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Chronic Pain, Memory, and Injury: Evolutionary Clues from Snail and Rat Nociceptors

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The sensory component of chronic pain is amenable to comparative study and evolutionary interpretations. Pain is usually initiated by activation of nociceptors, which detect damaging stimuli. A comparison of rats and a marine snail, *Aplysia*, shows that nociceptors in each group satisfy the same functional definition and exhibit similar functional alterations, including persistent hyperexcitability and synaptic potentiation following noxious stimulation. These alterations are also associated with conventional learning and memory. Because of the ancient divergence of these lineages, some similarities probably reflect independent evolution. However, the molecular signals linked thus far to known forms of long-term neuronal plasticity represent homologous processes that are found in all metazoan cells. Persistent plasticity mechanisms now used for chronic pain and memory may have evolved originally in the earliest neurons by selective recruitment of core cell signaling and effector systems for neuronal repair, sensory compensation, and protective functions related to peripheral injury.

Few investigators of chronic pain mechanisms have paid explicit attention to evolutionary considerations. Nevertheless, interesting clues about the evolution of pain mechanisms, like the evolution of other biological phenomena, can come from comparative studies at the behavioral, cellular, and molecular levels. Pain has been defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage (Merskey & Bogduk, 1994). This widely accepted definition of pain leads to two distinct sets of cross-species comparisons, which differ markedly in the range of species to be considered. Sensory responses to actual or potential tissue damage (noxious stimulation) could occur, in principle, in any animal possessing a sensory system, which means virtually all living species and extinct species possessing nervous systems. Thus, some of these mechanisms may be quite primitive. On the other hand, unpleasant emotional experiences associated with actual or potential tissue damage can only be addressed effectively in species in which such emotions are likely to occur (most plausibly in animals with complex brains and extensive behavioral repertoires), which may represent a small fraction of the animal kingdom (Walters, 2008). Indeed, because emotion is defined as a subjective experience, the emotional content of pain in other species is extremely difficult (some would say impossible) to identify (Allen, 2004). Consequently, much more comparative information is available about responses to actual or potential tissue damage (nociceptive responses) than about emotional aspects of pain. Let me stress that the human pain experience, and presumably pain in some animals, normally depends upon both the nociceptive component and the emotional component. Pain that is chronic (outlasting the healing of damaged

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tissue) is surprisingly common, occurring in about 20% of the world's population (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006), and often is quite resistant to treatment. Comparative studies at the behavioral, neural, and molecular levels should lead to a better understanding of the biology of chronic pain, which might eventually help in efforts to improve therapy. In particular, comparisons of long-term alterations in nociceptive neurons and other types of neurons may shed light on mechanisms contributing to the persistence of chronic pain. Here I discuss functional and mechanistic similarities between long-term sensitization that has been described in nociceptive pathways in both molluscan and mammalian species. I then consider possible evolutionary implications of the observation that these mechanisms for persistent alterations are shared with many that are considered fundamental to conventional learning and memory.

Functional Properties of Nociceptors Are Similar in *Aplysia* and Rats

Nearly all animals exhibit defensive behavioral responses to noxious stimuli, most commonly local or generalized withdrawal, escape locomotion, and sometimes aggressive retaliation, usually followed by prolonged immobility, enhanced vigilance, and recuperative behaviors (Walters, 1994). Nociceptors are sensory neurons specialized for detecting damaging and potentially damaging stimuli, and probably are strong activators of defensive responses in most animals (although defensive responses can also be activated by threatening stimuli that do not cause tissue damage, such as olfactory, auditory, or visual stimuli). Nociceptors have been examined in only a few species, most extensively in the laboratory rat (*Rattus norvegicus*) and, among invertebrates, in a mollusc, *Aplysia californica*. This large, soft-bodied marine snail (it lacks a shell) is found commonly along the coast of southern California. *Aplysia*'s large, individually identifiable neurons have greatly facilitated the discovery of various cellular mechanisms of neuronal function and plasticity. No neurons have been investigated as intensively in *Aplysia* as the mechanosensory neurons comprising the left E (LE) cluster in the abdominal ganglion and the ventrocaudal (VC) clusters in the two pleural ganglia. These highly plastic cells have been neurons of choice to investigate basic mechanisms of learning and memory (see Kandel, 2001). Both the LE neurons, which innervate the animal's siphon (Byrne, Castellucci, & Kandel, 1974) and the VC neurons, which innervate most of the ipsilateral surface of the body (Walters et al., 2004; Walters, Byrne, Carew, & Kandel, 1983a), were found initially to have low mechanosensory thresholds and are often regarded as receptors for light touch by investigators of learning and memory (e.g., Antonov, Antonova, Kandel, & Hawkins, 2001; Barco, Bailey, & Kandel, 2006). However, the LE and VC mechanosensory neurons are properly considered nociceptors rather than low-threshold touch receptors for the following reasons.

First, under natural, unrestrained conditions light touch rarely activates LE or VC sensory neurons; the low thresholds encountered in early studies were an artifact of applying test stimuli to pieces of the body wall that were tightly pinned

to firm substrates. This effectively reduces the natural compliance of the animal's soft body (increasing the effective intensity of weak stimuli) and produces peripheral sensitization, dramatically lowering the mechanosensory threshold (Clatworthy & Walters, 1993; Illich, Joynes, & Walters, 1994; Walters, 1987). Unless sensitized, these sensory neurons exhibit relatively high thresholds, graded responses to increasing stimulus intensities, and maximal responses to sharp, pinching stimuli that cause clear tissue damage. Second, these later studies demonstrated that the LE and VC mechanosensory neurons share a property that, among all sensory neurons, is unique to nociceptors—sensitization rather than adaptation to repeated stimulation. All other sensory neurons adapt or accommodate when repeatedly activated, whereas for at least the first several noxious stimuli, nociceptors become more sensitive and respond more vigorously to each successive stimulus. Maximal activation by noxious stimuli and sensitization by prior noxious stimulation are characteristic features of mammalian nociceptors (Illich & Walters, 1997; Woolf & Ma, 2007). Presumably these features represent widespread adaptations to ensure that the intensity of defensive responses matches the threat posed by a noxious or quasi-noxious stimulus, as well as the increasing threat presented by repeated or prolonged noxious stimulation. Although the sharing of features, such as these, by animals as distantly related as *Aplysia* and rats suggests that they may be quite general, functional properties of nociceptive neurons need to be compared in many more animal groups to distinguish general properties of nociceptors from taxon-specific or life-style-specific properties. Various other similarities are also found between rat and *Aplysia* nociceptors, but one that has interesting evolutionary implications, and perhaps implications for chronic pain mechanisms, is the capacity of these neurons to store long-term cellular "memory" of noxious stimulation.

Nociceptors in *Aplysia* and Rats "Remember" Noxious Stimulation

Persistent alterations of mammalian nociceptors are thought to contribute to several forms of chronic pain (Cheng & Ji, 2008; Walters et al., 2008; Woolf & Ma, 2007). Long-term, memory-like changes intrinsic to mammalian nociceptors following noxious stimulation are implied by numerous observations but rarely have been tested directly. This is because events sufficiently noxious to produce long-term changes in behavior in mammals cause inflammation in the region of injury. Persistent inflammatory signals impinging on peripheral branches of nociceptors, rather than long-term alterations intrinsic to the nociceptors, are commonly assumed to drive persistent pain. However, peripheral injury and inflammation cause clear changes in gene expression within nociceptors, including an upregulation of some ion channels and growth factor receptors (Ji, Samad, Jin, Schmoll, & Woolf, 2002; Mannion et al., 1999; Waxman, Kocsis, & Black, 1994; Woolf & Costigan, 1999), which strongly indicate long-lasting alterations of nociceptor function. Furthermore, peripheral nerve injury and inflammation produce regenerative and collateral growth of nociceptor axons (Doucette & Diamond, 1987; Shea & Perl, 1985; Lu & Richardson, 1991) and a transcription-

dependent enhancement of the nociceptor's growth state that continues to be expressed in vitro after isolation of the neurons (Lankford, Waxman, & Kocsis, 1998; Smith & Skene, 1997). In principle, an enhanced growth state might also promote growth of new synapses within the spinal cord. Strong evidence for inflammation- or injury-induced functional (electrophysiological) changes intrinsic to nociceptors can be provided by testing neurons in vitro, isolated from continuing extrinsic signals. Although such tests are often made on dissociated sensory neurons, they are usually performed in acute preparations, only a few hours after dissociation. However, long-term (24 h or longer) hyperexcitability of dissociated sensory neurons following prior injury or inflammation has been documented (Ma & LaMotte, 2005; Walters et al., 2008). While such observations are among the best evidence available for intrinsic cellular "memory", they usually do not exclude the possibility that this memory only lasts long enough to amplify long-term responses initiated by the cellular trauma of dissociation (Zheng, Walters, & Song, 2007).

Aplysia sensory neurons have served as an influential model system for memory studies, so it was natural to investigate long-term as well as short-term alterations of these noiciceptors produced by noxious stimulation within or close to their receptive fields. Indeed, one of the first publications about the VC tail sensory neurons described dramatic synaptic enhancement that lasted at least 75 min following noxious tail shock (Walters, Byrne, Carew, & Kandel, 1983b). It was then shown that nociceptors directly activated by tail shock display synaptic facilitation and hyperexcitability of their cell body (soma) lasting at least 24 hours (Walters, 1987). Peripheral injury, produced by either pinching and cutting the tail or by crushing the nerve that innervates the tail, produced effects on the nociceptors that lasted weeks or longer. These included peripheral axonal regeneration (Steffensen, Dulin, Walters, & Morris, 1995) and sprouting of neurites near a site of peripheral injury and within central ganglia (Steffensen et al., 1995; Billy & Walters, 1989). Functionally, peripheral injury caused a decrease in mechanosensory threshold in the damaged region (Billy & Walters, 1989; Dulin, Steffensen, Morris, & Walters, 1995), a decrease in electrical threshold of the nociceptor axon near a site of injury or intense depolarization (Weragoda, Ferrer, & Walters, 2004), and an increase in excitability (expressed as both a decrease in electrical threshold and an increase in repetitive firing) of the nociceptor soma (Gasull, Liao, Dulin, Phelps, & Walters, 2005; Ungless, Gasull, & Walters, 2002; Walters, Alizadeh, & Castro, 1991). A long-standing puzzle was why nociceptor somata demonstrate injury-induced plasticity, because in both *Aplysia* and rats the nociceptor soma is located at the end of a "blind alley", off the direct path connecting peripheral sensory receptors to the central presynaptic terminals. Recently a sensitizing function of soma hyperexcitability was revealed by showing that this hyperexcitability promotes afterdischarge in the soma when peripherally generated action potentials arrive. The afterdischarge is then relayed to other neurons in the central nervous system, amplifying the nociceptive input (Gasull et al., 2005). Finally, peripheral injury also produces synaptic facilitation (Walters et al., 1991), although it is not yet known whether the synaptic effect is intrinsic to

the nociceptor or due also or instead to other changes in the neural circuit, such as alterations in the postsynaptic neuron. As is true for the regenerative growth of mammalian nociceptors, injury-induced growth of *Aplysia* nociceptors demonstrates that at least some of the observed changes are intrinsic to the nociceptors rather than a reflection of continuing extrinsic modulation. Furthermore, an intrinsic set of mechanisms for hyperexcitability in *Aplysia* nociceptors is demonstrated by the finding that long-term hyperexcitability can be produced directly in isolated, dissociated neurons by injuring their neurites (Ambron, Zhang, Gunstream, Povelones, & Walters, 1996; Bedi, Salim, Chen, & Glanzman, 1998) or transient depolarization (Kunjilwar, Fishman, Englot, O'Neil, & Walters, 2009), and is also expressed in excised ganglia-nerve preparations in low-Ca^{2+} conditions that block ongoing release of extrinsic neuromodulators (Gasull et al., 2005; Kunjilwar et al., 2009).

Functional similarities of long-term plasticity in *Aplysia* and rat nociceptors led to a clinically relevant prediction about rat nociceptors based upon patterns of adaptive plasticity in *Aplysia* nociceptors. These patterns suggested that long-term responses of nociceptors in general to severe noxious stimulation represent a switch of the nociceptor into a persistent, intrinsically maintained, hyperfunctional state. This led us to predict that some of the most persistent and intractable forms of chronic pain in mammals depend, at least in part, upon the switch of mammalian nociceptors into a persistent hyperfunctional state after intense or prolonged exposure to signals of tissue and nerve injury. We have begun to test this idea in a model of chronic pain induced by spinal cord injury in rats. This sometimes devastating and untreatable form of pain, which occurs in a majority of human patients after spinal cord injury, was not previously thought to involve changes in nociceptors (Finnerup & Jensen, 2004). Specifically, we predicted that prolonged exposure of the central axons and terminals of nociceptors to signs of tissue injury (especially inflammatory signals) within the spinal cord would lead to hyperexcitability of nociceptors that could result in persistent spontaneous activity being generated in the somata of these neurons, as well as enhanced growth of nociceptor axons, with both effects causing central sensitization of pain pathways and spontaneous pain. These predictions have received support in preliminary studies, and suggest a new target – nociceptors – for treating this particularly resistant form of chronic pain (Walters et al., 2008).

Cellular Memory of Injury in Nociceptors Shares Mechanisms With Conventional Learning and Memory

Striking similarities exist in the behavioral responses of *Aplysia* and rats (as well as many other species) to noxious stimulation, including withdrawal reflexes, escape, guarding responses, and recuperative behaviors (Walters, 1994), and even the conditioning of fear-like responses to a context associated with noxious stimulation (Walters et al., 1981). As just described, these similarities are paralleled by functional similarities in their nociceptors, even though the neural circuits of molluscs and mammals differ as much as their gross anatomy does. It

turns out that the cellular and molecular mechanisms involved in persistent changes in behavioral responses and nociceptor excitability also are similar in *Aplysia* and rats. Furthermore, these mechanisms display substantial overlap with the mechanisms thought to underlie traditional forms of learning and memory, which are under intense investigation, especially in rodents, gastropod molluscs, and *Drosophila* (Alberini, 2009; Barco et al., 2006; Margulies, Tully, & Dubnau, 2005). In nociceptors and memory circuits these mechanisms are expressed as short- and long-term neuronal alterations; specifically, enhancement of synaptic transmission (e.g., Ji, Kohno, Moore, & Woolf, 2003; Lee & Silva, 2009) and enhancement of membrane excitability (e.g., Devor, 2006; Xu & Kang, 2005). The long-term synaptic enhancement can involve growth of new synapses (Bailey & Kandel, 2008; De Roo, Klauser, Garcia, Poglia, & Muller, 2008). In turn, these alterations are induced and sometimes maintained by the generation of numerous plasticity signals that are common to *Aplysia* sensorimotor systems, mammalian spinal sensory systems, and mammalian circuits in the hippocampus and other parts of the brain important for learning and memory. Shared plasticity signals include Ca^{2+} influx through NMDA receptor-gated channels opened during intense electrical activity (Glanzman, 2008; Ji et al., 2003; Rao & Finkbeiner, 2007), activation of cell signaling pathways by entry of Ca^{2+} or its release from intracellular stores, and by the binding of neuromodulators and growth factors to G-protein-coupled receptors and receptor tyrosine kinases (Barco et al., 2006; Ji et al., 2003; Lu, Christian, & Lu, 2008; Pezet & McMahon, 2006; Purcell & Carew, 2003). The resulting intracellular signals are highly conserved, including the second messenger, cAMP, and activated protein kinase or lipid kinase enzymes, notably PKA, PKC, ERK, and PI3K (Barco et al., 2006; Cheng & Ji, 2008; Lee & Silva, 2009; Obata & Noguchi, 2004; Sossin, 2008). Less extensive evidence suggests that cGMP and PKG (Aley, McCarter, & Levine, 1998; Lewin & Walters, 1999; Ota, Pierre, Ploski, Queen, & Schafe, 2008; Sung & Ambron, 2004; Sung, Walters, & Ambron, 2004; Zheng et al., 2007) and a protein kinase, TOR (mTOR in mammals), which promotes local protein synthesis in axons and dendrites (Casadio et al., 1999; Hu, Chen, & Schacher, 2007; Jimenez-Diaz et al., 2008; Price et al., 2007; Sossin, 2008; Weragoda et al., 2004), also contribute to both nociceptor sensitization and conventional memory. Long-term effects triggered by some of these signals require changes in gene transcription, with the transcription factor CREB playing an important role in prominent forms of long-term plasticity in the mammalian brain (Alberini, 2009; Lee & Silva, 2009) and in *Aplysia* nociceptors (Barco et al., 2006; Casadio et al., 1999; Lewin & Walters, 1999), and perhaps in mammalian nociceptors as well (Molliver, Cook, Carlsten, Wright, & McCleskey, 2002; Simonetti, Giniatullin, & Fabbretti, 2008; Tamura, Morikawa, & Senba, 2005; Teng & Tang, 2006). Thus, at the subcellular and molecular levels, the mechanisms of long-term neuronal plasticity revealed thus far seem remarkably similar when comparing molluscs to mammals, and comparing nociceptors to hippocampal neurons.

What Explains the Similarities in Mechanisms Associated with Nociceptor "Memory" and Conventional Memory in Distantly Related Animals?

The similarities reviewed above add to similarities across major phyla many have noted in various learning phenomena. Like those similarities (Papini, 2008), these additional parallels may reflect one or more of the following evolutionary relationships: far-reaching homology extending from molecular to functional levels, massive convergence, or parallel evolution. As argued by Papini for associative learning, homology across all levels can immediately be rejected because invertebrates and vertebrates diverged so long ago that specific neural circuits mediating learning and memory functions in different phyla, and (I assume) circuits mediating nociceptive functions in different phyla, probably arose independently following this early separation. For example, it is extremely unlikely that the pleural ganglia housing nociceptor somata in *Aplysia* and the dorsal root ganglia housing nociceptor somata in rats are homologous structures (although their development may well involve some homologous processes). Moreover, the functions of nociceptive systems and specialized memory systems differ, so the selection pressures shaping each type of system probably differ. These considerations indicate that some of the similarities across distantly related nociceptive systems and between nociceptive systems and specialized memory systems reflect common solutions to related problems that were arrived at independently. For example, at a functional level there are only two ways that a nociceptor can become more effective at sending information to the central nervous system: it can become more sensitive to its inputs and it can amplify its output. Thus, if, as seems likely, strong selection pressures have favored enhanced signaling effectiveness of surviving nociceptors in a region of injury (e.g., to compensate for lost sensory branches and to increase defensive responsiveness around wounds that attract predatory and parasitic attention; Walters, 1994; Weragoda et al., 2004), one would predict that either hypersensitivity (membrane hyperexcitability) or enhancement of synaptic output, or both, would be adaptations likely to appear in unrelated nociceptors subject to similar, strong selection pressures for enhanced nociceptive function after peripheral injury.

On the other hand, massive convergence of independently derived processes is unlikely to account for the large overlap in sets of cell signals critical both for long-term sensitization of nociceptors in different phyla and for long-term memory in different phyla. Indeed, at the subcellular level, the discovery of identical cell signals playing the same basic plasticity roles in each lineage and in each form of long-term alteration demonstrates that homologous, quite primitive (Ghysen, 2003), molecular processes subserve important parts of these alterations across phyla and across functionally distinct neural systems. The recent sequencing of expressed mRNAs in *Aplysia* indicates that most genes expressed in this mollusc have homologs in mammals, including genes that encode components of signal transduction and cellular regulatory pathways (Moroz et al., 2006). This advance, and the imminent sequencing of the *Aplysia* genome

(http://www.ncbi.nlm.nih.gov/nuccore/AASC00000000.2), will greatly facilitate molecular comparisons between *Aplysia* and other organisms. The available cellular observations indicate that both nociceptor "memory" and conventional memory in different phyla and diverse neural systems have utilized homologous cell signaling modules to trigger and maintain long-lasting neuronal alterations. In unrelated or distantly related nociceptive systems there probably has been parallel evolution – incorporating these core regulatory modules – to solve problems of sensory compensation and maintained vigilance following injury. In specialized memory systems, the same signaling modules appear to have been utilized in neuronal alterations shaped by divergent evolutionary pressures to solve problems of information storage. An interesting question is whether selection pressures evident today provide any clues about early selection pressures that shaped primitive plasticity systems that may be ancestral to those used today for diverse types of persistent neural plasticity.

Injury: A Potent Selection Pressure for Primitive Plasticity Mechanisms?

From a biological point of view, the emotional intensity and urgency of severe pain reflect the importance of injury-related selection pressures during evolution; an organism that cannot compensate for loss of sensory function after injury, or use nociceptive sensitization to reduce chances of further injury, is likely to die sooner and have less reproductive success than one that does. Sensitization around a wound that persists long enough for healing to occur appears to be highly adaptive, and is certainly a robust phenomenon in *Aplysia* and rats. Injury is particularly interesting as an evolutionary selection pressure because it should have been present at least as long as metazoans (Walters, 1994). Thus, unlike pressures to store information about the environment or about consequences of behavioral actions, which would have had little impact until neural circuits complex enough to begin to store such information had evolved, injury-related selection pressures have probably operated on neurons (or their antecedents) from the earliest stages of neural evolution. In other words, plasticity mechanisms selected as adaptive responses to injury may have evolved very early, before the appearance of forms of learning and memory requiring integration of activity in different neural pathways (e.g., associative learning). It seems likely that the earliest neurons were sensory and motor neurons, or combined sensory-motor neurons (Ward, Thomson, White, & Brenner, 1975; Westfall & Kinnamon, 1978). Early animals were quite small and lacked shells or hard exoskeletons, so the branches of primitive neurons were close to the soft body surface and exposed to peripheral trauma from inanimate, and possibly animate, sources. Thus, from the earliest stages of neural evolution, injury-related selection pressures may have been exerted directly on primitive neurons.

An implication of these considerations is that persistent neuronal plasticity mechanisms may have been selected originally in soft-bodied ancestors of most contemporary animals for their ability (1) to repair and regenerate peripheral

axonal branches, (2) to compensate for loss of sensory function within a damaged region, and 3) to reduce the chances of aggravating an injury by subsequent movements. A fourth function may have undergone selection after predation arose – sensitization around a wounded region to accelerate responses to subsequent attacks by predators or parasites attracted to the wound (Walters, 1991, 1994; Weragoda et al., 2004). The first set of mechanisms would result in regrowth of destroyed axonal branches while the second, third , and fourth sets could include hyperexcitability of surviving branches of damaged sensory neurons, hyperexcitability of the branches of nearby, undamaged sensory neurons, hyperexcitability of the soma or central branches of sensory neurons (which could amplify trains of sensory action potentials arriving from the periphery), enhanced release of neurotransmitter from central synapses of sensory neurons, and growth of new synapses from surviving sensory neurons. Again, these or similar functional changes have been observed in *Aplysia* and rat nociceptors, and also in neurons in structures, like the hippocampus, that appear specialized for learning and memory functions.

None of the molecular signals and cellular effectors associated thus far with nociceptor plasticity and with learning and memory (see above) is unique to these forms of plasticity; each has many other roles and is found in most metazoan cells. The molecular signals (e.g., second messengers, protein kinases, transcription factors) identified with neuronal plasticity to date represent parts of highly conserved, core regulatory systems (e.g., Gerhart & Kirschner, 1997), which are also involved in other processes, including development, differentiation, adaptation to different physiological conditions, and cellular responses to stress. Such signals may have become linked in primitive neurons to the stress of peripheral injury. Once linked to injury-induced plasticity in nociceptive sensory neurons, these regulatory modules could then be "co-opted" for use in other forms of neural plasticity as nervous systems evolved. Thus, while the phenomena of nociceptive behavioral sensitization in molluscs, chronic pain in mammals, and long-term memory in mammals are homoplasic at the psychological level, they may be products of parallel evolution, utilizing homologous molecular building blocks (see Papini, 2008). The linking of these building blocks to persistent changes in neuronal function might have occurred originally in response to ubiquitous injury-related selection pressures. If this linkage occurred in a common ancestor of contemporary animals, the *persistence* of these different psychological phenomena could be a homologous property. However, if such linkages occurred independently in different lineages or different types of neurons, the persistence of each form of behavioral modification would represent a homoplasic property.

In either case, contemporary nociceptors--both in vertebrates and in invertebrates--offer a special opportunity to discover fundamental mechanisms of neuronal plasticity that may prove important for understanding the persistence of long-term memory as well as chronic pain. Conversely, the hypothesis that peripheral injury was a preeminent selection pressure driving the evolution of mechanisms of neural plasticity underscores the value of using known learning and memory mechanisms to guide the search for mechanisms, in nociceptive sensory

neurons and their targets, that contribute to the persistence of some forms of chronic pain (e.g., Ji et al., 2003). More generally, an evolutionary perspective combined with an explicit comparative approach can yield novel predictions about cellular mechanisms that may contribute to clinically important problems, such as chronic pain following spinal cord injury. Such efforts are encouraged by the growing realization that evolutionary considerations can be a valuable part of biomedical research and medicine (Nesse, Stearns, & Omenn, 2006; Williams & Nesse, 1991).

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