THE PAIN OF BEING SICK: Implications of Immune-to-Brain Communication for Understanding Pain

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Abstract This review focuses on the powerful pain facilitatory effects produced by the immune system. Immune cells, activated in response to infection, inflammation, or trauma, release proteins called proinflammatory cytokines. These proinflammatory cytokines signal the central nervous system, thereby creating exaggerated pain as well as an entire constellation of physiological, behavioral, and hormonal changes. These changes are collectively referred to as the sickness response. Release of proinflammatory cytokines by immune cells in the body leads, in turn, to release of proinflammatory cytokines by glia within the brain and spinal cord. Evidence is reviewed supporting the idea that proinflammatory cytokines exert powerful pain facilitatory effects following their release in the body, in the brain, and in the spinal cord. Such exaggerated pain states naturally occur in situations involving infection, inflammation, or trauma of the skin, of peripheral nerves, and of the central nervous system itself. Implications for human pain conditions are discussed.

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INTRODUCTION

Interactions between the central nervous system and the body have generally been regarded as involving regulation of peripheral processes by the brain. However, a variety of recent research suggests that the interaction between brain and body is far more dynamic than previously recognized, with peripheral systems and products exerting potent effects on neural processes and thereby behavior. This bidirectionality of communication has become clear with regard to interactions between the brain and the immune system. Initial interest in brain-immune relationships focused on how neural processes could regulate immune function, but it is now clear that immune products signal the central nervous system and regulate its activity (for review see Maier & Watkins 1998). Immune-to-brain communication plays an unrecognized role in many psychological phenomena. The purpose of this review is to describe what is known about its role in pain.

A BRIEF OVERVIEW OF PAIN MODULATION

The sensation of pain is a dynamic, rather than passive, process. Research spanning well over a century has shown that highly organized neural circuits existing in the brain and spinal cord regulate pain. Some of these circuits suppress pain; others magnify it. Thus, a person’s perception of pain may have little to do with the actual intensity of the pain.

A central organizational theme revealed by the study of pain inhibitory (analgesia) and pain facilitatory (hyperalgesia) circuits is that, by and large, the central nervous system regulates pain perception by regulating the pain message while it is still in the spinal cord (Kelly 1986). Thus, regulation occurs before pain reaches a person’s consciousness (Figure 1). The analgesia and hyperalgesia circuits do this by modulating pain signals as they first arrive in the spinal cord from the body. In the absence of modulation, nociceptive (pain responsive) peripheral nerves become activated by intense stimuli (e.g. heat, crush, pinprick, acid), and this activation causes these nerves to relay electrical signals to neurons in the spinal cord dorsal horns. Here, the incoming sensory nerve fibers synapse, so neurotransmitters released in response to the incoming electrical signals carry the pain message forward to the second neuron in line. These spinal cord dorsal horn neurons become activated in turn, causing electrical signals encoding the pain message to be sent up to the brain, toward consciousness (Figure 1). From this description, it becomes clear that at the level of the spinal cord dorsal horns, there are two ways for pain to be modulated. One is to modulate how much neurotransmitter is released by the incoming nociceptive sensory nerves. The second is to modulate how excitable the spinal cord dorsal horn neurons are in response to the pain signals they receive. Analgesia and hyperalgesia circuits can regulate both (Figure 1), thereby allowing for dramatic suppression or enhancement...
Figure 1 Dynamic modulation of pain. The brain contains distinct circuits that either inhibit pain (pain inhibitory systems) or facilitate pain (pain facilitatory systems). Pain inhibitory systems are activated by opiate drugs such as morphine, by environmental dangers, and by learned danger signals. Pain facilitatory systems, in contrast, are activated by infection, inflammation, learned sickness signals, and learned safety signals. Once activated, pain inhibitory systems suppress pain by inhibiting neurons in the spinal cord dorsal horns that relay pain information from the body to the brain (pain transmission neurons in dorsal horn). Pain facilitatory systems, on the other hand, exaggerate pain by making these spinal pain transmission neurons hyperexcitable to incoming sensory information. +, Excitatory connection; −, inhibitory connection. Note: There is also dynamic modulation of the release of neurotransmitter from pain fibers arriving in the spinal cord from the body. Although not illustrated in the figure, pain inhibitory systems can inhibit release of neurotransmitter from these sensory fibers, and pain facilitatory systems can exaggerate the release of neurotransmitter from these sensory fibers.

Analgesia and Antianalgesia

Neural circuits that function to suppress pain are thought to have evolved to enhance survival of the organism during fight/flight. That is, suppressing the pain of wounds facilitates the ability of animals, including humans, to defend themselves during attack and to successfully escape from further harm. In keeping with such a notion, analgesia is produced by a variety of stressful environmental stimuli (e.g. environmental “dangers” such as electric shock, cold water, swims, conspecific aggression, the sight of a cat by a rat, military combat) (Kelly 1986). In addition, analgesia can be classically conditioned, whereby initially innocuous stimuli (e.g. lights or sounds) paired with an environmental danger (e.g. shock) become capable of eliciting analgesia by themselves (Watkins & Mayer 1986). Thus, learned danger signals, in addition to unlearned danger signals, can produce analgesia (Figure 1). Studies of the neural pathways and neurochemistries mediating these so-called stress-induced analgesias reveal that there are multiple pain suppression systems (Kelly 1986, Watkins & Mayer 1986). What these circuits have in common is that, in the end, they send axons from sites in the brain down to the spinal cord, where pain signals are inhibited (Figure 1). These circuits can also be activated directly, by systemic administration of drugs, such as morphine, or by implantation of either fine wires or tubes into discrete sites along these pathways that allow their activation by electrical stimulation or drug microinjection, respectively (Richardson 1995, Sandkuhler 1996, Yaksh 1997). Animal studies of analgesia produced by such direct activation of these pathways led to the development of many analgesic drugs and to the use of brain stimulators and epidural drug injections for control of pain in humans.

Although for many years only suppression of pain was thought to occur, this is not the case. Pain facilitation occurs as well (Figure 1). Two types of pain facilitation are now recognized: antianalgesia and hyperalgesia (Maier et al 1992). Antianalgesia, as the name implies, refers to removal of pain inhibition. Antianalgesia was predicted long before it was experimentally demonstrated (Maier et al 1992). As noted above, it has long been known that danger signals activate analgesia systems. However, what brought these analgesic states to an end was a mystery. Recent studies have demonstrated that analgesia produced by signals indicating danger can be actively terminated by signals indicating safety (Wiertelak et al 1992b). These so-called antianalgesia circuits are activated by learned safety signals that predict that danger will not occur. Antianalgesia is created by a brain-to-spinal cord circuit that is anatomically distinct from those creating analgesia (Watkins et al 1998). Where analgesia and antianalgesia circuits come together is in the spinal cord. Antianalgesia actively opposes the ability of analgesia circuits to suppress pain transmission at the level of the spinal cord dorsal horns (Watkins et al 1997b, Wiertelak et al 1992a). The power of antianalgesia goes beyond simply abolishing stress-induced analgesia. It can also abolish the analgesic effects of a variety of drugs, including
morphine (Watkins et al 1997b, Wiertelak et al 1992a). Learned safety signals abolish analgesia through the release of specific peptide transmitters within the spinal cord (Wiertelak et al 1992a, 1994). A family of such peptides has now been characterized, with cholecystokinin receiving by far the most study (Baber et al 1989, Cesselin 1995). Direct administration of cholecystokinin into the cerebrospinal fluid surrounding the spinal cord [intrathecal (i.t.) administration] effectively blocks analgesias produced by morphine, by environmental danger signals, and by learned danger signals (Baber et al 1989, Faris et al 1983). Animal studies led to the proposal that antianalgesic peptides may play a key role in the development and expression of morphine tolerance (Cesselin 1995, Kellstein & Mayer 1991, Payza et al 1993, Watkins et al 1984). Furthermore, animal studies have provided strong evidence that antianalgesic peptides such as cholecystokinin (a) may naturally suppress a variety of pain control procedures (e.g. morphine, acupuncture, placebo effects) (Benedetti & Amanzio 1997, Tang et al 1997, Watkins et al 1984) and (b) may be overexpressed in chronic pain states known to be resistant to such analgesic drugs as morphine (Nichols et al 1995, Xu et al 1994). Thus, the existence of antianalgesia systems has great implications for both normal and pathological pain states.

**Hyperalgesia and Allodynia**

In contrast to antianalgesia, hyperalgesia actually exaggerates pain transmission rather than simply oppose analgesia (Maier et al 1992). The existence of neurocircuitry that creates hyperalgesia has great implications for human pain and suffering, which is the focus of the remainder of this review. Like analgesia and antianalgesia, the actual modulation of pain occurs within the spinal cord dorsal horns. Also like analgesia and antianalgesia, hyperalgesia can be created by brain-to-spinal cord circuits (Kaplan & Fields 1991, Watkins & Maier 1997). Hyperalgesia is often assumed to also be created by direct peripheral nerve-to-spinal cord circuits. Events in the body that trigger exaggerated pain states include localized trauma, infection, and inflammation. It seems logical to assume that such events would cause exaggerated pain via their activation of peripheral nerves in the region, causing direct signaling to the spinal cord. Until recently, the possibility that the brain might be involved in creating such exaggerated pain states was not considered. It is therefore notable that in the few cases where the potential involvement of a brain-to-spinal cord circuit has been assessed, such a pathway again proved key for creating exaggerated pain states (Bian et al 1998, Pertovaara 1998, Ren & Dubner 1996, Wiertelak et al 1997).

The general term hyperalgesia is most accurately subdivided into two forms: hyperalgesia and allodynia (Willis 1992). Hyperalgesia, as used here, refers to a lowering of pain threshold such that stimuli that were not originally painful now are. Hyperalgesia is typically assessed in the laboratory using radiant heat stimuli. In the studies cited in this review, thermal hyperalgesia is almost always the form assessed. Hyperalgesia involves a “plastic” change in the spinal cord dorsal horn response (Liu & Sandkuhler 1998, Sandkuhler & Liu 1998), similar if not identical to the long-term potentiation (LTP) that some believe underlies learning and memory in the
hippocampus (Doyere et al. 1993). For both, LTP reflects a use-dependent increase in synaptic strength between presynaptic terminals of incoming nerve fibers and neuronal cell bodies within the region. Thus, such neuronal plasticity results in exaggerated electrical activity for a period of time, in response to synaptic input. This LTP-like process in spinal cord dorsal horn neurons can occur either after activation of a brain-to-spinal cord circuit or after “pain” neurons in this region receive a barrage of activity from peripheral nerves carrying pain messages. In either case, the signals arriving at the spinal cord dorsal horns release neurotransmitters, such as substance P and glutamate, that create a depolarization of spinal cord dorsal horn pain neurons that is sufficiently large and prolonged that N-methyl-D-aspartate ion channels become activated. When this key step occurs, the resulting influx of calcium ions sets into motion a whole cascade of intracellular events culminating in the formation of nitric oxide and prostaglandins (Willis 1992). Both nitric oxide and prostaglandins diffuse from the neuronal cell body where they are formed, causing dramatic increases in the excitability of the neuron that made them, of nearby neurons, and of presynaptic terminals of the peripheral sensory “pain” neurons that synapse in the region (Vasko 1995, Willis 1992). The end result is a dramatic change in spinal cord dorsal horn function. Sensory “pain” fibers arriving in the dorsal horn from the body release exaggerated quantities of transmitter. In response, spinal cord dorsal horn neurons overreact to the “pain” signals they receive from the body (Willis 1992).

Allodynia, on the other hand, is a less easily defined concept. Basically, allodynia (at least as assessed by laboratory animal behavior) may or may not be “pain” in the way that one normally thinks of pain. It refers to increased distress/reactivity to a stimulus that is normally innocuous (e.g. nonthreatening and nonstressful, in addition to nonpainful) (Willis 1992). The light touch of a wisp of cotton or the feeling of loose clothing against the body are examples of such innocuous stimuli. When allodynia occurs to such mechanical (touch/pressure) stimuli, the organism responds vigorously and often emotionally. Human pain patients complain of being greatly distressed by clothing, by bedsheets, or by a soft breeze across their skin (Gilmer 1995, Rowbotham & Fields 1996, Swanson et al. 1998). Allodynic rats begin motorically reacting and often vocalizing to light-touch stimuli that evoke nothing but curious investigation from control animals (Slart et al. 1997). How innocuous stimuli that do not release any of the “pain” neurotransmitters in the spinal cord dorsal horn become capable of causing distress and possibly pain in allodynic animals is a mystery. Many pain transmission neurons in the spinal cord dorsal horns are well known to receive sensory information from both sensory “pain” fibers and “light-touch” fibers arriving from the body. Under normal conditions, these dorsal horn neurons readily distinguish between pain and light-touch information, responding vigorously to pain and barely responding at all to light touch. Currently, the general view is that some (currently mysterious) process causes spinal cord dorsal horn pain transmission neurons to become so hyperexcitable that they respond to light touch as if it were pain. That is, light touch evokes a vigorous response by the pain transmission neurons comparable to that normally elicited only by pain.
Classically, hyperalgesia and allodynia have been assumed to be due entirely to alterations in neural function. For example, nerve crush or other trauma was thought to cause physical and functional changes in the membrane of the damaged nerve (Willis 1992). The abnormal nerve would then send barrages of electrical activity to spinal cord dorsal horn neurons, setting LTP-like processes within these neurons into motion. Thus, this view focused on direct damage to the nerve itself and the resulting neuronally mediated LTP-like cascades.

What is exciting is that this view is changing. The change is being brought about by the recognition that neurons do not simply act alone: They can be remarkably regulated by the immune system. The argument to be made is that substances released by immune cells can dynamically and dramatically modulate pain. Hyperalgesia and allodynia are the result of such immune-neuron interactions and occur following the release of immune cell-derived substances in the body, the brain, and/or the spinal cord. In the sections that follow, four interrelated aspects of immune modulation of pain are examined. First, hyperalgesia as a natural consequence of sickness is examined. It is then argued that hyperalgesia is simply one component of a brain-mediated constellation of responses to immune challenge. The second topic examines hyperalgesia and allodynia that result from infection and inflammation of the skin. It is argued that what has previously been thought of as purely neurally created exaggerated pain states actually arise via the release of immune-derived substances. The third topic focuses on nerve trauma and inflammation, and it is argued that hyperalgesia and allodynia resulting from even this classic pain model needs to be reevaluated in terms of mediation by immune cells. The fourth topic examines the pain modulatory role of immune-like cells of the central nervous system: astrocytes and microglia. The case is presented that creation of hyperalgesia and allodynia in the spinal cord dorsal horns actually results from dynamic interactions between neurons and these glia. It is argued that spinal cord microglia and astrocytes actually play an important role in allodynia and hyperalgesia observed following infection, inflammation, or injury in the body. Furthermore, the case is made that spinal cord glia activated by infection of the central nervous system are sufficient to create exaggerated pain states. The concluding section explores the implications of these new roles of the immune system and spinal cord glia for developing new strategies for pain control in humans.

IMMUNE-TO-BRAIN COMMUNICATION: ORGANIZING THE SICKNESS RESPONSE

Defense of the organism against infection by pathogens (e.g. bacteria, viruses, parasites) is an evolutionarily old, survival-oriented response (Hart 1988, Maier & Watkins 1998). Organisms as primitive as sponges have specialized cells called immunocytes that recognize “nonself,” causing foreign invaders to be attacked,
Immunocytes are a type of phagocyte (literally eating cell), similar in function to phagocytes in our own bodies (including macrophages, meaning big eaters). As more complex species evolved, their immune systems evolved as well, adding a wide variety of specialized cell types dedicated to performing various functions required for host defense (Kuby 1992).

Evolution of the vertebrate brain provides for the ability to orchestrate broad changes in behavior and physiology to further enhance host survival during immune challenge. This brain-mediated set of changes is called the sickness response (Hart 1988). The sickness response consists of a constellation of physiological changes (fever, increased sleep, alterations in blood chemistry), behavioral changes (decreased locomotion, decreased sexual behavior, decreased exploration, decreased aggression, decreased food and water intake), and hormonal changes (release of classic stress hormones from the sympathetic nervous system and hypothalamo-pituitary-adrenal axis). Sickness occurs rapidly, beginning within minutes to a few hours after immune challenge in organisms as diverse as reptiles, fish, birds, and mammals (Hart 1988, Kluger 1978, Maier & Watkins 1998).

It has been argued that the immune system signals the brain about infection because the brain-mediated sickness response enhances host survival (Hart 1988, Maier & Watkins 1998). The key feature of the sickness response appears to be fever. Fever raises the core body temperature to the point where viruses and bacteria do not readily multiply, bacteria lose their ability to form protective outer coats, the host’s white blood cells multiply rapidly, phagocytes are optimized for destruction of pathogens, and liver metabolism shifts to alter blood chemistry to deprive pathogens of nutrients and chemicals they need while maximizing the needs of the host (Kluger 1978, 1991). Although all these changes clearly enhance host survival, fever comes with a cost. Fever is extremely energy intensive, requiring a 10–15% increase in energy expenditure for every degree of fever (Kluger 1978, 1991). One can view many aspects of the sickness response as aimed at providing energy for fever, by saving energy used by nonessential behaviors (increased sleep, decreased exploration, decreased aggression, and so forth), and by releasing energy from bodily stores (one of the effects of classic stress hormones). Even decreased food and water intake can be viewed as “up front” energy saving if one takes into account the energy cost associated with running down prey and foraging, as well as the energy costs associated with digestion (Hart 1988, Maier & Watkins 1998).

Exactly how the immune system signals the brain is a matter of ongoing debate (Watkins et al 1995c). What is clear is that immune-to-brain communication occurs early in the immune response to infection and injury. During an immune challenge, macrophages and other immune cells rapidly create and release proteins called proinflammatory cytokines. These proteins are proinflammatory because they orchestrate the early immune response to infection and injury by communicating with white blood cells, attracting them to the site of infection/injury, and causing them to become activated to respond (Kuby 1992). The proinflammatory cytokine family includes tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6. These proinflammatory cytokines frequently are sequentially formed in a cascade, where typically TNF is
made first, causing the induction of IL-1, which in turn causes the induction of IL-6 (Kuby 1992). These proinflammatory cytokines (especially IL-1 and TNF) are thought to be key mediators of immune-to-brain communication (Maier & Watkins 1998, Watkins et al 1995c). They are both necessary and sufficient for eliciting sickness responses. That is, sickness responses can be blocked by administering antagonists that disrupt proinflammatory cytokine actions, and sickness responses can be elicited by administering proinflammatory cytokines in the absence of viral or bacterial challenge (Maier & Watkins 1998, Watkins et al 1995c).

What is far less clear is the signaling pathway between release of proinflammatory cytokines and brain activation. One popular idea is that proinflammatory cytokines build up at the site of infection/injury, spill over into the blood stream, and are carried by the blood to the brain. Because proinflammatory cytokines are large proteins that cannot passively cross the blood-brain barrier, they have been variously argued to (a) enter the brain at the few sites where the blood-brain barrier is weak or absent (e.g. circumventricular structures), (b) be actively transported across the blood-brain barrier, or (c) bind to receptors expressed in blood vessels of the brain, inducing the creation of other chemicals (such as prostaglandins) that can easily pass across the blood-brain barrier (Watkins et al 1995c). Although each of these views has its proponents, detractors point out that sickness responses can still be observed when infection is so localized that no proinflammatory cytokines can be detected in blood (Kluger 1991). Indeed, very localized infection/injury may most realistically model actual host defense against the initial stages of immune challenge. In this latter situation, immune-to-brain communication appears to be mediated by activation of specialized sensory nerves that carry immune information to the brain (Maier et al 1998).

To date, most research on this topic has focused on sensory nerves in the vagus as a neural pathway for immune-to-brain communication (Figure 2) (Maier et al 1998). Sensory nerves in the vagus are excited both by proinflammatory cytokines and by bacterial challenge, as evidenced by their increased expression of neuronal activation markers (e.g. cFos, an immediate-early gene product) (Gaykema et al 1998, Goehler et al 1998). Furthermore, a wide variety of sickness responses are blocked by cutting the vagus nerve, including fever, decreased food-motivated behavior, increased sleep, decreased activity, decreased social interaction, changes in brain activity, and release of stress hormones (Maier et al 1998). Substances released by activated immune cells may either directly (Ek et al 1998) or indirectly (Goehler et al 1997) activate sensory fibers in the vagus. For example, IL-1 can bind either to receptors expressed on sensory neurons of the vagus (Ek et al 1998) or to specialized sensory end-organs called paraganglia (Goehler et al 1997). These sensory end-organs synapse onto sensory vagal fibers, allowing communication to occur (Figure 2). Paraganglia are tiny chemoreceptive structures that have been called “the taste buds of the blood.” Their location along lymph capillaries and blood capillaries perfectly positions them to “sample” these fluids for substances released by immune cells (Goehler et al 1997). In addition, the connective tissues surrounding the paraganglia contain dense accumulations of immune cells (macrophages, dendritic cells, mast
Figure 2 Immune-to-brain communication. On encountering pathogens (bacteria, viruses, etc), phagocytic immune cells become activated. Activated phagocytes both engulf the pathogens and release proinflammatory cytokines including interleukin-1 (IL-1). IL-1 binds to and activates sensory paraganglia, which send sensory information to sensory nerve fibers in the vagus. Vagal sensory information is relayed to the nucleus tractus solitarius (NTS) of the medulla, which then relays this information to brain areas that create sickness responses, including the hippocampus (HIPP) and paraventricular nucleus of the hypothalamus (PVN). For hyperalgesia, the pathway includes the NTS, the nucleus raphe magnus (NRM), and the dorsal horns of the spinal cord. Activation of these brain circuits leads to the release of IL-1 from glia, leading to the production of sickness responses.

cells) (Goehler et al 1999). These immune cells respond to localized immune challenge by rapidly producing and releasing proinflammatory cytokines and other substances (Goehler et al 1999). Taken together, this immune-to-vagus-to-brain pathway appears to form a rapid response system for triggering brain-mediated sickness responses (Figure 2).

Given that sensory vagal fibers synapse predominantly in the nucleus tractus solitarius (see Figure 2) (Ritter et al 1992), it would not be surprising if this medullary structure played a key role in the generation of brain-mediated sickness responses. Indeed, the nucleus tractus solitarius sends axons to numerous brain areas that create the various aspects of sickness (Figure 2) (Maier & Watkins 1998, Ritter et al 1992). Studies of how the brain creates sickness, after it is signaled to do so by the immune system, revealed an intriguing finding. That is, that proinflammatory cytokines again play a pivotal role. Within the brain, glia (which are immune-like cells of the central nervous system) respond to immune-to-brain signaling by synthesizing IL-1 de novo (Laye et al 1995). The brain expresses receptors for IL-1, and blocking IL-1 actions in the brain blocks sickness responses (Maier & Watkins 1998, Rothwell & Luheshi 1994).

To summarize, infection/injury in the body leads to the activation of immune cells. In the early stages of this immune response, a variety of substances, including proin-
flammatory cytokines (TNF, IL-1, IL-6), are released at the infection/injury site. For abdominal immune activation at least, this may trigger the activation of sensory paraganglia that communicate to sensory nerves in the vagus. The vagus may also be activated by direct receptor binding of immune products. The sensory vagal fibers, in turn, trigger brain-mediated sickness responses via activation of brain circuitry originating within the nucleus tractus solitarius. In addition, systemic signals for sickness may travel via the blood to the brain, providing an additional blood-borne pathway for immune-to-brain communication. In either case, glia become activated and these immune-like cells make and release IL-1, a key mediator within the central nervous system for creating sickness responses.

**PAIN AS A NATURAL PART OF THE SICKNESS RESPONSE**

We have recently suggested that exaggerated pain responses (hyperalgesia) be added to the list of classic sickness responses reviewed above (Watkins et al 1995d). Hyperalgesia would be advantageous to the survival of the organism, by directing recupervative behaviors (like licking and favoring) to the site of injury or infection. Furthermore, by encouraging the organism to curl up and remain immobile, exaggerated pain would also serve to save energy. Thus, from several regards, hyperalgesia seems a logical candidate for a sickness response.

Such an argument leads to three predictions: (a) that experimental manipulations that elicit classic sickness responses should also elicit hyperalgesia, (b) that the neurocircuitry mediating classic sickness responses and hyperalgesia should at least partially overlap, and (c) that like classic sickness responses, hyperalgesia should be dependent on IL-1 released in the central nervous system, in addition to proinflammatory cytokines released at the site of infection. As is reviewed below, each of these predictions is true.

Hyperalgesia, like other sickness responses, is elicited by immune activation in the periphery. Intraperitoneal (i.p.) (intraabdominal) administration of either bacterial cell walls (endotoxin) or live bacteria elicits thermal hyperalgesia in rats (Mason 1993, Watkins et al 1995a,d). The fact that i.p. IL-1 and i.p. TNF can each produce hyperalgesia and allodynia supports the idea that proinflammatory cytokines are sufficient to elicit these responses (Ferreira et al 1988, Maier et al 1993, Oka et al 1996a, Watkins et al 1995b,d). Furthermore, proinflammatory cytokines are necessary for this so-called sickness-induced hyperalgesia because pharmacologically blocking the action of IL-1 or TNF prevents sickness-induced hyperalgesia induced by either bacterial cell walls or the proinflammatory cytokines themselves (Maier et al 1993, Watkins et al 1995d). A classic cytokine cascade is involved (Kuby 1992) because TNF actually creates hyperalgesia by inducing the release of IL-1 (Watkins et al 1995b).

Regarding similarity of neurocircuitry, what is known to date is that the initial portions of the circuit are shared by hyperalgesia and the other sickness responses. That is, cutting the vagus nerve disrupts sickness-induced hyperalgesias elicited
by i.p. administration of bacterial cell walls, IL-1, or TNF (Watkins & Maier 1999a). Sickness-induced hyperalgesia is also disrupted by lesions of the nucleus tractus solitarius (Wiertelak et al 1997), the major termination site of sensory vagal nerves (Ritter et al 1992). From this point, the neurocircuitry for each sickness response likely diverges as axons from the nucleus tractus solitarius project to the multiple brain regions mediating various sickness outcomes. From lesion studies it is known that sickness-induced hyperalgesia involves, at least, the nucleus tractus solitarius and the nucleus raphe magnus (see Figure 2), with the latter structure sending its axons down to the spinal cord dorsal horns where exaggerated pain responses are created (Watkins & Maier 1999a).

Like other sickness responses, sickness-induced hyperalgesia involves proinflammatory cytokines within the central nervous system (Oka & Hori 1999). By i.p. administration, IL-1 appears to produce thermal hyperalgesia via de novo production and release of IL-1 within the brain, because this hyperalgesia is blocked by intracerebroventricular (i.c.v.) (into the cerebrospinal fluid-filled ventricles of the brain) administration of alpha-melanocyte-stimulating hormone (α-MSH), an endogenous peptide that functions as an IL-1 antagonist (Oka et al 1996a). By i.c.v. administration, TNF (Oka et al 1996b), IL-1 (Oka et al 1993, Watkins et al 1994, Yabuuchi et al 1996), and IL-6 (Oka et al 1995b) are each sufficient to produce thermal hyperalgesia, and α-MSH blocks hyperalgesia produced by i.c.v. IL-1 (Oka et al 1993). A classic cytokine cascade (Kuby 1992) again appears to be involved because i.c.v. TNF creates hyperalgesia by inducing the release of brain IL-1 (Oka et al 1996b). IL-1 exerts its effects on pain by selectively exaggerating neuronal electrical responses to intense stimuli applied to the skin (Oka et al 1994a). One site of IL-1 action is the hypothalamic preoptic area because microinjection of IL-1 into this site is sufficient to produce thermal hyperalgesia (Oka et al 1995a). All three proinflammatory cytokines (TNF, IL-1, IL-6) produce hyperalgesia via the release of prostaglandins (Oka et al 1993, 1995b, 1996b; Yabuuchi et al 1996), substances repeatedly implicated in exaggerated pain states (Willis 1992) and known to produce hyperalgesia following i.c.v. administration (Oka et al 1994b). Indeed, in keeping with the idea that IL-1 acts via prostaglandin release, prostaglandin likewise selectively exaggerates neuronal electrical activity in response to intense stimuli applied to the skin (Oka et al 1997).

Although brain IL-1 can increase pain responses, spinal cord IL-1 is also key. By i.p. administration, injection of bacterial cell walls not only induces hyperalgesia (Maier et al 1993) and increases brain IL-1 (Nguyen et al 1998; KT Nguyen, T Deak, MK Hansen, M Flesher, LE Goehler et al, submitted for publication), it also rapidly increases IL-1 in the spinal cord dorsal horns (Watkins & Maier 1999a; KT Nguyen, T Deak, MK Hansen, M Flesher, LE Goehler et al, submitted for publication). This is important because the spinal cord dorsal horns contain the neurons that receive and modulate pain information arriving from the body (Willis 1992). The IL-1 produced in the spinal cord dorsal horns by peripheral immune activation is used to create hyperalgesia. This is so because preventing spinal cord IL-1 effects, by microinjecting a selective IL-1 receptor antagonist into the cerebrospinal fluid surrounding the spinal cord, blocks thermal hyperalgesia produced by inflammation of
a paw (Watkins et al 1997a). It has recently been reported that application of IL-1 directly onto the spinal cord, using electrophysiological techniques, causes exaggerated responses of spinal cord dorsal horn neurons only to incoming pain signals (Reeve et al 1998). Although the lack of IL-6 antagonists has prevented the potential role of IL-6 in sickness hyperalgesia from being tested, it should be noted that i.t. IL-6 produces hyperalgesia and allodynia in rats (DeLeo et al 1996).

Regarding the source of IL-1, spinal cord IL-1 is thought to be made and released by glia (astrocytes and microglia). As noted above, the neural circuit that leads to sickness-induced hyperalgesia involves a nucleus tractus solitarius—to—nucleus raphe magnus—to—spinal cord pathway. Spinal cord glia express receptors for, and are activated by, neurotransmitters released by the nucleus raphe magnus, including substance P and glutamate (Watkins & Maier 1999a). Activated astrocytes and microglia begin releasing glial products, including IL-1. IL-1 then likely acts on the cells in the region to stimulate further release of more IL-1 and, in addition, to stimulate the release of a variety of neuroactive substances, including nitric oxide, excitatory amino acids, and nerve growth factor (NGF). All these glially derived substances are known to be key mediators of sickness-induced hyperalgesia at the level of the spinal cord (Watkins & Maier 1999a, Watkins et al 1997a). Indeed, using light microscopy, spinal cord astrocytes and microglia are visibly activated in response to infection/inflammation in body. Immunohistochemical analyses of astrocyte- and microglial-specific activation markers reveal that both of these glial populations are activated by peripheral infection and inflammation (Fu et al 1998, Sweitzer et al 1999, Watkins et al 1995a). The importance of astrocytes and microglia in creating sickness-induced hyperalgesia is emphasized by the finding that hyperalgesia induced by infection and inflammation in the body is blocked by spinal administration of drugs that selectively disrupt glial function (Meller et al 1994; Watkins et al 1995a, 1997a).

ROLE OF THE IMMUNE SYSTEM IN PAIN

Skin Infection and Inflammation

Subcutaneous (s.c.) injection of a variety of immune stimuli causes thermal hyperalgesia and mechanical allodynia. Such stimuli include chemical irritants such as dilute formalin (Watkins et al 1997a), killed bacteria (Poole et al 1999, Poole & Woolf 1999), yeast cell walls (Meller et al 1994), and the algae protein, carrageenan (Poole et al 1999). These all recruit a variety of immune cells to the site of injection. Once there, these immune cells produce and release proinflammatory cytokines and NGF (Johnson & Krenger 1992, Kuby 1992).

A role for proinflammatory cytokines in creating such hyperalgesias is supported by the fact that s.c. injection of either IL-1 (Ferreira et al 1988, Follenfant et al 1989), TNF (Cunha et al 1992), or IL-6 (Cunha et al 1992) induces hyperalgesia and allodynia, with the following order of potency: IL-1 > TNF >>> IL-6 (Poole et al 1999). Such injections directly excite peripheral nociceptive fibers (e.g. nerves that
become excited by intense stimuli that would be perceived as pain by humans) (Sorkin et al. 1997, Xiao et al. 1996). By s.c. administration, proinflammatory cytokines also sensitize these nociceptive fibers to overrespond to subsequent stimuli (Sorkin et al. 1997, Xiao et al. 1996). Poole and colleagues have extensively characterized the response cascades initiated by a variety of s.c. immune activators (Poole et al. 1999, Poole & Woolf 1999). From their work, it is clear that all the proinflammatory cytokines act via release of IL-1. That is, hyperalgesias caused by all of the proinflammatory cytokines are reduced or abolished by blocking IL-1 actions with anti–IL-1 antibodies, IL-1 receptor antagonist, or the IL-1 functional antagonist α-MSH (Follenfant et al. 1989; Poole et al. 1992, 1999). In addition, at least TNF simultaneously exaggerates pain also via a second pathway, namely sympathetic activation (Poole et al. 1999).

IL-1 actions have been variously argued to (a) reflect direct IL-1 binding and activation of sensory nerves, (b) be dependent on the release of prostaglandins that sensitize pain fibers (Ferreira 1972), (c) work via pathways that are independent of prostaglandins, or (d) be dependent on the release of NGF (Poole et al. 1999, Poole & Woolf 1999). All four mechanisms actually do appear to mediate IL-1 actions to varying degrees, depending on the exact circumstances under study (Poole et al. 1999, Poole & Woolf 1999).

NGF clearly plays a role in exaggerated pain states. By s.c. administration, NGF produces both hyperalgesia and allodynia (Woolf et al. 1994), s.c. injection of killed bacteria causes the release of NGF, and hyperalgesia and allodynia produced by either NGF or killed bacteria are blocked by drugs that disrupt NGF action (McMahon et al. 1995, Woolf et al. 1994). During inflammation, NGF levels increase in immune cells at the site of infection, in inflammatory fluids (for example in the fluid space of inflamed joints), and in inflamed skin (Poole & Woolf 1999, Woolf et al. 1994). NGF exerts both direct and indirect effects on peripheral nerves. Direct actions are exerted by NGF binding to receptors on nociceptive (“pain” responsive) fibers, thereby altering excitability of these nerves. Indirect actions of NGF arise from its cytokine-like actions, which cause immune cells that accumulate at the site of infection/injury to release their cellular contents. Many of these substances can, in turn, excite nociceptive fibers (Poole & Woolf 1999).

Several lines of evidence indicate that IL-1 acts, at least in part, via NGF release. In tissue culture, IL-1 causes NGF release from immune cells (Lindholm et al. 1987, 1988). By s.c. administration, IL-1 also releases NGF (Safieh-Garabedian et al. 1995), and blocking NGF actions blocks hyperalgesia induced by s.c. IL-1 (Safieh-Garabedian et al. 1995). As reviewed above, because all proinflammatory cytokines release IL-1, this implies that NGF is likely a common pathway to pain. Furthermore, administering an IL-1 receptor antagonist blocks the ability of s.c.-killed bacteria either to produce hyperalgesia (Poole et al. 1999) or to increase NGF (Poole & Woolf 1999). Because TNF exerts at least part of its hyperalgesic actions by inducing the release of IL-1 (Poole et al. 1999), it is not surprising that TNF likewise releases NGF and, in fact, acts synergistically with IL-1 to do so (Hattori et al. 1993, Woolf et al. 1997).
Lastly, blocking NGF actions attenuates TNF-induced hyperalgesia (Woolf et al. 1997), again in keeping with TNF actions being mediated partially by IL-1.

Like hyperalgesia following i.p. injections (Watkins & Maier 1999b), hyperalgesia induced via peripheral nerve activation by s.c. immune activators ultimately results in exaggerated responses of pain transmission neurons in the spinal cord dorsal horns. In fact, parallel to the activation of spinal cord glia observed after i.p. injections (Watkins et al. 1995a, Watkins & Maier 1999b), s.c. injections of immune stimuli also activate glia in this key pain modulatory area. Both s.c. chemical irritants (formalin) (Fu et al. 1998, Sweitzer et al. 1999, Watkins et al. 1995a) and s.c. yeast cell walls (Sweitzer et al. 1999) activate microglia and astrocytes in the spinal cord dorsal horns. In addition, both s.c. formalin and s.c. yeast cell walls increase IL-1 production by spinal cord glia (Sweitzer et al. 1999). The importance of this glial IL-1 is illustrated by the fact that blocking spinal cord IL-1 actions abolishes s.c. formalin-induced hyperalgesia (Watkins et al. 1997a). That spinal cord glia are key to such changes in pain responsivity is supported by the finding that drugs that disrupt glial function block hyperalgesias elicited by both s.c. formalin (Watkins et al. 1997a) and s.c. yeast cell walls (Meller et al. 1994).

Nerve Infection and Inflammation

Both nerve trauma and nerve infection/inflammation create exaggerated pain states characterized by hyperalgesia and allodynia. Abnormal pain responses resulting from nerve trauma are referred to clinically as neuropathic pains, and they include such human pain conditions as deafferentation pain following loss of a body part or nerve crush, pain associated with diabetes, cancer pain, and pain that develops after viral infection of peripheral nerves (e.g. postherpetic neuralgia that results from shingles) (DeLeo & Colburn 1999, Willis 1992). When nerve infection/inflammation, rather than physical trauma, is the diagnosed cause, these same exaggerated pain responses are referred to clinically as neuritis. The potential of immune involvement in both neuropathic and neuritic pain states has now been recognized in such diverse species as the mollusk Aplysia and laboratory rats.

Like sponges (Smith & Hildemann 1986), the principle cell in mollusks that attacks, engulfs, and destroys foreign invaders is a phagocyte called an immunocyte. These immunocytes travel via the hemolymph (molluscan blood) and tissues to reach sites of injury and infection. They appear to be the source of IL-1- and TNF-like factors in hemolymph (Clatworthy 1999, Clatworthy et al. 1994, Hughes et al. 1992), IL-6-like factors have also been identified in mollusks (Clatworthy 1999), so these invertebrates appear to have the same proinflammatory cytokines as mammals. Certainly evidence to date is that molluscan proinflammatory cytokines cause the same biological responses as do their mammalian counterparts (Clatworthy 1999).

Responses to nerve injury in the mollusk Aplysia have been intensively studied. From single cell recordings, it is clear that sensory nerve injury induces dramatic increases in both excitability and synaptic transmission of nociceptive neurons (Clatworthy & Walters 1994, Walters et al. 1991). The changes appear to reflect both
direct effects at the site of trauma as well as indirect effects induced by axonal transport of signal molecules from the site of trauma back up to the cell body, causing excitability changes there as well (Gunstream et al 1995). Proinflammatory cytokines released from immunocytes attracted to the site of axonal injury appear to be the cause of all these changes (Clatworthy 1999). IL-1 and TNF increase excitability of neurons in mollusks such as Aplysia by altering ion channel function (Clatworthy 1999). Indeed, nerve damage is not even necessary for molluscan proinflammatory cytokine-induced excitability changes to occur. Simply attracting immunocytes close to the sensory nerves by “baiting” the area with killed bacteria leads to marked increases in neuronal excitability and synaptic transmission (Clatworthy & Grose 1997). Even in cell culture, Aplysia sensory neurons become hyperexcitable when incubated in solutions that previously contained immunocytes or when incubated in the presence of immunocytes stimulated by killed bacteria (Clatworthy & Grose 1997). Such data again implicate immunocyte-derived substances as the cause of the excitability changes.

Parallel to the situation just described in Aplysia, nerve trauma in rats is associated with attraction of macrophages and other phagocytic immune cells to the area and release of proinflammatory cytokines (DeLeo & Colburn 1999, Rotshenker et al 1992, Sommer & Schafers 1998) and NGF (Herzberg et al 1997) by these immune cells. In addition, Schwann cells that enwrap the damaged nerves become activated, causing these immune-derived cells to release proinflammatory cytokines and NGF as well (Myers et al 1999, Wagner & Myers 1996b). There is even evidence that sensory neurons begin creating NGF (Herzberg et al 1997) and proinflammatory cytokines (DeLeo & Colburn 1999, Richardson et al 1998) following trauma to their peripheral nerve fibers. The timecourse of hyperalgesia correlates well with the timecourse of phagocyte invasion into the area of damage (Sommer et al 1993). Indeed, if phagocyte invasion of the area is experimentally delayed, neuropathic pain is likewise delayed (Myers et al 1999, Sommer & Schafers 1998). Immune-derived substances are implicated in the development of hyperalgesia and allodynia following nerve damage because the exaggerated pain responses can be reduced by blocking TNF (Illich et al 1997; Sommer et al 1997, 1998b; Wagner et al 1998), IL-1 (Sommer et al 1998a,c), or NGF (Herzberg et al 1997) at the site of nerve trauma.

It is intriguing that the very same types of responses can be observed in the absence of physical trauma to nerves, simply by attracting and activating immune cells in the region. Schwann cells, for example, begin producing proinflammatory cytokines in response to local injections of killed bacteria, TNF, IL-6, or IL-1 (Bolin et al 1995). Simply injecting TNF onto the sensory nerve both elicits hyperalgesia and allodynia (Wagner & Myers 1996a) and directly activates peripheral nerves that normally respond only to painful stimuli in the skin (Sorkin et al 1997). As noted above for Aplysia (Clatworthy 1999), it has been proposed that hyperexcitability induced by TNF results directly from alterations of ion channels in the sensory neuron (Baldwin et al 1996, Kagan et al 1992). Placing killed bacteria (Clatworthy et al 1995, Eliav et al 1996), viral coat proteins (Herzberg et al 1998), algae protein (Eliav et al 1996), or a foreign body such as chromic gut surgical sutures (Maves et al 1993) near sensory
nerves also induces both hyperalgesia and allodynia. Taken together, these findings are striking in that they clearly demonstrate that proinflammatory cytokines can rapidly induce aberrant responses in peripheral nociceptive nerves, independent either of damage to the nerve or of any action at receptors expressed by peripheral nerve terminals (Sorkin et al 1997).

As was the case following either i.p. or s.c. injections of immune activators, there is growing evidence that neuritis and neuropathic pain models induce glial activation within the spinal cord dorsal horns. Damage of peripheral sensory nerves inducing neuropathic pain also leads to activation of both microglia and astrocytes within the spinal cord dorsal horns (Coyle 1998, DeLeo & Colburn 1999, Garrison et al 1991), correlated with increased spinal cord expression of the proinflammatory cytokines IL-1 (Coyle 1998, Sweitzer et al 1999), TNF (DeLeo & Colburn 1999), and IL-6 (DeLeo & Colburn 1999, DeLeo et al 1996). The importance of spinal cord IL-1 and IL-6 for exaggerated pain responses by the spinal cord was noted previously. Indeed, simply placing immune activators near sensory nerves, in the absence of trauma, causes intense activation of both astrocytes and microglia in the spinal cord dorsal horns, correlated with the expression of exaggerated pain responses (Herzberg et al 1998). Furthermore, we recently demonstrated a key role for spinal cord IL-1 in mediating neuritis-induced exaggerated pain states. We found that i.t. IL-1 receptor antagonists block exaggerated pain induced by immune activators (yeast cell walls) placed near healthy sciatic nerves (Hammack et al 1999).

Central Nervous System Infection and Inflammation

As noted above, infection and inflammation in the abdomen, in the skin, and around peripheral nerves all result in activation of astrocytes and microglia in the spinal cord. For s.c., periaxonal, and i.p. inflammation/infection, such glial activation actually mediates the exaggerated pain state (Hammack et al 1999; Meller et al 1994; Watkins et al 1995a, 1997a). This raises the issue of whether glial activation would be sufficient to create exaggerated pain states in the absence of infection, inflammation, or injury in the body.

This possibility presents itself because astrocytes and microglia are immunocompetent cells, which means these two types of glia act like immune cells within the central nervous system. They express specific receptors that recognize and bind bacteria and viruses (Becher et al 1996, Ma et al 1994, Peterson et al 1995, Sharpless et al 1992), and these glia become activated as a result. On activation, these cells begin releasing a variety of substances (nitric oxide, prostaglandins, IL-1, NGF, excitatory amino acids) that induce a positive feedback circuit (Watkins & Maier 1999b; ED Milligan K Mehment, JL Hinde, D Martin, SF Maier, et al, submitted for publication). That is, substances released by activated microglia stimulate nearby astrocytes to release substances that further excite microglia, and so forth. Furthermore, as noted previously, all these substances excite neurons and are key mediators within the spinal cord dorsal horns of exaggerated pain states (Willis 1992).
This leads to the hypothesis that exaggerated pain would be expected to occur on infection of the spinal cord. A number of bacteria and viruses are neurotropic; that is, they “home” to the central nervous system and invade it. An example of one such virus is HIV-1, the virus that causes AIDS in humans. Various strains of HIV-1 infect the brain and spinal cord early in the course of the disease and continue throughout disease progression (Diederich et al 1988). Within the central nervous system, a specific portion of the outer surface of HIV-1 binds to activation receptors expressed on microglia and astrocytes. The portion of HIV-1 that activates these glia is a glycoprotein called gp120 (Tyor et al 1992).

Rats do not get AIDS because HIV-1 simply cannot multiply inside infected rat cells. However, glial activation is a process distinct from glial infection. gp120 does indeed bind to and activate rat microglia and astrocytes (Codazzi et al 1996, Opp et al 1996). This glial activation occurs in a manner identical to that in humans, and the same neuroexcitatory substances are released from rat glia as a result. Thus, this similarity between rat and human cellular responses allows laboratory rats to be used to examine whether viruses such as HIV-1 might cause exaggerated pain states through activation of spinal cord glia.

We have recently undertaken such studies. Although still in its infancy, this work has already been revealing. When gp120 is administered i.t. into the cerebrospinal fluid space surrounding the lumbosacral cord (that is, to the spinal levels receiving sensation from the lower body), remarkable thermal hyperalgesia results (Watkins & Maier 1999b; ED Milligan, K Mehmert, JL Hinde, D Martin, SF Maier, et al, submitted for publication). Altered responsivity extends beyond thermal stimuli. By i.t. administration, gp120 induces allodynia as well (Milligan et al 1998, 1999; Watkins & Maier 1999b). Thus, gp120, like peripheral immune activation by infection and injury, alters responsivity in ways paralleling clinically relevant aspects of pain.

Spinal cord glia do appear to be key mediators of these effects of i.t. gp120. By i.t. administration, drugs that disrupt glial function abolish both gp120-induced hyperalgesia and alldynia, and anatomical evidence of glial activation can be readily observed using immunohistochemistry for glial activation markers (Milligan et al 1998, Watkins & Maier 1999b; ED Milligan, K Mehmert, JL Hinde, D Martin, SF Maier, et al, submitted for publication). Investigation into the mediators released from spinal cord glia in response to gp120 is just beginning. In cell culture, at least, gp120 is able to induce the release of a variety of substances previously implicated in exaggerated pain states, for example nitric oxide (Koka et al 1995), prostaglandins (Ushijima et al 1995), IL-1 (Koka et al 1995), excitatory amino acids (Vesce et al 1997), and IL-6 (Yeung et al 1995). To date, we have only examined gp120-induced changes in IL-1. Our preliminary studies (Watkins & Maier 1999b; ED Milligan, K Mehmert, JL Hinde, D Martin, SF Maier, et al, submitted for publication) indicate that gp120 rapidly increases IL-1 gene activation, as evidenced by increases in mRNA content in spinal cord dorsal horns. We also know that IL-1 protein rapidly increases as well, specifically in the lumbosacral spinal cord region where gp120 was injected. That this IL-1 protein is actually released, and thus biologically relevant, is supported by the fact that IL-1 protein released from lumbosacral spinal cord rapidly and dramat-
ically accumulates in the cerebrospinal fluid surrounding only this spinal cord level (Milligan et al 1998, 1999; Watkins & Maier 1999b). Spinal cord glia appear to be the source of this IL-1, given that drugs that disrupt glial function block gp120-induced increases in IL-1 protein both in spinal cord and in the surrounding cerebrospinal fluid (Milligan et al 1999). Lastly, and of key importance, gp120-induced thermal hyperalgesia and mechanical allodynia are both blocked by i.t. administration of a specific IL-1 receptor antagonist (Milligan et al 1999). These data provide strong support that IL-1 is a critical mediator of HIV-1 gp120-induced exaggerated pain states (Milligan et al 1998, Watkins & Maier 1999b).

IMPLICATIONS FOR HUMAN PAIN CONDITIONS

The finding in animal models that proinflammatory cytokines in the body, in the brain, and in the spinal cord create exaggerated pain states has major implications for human pain. Indeed, it has been stated that up-regulation of proinflammatory cytokines may well be the single most important and treatable factor linked to the development of chronic pain (Poole & Woolf 1999). As in the animal models reviewed above, implications for human pain states arise from the fact that proinflammatory cytokines can markedly influence pain at these levels: the peripheral nerve terminals, along the nerve bundles, within the brain, and within the spinal cord itself.

The role of spinal cord glia in creating exaggerated pain in humans is entirely unexplored. However, from the work reviewed above, this is clearly an issue that warrants serious consideration. In AIDS, as the example, upwards of 80% of patients suffer from chronic pain, and of these, a shockingly high percentage suffer from vague and diffuse pains of unknown origin (Breitbart et al 1996, Hewitt et al 1997). Clearly, AIDS patients suffer from pain from a variety of readily identifiable causes, including nerve damage, opportunistic cancers, and opportunistic infections, resulting both from the drugs used in therapy and from the disease process itself (Breitbart et al 1996, Hewitt et al 1997). Our work suggests that HIV-1 activation of spinal cord glia may also contribute to the pain and suffering. That is, HIV-1–induced glial activation in spinal cord would be expected to both create pain for which there is no definable etiology in the body and exaggerate pain resulting from identifiable peripheral causes.

Beyond the numerous bacteria and viruses known to “home” to the central nervous system, other triggers for spinal cord glial activation exist. For example, from the animal studies reviewed above, infection and damage of peripheral nerves leads both to exaggerated pain states and to astrocyte and microglial activation in the spinal cord (Coyle 1998, DeLeo & Colburn 1999). Although no studies of animal models of arthritis have yet examined spinal cord glial activation, the prolonged sensory pain fiber activity known to be induced by such conditions would cause prolonged release of pain transmitters into the spinal cord dorsal horns. As noted previously, this pattern of effects predicts glial activation at spinal levels. In none of these cases has the effect
of drugs that disrupt glial function or specific glial mediators yet been tested. Furthermore, spinal cord trauma recruits immune cells from the general circulation into the region (Carlson et al 1998, Popovich et al 1997), activates both astrocytes (Hadley & Goshgarian 1997) and microglia (Popovich et al 1997), and causes exaggerated pain states in both laboratory animals and humans (Christensen & Hulsebosch 1997, Wang et al 1997, Xu et al 1993). The potential role of glia and proinflammatory cytokines in these pain states has yet to be explored.

Proinflammatory cytokines also directly activate peripheral nerves that carry the sensation of pain. TNF and IL-1 have each been repeatedly implicated in directly activating the sensory nerve bundles as they course toward the spinal cord. Indeed, TNF has been linked to demyelination and degeneration of axons (Redford et al 1995, Said & Hontebeyrie-Joskowicz 1992), leading to the suggestion that peripheral demyelinating neuropathies and multiple sclerosis may be linked to TNF release (Myers et al 1999). Such findings in laboratory animals again suggest examination of human conditions involving infection, inflammation, and damage involving or contacting peripheral sensory nerves. Some of these sites of proinflammatory cytokine production may be less than obvious. For example, herniated disks, which are sites both directly apposed to sensory nerves and associated with exaggerated pain states, are also sites of greatly elevated proinflammatory cytokines (Kang et al 1997, Rand et al 1997). Whether these cytokines contribute to pain and suffering of the patient remains to be investigated.

Lastly, proinflammatory cytokines act at peripheral nerve terminals to exaggerate pain. Their release at sites of skin infection and damage has obvious implications for human pain. Sensory nerves are in intimate contact with immune cells that reside in the skin (Misery 1998); they are also affected by immune cells attracted to sites of infection and trauma. Sites of proinflammatory cytokine production where tissue damage is less obvious are more subtle. One example is rheumatoid arthritis. Remarkable accumulations of activated immune cells occur in joint linings and fluid within the joint space of arthritic sites (Martin 1999). From animal models it is known that IL-1 injected into joints causes arthritis and worsens preexisting arthritic states. Furthermore, injection of IL-1 into the joints of laboratory animals increases sensory nerve activity, which is supportive of pain transmission (Fukuota et al 1994, Kelly et al 1996). Because of the immediacy of the effects observed, it appears that IL-1 again is acting directly on the nerve itself to increase sensory signaling (Kawatani & Birder 1992). Human arthritis patients show elevated IL-1 levels both in the general blood circulation and in the affected joint. In addition, their immune cells are primed to overrespond to new challenges with exaggerated IL-1 release (Martin 1999). The key involvement of IL-1 in arthritic pain is supported by recent placebo-controlled double-blind clinical trials over a 6-month period in patients with rheumatoid arthritis. Patients given an IL-1 receptor antagonist to disrupt IL-1 actions showed significant reductions in tender joint scores and both physician and patient assessment of their condition, compared with patients given the placebo (Nuki et al 1997). TNF appears to be involved in human arthritis as well. TNF levels are greatly increased in the general circulation as well as in the joints and joint fluids of patients with rheumatoid
arthritis (Martin 1999). These elevations of TNF are correlated with joint pain, and TNF antagonists decrease symptoms in rheumatoid arthritis. Similar to the findings for IL-1, carefully controlled human clinical trials have provided evidence that TNF inhibitors produce significant improvement in patient quality of life indices and significantly reduce pain (Moreland et al 1997). Indeed, based on preclinical and clinical data, Martin has suggested that proinflammatory cytokines may be important targets for novel analgesic drugs for conditions such as phantom limb pain, reflex sympathetic dystrophy, traumatic nerve injuries, herpes zoster virus associated with both shingles and postherpetic neuralgia, trigeminal neuralgia, and diabetic neuropathy, all of which are currently poorly managed by available drugs and therapies.

CONCLUSIONS

Regardless of the precise details and the ultimate mechanisms that prove to be involved, it can be concluded that immune cells and products of immune cells signal the central nervous system and modulate pain. Indeed, activation of glia within the spinal cord dorsal horns and consequent release of IL-1 at this site may prove to be a final common pathway for many exaggerated pain states. Furthermore, a consideration of this immune regulation of pain may help to make functional sense out of what would not seem to be adaptive, namely hyperalgesia and allodynia. Thus, pain processes may participate in the larger scheme of host defense and be better understood in this context. The next few years will likely witness more attempts to understand immune-pain interactions, and we believe an unraveling of the mechanisms involved may well produce real advances in the ability to treat pain.

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