Neurotoxic Versus Neuroprotective Actions of Endogenous Opioid Peptides: Implications for Treatment of CNS Injury

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INTRODUCTION

Insults to the central nervous system (CNS) initiate a complex cascade of biochemical alterations that are remarkably consistent across different injury models (Panter and Faden 1992). These reactive changes include both the induction of endogenous autodestructive factors (Faden 1993a; McIntosh 1994) on the one hand and endogenous neuroprotective factors (Mattson and Scheff 1994) on the other. The balance between these opposing processes determines subsequent tissue damage and behavioral recovery.

Endogenous opioid peptides have been implicated as pathophysiological factors in CNS injury since 1981 (Faden et al. 1981a, 1981b). Studies using opioid receptor antagonists support a role for certain endogenous opioids in the pathophysiology of spinal cord trauma, cerebral ischemia, and traumatic brain injury (Faden 1993b). The diversity of endogenous opioids and opioid receptors has complicated the search for the patho-physiological opioids, although solid experimental results implicate dynorphin as one such factor (Faden 1990, 1993b). More recently, studies have demonstrated that certain opioid receptors may mediate neuroprotective actions (Hall et al. 1987; Hayes et al. 1990), suggesting the possible existence of one or more neuroprotective opioids as well. This chapter reviews the literature within the context of developing strategies for treating CNS injury.

ENDOGENOUS OPIOIDS AND OPIOID RECEPTORS

Since the discovery of the pentapeptide enkephalins nearly 20 years ago, a large number of endogenous opioids or opioid fragments have been identified (Cox 1982). These predominantly fall into three large classes: pre-proenkephalin A, pre-proenkephalin B (pre-

prodynorphin), and pre-proopiomelanocortin. In addition, at least three classes of opioid receptors have been found: μ, d, and k.

Enkephalins show some selectivity for μ and d receptors, whereas dynorphin is relatively selective for k receptors. ß-endorphin has activity at each of these receptors. The development of selective synthetic agonists and antagonists to these receptors has provided tools to examine the role of endogenous opioids and their receptors in a variety of physiological and pathophysiological functions, including CNS injury (Faden 1993b).

Endogenous Opioids as Pathophysiological Factors: Studies Using Opioid Receptor Antagonists

Faden and colleagues provided the first evidence to suggest a pathophysiological role for endogenous opioids by demonstrating that treatment with the opioid antagonist naloxone significantly reduced posttraumatic ischemia and improved behavioral recovery following impact injury to cat cervical spinal cord (Faden et al. 1981a, 1981b). This work was subsequently replicated by many laboratories using a variety of experimental animals, CNS injury models, and outcome measures (for review, see Faden 1993b). The high doses of naloxone required for optimal therapeutic actions in CNS injury suggested that non-μ receptors were involved, most likely d or k. Failure to observe a beneficial effect with a d-selective antagonist, combined with strong protective actions for k-active or k-selective opiate antagonists, provided support for the concept that k opioid receptors might mediate the pathophysiological actions of endogenous opioids (Faden et al. 1987).

Dynorphin as a Neurotoxic Factor: Its Potential Role in the Pathophysiology of CNS Injury

Many groups have demonstrated that intrathecal administration of dynorphin causes pathophysiological changes, including hind limb paralysis, decreased spinal cord blood flow, neurochemical changes (i.e.,release of fatty acids and excitatory amino acids), and histological changes (Bakshi et al. 1990; Faden and Jacobs 1983; Herman and Goldstein 1985; Long et al. 1987; Przewlocki et al. 1983). Whether these toxic effects of dynorphin are mediated by opioid receptors has been debated, but best evidence now suggests that both opioid receptor-mediated and nonopioid mechanisms are involved (Bakshi et al. 1990; Faden 1990). At low doses of intrathecal dynorphin, pathophysiologic effects are largely reversed by a variety of opioid

receptor antagonists, including k-active and k-selective antagonists (Bakshi et al. 1990, 1992; Faden 1990). However, at higher doses of dynorphin, paralysis and other physiological effects are not reversed by opioid receptor antagonists, and these actions are duplicated by dynorphin 2-17 or dynorphin 3-13, which are inactive at opioid receptors (Faden 1990; Long et al. 1987).

That dynorphin may be involved in the pathophysiology of CNS injury has been suggested by several observations. Dynorphin administered at subinjury levels significantly shifts the curve of traumatic injury to the left, both after spinal cord injury (Faden 1990) and brain trauma (McIntosh et al. 1994). In addition, following brain or spinal cord trauma, dynorphin increases in injured tissue in direct proportion to injury severity, and it is well localized to those sites showing maximal injury (Faden et al. 1985; McIntosh et al. 1987a). Perhaps more critically, however, treatment with polyclonal antibodies to dynorphin but not antisera to other endogenous opioids significantly attenuates behavioral deficits following traumatic spinal cord injury (Faden 1990).

The responses to trauma and ischemia may differ. Ischemic brain injury has not been associated with accumulation of dynorphin immunoreactive material in injured tissue (Andrews et al. 1989; Fried and Nowak 1987). Moreover, several groups have reported protective, albeit inconsistent, effects of treatment with high systemic doses of dynorphin in experi-mentally induced cerebral ischemia (Baskin et al. 1984; Handa et al. 1988; Tang 1985). However, k opioid receptors appear to be upregulated after both cerebral ischemia (Scavini et al. 1990) and spinal cord trauma (Krumins and Faden 1986), yet downregulated after brain trauma (Perry et al. 1992).

Mechanism for Dynorphin's Neurotoxic Actions

Caudle and Isaac (1988) first suggested that the pathophysiologic actions of dynorphin following intrathecal administration may result from induction of N-methyl-d-aspartate (NMDA)-mediated receptor actions. This concept is supported by results from a number of investigators (Bakshi and Faden 1990a, 1990b; Bakshi et al. 1992; Long et al. 1989). These studies have shown that NMDA antagonists, including competitive, noncompetitive, and glycine modulatory site antagonists, can antagonize the paralytic effects of intrathecal dynorphin (Bakshi and Faden 1990a, 1990b; Bakshi et al. 1992; Long et al. 1989).

NMDA antagonists have also been found to attenuate electrophysio-logical (Isaac et al. 1990) and histological changes (Bakshi et al. 1992) produced by dynorphin. A possible mechanism may well be that endogenous opioids presynaptically modulate the release of excitatory amino acids. For example, dynorphin administered through a micro-dialysis probe caused dose-dependent release of glutamate in both brain (Faden 1992) and spinal cord (figure 1). In addition, an opioid receptor antagonist administered prior to brain ischemia attenuated postischemic glutamate release in a stereospecific fashion (Graham et al. 1993).

IS THERE ALSO A NEUROPROTECTIVE ACTION MEDIATED BY ENDOGENOUS OPIOIDS OR OPIOID RECEPTORS?

Hayes and colleagues suggested that μ opioid receptors may modulate neuroprotective actions in brain injury. This is based upon the observation that very low doses of naloxone may exacerbate effects of traumatic brain injury (Hayes et al. 1990) in contrast to very high doses of naloxone, which are protective (Hayes et al. 1983). In addition, this group has shown that μ agonist compounds such as morphine sulfate or D-Ala2-MePhe4Gly-ol5 enkephalin (DAGO) can attenuate the behavioral consequences of traumatic brain injury. Interestingly, DAGO attenuates the behavioral deficits produced by intrathecal dynorphin administration in a dose-dependent fashion (Faden, unpublished observations).

In addition to a potentially protective role provided by μ receptors, a number of studies have shown that certain k agonists may also protect against both brain and spinal cord injury (Birch et al. 1991; Cordon et al. 1990; Hall et al. 1987). Although this would seem to contradict studies showing protective effects of k-selective antagonists such as norbinaltor-phimine (Faden et al. 1987; Vink et al. 1991), these differences most likely relate to the well-established existence of k isoreceptors (Horan et al. 1993; Rothman et al. 1990; Zukin et al. 1988). Considerable evidence supports the existence of both high- and low-affinity k receptors. Whereas dynorphin is active at both types of k receptors (Zukin et al. 1988), kagonist compounds showing neuro-protective actions may be selective for the high affinity k1 site. In contrast, the neurotoxic actions of dynor-phin that are mediated by opioid receptors may involve the low-affinity or k2 site, which itself may have distinct subpopulations (k2a, k2b) (Rothman et al. 1990). Interestingly, the benzomorphan opioid antagonist WIN44,441-3, which has perhaps the highest potency and effectiveness of any opioid antagonist in CNS injury (Faden and Jacobs
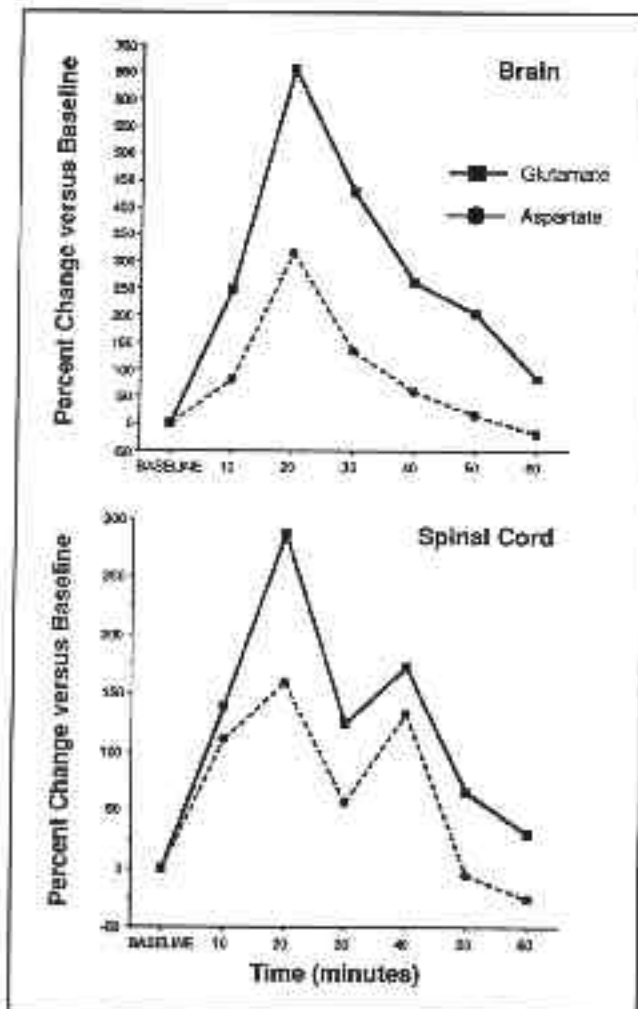
FIGURE 1. *Effect of dynorphin A(1-17) [100 nanomolars (nmol)] on extracellular glutamate and aspartate levels following administration through microdialysis probe in rat hippocampus (top) or spinal cord (bottom). Other studies showed these effects to be dose dependent.*

1985; McIntosh et al. 1987b), has high affinity for the k2b receptor (Horan et al. 1993; Rothman et al. 1990). Moreover, the author and colleagues have recently found that traumatic spinal cord injury in rats selectively upregulates k2 receptors (Sun and Faden, unpublished observations).

LESSONS LEARNED: IMPLICATIONS FOR FUTURE PHARMACOTHERAPY

If one accepts the existing data regarding the protective actions of μ-agonists and k antagonists, then it would seem logical to consider treating patients either with a combination of such agents or with a compound that has this pharmacological profile. Buprenorphine is a mixed μ-agonist/k-antagonist compound (Leander 1987; Sadée et al. 1982) that has been used to treat various forms of addiction in humans (Bracken and Holford 1993; Kosten et al. 1989). In preliminary studies (Johnson et al. 1989), buprenorphine administered 30 minutes after fluid percussion-induced traumatic brain injury in rats significantly improved neurological outcome at 4 weeks as compared to saline-treated controls (figure 2).

Opiate antagonists have been shown to be of benefit in spinal cord injury (Bracken and Holford 1993) and possibly cerebral ischemia (Adams et al. 1986; Estanol et al. 1985) in humans. Given these preliminary experi-mental data and the established safety of buprenorphine treatment in humans, buprenorphine appears to be a potentially attractive therapy for acute brain or spinal cord injury in humans.

Potential Implications for Addiction Treatment

Dynorphin peptides have been found to suppress opiate withdrawal as well as antinociceptive tolerance in morphine-dependent mice (Takemori et al. 1992). Similar observations have been made in a variety of other species, including rats (Green and Lee 1988), monkeys (Aceto et al. 1982), and humans (Wen et al. 1984). From these studies it has been suggested that "Usage of an endogenous opioid peptide may be a safe and useful way to manage opiate withdrawal in human opiate addicts" (Takemori et al. 1992, p. 223). However, given the neurotoxic effects of dynorphin administered intrathecally as well as the ability of dynorphin to shift the curve of CNS trauma to the left, the issue of dynorphin's safety must be considered. Particularly relevant in this regard are the
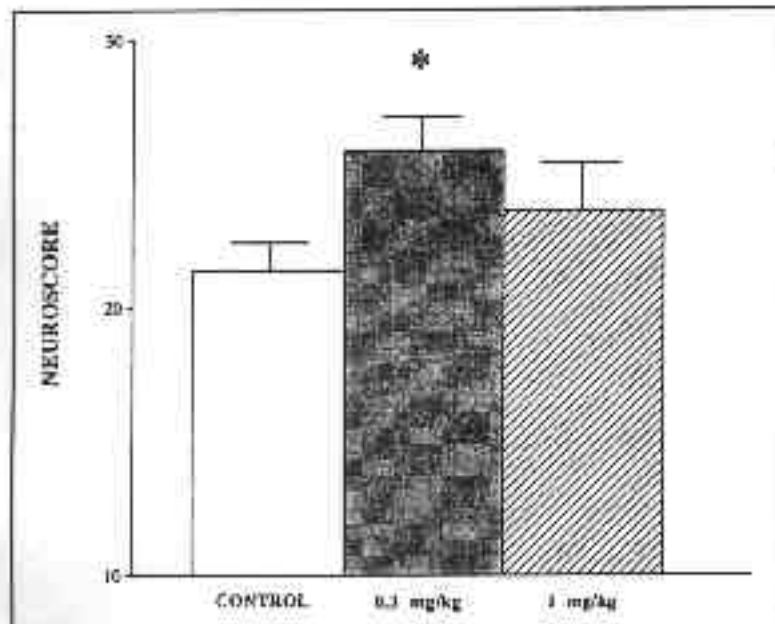
FIGURE 2. *Effect of treatment with buprenorphine on neurological outcome 2 weeks after fluid percussion-induced traumatic brain injury in rats. Neuroscore represents the summation of 7 separate motor function scores, each ranging from 0 (no function) to 5 (normal function). Treatment was administered as single bolus injection at 30 minutes after injury.*

structure-activity studies by Takemori and colleagues (1992) relating to dynorphin suppression of the expression of opiate withdrawal and tolerance in morphine-dependent mice. This therapeutic profile is remarkably similar to that which produces paralytic injury following intrathecal dynorphin administration in rats. Given the other forms of therapy for opiate withdrawal currently being studied, it would be wise to carefully evaluate its safety before proceeding with this form of therapy. Another finding that may be relevant is the recent work by Hurd and Herkenham (1993) demonstrating increases in dynorphin-like immuno-reactive material as well as upregulation of k opiate receptors in cocaine addicts shortly after death. Animal studies have also shown that cocaine administration increases dynorphin levels (Hurd et al. 1992; Sivam 1989).

SUMMARY

Endogenous opioid systems seem to have both neurodestructive and neuroprotective roles in CNS injury. Whereas μ and k1 receptors appear to mediate neuroprotective actions, k2 receptors may be involved in secon-dary injury responses. Among the endogenous opioids, dynorphin has marked neurotoxic effects when given intrathecally to rats; when admin-istered in subinjury doses, dynorphin exacerbates the response to brain or spinal cord trauma. Because of the neurotoxic effects of dynorphin, one should employ this compound with great caution in human studies of addiction treatment. It has not been established which endogenous opioids might be protective. Taken together, these observations may suggest novel approaches to the treatment of CNS injury using selective mixed opioid agonist-antagonist compounds such as buprenorphine.

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ACKNOWLEDGMENTS

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