ORIGINAL ARTICLE

Opioids and brain imaging

Shyam Balasubramanian, MBBS, MD, FRCA
Patricia Morley-Forster, MD, FRCPC
Yves Bureau, PhD

ABSTRACT

Since the introduction of the gate-control theory, a plethora of evidence to support the spinal processing of pain signals has come to light. Cognitive and affective aspects of the pain experience indicate the importance of supraspinal structures, but the biological mechanisms have remained inadequately explored. Within the past decade, imaging techniques have emerged that enable in vivo assessment of the central opioidergic system and the central processing of pain. The two most important imaging modalities to this end are functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). This article will describe the underlying principles of these techniques and explain their importance in determining the loci of opioidergic pathways and their neuromodulatory influence on acute and chronic pain conditions, role in placebo effects, implication in drug dependence, and potential role in studying the analgesic efficacy of new drugs.

Key words: brain imaging, fMRI, PET, central opioid pathways, central pain processing

INTRODUCTION

The development of modern imaging techniques has allowed clinical researchers and other scientists to better appreciate the functional organization of the central nociceptive system and its modulation by opioids. Cognitive and affective aspects of the pain experience indicate that the brain is one of the most potent centers for modulation of pain signals.[1,2] Prior to the advent of functional neuroimaging technologies, these mechanisms had been studied only cursorily.[3] Regional cerebral blood flow (CBF), as a reflection of the activity of regional synapses, can be quantified with radiographic techniques. Pain intensity-related hemodynamic changes have been identified in a widespread, bilateral brain system that includes the parietal, insular, cingulate, and frontal cortical areas. Changes have also been noted in the thalamus, amygdala, and midbrain.

Neuroimaging studies have also contributed to our knowledge of the role of endogenous opioids in the placebo effect and of the effects of substance misuse and abuse on the brain. We now understand that the mechanism of action of opioids is more complex than simple inhibition of neural activation. Recent technology has allowed for demonstrations of opioid receptor distribution, neurophysiology at the receptor level, delineation of neurochemical pathologies in disease states, and changes in neurotransmission.[4] The hope is that, based on information gained from brain imaging, pathway-targeted interventions will be developed.

POSITRON EMISSION TOMOGRAPHY

Positron emission tomography (PET) is the only neuroimaging technology that allows three-dimensional determination of the central opioid receptor distribution in fully conscious humans. The first human opioid receptor imaging study using PET was conducted on May 24, 1984,[5] and the first PET report on human pain was published in 1991.[6] The basic underlying principle of the technique is that neurons within active areas of the brain require more glucose and oxygen compared to neurons at a baseline condition within the same area. Thus, in response to the increase in metabolism in the active neurons, regional cerebral blood flow (CBF) increases. Radiolabeled glucose, such as ^{18}F fluorodeoxyglucose (F-18 FDG), is readily taken up by neurons, even more so by active neurons. Gamma rays released from the interactions of these radiolabeled molecules with electrons within the body are detected and processed by external sensors, and this external equipment produces an image.[7] PET scanners can map the concentration of the radiolabeled molecule and the binding of pharmacological agents over time. However, PET as a tool for assessing task-related brain activity is restricted by its relatively long measuring time.

FUNCTIONAL MAGNETIC RESONANCE IMAGING

The first functional magnetic resonance imaging

(fMRI) report on human pain was published in 1995,[8] and the experiment used electrical stimulation of an extremity to demonstrate activation of the somatosensory cortex. MRI measures the different magnetic spins between oxygenated and deoxygenated hemoglobin, the levels of which change with neuronal oxygen consumption. In the original studies, longer periods of painful stimulus were used for brain imaging studies. This introduced confounding factors to the study of pain, due to the effects of skin damage, subject compliance, interstimulus interaction, etc. It was proven that the changes in signal intensity during periods of short, repetitive stimuli and longer periods of painful stimuli were similar.[9] Consequently, more tolerable, shorter stimuli that do not have the desensitizing effects of longer stimuli are now used in these neuroimaging studies.

While PET can be used to measure available receptors and uptake sites, fMRI measures the indirect effects of drugs on the brain through their effects on CBF.[10] Compared to PET, fMRI has greater temporal (seconds vs. minutes) and spatial (about 1 mm vs. 4 mm) resolution, allowing for better localization of brain activity during complex event-related tasks.[11] Recently, novel approaches using a combination of fMRI and PET used to measure concurrent changes in CBF and regional cerebral metabolic rate during human brain activity have been reported.[12]

HYBRID IMAGING

PET/CT

A frequent complaint in receptor binding investigations is the lack of accuracy in determining the location of ligand-receptor binding in the brain.[13,14] Accuracy in determining brain regions of interest with PET signals is better accomplished by combining PET images with computed tomography (CT) images.[13,15] Early experiments required that the subjects/patients be imaged in a PET scanner first and in a CT scanner later. This necessitated moving the patient from one machine to another and sometimes making a second appointment. Furthermore, the separate images had to be either visually compared side by side or co-registered using software that merged the images. The software method did not always result in perfectly co-registered images, making analyses somewhat unreliable.

Within the last few years, dual PET/CT scanners have been developed.[14] Essentially, they are a combination of dedicated PET and dedicated CT scanners within the same chassis. Thus, even though patients can be scanned by PET and CT in a single experiment without having to move to a different machine, the scans will still be sequential as opposed to simultaneous. The advantage of dual PET/CT scanners is that inaccuracies due to repositioning are minimized. That being said, the bed on which the patient is lying does move so that the body part of interest is positioned in the right place for the chosen scan. Consequently, there is still some repositioning artifact, but the results are vastly preferable to those obtained by independent machines.

There are exciting possibilities for opioid research with combination PET/CT scanners. However, to date little has been done in opiate receptor or pain research with this hybrid technology. A dedicated PET scanner on its own is still the machine of choice for opiate imaging research because of its relatively low cost and the fact that PET/CT scanners are relegated mostly to clinical diagnostic work, often for use in cancer staging.

PET/MRI

As mentioned, current PET/CT machines do not allow for simultaneous PET and CT images. Simultaneous imaging using separate modalities is key for a machine to be a true hybrid. MRI uses strong magnetic fields for imaging purposes, and these fields may negatively interact with the detectors used in most PET scanners. Nevertheless, there are prototypes of PET/MRI hybrids being built today that may be the predecessors of better machines to come. Advantages of such technology include better soft-tissue images from MRI (compared to CT) in combination with simultaneous PET images that can be co-registered with greater accuracy. There are no repositioning artifacts, as the patient would not be moved to another machine or have the bed shifted when a different scanning modality was enacted. So far, only mouse images have been acquired in this way, using small-bore PET/MRI machines.[16] But this technology is promising and eagerly anticipated by the imaging community.

OPIATE RADIOLIGANDS

A tracer is a high affinity ligand that has a slow receptor dissociation rate and thus prolonged retention at the receptor. Derivation of the mathematical model that determines receptor-ligand binding properties for opioid receptors has been very helpful in PET imaging. In pain studies, commonly the μ-opioidergic agonist ^{11}C-carfentanil and the nonspecific opioid receptor antagonist ^{11}C-diprenorphine are utilized. Diprenorphine is a higher-affinity ^{3}H opiate ligand developed for visualizing opioid receptors. It lacks opiate receptor subtype specificity and has similar affinity for the μ, δ, and κ subtypes.[17] Diprenorphine also shows variability in its in vivo and in vitro binding characteristics because of the presence of sodium. Earlier studies used a highly potent μ-selective opioid agonist, lofentanil, but since it was not easily amenable to radiolabeling, it has been replaced by carfentanil.[18] Unlike diprenorphine, carfentanil, and newer

potent opiate agonists show similar in vivo and in vitro binding characteristics.

Radiotracers based on ^{11}C have a half-life of about 20 minutes and are suitable only for short imaging protocols lasting less than one hour after a bolus injection. For longer imaging requirements, an infusion is necessary following the bolus. This increases the total dose of opiate radioligands, imposing safety concerns. Compared to ^{11}C, an ^{18}F-labeled μ-selective ligand with a half-life of about 110 minutes improves signal quality and can be used for long-lasting imaging protocols, even with a single bolus injection. The recently developed ^{18}F-sufentanil is a promising tracer for extended protocols in μ-opioid mapping and quantification with PET.[19]

Discovery of a newer radioligand for the κ-opioid system, GR 103545,[20] now provides a unique opportunity to assess the opioidergic system in drug-dependent humans and in some neuropsychiatric disorders.

APPLIED NEUROANATOMY

Familiarity with basic neuroanatomy is essential in order to appreciate the importance of brain structures identified with functional brain imaging (Table 1). μ-receptor-mediated neurotransmission has been observed in both higher-order and subcortical brain regions. The prominent endogenous opioid transmission and μ-receptor populations are present in the prefrontal, cingulate, temporal, insular cortex, thalamic, hypothalamic, amygdala, basal ganglia, and brain stem regions.

The limbic system is a collective name for the structures involved in emotions, emotional responses, hormonal secretions, mood, motivation, pain, and pleasure sensations. It includes cortical and subcortical brain structures. The cortical structures include the prefrontal, anterior cingulate, and insular cortices. The subcortical structures include the thalamus, hypothalamus, amygdala, and hippocampus.

The nuclei that make up the basal ganglia are the striatum, globus pallidus, subthalamic nuclei, and substantia nigra. The striatum is further subdivided into the putamen, caudate nucleus, and nucleus accumbens. Although there is no clearly identified role for the basal ganglia, it may be important for motor function and learning. In particular, the nucleus accumbens, also called the ventral striatum, is rich in opioid receptors and is implicated in emotion and behavior.

OPIOID RECEPTORS AND ENDOGENOUS OPIOIDS

The endogenous opioid system is implicated not only in pain processing but in neuroendocrine function and immune modulation. In 1973, the receptors were first demonstrated in nervous tissue by the use of radioligand binding assay.[21] Bencherif et al.[22] studied the role of the supraspinal endogenous opioid system in pain processing using PET imaging of ^{11}C-carfentanil in eight healthy volunteers. They applied topical capsaicin to inflict acute pain and found that the supraspinal μ-opioid system was activated. They hypothesized that endogenous opioid peptides such as beta-endorphin, metenkephalin, endomorphin, or other opioid peptides are released in response to pain.

The contralateral insula is consistently one of the most significantly active regions involved in pain processing in studies using fMRI.[23] The medial nucleus of the thalamus projects to the anterior cingulate and prefrontal cortices. These areas partly comprise the median pain system that is thought to mediate affective-motivational aspects of pain perception.[24] The PET ligand studies of Zubieta et al.[25] revealed increases in μ-opioid receptor availability with advancing age in neocortical regions and the putamen. They also observed that women had higher opioid binding potential than men during the reproductive years, but binding decreased below that of men after menopause. Investigations regarding opioid receptors in the adult human cerebellum have been limited, but one PET study with ^{11}C-diprenorphine has provided strong evidence for opioid circuitry in the cerebellum.[26]

OPIOID AGONISTS

Neuroimaging technology is proving that opioid receptor activation has complex effects. The PET study conducted by Adler et al.[27] challenged the commonly believed hypothesis that, given the inhibitory effects of opioids on neuronal activity, there will be suppression of pain-evoked responses in distinct brain areas. They observed both decreases and increases in regional brain activity with fentanyl. The decrease in activity was noted bilaterally in the thalamus and posterior cingulate, while activation was observed in the anterior cingulate and contralateral motor cortex. The particular sector of the anterior cingulate that was activated by fentanyl has been implicated in attentional and affective processes in the past.[28] Thus, the mechanism of action of fentanyl analgesia is more than simple inhibition of regional cerebral neuronal activation. The modulation of attentional and affective processes may also contribute to fentanyl analgesia. Similarly, blood flow increases reflecting increased neuronal activity were detected in the orbitofrontal and medial prefrontal regions and the anterior cingulate cortex (ACC).[29] These brain regions are known to contribute to the processing of painful stimuli, as well as of attention and emotions.

Some fMRI studies have shown robust pain-related activity in the insular cortices that is significantly modulated by steady-state infusion of remifentanil. Wise et al.[30] were the first to use fMRI to calculate pharmacokinetic parameters describing the time of onset and offset of

Table 1. Applied neuroanatomy		
Structure	**Location**	**Role**
Prefrontal cortex	Anterior part of the frontal lobes of the brain; divided into lateral, orbitofrontal, and medial prefrontal areas	Implicated in planning complex cognitive behaviors; orbitofrontal cortex involved in decision making
Anterior cingulate cortex (ACC)	Located in middle of brain, just behind prefrontal cortex	Attention, cognitive modulation
Insular cortex	Buried deep in the lateral sulcus	Anterior part: emotion Posterior part: ascending visceral symptoms
Thalamus	Large, dual-lobed mass of gray-matter cells, located at top of brain stem	Receives auditory, visual, and somatosensory signals and relays them to the cerebral cortex
Hypothalamus	Posterior to optic chiasma, below the thalamus	Autonomic and endocrine functions, homeostasis, emotions, motor function; regulates food and water intake, sleep-wake cycle
Amygdala	Almond-shaped mass of nuclei, located deep within temporal lobes; lies medial to hypothalamus and adjacent to hippocampus	Arousal, aggression, fear, emotional responses, hormonal secretions
Hippocampus	Horseshoe shaped; located within temporal lobes, adjacent to amygdala	Consolidation of new memories, emotions, navigation, and spatial orientation
Nucleus accumbens	Lateral to septum pellucidum	Reward, pleasure, and addiction

remifentanil action based on changes in pain-related brain function.

OPIOID ANTAGONISTS

In 1975, Snyder and co-workers[17] demonstrated that opiate receptors could be labeled in vivo following an intravenous injection of an opiate antagonist, ^{3}H-naloxone. This was a landmark study, the first to investigate in vivo labeling of any receptor. The effects of naloxone on experimental and clinical pain have been widely reported. Naloxone enhances baseline clinical pain and diminishes the analgesic effectiveness of placebo.[31]

Borras et al.[32] conducted a study to determine the effect of naloxone on brain activity as measured by fMRI. They assessed the effects of naloxone on endogenous opioid systems and also evaluated its effect on central nervous system response to noxious heat. They observed that naloxone-specific activation changes were found in a number of cortical and subcortical regions and in the cerebellum. Cortical activation was induced in regions including the cingulate, prefrontal cortex, and insula. Subcortical regions showing increased signal change included the thalamus, hippocampus, and entorhinal cortex. These activated areas are the sites of action of endogenous opioid pathways involved in regulating central nervous system response to aversive stimuli.

PLACEBO ANALGESIA

There is overwhelming evidence that the endogenous opioid system is involved in placebo analgesia. In an elegant, widely cited PET study, Petrovic et al.[33] analyzed the brain regions that are affected both by placebo analgesia and remifentanil. In both cases, regional CBF changed in similar areas of the anterior cingulate, lateral orbitofrontal cortex, and brain stem, suggesting that placebo activates the same opioid receptor system to which remifentanil binds. However, this study did not include an anticipation period and so could not discriminate neural responses during anticipation from changes associated with the painful stimulus itself.

Amanzio and Benedetti[34] investigated the mechanism underlying the activation of endogenous opioids in placebo analgesia in humans by using a model of experimental ischemic arm pain. In their study, they produced different types of placebo response that could be totally blocked, partially blocked, or totally unaffected by naloxone. They speculated that placebo analgesia can be dissected into opioid and nonopioid components, depending on

the procedure used to induce the placebo response. By adding expectation cues, an opioid component is observed. The two fMRI experiments conducted by Wager et al.[35] found that placebo analgesia was related to decreased brain activity in pain-sensitive brain regions, including the thalamus, insula, and ACC, and was associated with increased activity during anticipation of pain in the prefrontal cortex, providing evidence that placebos alter the experience of pain.

More recently, Zubieta and colleagues[36] provided the first direct evidence that the administration of a placebo with implied analgesic properties activated the endogenous opioid system. They observed that neurotransmitter activity took place directly in higher-order brain regions, namely the rostral ACC; the dorsolateral, prefrontal, and insular cortices; and the nucleus accumbens. With the exception of the nucleus accumbens, these findings are similar to those of the fMRI studies of Wager et al.[35] It should be noted that nucleus accumbens signals are difficult to obtain with fMRI techniques.

ACUTE AND CHRONIC PAIN

There are differences in brain images acquired during acute and chronic pain states. Studies with ^{11}C-carfentanil revealed reduced μ-opioidergic binding, following induction of acute pain in masseter muscles, in the dorsal ACC, insula, thalamus, hypothalamus, amygdala, and lateral prefrontal cortex. It was also noted that with activation of the opioidergic system in the amygdala, thalamus, and nucleus accumbens, sensory pain scores were lower. Similarly, there was a negative correlation with affective pain ratings with activation of the ACC, thalamus, and nucleus accumbens.[37]

In chronic pain, PET studies have shown a decrease in radioligand-opiate receptor binding. Rheumatoid arthritis, trigeminal neuralgia, and central poststroke pain all lead to decreased ligand binding in pain-processing regions during painful periods in comparison to pain-free intervals or in healthy subjects. Willoch et al.[38] presented a case report of central pain following pontine infarction that was associated with changes in opioid receptor binding. Jones et al.[39] were the first to systematically demonstrate reduction in opioid receptor binding capacity in neurons within the human nociceptive system in four patients with central neuropathic pain. These findings may explain why certain patients with central pain require high doses of synthetic opiates to achieve optimum analgesia.

Although the decrease in ligand-opiate receptor binding is a common factor in acute and chronic pain, the underlying mechanisms may be different. In chronic pain, the decrease may be due to a combination of the following factors: increased endogenous opioid release, receptor internalization, receptor down-regulation, decrease in affinity of opioid receptors for radioligands, or loss of neurons carrying these receptors.[4] In contrast, in acute pain, the decrease in radioligand binding observed in healthy controls is more likely to be due to endogenous peptide release, or possibly agonist-induced internalization and recycling of μ-opioid receptors, than to receptor down-regulation and changes in affinity.[22]

ADDICTION AND DRUG DEPENDENCE

The presence and quantity of μ-opioid receptors have been suggested to indicate opioid abuse potential.[40] Zubieta and co-workers[41] were the first to observe increased μ-opioid binding, using PET with ^{11}C-carfentanil, in certain brain regions of cocaine addicts; these increases correlated with the severity of cocaine craving experienced at the time.

Different drugs stimulate dopamine release in the nucleus accumbens, part of the ventral striatum. Striatal dopamine release is stimulated by μ-opioid receptor activation but inhibited by striatal κ-opioid receptors. In view of the current interest in the opioid system in neuropsychiatric disorders, recent studies have focused on identifying the ideal radioligands for brain imaging of the κ-opioid system.[42] The newer radioligand for κ-receptors, GR 103545, now provides an opportunity to assess the opioidergic system in drug-dependent humans, though the application of this knowledge in management of addiction is still in its infancy.

Brain imaging has been used to investigate opioid dependence. PET imaging in methadone-maintained addicts failed to demonstrate widespread reduced uptake of tracers in the brain, as would be expected if methadone were occupying opioid receptors.[43,44] This suggests that the efficacy of methadone may not depend upon receptor blockade or reduction; instead, it may act by desensitizing receptors to opioids.[10] On the other hand, PET studies in patients on buprenorphine clearly show that μ-opioid receptors are occupied in a dose-dependent fashion. Hence, receptor blockade may contribute to the effectiveness of buprenorphine.[45]

LIMITATIONS

The sensation of pain is the result of an intricate interaction of peripheral chemical and electrical signaling, central modulation, emotion, and behavior. This partly explains why effective relief of persistent pain can not be achieved by neurosurgical ablative procedures.[46] It is unrealistic to expect brain imaging technology to accurately quantify the source or intensity of pain, as there is interindividual variability. Review of PET/fMRI neuroimaging shows only 50 to 85 percent consistency on the sites, sides, and intensities.[7] Nevertheless, in the past

decade, neuroimaging studies in humans have formed the basis for our understanding of the brain's processing of pain.

In most brain imaging studies, the observed effects were assumed to be a direct consequence of the administered drug. Since there have been no concurrent pharmacokinetic studies to verify it, this assumption could be erroneous. Similarly, when investigating relative regional CBF changes using PET or fMRI, it is assumed that global CBF and arterial oxygen and carbon dioxide tensions do not change across the investigated conditions. But intense pain can increase sympathetic activity and hyperventilation, both of which can potentially alter these parameters.[47]

The basic mechanisms of ligand activation are yet to be completely understood. Although the changes in ligand binding observed with PET are currently assumed to be related to competition of the ligand with the endogenous transmitters, the underlying mechanism may be more complex.[4]

CONCLUSION

The development of noninvasive brain imaging technologies has led to exciting discoveries regarding central opioidergic function and dysfunction. This has opened up new possibilities in the diagnosis and treatment of painful conditions. The opportunity afforded by fMRI to compare time courses of drug effects in different brain regions has helped to identify the neural networks essential for analgesia. This knowledge will aid in designing treatments to target specific brain systems for maximum therapeutic effect. The altered opioid receptor binding noted in patients with chronic pain conditions raises the possibility of new pharmacological approaches to treatment.

More exploration of opioidergic circuitry and opioid receptor distribution within the cerebellum will promote better appreciation of the role of opioids in cerebellar function.[26,48] The future will witness more-focused treatment for conditions that remain poorly treated, such as substance abuse. Physicians must gain a basic understanding of these technologies in order to take advantage of their clinical implications.

Shyam Balasubramanian, MBBS, MD, FRCA, Clinical Fellow, Interdisciplinary Pain Program, Schulich School of Medicine, St. Joseph's Health Care London, London, Ontario, Canada.
Patricia Morley-Forster, MD, FRCPC, Medical Director, Interdisciplinary Pain Program, Schulich School of Medicine, St. Joseph's Health Care London, London, Ontario, Canada.
Yves Bureau, PhD, Research Scientist, Lawson Health Research Institute, University of Western Ontario, London, Ontario, Canada.

REFERENCES

1. Melzack R, Casey KL: Sensory, motivational and central control determinants of pain. In Kenshalo DR (ed.): *The Skin Senses*. Springfield: Thomas, 1968.
2. Weisenberg M, Schwarzwald J, Tepper I: The influence of warning signal timing and cognitive preparation on the aversiveness of cold-pressor pain. *Pain*. 1996; 64: 379-385.
3. Petrovic P, Ingvar M: Imaging cognitive modulation of pain processing. *Pain*. 2002; 95: 1-5.
4. Sprenger T, Berthele A, Platzer S, et al.: What to learn from in vivo opioidergic brain imaging? *Eur J Pain*. 2005; 9(2): 117-121.
5. Frost JJ, Wagner HN Jr, Dannals RF, et al.: Imaging opiate receptors in the human brain by positron tomography. *J Comput Assist Tomogr*. 1985; 9(2): 231-236.
6. Talbot JD, Marrett S, Evans AC, et al.: Multiple representations of pain in human cerebral cortex. *Science*. 1991; 251: 1355-1358.
7. Chen AC: New perspectives in EEG/MEG brain mapping and PET/fMRI neuroimaging of human pain. *Int J Psychophysiol*. 2001; 42(2): 147-159.
8. Davis KD, Wood ML, Crawley AP, et al.: fMRI of human somatosensory and cingulate cortex during painful electrical nerve stimulation. *Neuroreport*. 1995; 7(1): 321-325.
9. Davis KD, Kwan CL, Crawley AP, et al.: Event-related fMRI of pain: Entering a new era in imaging pain. *Neuroreport*. 1998; 9(13): 3019-3023.
10. Lingford-Hughes A: Human brain imaging and substance abuse. *Curr Opin Pharmacol*. 2005; 5: 42-46.
11. Tracey I: Prospects for human pharmacological functional magnetic resonance imaging (phMRI). *J Clin Pharmacol*. 2001; 41: 21S-28S.
12. Newberg AB, Wang J, Rao H: Concurrent CBF and CMRG1c changes during human brain activation by combined fMRI-PET scanning. *Neuroimage*. 2005; 28: 500-506.
13. Schulthess GK: Positron emission tomography versus positron emission tomography/computed tomography: From "unclear" to "new-clear" medicine. *Mol Imaging Biol*. 2004; 6(4): 183-187.
14. Beyer T, Antoch G, Müller S, et al.: Acquisition protocol considerations for combined PET/CT imaging. *J Nucl Med*. 2004; 45: 25S-35S.
15. Vogel WV, Oyen WJG, Barentsz JO, et al.: PET/CT: Panacea, redundancy, or something in between? *J Nucl Med*. 2004; 45: 15S-24S.
16. Pichler BJ, Judenhofer MS, Catana C, et al.: Performance test of an LSO-APD detector in a 7-T MRI scanner for simultaneous PET/MRI. *J Nucl Med*. 2006; 47(4): 639-647.
17. Frost JJ: PET imaging of the opioid receptor: The early years. *Nucl Med Biol*. 2001; 28(5): 509-513.
18. Dannals RF, Ravert HT, Frost JJ, et al.: Radiosynthesis of an opiate receptor binding radiotracer: [11C]carfentanil. *Int J Appl Radiat Isot*. 1985; 36(4): 303-306.
19. Henriksen G, Platzer S, Hauser A: ^{18}F-labeled sufentanil for PET-imaging of μ-opioid receptors. *Bioorg Med Chem Lett*. 2005; 15: 1773-1777.
20. Talbot PS, Narendran R, Butelman ER, et al.: 11C-GR103545, a radiotracer for imaging kappa-opioid receptors in vivo with PET: Synthesis and evaluation in baboons. *J Nucl Med*. 2005; 46(3): 484-494.
21. Pert CB, Snyder SH: Opiate receptor: Demonstration in nervous tissue. *Science*. 1973; 179(77): 1011-1014.
22. Bencherif B, Fuchs PN, Sheth R, et al.: Pain activation of human supraspinal opioid pathways as demonstrated by [11C]-carfentanil and positron emission tomography (PET). *Pain*. 2002; 99(3): 589-598.
23. Peyron R, Laurent B, Garcia-Larrea L: Functional imaging of

brain responses to pain. A review and meta-analysis. *Neurophysiol Clin.* 2000; 30(5): 263-288.
24. Albe-Fessard D, Berkley KJ, Kruger L, et al.: Diencephalic mechanisms of pain sensation. *Brain Res.* 1985; 356(3): 217-296.
25. Zubieta JK, Dannals RF, Frost JJ: Gender and age influences on human brain mu-opioid receptor binding measured by PET. *Am J Psychiatry.* 1999; 156(6): 842-848.
26. Schadrack J, Willoch F, Platzer S, et al.: Opioid receptors in the human cerebellum: Evidence from [11C]diprenorphine PET, mRNA expression and autoradiography. *Neuroreport.* 1999; 10(3): 619-624.
27. Adler LJ, Gyulai FE, Diehl DJ: Regional brain activity changes associated with fentanyl analgesia elucidated by positron emission tomography. *Anesth Analg.* 1997; 84: 120-126.
28. Corbetta M, Miezin FM, Dobmeyer S, et al.: Selective and divided attention during visual discriminations of shape, color, and speed: Functional anatomy by positron emission tomography. *J Neurosci.* 1991; 11(8): 2383-2402.
29. Sprenger T, Wagner K, Willoch F, et al.: Hot-spots of opioid receptor activation by μ-agonists—a fusion study of [11C]-diprenorphine and H215O-PET. *J Cereb Blood Flow Metab.* 2003; 23(suppl. 1): 715.
30. Wise RG, Williams P, Tracey I: Using fMRI to quantify the time dependence of remifentanil analgesia in the human brain. *Neuropsychopharmacology.* 2004; 29(3): 626-635.
31. Grevert P, Albert LH, Goldstein A: Partial antagonism of placebo analgesia by naloxone. *Pain.* 1983; 16(2): 129-143.
32. Borras MC, Becerra L, Ploghaus A, et al.: FMRI measurement of CNS responses to naloxone infusion and subsequent mild noxious thermal stimuli in healthy volunteers. *J Neurophysiol.* 2004; 91: 2723-2733.
33. Petrovic P, Kalso E, Petersson KM, et al.: Placebo and opioid analgesia—imaging a shared neuronal network. *Science.*2002; 295: 1737-1740.
34. Amanzio M, Benedetti F: Neuropharmacological dissection of placebo analgesia: Expectation-activated opioid systems versus conditioning-activated specific subsystems. *J Neurosci.* 1999; 19(1): 484-494.
35. Wager TD, Rilling JK, Smith EE, et al.: Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science.* 2004; 303(5661): 1162-1167.
36. Zubieta JK, Bueller JA, Jackson LR, et al.: Placebo effects mediated by endogenous opioid activity on μ-opioid receptors. *J Neurosci.* 2005; 25(34): 7754-7762.
37. Zubieta JK, Smith YR, Bueller JA, et al.: Regional mu opioid receptor regulation of sensory and affective dimensions of pain. *Science.* 2001; 293(5528): 311-315.
38. Willoch F, Tolle TR, Wester HJ, et al.: Central pain after pontine infarction is associated with changes in opioid receptor binding: A PET study with 11C-diprenorphine. *AJNR Am J Neuroradiol.* 1999; 20(4): 686-690.
39. Jones AK, Watabe H, Cunningham VJ, et al.: Cerebral decreases in opioid receptor binding in patients with central neuropathic pain measured by [11C]diprenorphine binding and PET. *Eur J Pain.* 2004; 8(5): 479-485.
40. Roache JD: Performance and physiological measures in abuse liability evaluation. *Br J Addict.* 1991; 86(12): 1595-1600.
41. Zubieta JK, Gorelick DA, Stauffer R, et al.: Increased mu opioid receptor binding detected by PET in cocaine-dependent men is associated with cocaine craving. *Nat Med.* 1996; 2(11): 1225-1229.
42. Machulla HJ, Heinz A: Radioligands for brain imaging of the kappa-opioid system. *J Nucl Med.* 2005; 46(3): 386-387.
43. Kling MA, Carson RE, Borg L, et al.: Opioid receptor imaging with positron emission tomography and [(18)F]cyclofoxy in long-term, methadone-treated former heroin addicts. *J Pharmacol Exp Ther.* 2000; 295(3): 1070-1076.
44. Melichar JK, Hume SP, Williams TM, et al.: Using [11C]-Diprenorphine to image opioid receptor occupancy by methadone in opioid addiction: Clinical and preclinical studies. *J Pharmacol Exp Ther.* 2005; 312(1): 309-315.
45. Greenwald MK, Johanson CE, Moody DE, et al.: Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology.* 2003; 28: 2000-2009.
46. Xu X, Fukuyama H, Yazawa S, et al.: Functional localization of pain perception in the human brain studied by PET. *Neuroreport.* 1997; 8(2): 555-559.
47. Porro CA: Functional imaging and pain: Behavior, perception, and modulation. *Neuroscientist.* 2003; 9(5): 354-369.
48. Bucher SF, Seelos KC, Oertel WH, et al.: Cerebral generators involved in the pathogenesis of the restless legs syndrome. *Ann Neurol.* 1997; 41(5): 639-645.

CORRECTION

Journal of Opioid Management 2.2, March/April 2006, pp 105-112

The article "Effect of drug and medical treatment on wide geographic variations in repeated emergency department use by HIV-infected drug users" was headed as a Literature Review in error. It is an original article using a database that the authors assembled themselves. We apologize for the error.