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The discovery of endogenous opioid systems: what it has meant for the clinician's understanding of pain and its treatment

Jane C. Ballantyne, MD, FRCA[1]

Mark D. Sullivan, MD, PhD[2]

[1]Department of Anesthesiology and Pain Medicine, University of Washington School of Medicine, Seattle, Washington

[2]Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, Washington (sullimar@uw.edu)

Corresponding author

Jane C. Ballantyne, MD, FRCA

Professor, Department of Anesthesiology and Pain Medicine, Box 356540

University of Washington School of Medicine, Seattle, WA 98195-6560

Phone: (206) 543 2568, Fax: (206) 543 2958 email: jcb12@uw.edu

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ABSTRACT

Before the discovery of the endogenous opioid system in the 1970s, opioids were understood only through the lens of opioid drug effects. Opium produced sleep, pain relief and addiction. Once a variety of opioids had been extracted from opium, and still others synthesized chemically, it became clear that there must be endogenous receptors to explain differential drug effects. So, the search was on to identify the receptors, and subsequently, their endogenous ligands. Even then, the consequential ways in which the endogenous opioid system influences the way we respond to the environment and survive took time to unravel. Today's understanding extends far beyond simply accepting pain relief and addiction as separate processes, to the realization that the endogenous opioid system achieves constant adjustments between punishment (pain) and reward in communicating areas of the brain previously thought to subserve separate functions. The system also plays a crucial role in socialization. Taken together, these two lines of research have led to new insights into why the endogenous opioid system is so important in terms of evolution, individual survival and day-today function, and how important it is to consider opioid medications within the context of these critical natural functions.

Keywords: Opioids; endogenous opioids; pain; dependence; socialization

Introduction

The word "pain" derives from the Latin "poena" meaning penalty or punishment. In fact, this is still the first definition of pain provided in the current Oxford English Dictionary (OED).[1] The second definition of pain in the OED is "the punishment or suffering thought to be endured by souls in hell." It is only with the third OED definition that we encounter the usual biomedical meaning of pain, "Physical or bodily suffering; a continuous, strongly unpleasant or agonizing sensation in the body…" This ranking of pain definitions reminds us that our culture asked "why" questions about the meaning of pain, before we asked "how" questions about the

mechanism of pain. In this sense, the kinship of pain with reward and punishment is more basic and primitive than its kinship with nociception and sensation. We will argue that we are led back to this kinship when we consider how the endogenous opioid system embeds the experience and the physiology of pain in the broader issues of punishment and reward.

Though it could be demonstrated that pain was modified by events and contexts outside the body, for centuries there was no known mechanism within the body that could explain how these contexts could change the physiology and the experience of pain. The groundbreaking insight into this mechanism came in 1973 when Candace Pert and Solomon Snyder, researchers at The Johns Hopkins University School of Medicine, identified opioid receptor sites in the brain by means of naloxone binding studies.[133] Before this discovery, during the many centuries that opium and its derivatives were used for pain, the efficacy of opiates was often attributed to divine benevolence. Thomas Sydenham, the 17th-century "English Hippocrates", wrote *"Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium."* Sir William Osler called opium, "God's Own Medicine." Even those who shunned supernatural explanations of the efficacy of opium, thought it was a happy accident that opium provided potent relief for human pain. But Pert and Snyder made it clear that opioids were an intrinsic and essential part of the pain system. We still struggle to understand the full implications of their discovery for how we understand the relationships between pain and pain relief, between punishment and reward, and most crucially, how these concepts relate to each other.

The neurobiological basis of addiction

Decades of biophysical and pharmacologic research in both addiction and pain fields led to the search for endogenous opioid receptors, since it became clear that differential opioid drug effects could only be explained by the existence of specific receptors.[102] The existence of endogenous receptors alone would have been enough to explain differential drug effects, but as history relates, the discovery of two distinct endogenous opioids (enkephalin and endorphin) followed rapidly in the wake of the discovery of receptors.[72] Because the research that led to the discovery of an endogenous opioid system had arisen from the study of drug effects, it was not immediately clear what the discovery meant in terms of understanding a much broader role for opioids beyond producing addiction and pain relief. We will explore this broader role after we briefly describe our current understanding of the neurobiology of addiction and pain.

Addiction-related brain research has led to understanding drug addiction as an irreversible neurobiological disease produced by repeated exposure to an addictive drug, coupled with drug seeking behaviors.[91] The brain activity that produces the reward that can lead to addiction was found to be centered in the so-called "reward" center which consists of neuronal circuits within mesocorticolimbic dopamine systems originating in the ventral tegmental area (VTA) and projecting to the nucleus accumbens (NAc), amygdala and prefrontal cortex (PFC). It is now known that all addictive drugs act through the dopamine circuits in this center, produce reward, and reinforce drug seeking – so-called positive reinforcing effects.[73,74,89,90] Opioids induce dopamine activity via opioid receptors in the mesocorticolimbic system, both directly and indirectly by decreasing GABA inhibition.[26,35,73,81,96,121] It appears that dopamine circuits are chiefly involved in reward-driven actions and behaviors ("wanting"), and

less involved in driving the hedonic experience ("liking"), which is more strongly linked with opioids.[73,74,160] Although there is considerable certainty about the central role of dopamine in the "reward" circuits, there is still considerable uncertainty about how reward progresses to the state of addiction.

One way to think about drug addiction is as a behavioral state that arises because drug-seeking behaviors become established through repetition and learning, to the point that they are difficult to eradicate.[143,152] By this theory, addiction occurs when repeated drug taking is combined with drug seeking behavior that has advanced from impulsive to compulsive. In the case of opioids, dependence is a key factor driving drug seeking. Chronic exposure to opioids produces tolerance to the euphoric, and in time, also to the analgesic effects of opioid drugs.[18,19,144] The natural progression of opioid dependence is to lose the ability to obtain euphoria or analgesia, to the point of eventually needing opioid to simply feel normal and avoid unpleasant withdrawal symptoms, including withdrawal hyperalgesia and anhedonia (*drug-opposite responses*). This dysfunction may be based on *drug-opposite responses* experienced on a constant basis.[177] When this occurs, opioid seeking occurs because of negative reinforcement, or avoidance of withdrawal, which characterizes the state of dependence.[35,89] As long as this state is reversible, and opioids can be successfully discontinued, it would not be considered addiction. What is necessary for addiction is that opioid seeking behaviors have become established as memories.[39,73,117] Once these memories are established, opioid use can be rekindled at any time by stress or by contextual clues, hence the irreversibility of addiction. Opioid addiction can be controlled by opioid maintenance treatment that fully occupies μ receptors and lessens the effect of taking non-therapeutic or illicit opioids. Pain patients who

take opioids continuously and long-term (e.g., using round the clock opioid regimes) may not manifest opioid seeking behaviors.[19] Opioid seeking may not emerge until or unless efforts are made to cut down an opioid dose, or circumstances prevent a patient from continuing to obtain opioid. It is difficult to know when or if addiction has developed in a patient taking prescribed opioids for pain, partly because their behaviors are centered on obtaining pain relief and do not resemble the opioid seeking behaviors of illicit users, and partly because behaviors may be suppressed by continuing opioid pain treatment.

The neurobiological basis of pain

The most straightforward part of pain processing is the transmission of injury-induced pain via primary afferent nociceptors arising from the dorsal root ganglion, synapsing in the dorsal horn where an immediate reflex withdrawal can be produced, crossing to the contralateral spinothalamic tract to the thalamus and then to the cortex where pain is localized and subsequent actions may be processed.[22,84 11,44,106] The pain picture became infinitely more complicated when pain neuroscientists of the early 20th century recognized that pain is not simply carried along a line labelled system from periphery to brain, but is subject to modification by a parallel system descending from brain to periphery. Henry K Beecher recognized that it was possible to perceive no pain after injury in the circumstance of war, and was frustrated that many investigators did not recognize that "there is no simple relationship between stimulus and subjective response".[24] Ronald Melzack and Patrick Wall proposed in the gate control theory of pain that neurons in the dorsal horn were subject to powerful control from supraspinal sites. They were equally frustrated when their colleagues did not accept the concept of pain plasticity.[113,172] Subsequent work has unraveled many of the complex top-

down processes that modulate pain, leading to a vastly improved, but not completely clear, understanding of pain modulation and its role in how patients actually perceive pain.[22,23] It has recently been proposed that nociception is a fundamental physiological learning process that occurs continuously, often without concurrent pain perception. Underlying this proposal is the concept that this continuous nociception can come into consciousness due to changes in central processing, e.g., in the periaqueductal grey.[15] The periaqueductal grey (PAG) is the main pain-relevant output pathway of the limbic system. The PAG receives projections from limbic forebrain areas including the anterior cingulate cortex (ACC), the hypothalamus and the amygdala, which respond to external stimuli as well as motivations. The output from the PAG alters pain transmission in the dorsal horn via the rostral ventromedial medulla (RVM). The effects may be either facilitatory or inhibitory.[59,60,137,165]

Opioids play a large role in the pain modulatory system.[107,187] Opioid receptors are present in all of the supraspinal pain processing sites as well as the dorsal root ganglion and dorsal horn. Activation of inhibitory GABA supraspinal neurons by opioids accounts in large part for opioids' analgesic effects. Endogenous opioids mediate relays between the component nuclei of the pain modulatory system. Furthermore, opioid activity triggers the dopaminergic network of the PAG and RVM to participate in descending inhibition via D1 dopamine receptors.[179,180]

While the preceding describes a pain and pain modulatory system that is quite separate from the "reward" system, anatomic and biologic links between the two are being revealed and have become the focus of present day exploration into understanding the links between pain and reward. Functional imaging in humans has demonstrated extensive overlap between areas

that respond to pain and reward cues.[27,61,79,87,120] Afferent sensory information that reaches the insular cortex after injury may project to dopamine circuits in the NAc and amygdala where the pain perceived could be altered by induced reward (see below), and where pain's aversive value and motivational salience may be processed. The concept of pain perception, as distinct from nociception, being shaped by emotional learning and perceived danger, moves us closer to understanding pain as a motivational state that consciously or unconsciously drives behaviors.[10,15-17,68]

Understanding pain as a behavioral drive

We think of pain and pleasure as feelings, long considered opposites. Yet the feelings of pain and pleasure cannot be understood in isolation from the organism's and the species quest for survival. Pain is not just a feeling, but also a behavioral drive.[44] As Porreca and Navratilova have recently written, "Pain is a call to action. Like hunger, thirst, and desire for sleep, pain is a part of the body's survival systems that collectively are responsible for protecting the organism."[136] This emotional-drive aspect of pain has been recognized since 1968 when Melzack and Casey replaced a purely sensory model of pain with a multidimentional model that recognized not only sensory/discriminative aspect of pain but also affective/motivational features.[112] Recognition of the affective dimension of pain is now widespread, but the idea that the sensory dimension is subordinated to the affective dimension is more novel. The affective apparatus of the limbic system dampens or amplifies the pain experience according to the overall situation of the organism. What is actually felt, be it perceived pain or pleasure, is the product of calculation within the reward and limbic systems,

which aligns nociceptive processing more closely with reward than with pleasure. (Table 1) *This is how we begin to understand that the endogenous opioid system, rather than having two separate functions – stimulation of reward and reduction of pain – has a key role in integrating reward and pain in order to bring about behaviors that are advantageous.*[44,76]

Functional neuroimaging studies have shown that approximately 15% of the cortex is responsive to nociceptive stimuli.[15] But these responsive regions are not dedicated or specific to nociceptive processing.[75] Multiple authors have recently argued that what was formerly called the "pain neuromatrix" of brain centers active in pain perception are more properly considered a multisensory "salience network".[28,95,98] This salience network is activated by various events that threaten the body's integrity, including not only nociceptive stimuli, but also the non-nociceptive stimuli that provide the context within which the salience or relevance of nociception to organismic survival is determined. Thus the activity in the brain areas that respond to nociceptive stimuli is not a reflection of pain intensity, but of pain salience. As Moseley has argued, this network is more of a danger-detection system than a damage-detection system.[116]

The endogenous opioid system is one of the mechanisms by which the limbic system tunes the responsiveness of the organism to nociceptive input. Recent research by Navratilova et al using conditioned place preference (CPP) in rats as a measure of pain relief showed that endogenous opioid signaling in the rostral anterior cingulate cortex (rACC) appears to be both necessary and sufficient for relief of pain aversiveness. [119] They showed that blockade of opioid signaling in the rACC blocks this relief (assessed by CPP and NAc dopamine signaling) from non-opioid pain treatments. These studies are consistent with previous research that demonstrated

the importance of rACC opioids in placebo analgesia [171,188] and in the response to sustained pain.[186] Navratilova et al also showed that morphine produced reward (CPP and NAc dopamine signaling) in injured, but not pain-free rats. This shows that the rewarding effects of pain relief can be distinguished from the intrinsically rewarding effect of opioids. In fact, opioids appear to preferentially reduce the affective dimension of pain experience rather than the sensory dimension.[136,139] Opioids have been found to reduce activation of affective areas of the brain at lower doses than sensory areas in fMRI studies.[125]

Much of addiction research has been focused on dopamine circuits within the so-called "reward" centers. Dopamine pathways are the final common pathways for many actions of endogenous opioids, and have traditionally been considered more involved with reward and addiction than with pain. However, with increased appreciation of the role of reward centers in pain processing, comes an increased appreciation of the role of dopamine in pain and pain processing. Dopamine encodes the motivational salience of pain, contributing to decisions whether pain should be endured to obtain rewards such as food, sex or social status.[46,161] Thus, it is not only survival behaviors such as feeding, food seeking, sexual activity, nurturing and socialization that are mediated through dopamine and the reward centers, but pain, and relief thereof, also becomes encoded as punishment or reward through dopamine in reward centers where pain's aversive value and salience are processed, ultimately imprinting motivation to avoid such stimuli.[109,110] Both the motivational salience (relevance and awareness) and the motivational valence (positive or negative) of pain is adjusted by the dopamine system.[160] It has also become clear that dopaminergic circuits in reward centers include opponent pathways that elicit punishment,[30,31,61] and that these separate pathways inhibit reward seeking and have

an aversive effect which is distinct from the pathways that promote reward seeking and positive reinforcement.[61,69,93,97,179,180]

Elman and Borsook have argued that chronic pain is not so much a sensory problem as a reward problem.[56] Reward is a broader concept than pleasure or euphoria. (Table 1) Reward may be obtained from pain relief. This is because pain experience exists within a broader context of hedonic homeostasis. They further suggest that neural changes are similar between chronic pain and long-term substance abuse, thus proclivity for addictive behavior is ingrained in pain neuropathology. Similar to long-term substance abuse, chronic pain produces a state of reward deficiency or anhedonia that is reflected in both a diminution of drives and in capacity to experience pleasure.[150] Both wanting (dopamine-mediated) and liking (opioid-mediated) for most rewards are diminished. And in the case of persistent pain, salience and reward associated with pain relief are increased. In this way, both pain and anhedonia set up the patient for incentive sensitization and craving. This would imply that patients with chronic pain are at increased risk of developing addiction, a possibility that remains under debate. Quantifying addiction risk and occurrence in opioid-treated pain patients is challenging because of the different circumstance of pain treatment compared with illicit use.[18,19] However, accumulating evidence suggests that addiction risk is as high in opioid-treated chronic pain patients as in opioid-exposed individuals in the general population, and vastly higher than in non-exposed pain patients or the general population.[3,6,29,70,94]

The role of the endogenous opioid system in socialization

Although analgesia is the most well-known and documented effect of the endogenous opioid system, it is far from the only important function of this system. In humans, endogenous opioids are also involved in multiple forms of reward and addiction, sexual activity, mental illness, mood states, learning and memory, digestion, childbirth, respiration, appetite and thirst, renal function, temperature regulation, metabolism, stress hormone modulation, immunity and cardiovascular regulation.[25] As animal behavior becomes more socially complex, the endogenous opioid system comes to serve more complex social functions. There is no endogenous opioid system in invertebrate animals. The endogenous opioid system in amphibians, reptiles, and fishes appears to be restricted to analgesic functions. In non-mammalian animals, opioids have the same antinociceptive effects they have in mammals.[156] However, in mammals, endogenous opioids play an additional role in social bonding that is crucial to survival for these species. Sociable behaviors (e.g., sexual activity, social grooming, play) increase endogenous opioids, while exogenous opioids decrease social interactions with conspecifics. It has long been noted that opioids relieve separation distress in rodents.[128] Indeed, mouse pups lacking the mu-opioid receptor gene do not attach normally to their mothers.[115] Recently, it has been shown that targeted deletion of this opioid receptor gene (Oprm1) in mice produced pronounced modifications of functional connectivity of the reward-aversion connectome, with a major influence on negative affect centers.[111] Opioids may play a crucial role in extending mammalian social behavior beyond that directly related to parturition and sexual activity that is supported by the oxytocin and vasopressin system.

Dunbar and colleagues (following Panksepp) have proposed the Brain Opioid Theory of Social Attachment (BOTSA).[103] They contend that research on rodents has led us to overemphasize the role of hormonal control and sensory stimuli in pair bonding. Primates are characterized by prolonged periods of dependence in offspring as well as great expansion of the neocortex at the expense of olfactory areas. This results in relationships among primates that are much more diverse, long-lived, and complex than those among rodents. These relationships require a maintenance mechanism that is not tied to sexual interaction or childbirth. BOTSA asserts that endogenous opioids are this important missing link in primate and human bonding. BOTSA draws upon the long-noted similarity between dependence on a love relationship and dependence on exogenous opioids.[77,100,127] Primates are distinguished from other mammals by both the rates of encephalization during development and the role of bonded social systems in species survival. While primate groups are not as large as those of some ungulate herd animals (e.g., wildebeest), primate groups are much more stable, cohesive and structured.[49]

Social bonding in primates is supported by physical proximity and intense social grooming, initially exclusive to a dyad. This grooming triggers beta endorphin release, which relaxes the animal and allows it to "continue interacting with another individual long enough to build a cognitive relationship of trust and obligation".[49] Group living offers many advantages to primates, but it also creates multiple stresses that would result in breakdown of the group. BOTSA postulates that the endogenous opioid system helps manage and defuse these stresses. In contrast, the oxytocin/vasopressin system is likely "too fragile and short-lived to be effective in managing long-lasting social bonds." Primate evolution has co-opted for this social purpose the endorphin system that serves only analgesic functions in lower animals. Endorphin release

during grooming helps assure that core relationships among primates will be available when they are necessary for group survival.

Daniel Carr has recently argued that pain modulation by endogenous opioids is secondary in importance for humans to "behavioral fine-tuning to help the population as a whole survive threats beyond trauma to the individual".[36] He cites the work of Krahe and Panksepp demonstrating that opioids relieve both physical pain and the pain of social isolation/separation in animals from chickens to monkeys.[92,128] He discusses the work of Alexander that showed less self-administration of opioids by rodents in physically and socially enriched environments.[5] Indeed, naloxone blocks the analgesic effect produced by the presence of sibling mice, just as naltrexone reduces human feelings of social connection.

BOTSA also postulates that human social bonding depends on endogenous opioids. A recent PET study verified that social touch modulates opioid activation in humans. Being caressed by partners while in the PET scanner produced pleasure and increased mu opioid receptor (MOR) availability in the thalamus, striatum, and frontal, cingulate, and insular cortices.[124] But human social bonds are more extensive and complex than those of other primates. "Group sizes of around 50 represent the upper limit that can be bonded by the conventional primate mechanism of social grooming: this is because ecological constraints on the time that can be devoted to social interaction (e.g., grooming) place an upper limit at about 20% of total daytime on grooming time for living primates".[49] Human have these same time constraints and therefore need another mechanism to allow larger groups (up to 150) to be bonded.

Dunbar and colleagues have studied different mechanisms for triggering endorphin release and supporting bonding in larger human groups. These include: laughter, singing, dancing, and watching drama. Laughter is shared with chimps as a "primitive wordless chorusing vocalization" and is a potent mechanism for endorphin release and pain relief as famously documented in Norman Cousins's *Anatomy of an Illness*.[43] Laughter is much more likely to occur in social situations, is highly contagious, and makes social interactions more satisfying. "In effect, it functions as a form of grooming-at-a-distance in which the need for physical contact to trigger the endorphin effect has now been replaced by a visual or vocal stimulus".[49] Since laughter may require face-to-face contact, it may not be able to support group sizes larger than 100. For larger groups, other endorphin releasing bonding strategies such as singing,[130] dancing,[158] drama viewing,[50] and shared religion may have been necessary.

There is some evidence of opioid involvement in adult human social bonds. Among adult humans, their style of intimate attachment is associated with cerebral opioid receptor availability. Adult attachment varies according to anxiety (about worthiness for attachment) and avoidance (concerns about trustworthiness of others). In a PET study with healthy subjects, the avoidance dimension of attachment, but not the anxiety dimension, was negatively associated with mu opioid receptor availability in thalamus and anterior cingulate cortex, frontal cortex, amygdala and insula.[123] Bandelow and colleagues have argued that borderline and antisocial personality disorders, which are defined by an impaired ability to form stable social bonds, are characterized by a dysregulation of the endogenous opioid system.[20,21] It is interesting that these disorders are also characterized by high rates of opioid and other addictions, risky sexual behavior, and self-injury.

Pain chronification

Insights provided by functional imaging support a model for the development of chronic pain that builds on the idea that pain perception is dependent on circuitry in the limbic system.[104] This model proposes that brain properties are the primary determinants of risk for chronic pain, and that chronic pain is primarily a neurological disorder, with nociceptive input being less dominant.[10,15,16,48,162,163,166] The basic assumption underlying the proposed model is that genetic or developmental forces embedded in the limbic system could account for differences between individuals in the way pain is processed.[16] It is normal for people to cope with acute injury-induced pain, and in time return to a healthy state. But for certain vulnerable individuals, there is amplification of the nociceptive input, and ensuing brain changes create the chronic pain state.[27,56,83]

Building on the idea that susceptibility to the development of chronic pain resides primarily in the brain, accumulating evidence suggests that the human brain undergoes extensive reorganization in chronic pain states, and that the brain in chronic pain differs from the brain experiencing prolonged acute pain.[10,15,47,162] Chronic pain is thus seen as primarily a maladaptive neuropathological disease, where nociceptive input plays a lesser role. The proposal is that threshold shifts in the conversion of nociception to pain perception, in turn dependent on learning-based synaptic reorganization (similar to learning-based establishment of addictive behaviors),[144,169,170] result in a lowered mesolimbic threshold for the conscious perception of pain.[8,9,17,80] This model raises the intriguing question of whether ongoing nociceptive input might not be perceived as painful by some individuals. A more recent

longitudinal study of patients with back pain demonstrated how, over a year follow-up, brain activity related to back pain shifts away from sensory brain regions to emotional/limbic regions.[68] In the early phase of back pain (10–15 weeks), fMRI reveals brain activity in sensory regions that is similar to the activity produced by acute pain. However, after a year, patients with persistent back pain show decreased activity in sensory regions and increased activity in limbic areas such as the medial prefrontal cortex and amygdala. This occurs even though the back pain feels unchanged to the patients. Thus, as back pain becomes chronic, the limbic or emotional brain becomes more involved. The "chronification of pain" is associated with gray matter and corticostriatal functional connectivity reorganization.

Chronification of pain arising through these types of functional brain reorganization is accompanied by a reduced capacity to activate opioid neurotransmission in the brain.[107] In addition, individuals with dysfunction of endogenous pain inhibition may be more likely to develop chronic pain.[27,56,83] Deficient endogenous pain inhibition has been implicated in fibromyalgia, irritable bowel syndrome, osteoarthritis pain, and rheumatoid arthritis pain.[148,178] Reduced capacity for conditioned pain modulation (where acute pain inhibits ongoing chronic pain) has been documented in many of the most common functional pain syndromes as well as acute and chronic post-operative pain.[86,182,183] Fibromyalgia-like symptoms predict post-op pain relief and opioid requirements after joint replacement and other orthopedic surgeries. [32,33,64,82] In fact, in a recent large population study, new persistent opioid use after surgery was found to be predicted by the presence of pain, mood and substance use disorders before surgery, and not by whether major or minor surgery was performed.[34]

The unraveling by neuroscientists of brain adaptations that contribute to chronic pain are fundamental to answering a perplexing question that faces clinicians treating chronic pain: why does chronic pain develop in some individuals and not others with seemingly equivalent pathology (or no obvious pathology)? No explanation other than the changed brain offers such a satisfactory hypothesis, or involves the endogenous opioid system (the focus of this paper) to the same extent. However, it must not be forgotten that there is a whole spectrum of chronic pain conditions, some of which have a more peripheral focus (neuropathic pain and joint pain for example),[9] for some of which inflammatory processes predominate (Lyme disease mimicking fibromyalgia for example),[155] and for others sensitization processes in the spinal cord become crucial drivers for subsequent brain sensitization and other adaptations (postsurgical pain for example).[181] Repetitive nociceptive input or other stressors can lead to a wide range of maladaptive hormonal and neuronal changes, largely mediated by the hypothalamic-adrenal axis, which underlie stress-related disorders often associated with chronic pain, including anxiety and depression. There are hundreds of molecular processes which give rise to heightened sensitivity in the periphery,[84] spinal cord[147] and brain.[15,142] Fibromyalgia, the archetypal "central" pain condition, seems to be a heterogenous condition that could range from one that is purely peripherally driven, with a possible role from systemic inflammation, to one that is purely centrally driven.[155]

Stress – a common factor for chronic pain, addiction and negative emotional states

Following on the concept that both chronic pain and addiction are learned states, chronic stress emerges as a dominant and common factor in the production of both these

states. At the same time, there is an established role for repeated stress, or even a single severe stress, in the production of psychiatric states including major depression, anxiety and post-traumatic stress disorder (PTSD).[15,56,174] Recent neuroimaging studies have documented that many brain areas thought active in the experience of pain or depression are active in both processes. These cortical areas (e.g., the anterior cingulate cortex [ACC], the insula, amygdala, and the dorsolateral prefrontal cortex [DLPFC]) form functional units through which psychiatric co-morbidity may amplify pain.[15,75] They are also laden with opioid receptors.[134] Baliki and Apkarian have proposed that pain perception, as distinct from nociception, is part of a continuum of aversive behavioral learning that is manifest by pain, depression or anxiety, depending on pre-existing vulnerabilities.[15] They envisage pain and negative moods as a continuum of aversive behavioral learning, which enhances survival by protecting against threats. Thus, their framework for the transformation of nociception into behavior selection through learning is extended to incorporate negative moods.[42]

Stress responses exist to maintain homeostasis and improve survival. Stress responses may occur through attempts to balance punishment with reward within the pain salience network (endogenous opioids being critically involved),[28,95,98,136] or to balance increased arousal, avoidance behaviors and negative affect (mediated by hypothalamic-pituitary-adrenal hormones) with anti-arousal mechanisms (often endogenous opioid mediated).[131,140,167] The responses could be either functional and advantageous, or dysfunctional leading to disease states. What emerges is that because of the central role played by endogenous opioid systems in many aspects of survival-promoting stress responses, endogenous opioid dysfunction commonly underlies stress-induced pathological states.

It is known that targeted rejection events, which involve intentional social rejection and the severing of important social bonds (e.g., being broken up with or fired) are among the strongest proximal risk factors for depression. These rejections are obviously threats to survival for intensely social primate species. These social rejections are associated with a 22-fold increase in risk for major depressive disorder and precipitate major depressive disorder three times faster than other life events of comparable severity.[85] A functional single nucleotide polymorphism (SNP) in the opioid receptor gene (*OPRM1*, rs1799971) leads to differences in sensitivity to both physical pain and social rejection. Patients with at least one G allele experience greater pain intensity after surgery, and require larger doses of opiates post-operatively.[153] G allele carriers also show greater neural and behavioral responses to social rejection.[154,175] In fact, G allele carriers tend to show a fearful pattern of adult attachment to significant others regardless of the quality of their early maternal care.[164] In further PET neuroimaging research, reactions to social rejection were compared in major depressive disorder patients and controls. Despite strong, sustained negative affect during social rejection in both groups, μ opioid receptor *activation* in multiple brain regions was found only in healthy controls, whereas MDD patients showed MOR *deactivation* in the amygdala, as well as slower emotional recovery from the rejection.[71]

Prevalence rates of major depression among patients with chronic pain have varied widely depending on the method of assessment and the population assessed. Rates as low as 10% and as high as 100% have been reported.[145] The majority of studies report depression in more than 50% of chronic pain patients sampled [14,63]. Patients and clinicians frequently ask whether the pain causes the depression or the depression causes the pain. There is evidence

for both. Prospective studies of patients with chronic musculoskeletal pain have suggested that chronic pain can cause depression,[13] that depression can cause chronic pain,[105] and that they exist in a mutually reinforcing relationship.[146] The opioid biology shared between pain and depression means that depression cannot be understood simply as an emotional reaction to an aversive sensation. Generalized or centralized pain may show the strongest biological links with depression. The number of pain sites or conditions is a much better predictor of major depression than pain severity or pain persistence.[41,52]

Similar alterations in endogenous opioid activity to those found in depression have been shown in chronic pain conditions with generalized or centralized features. Research has focused on patients with fibromyalgia. It is well-documented that patients with fibromyalgia have higher rates of depression, psychological trauma, and PTSD than patients with arthritis.[7,12] In healthy human subjects, increased μ opioid binding potential is associated with reduced pain sensitivity and more effective endogenous analgesia.[66] This μ opioid binding potential is reduced in the brains of patients with fibromyalgia.[67] It has recently been shown in a combined fMRI/PET study that this reduced μ opioid binding potential is associated with increased pain affect and evoked brain activity in the dorsolateral pre-frontal cortex and rostral anterior cingulate of patients with fibromyalgia.[148]

Recent research has shown that reduced μ opioid receptor availability within antinociceptive brain regions, such as the dorsolateral prefrontal cortex and anterior cingulate cortex was associated with lower clinical affective pain ratings, decreased pain-evoked neural activity and lower brain activation in the nucleus accumbens (NAc). This means that dysregulation of the endogenous opioid system in fibromyalgia could lead to less excitation of

antinociceptive brain regions by incoming noxious stimulation, resulting in the hyperalgesia and allodynia commonly observed in patients with fibromyalgia. This has led researchers to propose a conceptual model of affective pain dysregulation in fibromyalgia. High tonic levels of endogenous opioids are thought to downregulate μ opioid receptors on GABA inhibitory neurons that normally keep antinociceptive neurons switched off. Phasic release of endogenous opioids normally switches these inhibitory neurons off, thereby turning the antinociceptive neurons on and decreasing experienced pain. But the high ongoing activity in the endogenous opioid system typical of FM patients, downregulates these μ opioid receptors and keeps the endogenous opioid system from modulating pain in fibromyalgia.[148] This line of research helps explain both the lack of efficacy of exogenous opioid therapy and the efficacy of the opioid antagonist naltrexone therapy for fibromyalgia pain.[132,184] It also provides a mechanism for the clinical similarity of opioid-induced hyperalgesia and fibromyalgia.[173]

Corticotrophin Releasing Factor (CRF) is a brain neuromodulator that coordinates autonomic, behavioral and cognitive responses to stress with the endocrine system. In states of acute stress, CRF helps induce a high tonic firing in the brain stem nucleus that mediates physiological responses to stress and pain, the locus coeruleus (LC), to increase arousal, attention, and behavioral flexibility. Endogenous opioids have effects in the LC that are the direct opposite of CRF, biasing the LC to phasic discharge and reducing the tonic firing rate.[185] Thus opioids help LC neurons and the organism recover after the stressor disappears. The CRF and opioid systems work well to balance each other during acute stress. However, with chronic stress, the opioid system becomes dominant.[38,167] Although this protects against the negative consequences of the excitatory response, it comes at a cost. It has been suggested that

because of increased opioid tone, individuals that have suffered repeated stress may show equivalency to individuals that have developed opioid tolerance because of chronic opioid use: they may to tolerant to opioid analgesics and vulnerable to opioid abuse in an effort to avoid the negative effects of withdrawal.[167,177] In effect, chronic stress has induced a state of endogenous opioid-induced tolerance and dependence similar to chronic exposure to exogenous opioids. These effects may be particularly relevant in patients with PTSD who tend to have high use of analgesics and substantial comorbidity with opioid abuse, underlying which may be an over-responsive opioid system that was initially engaged to counteract responses to trauma. [58,78,149] This is an example of stress-related pathology arising from dysfunction in a system designed to oppose stress.

Why not opioids for chronic pain

We should now ask how our rapidly growing knowledge of the endogenous opioid system can contribute to correcting the missteps in opioid prescribing that have led to a societal catastrophe in the United States,[126,129] with other developed countries at risk of following a similar course.[2,62,65,168] The discovery of the existence of an endogenous opioid system in the 1970s was a pivotal point after centuries of understanding opioids as plant-derived drugs that fortuitously relieve pain and distress but at the risk of addiction.[133] Suddenly opioids could be seen as the body's own analgesics and euphorics. Research progressed along the lines one might expect. Addiction scientists focused on the role of opioid drugs in reward, and the subsequent learning that produces the state of opioid addiction. Pain scientists focused on mechanisms of pain and its modification at various points along pain

pathways (mostly distinct from reward centers), and the role of endogenous opioids in pain modification. These lines of research perpetuated the idea that addiction was an unfortunate byproduct of opioid analgesia, but not related to pain.

The next stages of research, however, were much more revealing. They revealed that pain is not just a warning system, or in the case of chronic pain, a warning system gone wrong. Pain exists to drive behaviors, not simply a withdrawal from an immediate threat, but a systematic, complex and calculated strategy to adjust to the environment and survive.[44,76,136] Such calculations depend on constant adjustments between punishment (pain) and reward taking place in reward centers, limbic areas and the cerebral cortex.[15,75] Pain is not separate from reward, but integrated closely with it, and the endogenous opioid system plays a critical role in this integration.[118] Pain processing takes place in areas of the brain that were traditionally thought of as pertaining only to reward and addiction.[171,186,188]

Addiction has long been understood as a maladaptation of reward occurring in the brain, often linked with addictive drug taking. Meanwhile, the tendency has been to understand chronic pain simply in terms of peripheral events such as inflammation and neuropathy, not fully appreciating the crucial role of the brain in pain chronification. Newer research reveals that a learning process similar to that involved in the development of addiction and involving overlapping areas in the brain, contributes significantly to the establishment of chronic pain.[10,15,47,162] Chronic pain can be thought of as a maladaptation of physiological pain that involves learning, where addiction is a maladaptation of reward.[15,44,99] (Table 1) Endogenous opioid systems are involved in both these learning processes. The link between the two lies in the fact that vulnerability to this type of maladaptation is shared.[56,83,174]

Parallel lines of enquiry have provided additional insights: there is also a critical role for the endogenous opioid system in socialization. Whereas our pre-1970s understanding of social bonding was based on knowing, for example, that pituitary hormones (e.g ., oxytocin) mediate maternal-infant bonding, discovery of an endogenous opioid system vastly expanded what can now be seen was a rudimentary appreciation of what drives social behaviors necessary for survival.[103] Just as we can now understand that endogenous opioids, not just the long established hypothalamic-pituitary-adrenal stress hormones (eg cortisol and adrenalin), play a central role in fight and flight, we also understand that endogenous opioids play a central role in socialization.[100,128] Coupled with the more traditional stress hormones, endogenous opioids are necessary for social bonding and mediate responses to social disruption such as rejection and abuse.[55,123] During acute stress, the arousing and protective effects of traditional stress hormones is balanced not only by their own feedback loops, but also by the "anti-stress" activity of endogenous opioids. Repeated or inescapable stress, however, appears to tip the balance towards opioid regulation.[167] For some (resilient) individuals, this helps maintain a beneficial homeostasis; for others the response becomes dysfunctional, and is thought to underlie many neuropsychiatric diseases, including PTSD, chronic pain, substance abuse and depression. While a discussion of resilience is beyond the scope of the present article, early research on 'opioidergic' tone suggests the innate properties of the endogenous opioid system coupled with adaptations to this system that could arise as an individual is confronted with stress, particularly childhood rejection and abuse, could contribute to changes in resilience.[27,83,120,138]

What now of the epidemic of opioid abuse and deaths seen in the United States? One of the most important insights gained from two decades of unfettered prescribing of opioids for chronic pain in the US, is that bad outcomes tend to arise in patients where there is already a high risk. Many patients are prescribed opioids but abandon them for a variety of reasons; they are often the patients already at low risk. Other patients take opioids long-term at stable, non-escalating doses; they are largely not at risk. But an examination of recent clinical data makes it clear that adverse outcomes, including poor pain control, loss of control over use and overdose deaths, are occurring in the population that paradoxically gains the most and loses the most from taking opioids over prolonged periods.[53,54,108,135,141,149,151,157,176] Adverse outcomes have been linked to high dose use.[4,40,45,51,108,114,159] But this progression to high dose use is associated with risk factors such as chronic pain that is not helped by any other means, craving, loss of control over use, and an unshakable belief in the supremacy of opioids. Is the ultimate root of the opioid epidemic the use of high dose opioids or the people that self-select to high dose use? Distressed people in the US are manifesting their distress as a number of stress related health conditions, including chronic pain.[37] Now we can understand the extent to which derangements in stress responses, including opioid responses, contribute to their ill health. The reward deficiency and emotional numbing that accompanies psychiatric disorders makes these individuals turn to opioids because opioids provide them with the relief that a healthy brain does not need.[57,122,167,177] If it were not for the disabling and sometimes fatal effects of prescribing to these individuals, we would have no ethical dilemma in providing opioids in order to relieve the desperation they feel when nothing else provides relief, be it from depression, anxiety, pain or loneliness.

It is now clear, if only from the patients who were once dependent on high dose opioid therapy but have now discontinued this therapy, that chronic continuous opioid therapy has profound effects on people's ability to function socially and emotionally. Dependence on opioids is not the topic of this paper, suffice it to say that dependence alone alters people's motivations.[74,88,89] Social relations are altered, personalities are changed, ability to function in the workplace is compromised, the ability to recruit normal (often endogenous opioid mediated) relief mechanisms is destroyed. A new homeostasis is reached that can only be maintained with continued drug taking, so drug taking becomes a priority. A highly tuned and complex reward system has had its subtleties flooded out of it.

A greater understanding of endogenous opioid systems does not provide a complete solution to the quandary of whether opioid drugs help or harm, or whether they should be used or avoided in chronic pain management, but it does suggest that there are powerful ways we could tap the endogenous opioid system that have been neglected recently in favor of prescribing, because prescribing is easier and more immediately satisfying. Before opioids became widely available, and before the existence of an endogenous opioid system was even imagined, self-management (utilizing for example exercise, yoga, meditation, tai chi, music, laughter, theater, faith, biofeedback) or other ways to tap the endogenous opioid system such as acupuncture, was the way people dealt with pain, and it had many successes. A fuller understanding of the endogenous opioid system helps us understand why self-management works, and why widespread opioid prescribing has had such catastrophic iatrogenic effects on the US population and society. This understanding points pain treatment towards strategies to support the endogenous opioid system by retraining brains through early intervention, to avoid

maladaptive learning and recruit powerful innate mechanisms to achieve homeostasis and stability without drugs.

Conclusion

The discovery of the endogenous opioid system in the 1970s heralded a whole new understanding of pain itself, why opioids relieve pain and why they are addictive. For many centuries before, opioids were considered simply drugs that for unknown reasons provided pain relief, produced euphoria and rest, but risked producing addiction. Even early after the discovery of endogenous opioids, addiction processes appeared confined to "reward" centers, while pain modification appeared confined to pain pathways. But subsequent research has revealed pain's role in maintaining bodily homeostasis, pain's interactions with the opposing motivator reward, pain as a behavioral drive and motivational state, shared processing of pain and reward in the limbic system leading to learned behaviors including learned pain and addiction, all processes in which the endogenous opioid system plays a central role. Beyond these new insights into pain and reward as inextricably bound, we are now able to appreciate that in primates and humans, endogenous opioid systems play an important role in survival behaviors that were previously attributed solely to the pituitary-hypothalamic-adrenal axis, such as fight and flight and social bonding. When we use exogenous opioids chronically and continuously, we sacrifice normal healthy motivational behaviors, socialization and coping. If we overuse opioids, the damage is not only to individuals, but also to families, communities and society. It is to be hoped that the lessons of the US "epidemic" of opioid abuse that has produced catastrophic and ongoing effects on US society, combined with the lessons from basic

science that reveal the critical role of endogenous opioids in natural and often effective responses to trauma and pain, will combine to discourage overprescribing of opioids for chronic pain in future. With our increased knowledge of the endogenous opioid system, we can be wiser about enlisting its assistance in the treatment of chronic pain. Endogenous opioids are likely involved in many of the evidence-based treatments for chronic pain.[101] By understanding the role of endogenous opioids, we can better target, titrate and combine these treatments for patients' benefit.

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Table 1. A construct for understanding perceived pain and pleasure as learned states arising from nociception and reward, where chronic pain and addiction are learning maladaptations

Pain terms	Reward terms
Perceived pain (pain that is felt)	Pleasure, hedonia, euphoria (reward that is felt)
Nociception, sometimes physiological (not necessarily felt)	Reward (not necessarily felt)
Persistent or pathological pain (a maladaptation of a physiological state)	Addiction (a maladaptation of a physiological state)

This construct is based on neuroscience theory. The construct proposes a terminology that helps distinguish perceived pain from transmitted pain (nociception), and perceived pleasure from reward. The underlying principle is that nociceptors and reward processing are continuously active (physiological) as well as reactive (induced), and are integrated to process survival behaviors.[15,17,44,99] Whether or not pain or pleasure are perceived depends on circumstance and learning, both evolutionary and developmental, as the individual responds to circumstances and stress. Persistent or pathological pain and addiction are seen as maladaptations of natural learning.[10,15,47,91,162] Persistent or pathological pain is pain that cannot be completely explained by diagnosable pain generators. A parallel is suggested between learning that leads to addiction, and learning that leads to chronic pain.[144,169,170]