficult symptoms to treat," said Allan I. Basbaum, PhD, FRS, of the University of California, San Francisco, press conference moderator and expert on the neurobiology of pain. "These studies and others are helping us better understand the complex neural pathways involved in pain and the long-term consequences of injury. With this, researchers will be better poised to develop approaches to alleviate pain and aid in recovery from injuries."

This research was supported by national funding agencies, such as the National Institutes of Health, as well as private and philanthropic organizations. Dr. Basbaum has consulted with Nektar Therapeutics, Inc., but was not involved in research presented today.

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Related Presentations:

Nanosymposium: **Pain Imaging and Perception II**
Tuesday, Nov. 15, 1–3:15 p.m., Room 147B

Minisymposium: **The Neurobiological Bases of Social Pain**
Sunday, Nov. 13, 1:30–4 p.m., Room 145B

Special Lecture: **Gating Pain: From Normal to Pathological Transmission in the Spinal Cord**
Sunday, Nov. 13, 8:30–9:40 a.m., Hall D
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Abstract 178.12 Summary

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Research Suggests Triggers for Morphine's Uncomfortable Side Effects

Cellular study finds morphine activates immune cells in brain

Two of morphine's most common side effects — itch and headache — may be due to the drug's effect on inflammatory cells found in the membrane covering the brain and spinal cord, according to a new study. The research was presented at Neuroscience 2011, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Morphine is commonly used to treat pain, including the severe pain of both tension and migraine headaches. Ironically, repeated use of morphine can induce headaches as well as relentless itching (pruritis) of the skin. These side effects are poorly understood and thus poorly controlled.

The current study, led by Julie L. Wieseler, PhD, of the University of Colorado at Boulder, found that morphine binds to a specific protein called toll-like receptor 4 (TLR4) found on immune cells called mast cells in the meninges — the membrane that covers the brain and spinal cord. Morphine activated the mast cells to produce inflammatory substances, including histamine and interleukin (IL)1, that can cause itch and pain.

"These data support a potential role for TLR4 in morphine-induced headaches and itch," said Wieseler. "Future research may lead to interventions that could mitigate the unwanted side effects that frequently occur when morphine is used to relieve pain."

Research was supported the National Institutes of Health, National Institute on Drug Abuse and National Institute on Alcohol Abuse and Alcoholism.

Scientific Presentation: Sunday, Nov. 13, 11–12 p.m., Halls A–C

178.12, Morphine modulates mast cell activity via TLR4: implications for medication overuse headache and pruritus.
A. MCFADDEN[1], **J. WIESELER[1]**, Y. ZHANG[1], L. LORAM[1], N. MILES[1], M. R. HUTCHINSON[2], K. C. RICE[3], S. F. MAIER[1], *L. R. WATKINS[1]; [1]Dept Psychology & Neurosci., Univ. Colorado At Boulder, BOULDER, CO; [2]Univ. of Adelaide, Adelaide, Australia; [3]Chem. Res. Br., Natl. Inst. on Drug Abuse & Natl. Inst. on Alcohol Abuse & Alcoholism, Rockville, MD

TECHNICAL ABSTRACT: Opioids are commonly used to treat pain, with morphine being the prototypical opioid. Morphine is given to treat tension-type headache and migraine headache, with repeated usage leading to medication overuse headache (MOH). Morphine is also commonly used to control pain in obstetrics, with the development of a common side effect, itch/pruritus, a symptom known to be dependent on the histamine released from mast cells. Here, we suggest that both of these phenomena associated with morphine are the result of toll like receptor (TLR) 4 activation of meningeal mast cells.
The meninges are implicated in the development of migraine headache. While often thought of as a basic barrier to protect the central nervous system, the understated significance of the meninges is that 1) they are innervated by afferent C-fiber, and 2) they house immune cells, including mast cells. As such, the meninges are well positioned to be a key interface between the central nervous system and peripheral immune system, as well as serve as a target for morphine. Mast cells release a host of inflammatory signals including histamine and interleukin (IL)1, and express TLR4. In migraine, mast cells are thought to release these inflammatory signals that then stimulate local nociceptors. Histamine is also a well-known mediator of itch, whereas TLR4 and IL1 are known to play critical roles in chronic pain. Lastly, systemic morphine increases expression of TLR4 and IL1 in the dorsal spinal cord, and repeated administration potentiates chronic pain. We investigated the effects of morphine on mast cell and TLR4 activity *in vitro* and *ex vivo*. Mast cell activity was inferred based on gene expression for IL1 and histidine decarboxylase (converts histidine to histamine) in the MC9 mast cell line as well as rat meninges. Mast cell TLR4 activity was inferred based on gene expression changes of IL1 and histidine decarboxylase in response to the classical TLR4 antagonist, Rhodobacter sphaeroides lipopolysaccharide (LPS-RS), and the novel *non*-opioid TLR4 antagonist, (+)-naloxone. Gene expression analysis followed 4 or 24 hr incubations in the various conditions. Morphine increased IL1 and histidine decarboxylase, supporting that morphine can activate mast cells. Co-administration of morphine with (+)-naloxone decreased IL1 and histidine decarboxylase gene expression, and dramatically decreased TLR4 expression. These data are the first to show that morphine activates mast cells beyond simply inducing degranulation. These data support a potential role for TLR4 in morphine induced MOH and morphine induced itch.

Abstract 72.03 Summary

Lead author: Laura Case (781) 223-1213
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"Mirror Box Therapy" Helps Reduce Arthritis Pain

Finding may lead to new non-drug treatments

A visual feedback technique called mirror box therapy can help reduce hand pain in patients with arthritis. These findings — among the first attempts to extend visual treatments to pain originating in intact limbs — was presented at Neuroscience 2011, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

An estimated 50 million Americans experience daily pain and restricted movement due to arthritis. "Our findings suggest that simple and inexpensive materials like mirrors could be used to reduce the pain and suffering caused by this common disease," said lead author Laura Case of the University of California, San Diego (UCSD).

For the study, Case and her colleagues had patients with osteoarthritis or rheumatoid arthritis in their hands undergo a variant of mirror visual feedback therapy. The experimenter and patient volunteer positioned their hands before and behind a mirror so that the experimenter's healthy hand appeared to be where the patient's hand would be. The participant was then instructed to mimic the slow hand movements made by the experimenter so that the participant felt as though the reflected hand was his or her own.

"Many patients reported a reduction in pain and stiffness during this illusion," said Case. Other visual feedback procedures, including one that involved viewing the hand through a shrinking lens, also reduced the patients' pain, but not as effectively as mirror therapy.

Previous research at UCSD and elsewhere has demonstrated that visual feedback can reduce pain caused by amputation-induced phantom limbs and complex regional pain syndrome (CRPS), or aid in motor recovery after stroke-induced paralysis. The current study is one of the first to investigate whether visual treatments can help treat arthritis and other pain that originates in intact limbs.

Scientific Presentation: Saturday, Nov. 12, 3–4 p.m., Halls A–C

72.03, Mirror and other visual feedback techniques reduce chronic central pain including osteoarthritis
L. K. CASE[1], D. J. BRANG[1], H. K. GROVES[2], V. RAMACHANDRAN[1]; [1]Dept. of Psychology, [2]Sch. of Med., UCSD, La Jolla, CA

TECHNICAL ABSTRACT: Mirror visual therapy (MVF) was originally introduced by our group as a novel, noninvasive visual treatment for phantom limb pain and complex regional pain syndrome. MVF demonstrated the powerful role of visual feedback in reducing chronic pain and inspired the use of other visual feedback techniques such as visual minification, visual displacement or distortion, and virtual reality. These treatments have shown initial promise in the treatment of a variety of chronic pain conditions, both in phantom and intact body parts. MVF, however, has not been tested in a wider variety of pain conditions such as arthritis. First, we present evidence for strong central contributions to arthritic pain. We employed the size weight illusion, in which one object is felt to be 30% heavier than another simply because it is smaller, even though they are of identical mass. Arthritic patients felt substantially more pain lifting the small weight even though the weights stimulated peripheral pain receptors equally. This demonstration of central modulation of arthritic pain suggests the utility of extending visual feedback techniques to this condition. Second, we present results from testing novel variants of mirror visual feedback therapy. Patients with chronic pain were tested using mirror box therapy, optical distortion, minifying lenses, and control procedures. Mirror box treatment significantly reduced pain and stiffness ratings for patients with osteoarthritis, in addition to increasing range of motion. Our variant of mirror box therapy substitutes an image of a healthy hand for the patient's arthritic hand by visually superimposing the healthy arm of an experimenter onto one of the patient's arms and asking the patient to mimic the slow, purposeful movements of the experimenter. An additional, yet less striking reduction in pain occurred from visual feedback of massage. Here, the experimenter's hand, superimposed in the mirror box onto the patient's, is massaged, reducing pain in the patient's limb. In addition, patients with phantom limb pain were helped if they simply watched the experimenter's hand (virtual massage), presumably through activation of the mirror neuron system. Finally, in a variant of MVF, a warm compress placed on the ipsilateral face or placed on the intact arm in a mirror box referred sensations of warmth and rubbing to phantom limbs, reducing pain. These advances demonstrate the powerful modulation of pain and paralysis, whether in phantom or intact limbs, using simple, noninvasive visual techniques. The results are of theoretical interest in understanding modulation of central pain and of practical interest in therapeutic practice in the clinic or home.

Abstract 178.10 Summary

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San Francisco, Calif.

Next-Generation Painkiller for Acute Pain Identified

Animal study suggests drug acts quickly but without dangerous side effects of opioids

Using a new polymer technology, scientists have developed a fast-acting drug that has been shown in animal studies to relieve acute pain without the side effects associated with opioid painkillers such as morphine. The research was presented at Neuroscience 2011, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Although prescription opioids are considered the most effective treatment for moderate-to-severe pain, their abuse has been identified by the U.S. Food and Drug Administration as a significant public health issue. One reason for opioid abuse is the rapid manner in which the drugs enter the brain, frequently causing a euphoric effect that can lead to dependency and abuse. Opioids can also cause excessive sleepiness and respiratory depression.

The drug, NKTR-192, binds to the mu-opioid receptors in the brain and in the periphery, believed to be the primary mechanisms of pain relief for opioids. The compound was selected for development because of its ability to provide acute pain relief while also entering the brain at a slower rate compared to current opioid drugs. Rodent tests showed that the compound worked quickly at relieving pain — about 15 minutes after ingestion. Further tests showed that the drug did not appear to be highly sedating or lead to abuse at the doses effective for pain relief.

"By providing effective analgesia with reduced side effects, this new drug may help transform the treatment of pain," said lead study author Stephen Harrison, PhD, of Nektar Therapeutics, Inc.

At Neuroscience 2010, Nektar Therapeutics presented another drug, NKTR-181, which has many of the same characteristics of NKTR-192, but is long-acting. It is being developed to treat chronic pain, and is currently in Phase 1 clinical testing.

Scientific Presentation: Sunday, Nov. 13, 9–10 a.m., Halls A–C

178.10, Pharmacological characterization of an orally active opioid analgesic with rapid onset of activity and low abuse liability.
S. D. HARRISON[1], C. ALI[2], C. IRENE[2], J. EVANS[2], S. FISHBURN[2], K. GOGAS[2], M. GUILLON[2], H. GURSAHANI[2], G. KIM[2], M. LEE[2], B. MANGADU[2], D. MCWEENEY[2], J. PFEIFFER[2], P. QUACH[2], J. RIGGS[3], G. STEPHENSON[3], P. TRINCHERO[2], S. WONG[2], T. RILEY[3]; [1]Res., Nektar Therapeutics, Inc, San Francisco, CA; [2]Nektar Therapeut., San Francisco, CA; [3]Nektar Therapeut., Huntsville, AL

TECHNICAL ABSTRACT: Opioids are widely prescribed for the treatment of moderate to severe acute pain but are limited by their CNS-mediated side effects, notably abuse liability. Stable polymer conjugation has been successfully applied to slow CNS entry of NKTR-181, an opioid with a prolonged duration of analgesic action for the chronic treatment of moderate to severe pain, but with markedly reduced abuse liability and CNS side effects. Using novel polymer conjugation we are developing a peripherally-restricted opioid (NKTR-192) for the treatment of acute pain, differentiated from NKTR-181 by a rapid onset of analgesic activity, predicted short duration of action, low CNS side-effects and abuse liability in rodent models. We have identified several candidate compounds to meet the NKTR-192 profile. One of these, NKTR-192-A, binds to the mu opioid receptor (Ki = 76 nM) and displays full agonist efficacy in vitro. Oral NKTR-192-A produces full efficacy in the rat formalin test and rat CFA-evoked hyperalgesia model of inflammatory pain (ED50 = 30-100 mg/kg po). Activity in the formalin paw test was seen within 5 min, consistent with attainment of peak plasma concentrations 5-15 mins after oral dosing in rats, suggesting a rapid onset of analgesic effect. NKTR-192-A also demonstrated oral efficacy in the mouse acetic-acid writhing test and its analgesic effect in this model was blocked by pre-treatment with the opioid receptor antagonists Naloxone and Naloxone Methiodide [NXMT]. The blockade by NXMT, which does not enter the CNS at the doses tested, supports a role for peripheral opioid receptors in the mediation of this analgesic effect. Doses of NKTR-192-A that produced a greater than 50% reduction in the time spent on the rotarod were substantially higher than doses that were associated with efficacy in the pain models, suggesting a significant separation of the analgesic and CNS side effects. These data were consistent with *in vivo* pharmacokinetic and *in situ* brain perfusion data in rats showing a 10-100 fold reduction in brain entry compared with marketed opioids. Finally, when evaluated in a rodent self-administration model, NKTR-192-A showed low abuse potential relative to marketed comparator opioids, producing progressive ratio breakpoints that were comparable to saline. These preclinical data suggest that NKTR-192-A is a mu-opioid agonist with low abuse liability and CNS side effects that produces a rapid onset of analgesic activity by acting predominantly at peripheral mu opioid receptors. NKTR-192-A has the potential to be an effective analgesic with a reduced CNS side-effect profile and lower abuse potential compared to currently marketed products for this indication.

Speaker's Summary

Speaker: David Fink, MD (734) 936-9070
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Gene Therapy for Pain: Results of a Phase I Clinical Trial (72.14)
Poster Session: Treatments for Persistent Pain
Saturday, Nov. 12, 2–3 p.m., Washington Convention Center, Halls A–C

Chronic pain is a difficult problem, one that is often refractory to medical management using available treatments.

In previous work, we constructed a gene transfer system (Nerve Targeting Drug Delivery System: NTDDS) that allows us to target the expression of pain-relieving substances to selected peripheral nerves by inoculation of the vector in the skin. Release of the pain-relieving substance from central terminals of those nerves into the spinal cord can be used to selectively block pain sensation. In preclinical studies using animal models of pain caused by inflammation, by damage to nerves, or by cancer in bone we previously demonstrated that this approach was effective in reducing pain-related behaviors. Based on the animal study results, we proceeded to a human clinical trial of a vector (NP2, Diamyd Incorporated) that was engineered to release naturally occurring morphine-like peptides termed enkephalins, in patients with intractable pain from cancer.

In the study that we are reporting at this meeting, 10 patients with severe pain unresponsive to high dose opiates were treated by injection of NP2 into the area of skin that corresponded to the distribution of radiating pain from their cancer. Three different doses of the vector were tested. Patients in the low dose group showed no response to the treatment. Patients in the two higher doses showed a substantial and dose-related reduction in their pain.

This first human study was designed as a Phase I clinical trial, to determine whether the NTDDS approach to treat pain was safe. The study was successful since no serious vector-related side effects were observed. Because it was a Phase I trial there were no patients treated with an inactive agent (i.e. no placebo controls) which limits our ability to draw conclusions about the pain relieving properties of NP2. However, the observation that increasing doses of the vector produced progressively greater pain relief is encouraging, and early this year Diamyd Incorporated initiated a Phase II blinded, placebo-controlled clinical study that is currently enrolling subjects which we expect to conclude around the end of the year.

Speaker's Summary

Speaker: Ching-Yi Lin, PhD (216) 445-5047
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Fibronectin Administration Inhibits Chronic Pain Development After Spinal Cord Injury (64.04)
Poster Session: Spinal Cord Injury: Therapeutic Strategies I
Saturday, Nov. 12, 4–5 p.m., Washington Convention Center, Halls A–C

More than 1 million Americans suffer from spinal cord injuries (SCI), with an estimated 11,000 new SCI each year. After SCI, chronic pain develops, which is among the most difficult SCI symptoms to treat or manage. When compared to other symptoms, SCI patients ranked relief from chronic pain as a high priority for improving their quality of life. Most importantly, individuals who have been suffering from SCI longer, rank pain relief higher than those whose injury is newer. This is probably because chronic SCI pain does not significantly improve over time when SCI patients receive current clinical treatment regimens, such as morphine administered systemically or by indwelling intrathecal pump systems. In order to improve the prognosis and quality of life of SCI patients, novel strategies to inhibit chronic SCI pain are needed. The long-term goal of our research is to develop a clinically feasible and mechanism-driven intervention for chronic pain. Fibronectin is a naturally occurring protein that supports the survival and growth of neurons in the brain and spinal cord. There is evidence that binding of fibronectin to its specific receptor (integrin) after injury can stimulate axonal growth, regulate inflammation, reduce tissue loss, and in some cases improve functional outcome. These properties of fibronectin suggested the possibility of using fibronectin in our studies to ameliorate SCI related pain.

Both mechanical allodynia and thermal hyperalgesia are pain-associated behaviors that can be assessed using von Frey filaments and radiant infrared heat, respectively, in animal models. Our study has demonstrated, for the first time, that a one-time intraspinal injection of fibronectin delivered acutely robustly inhibits the development of mechanical allodynia (non-noxious stimuli become noxious) but not thermal hyperalgesia (noxious stimuli become more noxious) over an extended observation period following spinal cord dorsal column crush injury. This indicates that a single, acute fibronectin injection was sufficient to desensitize injured animals such that they never developed allodynia to non-noxious mechanical stimuli over a 6-month observation period.

By applying various fibronectin fragments as well as competitive inhibitors, these anti-allodynia effects were shown to be dependent on the CS-1 motif of fibronectin. Furthermore, we found that acute fibronectin treatment diminished inflammation and blood vessel permeability in the spinal cord, which in turn led to enhanced fiber sparing and sprouting. In particular, the reduction of serotonin caused by spinal cord injury in the superficial dorsal horn, an important descending system in the modulation of pain, was reversed with fibronectin treatment. We conclude that treatment of SCI with fibronectin in our model preserved sensory regulation and prevented the development of chronic allodynia, providing the framework for a potential therapeutic intervention to treat chronic pain following SCI.