1. Introduction

Our knowledge of the existence of endogenous descending pain modulatory systems spans at least three decades and we now know that brain stem descending pathways constitute a major mechanism in the control of pain transmission (for comprehensive reviews, see Fields and Basbaum, 1999; Millan, 2002). The basis for an endogenous descending pain modulatory circuit linking the periaqueductal gray (PAG), the rostral ventromedial medulla (RVM) and the spinal cord, has now been well established (Gebhart, 1986; Fields et al., 1991; Fields and Basbaum, 1999; Millan, 2002 for reviews). Recent studies indicate that hyperalgesia in animal models of inflammatory and neuropathic pain is closely linked to activation of descending modulatory circuits involving both inhibition and facilitation. This review will discuss recent conceptual advances in our understanding of descending modulation and its role in persistent pain. The following issues will be described below: (1) the existence of bidirectional descending control; (2) descending modulatory influences after tissue and nerve injury; (3) dynamic shifts in descending modulation after injury; and (4) molecular mechanisms of activity-dependent plasticity in descending modulatory circuitry. The clinical implications of the findings will then be discussed.

2. Bidirectional descending control

Although the earliest studies focused on descending inhibitory control in response to transient noxious stimulation, we now know that there are parallel descending facilitatory mechanisms. Descending facilitation was likely not recognized in the original reports because it often is masked by the more intense electrical stimulation or higher drug doses used to produce descending net inhibition (see below). In the RVM, two types of neurons, on-cells and off-cells, have been identified as pain modulatory neurons (see Fields et al., 1991). On-cells are characterized by a sudden increase in firing immediately before, and off-cells exhibit a pause in activity just prior to, the initiation of a nocifensive response. While off-cells are usually associated with the inhibition of a nocifensive behavior, the activity of on-cells is correlated with a facilitation of nocifensive behavior. Brain stem descending pathways facilitate nociceptive transmission at the spinal level. Excitation and inhibition of dorsal horn neurons can be produced by stimulation of the dorsolateral funiculus of the spinal cord, nucleus raphe magnus (NRM) and nucleus reticularis gigantocellularis (NGC) (Ren et al., 2000 review). In the NGC, low intensity electrical stimulation or microinjection of neurotensin, a low dose of glutamate, or a high dose of baclofen, a GABA<sub>B</sub> receptor agonist, all produce facilitation of spinal behavioral and dorsal horn neuronal responses to noxious stimulation (Zhuo and Gebhart, 1992; Thomas et al. 1995; Urban and Gebhart, 1997). RVM neurons may exert bi-directional control of nociception through descending serotonergic and noradrenergic pathways (Zhuo and Gebhart, 1991; Holden et al., 1999). In addition, vagal afferent stimulation produces facilitation and inhibition of nociception and the neural relays include sites within the RVM (Randich and Gebhart, 1992).

3. Persistent pain and descending modulation

Earlier studies of descending modulation have mainly focused on responses to acute or transient stimuli. In contrast, recent studies have examined the effects of pain that last for hours, days or longer following tissue damage or nerve injury. These persistent, or chronic pain conditions are associated with prolonged functional changes in the nervous system, evidenced by the development of dorsal horn hyperexcitability, or activity-dependent plasticity, also commonly referred to as spinal central sensitization (see Dubner and Ruda, 1992; Woolf and Salter, 2000, for reviews). There is now considerable evidence that there is enhanced net descending inhibition after inflammation at sites of primary hyperalgesia. In cats with knee joint inflammation, descend-
ing inhibition is greater in neurons with input from the inflamed knee as revealed by reversible spinalization with a cold block (Schaible et al., 1991). In rats with hindpaw inflammation, thoracic lidocaine block leads to an enhanced activity of dorsal horn nociceptive neurons that is greater in inflamed than that in non-inflamed rats (Ren and Dubner, 1996). A similar conclusion can be reached by using Fos protein expression as a marker of neuronal activation. There are more inflammation-induced Fos-immunoreactive neurons in the dorsal horn in spinally transected or dorsolateral funiculus-lesioned rats, when compared to sham-operated inflamed rats (Ren and Ruda, 1996; Wei et al., 1998). Kauppila et al. (1998) showed that thermal but not mechanical nociceptive responses were further enhanced in hindpaw-inflamed and spinal nerve-ligated rats after midthoracic spinalization. Finally, hyperalgesia is intensified in rats with lesions of the dorsal lateral quadrant of the spinal cord after inflammation or formalin injection (Abbott et al., 1996; Ren and Dubner, 1996). These studies reveal the net descending inhibitory effects of activation of multiple supraspinal sites. The findings suggest that injury-induced dorsal horn hyperexcitability and hyperalgesia are dampened by descending pathways, due to enhancement of descending net inhibition.

The source of the enhanced inhibition can be traced back to brain stem structures. Local anesthesia of the RVM results in a further increase in dorsal horn nociceptive neuronal activity in hindpaw-inflamed rats (Ren and Dubner, 1996). Focal lesions of the RVM and locus coeruleus are followed by an increase in spinal Fos expression and hyperalgesia after inflammation (Tsuruoka and Willis, 1996; Wei et al., 1999). Interestingly, there appears to be laminar selectivity in the effect of RVM serotoninergic and locus coeruleus noradrenergic descending pathways (Ren et al., 2000). It appears that both RVM and locus coeruleus descending pathways are major sources of enhanced net inhibition in inflamed animals.

Descending facilitation not only parallels inhibition but also can be an active and dominant effect. The selective destruction of the NGC with a soma-selective neurotoxin, ibotenic acid, leads to an attenuation of hyperalgesia and a reduction of inflammation-induced spinal Fos expression (Wei et al., 1999). The descending facilitatory effect may also originate from the medullary dorsal reticular nucleus (Lima and Almeida, 2002) and other brain sites such as the anterior cingulate cortex (Calejesan et al., 2000).

A descending facilitatory drive contributes to the pathogenesis of certain types of persistent pain, particularly those associated with secondary hyperalgesia or nerve injury (Porreca et al., 2002). Spinalization blocks mustard oil-produced secondary mechanical allodynia and mechanical hyperexcitability of spinal nociceptive neurons (Mansikka and Pertovaara, 1997). Hindpaw formalin-induced hyperalgesia is prevented by RVM lesion (Wiertelak et al., 1997). RVM lesions inhibit secondary hyperalgesia produced by topical application of mustard oil (Urban and Gebhart, 1999). The same phenomenon occurs in models of neuropathic pain. The tactile allodynia after nerve injury is dependent upon a tonic activation of net descending facilitation from supraspinal sites (Ossipov et al., 2000). In nerve injured rats, lesions of the dorsolateral funiculus, local anesthetic block of the RVM and lesions of RVM mu-opioid receptor expressing cells do not prevent the onset, but reverse the later maintenance of tactile and thermal hypersensitivity (Porreca et al., 2001; Burgess et al., 2002). These observations point to an ascending-descending loop that is activated in response to prolonged stimulation to facilitate nociception at the spinal level. The ascending dorsal column pathways may contribute to this pain facilitatory circuitry in neuropathic pain models (Miki et al., 2000). There is no evidence of activation of the dorsal column pathway in models of inflammatory primary and secondary hyperalgesia.

Thus, descending modulation of persistent pain involves both inhibition and facilitation. Although there may exist selective circuitry that is responsible for multiple phases of modulation, it is rather surprising that the facilitatory sites in the rostral medulla generally overlap with the sites that also produce inhibition. The inhibition and facilitation may also share some synaptic mechanisms with subtle difference in sensitivity. It is well known that a manipulation at the same site, such as electrical stimulation given at lesser or greater intensities, or receptor agents administered at lower or higher doses, produce opposing effects on nociceptive transmission. After tissue or nerve injury, there is an increase in synaptic strength for both descending inhibition and facilitation. Both facilitatory and inhibitory circuitry may be activated by ascending input after injury (Herrero and Cervero, 1996; Gozariu et al., 1998). There is an increase in on- and off-cell activity after inflammation (Miki et al., 2002, and see below). What appears to be important, then, is the balance between synaptic excitation and inhibition under different conditions. It has been shown previously that the NGC plays a role in descending facilitation of nociceptive transmission after transient noxious stimuli (Zhuo and Gebhart, 1992). Lesions of the NGC produce an attenuation of hyperalgesia and spinal Fos expression after inflammation (Wei et al., 1999). However, combined NGC and NRM lesions reverse the opposite NGC or NRM lesion-induced effects. It is possible that severe persistent pain may be enhanced when the facilitatory network overrides the inhibition.

4. Dynamic shifts in descending modulation after injury

Recent studies indicate that the enhancement of descending inhibition in response to tissue injury appears to build up gradually (Schaible et al., 1991; Ren and Dubner, 1996; Danziger et al., 1999; Dubner and Ren, 1999; Hurley and Hammond, 2000). The difference in inflammation-induced Fos expression between transected and sham controls is...
clear at 3 days but not apparent shortly (2 h) after inflammation (Ren and Ruda, 1996). In early stages of inflammation the dynamic response is similar in both the spinally intact and transected rats, suggesting that descending inhibitory inputs play less of a role in the early response to peripheral inflammation. In contrast, at 3 days after inflammation, descending inhibition is enhanced to counteract continuous noxious input. The results from electrophysiological studies also suggest a progressive enhancement of descending inhibition of dorsal horn neurons during the development of inflammation (Schaible et al., 1991). An effect of Freund’s adjuvant on the contralateral spinal cord may also be subject to the inhibitory control of descending inputs as suggested by a clear contralateral increase in Fos-positive cells in transected rats after inflammation (Ren and Ruda, 1996). It appears that following inflammation brainstem descending pathways become progressively more involved in suppressing incoming nociceptive signals in primary hyperalgesic zones. Injury-related primary afferent input is probably responsible for triggering this ascending-descending feedback circuit. This enhancement of descending inhibition appears to be present when the animal is subject to continuous, persistent noxious stimulation.

The dynamic changes in descending inhibition after inflammation can be examined over time by monitoring antinociceptive responses in lightly anesthetized rats during RVM stimulation (Terayama et al., 2000; Guan et al., 2002b). In these studies, persistent inflammation induces dramatic changes in the excitability of RVM pain-modulating circuitry suggesting that there are dynamic temporal changes in synaptic activation in the brain stem after inflammation. Early (up to 3 h) in the development of inflammation there is an increased descending facilitation as shown previously (Urban and Gebhart, 1999), which reduces the net effect of the inhibition. Over time, the level of descending inhibition increases, or descending facilitation decreases, leading to a net enhancement of antinociceptive behavior. Direct stimulation of the dorsolateral funiculus that bypasses brain stem synaptic mechanisms does not produce a dynamic change in excitability indicating that the changes are due to supraspinal mechanisms at the level of the RVM or higher.

What are the cellular mechanisms that underlie these changes? Excitatory amino acids (EAAs) previously have been shown to mediate descending modulation in response to transient noxious stimulation and early inflammation (Urban and Gebhart, 1999 for review; Heinricher et al., 1999) and they appear to be involved in the development of RVM excitability associated with inflammation and persistent pain (Terayama et al., 2000; Guan et al., 2002b; Miki et al., 2002). N-methyl-d-aspartate (NMDA), the prototype NMDA receptor agonist, microinjected into the RVM, produces effects that are dependent upon the post-inflammatory time period. At 3 h post-inflammation, low doses of NMDA produce facilitation of the response to noxious heat of the inflamed hindpaw and the non-inflamed hindpaw and tail, supporting previous findings that descending facilitatory effects are NMDA dependent and occur early after inflammation (Urban and Gebhart, 1999). Higher doses of NMDA at 3 h post-inflammation only produce inhibition. At 24 h post-inflammation, NMDA produces only inhibition. All of these effects are blocked by administration of NMDA receptor antagonists. α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), a selective AMPA receptor agonist, produces dose- and time-dependent inhibition at 3 and 24 h post-inflammation that are blocked by an AMPA receptor antagonist. The above findings indicate that there is a leftward shift of the dose-response curves of NMDA- and AMPA-produced inhibition at 24 h post-inflammation as compared to 3 h. The leftward shift of the dose-response curves of EAA receptor agonists parallels the time-dependent enhancement of net descending inhibition produced by RVM electrical stimulation, which is also attenuated by NMDA receptor antagonists (Terayama et al., 2000). The results suggest that the time-dependent functional changes in descending modulation are mediated, in part, by enhanced EAA neurotransmission.

The time-dependent plasticity in descending pain modulatory circuitry also involves changes in the response profiles of RVM neurons. In previous studies, the responses of three classes of neurons in the RVM, on-, off- and neutral-cells have mainly focused on animals without preexisting injury (Fields et al., 1991; Heinricher et al., 1999). We have used paw withdrawal as a behavioral correlate to assess the relationship between nociceptive behavior and RVM neural activity (Miki et al., 2002). On-like, off-like and neutral-like cells were described according to the relationship of their responses to the paw withdrawal behavior. Importantly, we found that some neutral-like cells changed their response profile and were reclassified as on- or off-like cells during continuous recordings of 5 h or more during the development of inflammation. The switch in the response profile of RVM neurons correlated with the temporal changes in excitability in the RVM after inflammation (Terayama et al., 2000). This phenotypic change of RVM neurons was verified in a population study that showed a significant increase in the percentage of on- and off-like cells, and a decrease in the neutral-like cell population 24 h after inflammation as compared to control animals (Miki et al., 2002). The studies of RVM neurons also support our conclusion that enhanced descending modulation after inflammation involves both facilitation and inhibition since there were also changes in the responses of on- and off-like cells. After inflammation, there was a greater increase in on-like responses before the onset of paw withdrawal as compared to on-like responses in naïve controls. On-like cell activity is associated with facilitation of nociceptive behavior (Fields and Basham, 1999). In contrast, off-like responses were reduced after inflammation indicated by a less reduction in neuronal activity after the noxious stimulus, and a lack of a complete pause. The
pause in off-like cell activity is associated with disinhibition; the lack of the pause and the less reduction in neuronal activity suggest an increase in inhibition. However, it is difficult to predict the net effect of descending modulation from changes in single neuronal activity without recording from very large populations of neurons. Further studies are required to identify the subclasses of RVM neurons that exhibit profile changes after inflammation and are also modulated by glutamatergic transmission. Rats with inflammatory hyperalgesia exhibit an increased sensitivity to opioid analgesics (Neil et al., 1986). Typically, there is a leftward-shift of the dose-response curve for opioids from the inflamed hyperalgesic paw when compared to the non-inflamed paw (Hylden et al., 1991). Kayser et al. (1991) suggested that this increased opioid sensitivity in inflamed animals was related to a peripheral mechanism as it is significantly attenuated after local injections of very low doses (0.5–1 μg) of naloxone. Recent observations indicate that the increased opioid sensitivity after inflammation may also reflect changes in central pain modulating pathways. Hurley and Ham mond (2000, 2001) have demonstrated enhancement and plasticity of the descending inhibitory effects of mu and delta-2 opioid receptor agonists microinjected into the RVM during the development and maintenance of inflammatory hyperalgesia. It is likely that opioid peptide activation or GABA disinhibition (Fields and Basbaum, 1999) are also important in the initiation and maintenance of RVM plasticity.

5. Molecular mechanisms of activity-dependent plasticity in descending modulatory circuitry

The increased sensitivity of EAA receptors during the development of inflammation appears related, in part, to transcriptional and translational modulation of the receptors. Examination of the messenger RNA expression of the NR1, NR2A and NR2B subunits of the NMDA receptor in the RVM reveals an upregulation that parallels the time course of the RVM excitability changes (Miki et al., 2002). This is accompanied by an increase in NMDA receptor protein. Western blot analysis also reveals a time-dependent increase in the AMPA receptor GluR1 subunit levels in the RVM at 5 and 24 h post-inflammation as compared to naive animals (Guan et al., 2002a). Using an antibody that recognizes the phosphoGluR1 subunit at the serine 831 residue, Western blots also demonstrated that GluR1 phosphoprotein levels were increased as early as 30 min and were time-dependent, suggesting that posttranslational receptor phosphorylation may also contribute to the enhanced AMPA transmission (Guan et al., 2002a).

This activity-induced plasticity in pain modulating circuitry complements the activity-dependent neuronal plasticity in ascending pain transmission pathways (Dubner and Ruda, 1992). Inflammation leads to peripheral sensitization of nociceptors and central sensitization or activity-dependent plasticity of spinal nociceptive neurons. The spinal plasticity is dependent upon increased activation of nociceptors at the site of injury and its initiation and maintenance is dependent upon transcriptional, translational and posttranslational modulation of EAA receptor subunits. The increased neuronal barrage at the spinal level activates spinal projection neurons which then activate glutamatergic, opioidergic and presumably GABAergic neurons at the brain stem level leading to a similar but not identical form of activity-dependent plasticity. It is likely that transmission sites at multiple levels in nociceptive pathways exhibit enhanced sensitivity and plasticity in response to a persistent neuronal barrage associated with tissue or nerve injury.

6. Clinical implications of enhanced descending modulation after injury

The intensity of perceived pain under normal conditions and persistent pain as a result of injury are modulated by descending pathways. Descending modulation and activity-dependent plasticity are normal functions of the brain and presumably are activated to protect the organism from further environmental injury. We propose that the dynamic changes in descending modulation after inflammation and primary hyperalgesia and allodynia are protective. The early facilitation may function to enhance nocifensive escape behavior whereas the dominant late inhibition may provide a mechanism by which movement of the injured site is suppressed or reduced to aid in healing and recuperation. Enhanced modulation clearly includes shifts in the balance between inhibitory and facilitatory components. Present evidence suggests that there is a different balance in neural networks receiving input from zones of secondary hyperalgesia where there is no primary injury. The balance towards facilitatory influences appears to be maintained for longer periods. Activation of these sites would lead to an enhancement of movement behavior that could also be protective.

Injury to neural tissues will also upset the balance between facilitation and inhibition. The dynamic plasticity of descending pathways after peripheral nerve injury leading to neuropathic pain may render the system vulnerable and lead to pathological consequences. In this situation the initiation of hyperalgesia is not dependent upon descending facilitation whereas the maintenance of the hyperalgesia for long periods of time is dependent on such descending facilitation (Burgess et al., 2002). Nerve injury may activate a descending nociceptive system that normally is protective but can become a source of persistent pain after pathology in the nervous system.

The imbalance between these modulatory pathways may also be one mechanism underlying variability in other persistent or chronic pain conditions, especially those involving deep tissues such as muscle and viscera. Inputs from deep tissues produce more robust dorsal horn hyperexcitability and plasticity than inputs from cutaneous tissues.
Primary afferent and spinal neurons originating from muscle and viscera are often multimodal and responsive to innocuous as well as noxious stimuli. An imbalance of descending modulatory systems in which there is an increase in endogenous facilitation could lead to innocuous input being perceived as painful. For patients suffering from deep pains such as temporomandibular disorders, fibromyalgia, irritable bowel syndrome and low back pain, the diffuse nature and amplification of persistent pain, in part, may be the result of a net increase in endogenous descending facilitation.

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