Descending antinociceptive mechanisms in the brainstem: Their role in the animal’s defensive system

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Summary — The identification of specialized mechanisms in the mammalian brainstem that function to inhibit the rostral transmission of nociceptive (pain-related) information in the spinal cord led to an explosion of research into the neuroanatomical and neurochemical substrates of these antinociceptive systems. As outlined in the present paper, most attention was directed at those mechanisms in the periaqueductal grey (PAG) and rostral ventromedial medulla (RVM). However, comparatively little attention has been paid to the functional role of these mechanisms in animal behaviour. The purpose of the present paper is to review research into the behavioural significance of those antinociceptive mechanisms in the PAG and RVM. It is concluded that these mechanisms function as part of the animal’s fear or defensive system, serving to make a threatened animal insensitive to noxious stimulation and thereby allowing that animal to engage in defensive responses instead of recuperative activities. Further, it is argued that the organization of these antinociceptive circuits reflects the animal’s increasing capacity for early detection of danger. Specifically, nociception itself is held to signify the presence of immediate threat, and consequently, nociceptive input directly activates antinociceptive circuits at either the spinal level (during intense noxious stimulation) or RVM (following exposure to moderate noxious stimulus). In contrast, events that are themselves innocuous but which signal threat (either learned or innate danger signals) activate fear and defensive systems in the amygdala and PAG which engage the descending antinociceptive projections in the RVM.

antinociceptive mechanisms / brainstem / periaqueductal grey / rostral ventromedial medulla / defensive systems

Introduction

Over the past two and a half decades, there has been an enormous research effort devoted to examining mechanisms in the brain that serve to disrupt the transmission of nociceptive information. Such mechanisms have been indentified in numerous brainstem structures including the nucleus of the solitary tract, the lateral reticular nucleus, the lateral paragigantocellular reticular nucleus, and the locus coeruleus and subcoeruleus, as well as in forebrain structures including the hypothalamus and cortex (reviewed by Jones, 1992). However, the vast majority of research has focused on descending mechanisms in the periaqueductal grey (PAG) and nuclei in the rostral ventromedial medulla (RVM) which disrupt the transmission of nociceptive information in the dorsal horn of the spinal cord (see Basbaum and Fields, 1984; Fields and Basbaum, 1989, for reviews). The impetus for much of this research has come from the recognition that these mechanisms mediate the pain-relieving properties of many analgesic drugs such as morphine (eg, Yeung et al, 1977; Yeung and Rudy, 1980). However, most of this research ignored the obvious question: Why do animals possess antinociceptive mechanisms? In particular, what possible function could such mechanisms serve given the obvious importance of nociception in animal survival? Nonetheless, the specificity and apparent specialization of these mechanisms in modulating nociception suggest that they evolved to serve a particular purpose in the control of animal behaviour (cf Kavaliers, 1988a). Arguably the most compelling account of why antinociceptive mechanisms should exist was offered by Bolles and Fanselow (1980). They pointed out that defensive behaviours and nociceptive responding are incompatible activities, yet when an animal is in a dangerous situation it needs to be able to engage in appropriate defensive responses without hindrance from a conflicting motivation to engage in recuperative behaviours. Consistent with this view, there is a growing body of evidence indicating that the descending antinociceptive mechanisms in the PAG and RVM underlie the antinociceptive responses observed in animals tested in the presence of either innate or learned danger signals. Accordingly, it is the intention of the present paper to review this evidence and to show that it reveals the existence of a hierarchically organized antinociceptive system that functions as part of the animal’s defensive system by making the animal antinociceptive during exposure to danger.

Antinociceptive responses elicited by environmental events

A wide variety of environmental events can provoke antinociceptive responses and these responses have been documented in a number of mammalian species, including rats, mice, rabbits, cats, monkeys and humans (reviewed by Amit and Galina, 1986; see also Kelly, 1986) and have even been reported to occur in such phyllogenetically distant species as slugs and snails (Ka-
Antinociception and defensive systems

The occurrence of antinociceptive responses in animals from different phyla suggests that the inhibition of nociceptive information is of fundamental importance in animal survival strategies. As mentioned above, it has been suggested that activation of antinociceptive mechanisms represents an important part of animal defensive systems because a decrease in nociceptive sensitivity allows a threatened animal to engage in necessary defensive behaviours such as freezing, fleeing or even fighting, without being impeded by a competing motivation to attend to an injury (Bolles and Fanselow, 1980; Fanselow, 1986, 1991a). This is particularly important because animals are most likely to incur an injury during encounters with a predator or with an aggressive conspecific. Thus, a reduction in nociceptive sensitivity during danger would improve an animal's chances of survival. In support of the argument that antinociception is a defensive response, Fanselow and colleagues have documented a mutual exclusion between species-specific defensive responses and recuperative behaviours provoked by injury when animals are tested in dangerous or safe environments (eg, Fanselow and Baackes, 1982; Fanselow and Sigmundi, 1986). For example, Fanselow and Baackes (1982) reported that rats freeze and cease responding to a formalin-injected paw when placed in a 'dangerous' environment where previously they had been shocked, but do not freeze and resume responding to their formalin-injected paw when placed in a 'neutral' environment not associated with shock. Moreover, these conditionally elicited antinociceptive responses can be 'extinguished' by repeatedly exposing the animal to the danger signals in the absence of the noxious event (Ross and Randich, 1985; Westbrook et al, 1991).

There are also several demonstrations that antinociceptive responses can be elicited by innate danger signals, such as the presence of a natural predator (Lester and Fanselow, 1985; Kavaliers, 1988b) or odours from a stressed conspecific (Fanselow and Sigmundi, 1986). Indeed, Fanselow (1989, 1991b) has argued that noxious stimuli themselves should be viewed as innate signals for immediately proximal danger, and therefore, as capable of activating defensive systems including antinociceptive mechanisms. In support of this assertion is the abundance of studies reporting that varying degrees of antinociception can be elicited by exposure to noxious stimuli, most commonly electric shock delivered to the paws (through a grid floor) or to the tail (from electrode attachments) (eg, Lewis et al, 1980; Watkins et al, 1982a, b; Maier et al, 1992, 1993a; Watkins et al, 1994). One interesting finding in this regard was recently reported by Franklin and Abhott (1993) who provided evidence that the temporary 'dip' in nociceptive responding seen during the fifth to tenth minutes of the formalin test is an antinociceptive response, presumably elicited by the noxious stimulation present in the first 5 min following the subcutaneous injection of formalin.

The relationship between danger and antinociception has received further confirmation by a series of recent studies showing that, while danger signals (which predict an aversive event) provoke antinociceptive responses, safety signals (which predict the nonoccurrence of an otherwise expected aversive event) provoke anti antinociceptive responses that can even reverse the algiesic effects of systemic morphine (Wiertelak et al, 1992a, b).

The role of fear in antinociceptive responses

Consistent with their presumed role in defensive systems, several investigators have argued that fear plays a critical role in some environmentally induced antinociceptive responses (Bolles and Fanselow, 1980; Chance, 1980). Evidence that antinociceptive responses are dependent on the arousal of fear can be grouped into three categories. First, there are numerous demonstrations that antinociceptive and fear responses co-occur in animals exposed to innate or learned danger signals (Blanchard and Blanchard, 1972; Fanselow and
Role of descending mechanisms in antinociceptive responses to danger

There is an abundance of evidence that antinociceptive responses elicited by 'danger signals' are mediated by antinociceptive mechanisms in the PAG, RVM and spinal cord. However, there are also clear differences in the anatomical and neurochemical substrates of the antinociceptive responses elicited by different danger signals, as reviewed below.

Mechanisms mediating antinociception elicited by noxious stimuli

There are several demonstrations that exposure to intense noxious stimuli can elicit antinociceptive responses that are mediated by antinociceptive circuits located wholly within the spinal cord. For example, Watkins et al. (1982c) reported that a significant amount of antinociception produced by a 90-s hind paw shock on the tail-flick test was preserved in rats with complete transection of the spinal cord at the thoracic level. This antinociception has also been shown to be abolished by combined intrathecal injection of a μ opioid receptor antagonist with a κ- or δ-opioid receptor antagonist, indicating that the antinociception is mediated by endogenous opioids (Watkins et al., 1992). Other researchers have shown that the contribution of intraspinal circuits to shock-induced antinociception depends on the intensity of the shock. Specifically, exposure to intense shock (3.0 mA) elicits antinociception on the tail-flick test which survives transection of the rostral spinal cord, whereas the antinociception elicited by moderate levels of shock (1.0 mA) is abolished by spinal transection (Meagher et al., 1990, 1993). Unfortunately, despite the abundance of evidence that GABAergic mechanisms contribute to intraspinal antinociception (Curtis et al., 1959, 1968; Young and Kuhr, 1980, Hunt et al., 1981, Barber et al., 1982; Goodchild and Serrao, 1987; Magoul et al., 1987; Todd and McKenzie, 1989; Clavier et al., 1992), there have been no studies investigating the role of GABA in the intraspinal antinociception elicited by intense shock.

Direct evidence that nuclei in the RVM are involved in antinociceptive responses elicited by noxious stimuli came from the demonstration that the antinociception produced by front paw shock was virtually eliminated by combined lesions of the nucleus raphe magnus and lateral paragigantocellular nucleus, but not by selective lesion of either structure alone (Watkins et al., 1983a). That shock to the back paws should elicit an intraspinal-mediated antinociception (see above) whereas identical shock delivered to the front paws should elicit an antinociception mediated by supraspinal structures may indicate that the intraspinal antinociceptive circuits only extend a few segments from the level at which they are engaged. In other words, intense shock to the back paws engages antinociceptive circuits within the lumbo-sacral spinal cord which affect nociceptive input from the tail, whereas the same shock to the front paws may activate antinociceptive circuits within the cervical spinal cord which do not extend to the sacral level and thus do not affect the tail-flick response.

Confirmation of the role of RVM nuclei in antinociceptive responses elicited by shock has come from the demonstrations that the antinociception elicited by front paw shock is abolished by lesion of the dorsolateral funiculus (dlf) of the spinal cord (Watkins et al., 1982c), which carries the descending projections from the RVM nuclei (Basbaum and Fields, 1979; Bowker et al., 1981a, b; Watkins et al., 1981). The role of descending projection from the RVM in the antinociception elicited directly by shock is further supported by demonstrations that this antinociception is mediated at the spinal level by serotonergic and α₂- (but not α₁-) adrenergic receptors (Watkins et al., 1984a; Chance, 1986; Danyysz et al., 1986; Minor et al., 1988), which corresponds to the spinal neurochemical substrate of RVM antinociceptive mechanisms (Hammond and Yaksh, 1984; Bararo et al., 1985; Hammond et al. 1985; Aimone et al., 1987; Abhold and Bowker, 1990).

A potential problem that may confound conclusions about changes in nociceptive sensitivity in many of these studies is that nociception was assessed using the tail-flick test which is also sensitive to changes in posture and vasomotor tone (eg, Berge et al., 1988). However, studies (eg. Danyysz et al., 1986; Minor et al., 1988) in which nociception was assessed by other means, such as the hot-plate test, have shown that antinociception is readily elicited by shock, and that antinociception is mediated by spinal noradrenergic systems. These findings are thus consistent with the conclusion...
Mechanisms mediating antinociception elicited by learned danger

There are numerous reports confirming that the antinociceptive responses elicited by learned danger signals are mediated by serotonergic and ø2-adrenergic mechanisms in the spinal cord that are engaged by descending projections in the RVM. For example, expression of the immediate early gene c-fos as a marker of activity in spinal neurons, we (Harris et al., 1995) have recently demonstrated that nociceptive processing in the spinal cord is suppressed during exposure to a learned danger signal (an environment where the rats had previously been exposed to a 54°C floor). Both the antinociception and suppression of spinal c-fos expression were reversed by prior administration of the µ-opioid receptor antagonist naloxone (Harris et al., 1995). Further, conditionally elicited antinociceptive responses can be reversed by intrathecal injection of methysergide or yohimbine, but not by phenotamine (Chance, 1986; Lichtman and Fanselow, 1991; Rochford et al., 1992). The role of descending input from the RVM is indicated by the demonstrations that the antinociception elicited by a learned danger signal is abolished by lesion of the dlf (Watkins et al., 1982b) or RVM (Watkins et al., 1983a; Helmstetter and Tershner, 1994).

Several studies have provided evidence for a role of the PAG in conditioned antinociceptive responses. First, lesions of the PAG abolish the antinociception conditionally elicited by a signal for shock (Kinscheck et al., 1984; Helmstetter and Tershner, 1994). Further, pharmacological studies have identified that conditionally elicited antinociceptive responses are mediated by opioid and GABAergic mechanisms in the PAG. Specifically, antinociceptive responses elicited by a learned danger signal are reduced by microinjection of naloxone directly into the ventral PAG (Helmstetter and Landeira-Fernandez, 1990). Similarly, we have reported that microinjection of a benzodiazepine into the ventral, but not dorsal, PAG antagonizes the naloxone-reversible antinociceptive response displayed by rats tested in a dangerous environment (Harris and Westbrook, 1995). These findings are consistent with evidence that antinociceptive mechanisms in the PAG are under tonic inhibition from local GABAergic neurons, and that µ-opioid receptor ligands act to inhibit these GABAergic neurons and, thus, to activate the antinociceptive mechanisms in the PAG (Basbaum and Fields, 1984).

Sensitization of PAG antinociceptive mechanisms by exposure to inescapable shock

If antinociceptive responses are to be identified with a defensive motivational system, then these responses should be affected by events which impact upon the animal's motivational state and which affect other defensive responses. One event which has enduring effects on an animal's motivational state is prolonged exposure to inescapable shock (Overmier and Seligman, 1967; Maier and Seligman, 1976; Murison and Overmier, 1993). Importantly, inescapable shock does alter the induction and/or expression of antinociceptive responses in a manner consistent with their role in a defensive motivational system.

The majority of work investigating the impact of uncontrollable shock on the development of antinociception has been performed by Maier and colleagues. Initial studies demonstrated that exposure to a large number (eg, 80) of escapable shocks (shocks that could be terminated if the rat performed some operant response) produced a naloxone-insensitive hypoalgesia that decayed after about 10 min and had no apparent impact on the rat's hypoalgesic responses 24 h later. In contrast, yoked rats that received an identical pattern of inescapable shocks showed a profound antinociception that lasted for several hours,
and for the next 2 days these rats displayed exaggerated antinociceptive responses to small amounts of shock and increased sensitivity to the antinociceptive effects of morphine (Jackson et al., 1979; Lewis et al., 1980; Grau et al., 1981; Hyson et al., 1982; Maier et al., 1983; Drugan et al., 1985; Maier, 1989; Maier and Warren, 1988; Lea et al., 1994).

The various behavioural changes that are induced by exposure to many inescapable, but not escapable, shocks have been collectively termed 'Learned Helplessness' (Overmier and Seligman, 1967; Maier and Seligman, 1976; Murison and Overmier, 1993). The presumed involvement of learning processes in mediating the antinociceptive responses elicited by inescapable shock is consistent with demonstrations that the responses are blocked by a 'distractor' stimulus (Maier and Keith, 1987), by midcollicular decerebration (Klein et al., 1983) and by pentobarbital anaesthesia (Terman et al., 1984; Maier, 1989). Further, based on pharmacological and behavioural studies, it has recently been argued that the behavioural changes produced by exposure to inescapable shock reflect a transient 'anxiety' or generalized fear state that persists without a specific fear-provoking stimulus (Drugan and Holmes, 1991; Maier, 1993; Short and Maier, 1993). Accordingly, given the tendency for anxiety states to potentiate specific fear and defensive responses (e.g., Gray, 1982; Maier et al., 1993b), then the induction of 'anxiety' represents a likely means by which exposure to inescapable shock potentiates antinociceptive responses.

Lesion studies have indicated that the potentiated antinociceptive responses provoked by inescapable shock are mediated by the same descending antinociceptive mechanisms in the PAG and RVM that underlie the antinociception conditionally elicited by learned danger signals. Specifically, lesions of the PAG abolish the potentiated antinociceptive responses provoked by prolonged exposure to inescapable shock (Bragin et al., 1983). Consistent with this, Terman et al. (1985) reported that the antinociceptive responses induced by many inescapable shocks show cross-tolerance with the antinociception produced by electrical stimulation in the ventral PAG. Further, the antinociception elicited by inescapable shock is also abolished by lesion of the dlf (Watkins et al., 1984b), implicating descending projections from the RVM to the PAG in the production of the antinociception. Finally, like the antinociception elicited by learned danger signals, the potentiated antinociception produced by exposure to inescapable shock is blocked by deep pentobarbital anaesthesia (Terman et al., 1984; Maier, 1989) and is also abolished by midcollicular decerebration (Klein et al., 1983), indicating that forebrain structures are involved in the sensitization of antinociceptive mechanisms elicited by learned danger signals or inescapable shock. However, unlike antinociceptive responses conditionally elicited by learned danger signals, the potentiated antinociception following exposure to inescapable shock is not affected by lesions of the amygdala (Watkins et al., 1993a). Thus, this potentiated antinociception must be mediated by sources other than the amygdaloid inputs thought to engage antinociceptive mechanisms during fear and learned danger.

Pituitary and adrenal hormones have been shown to be involved in the sensitized antinociceptive responses which result from prolonged exposure to inescapable shock. Specifically, both the immediate and the re-instated antinociceptive responses are significantly reduced by hypophysectomy or adrenalectomy, or by pre-treatment with dexamethasone, manipulations that do not affect the antinociceptive responses elicited by fewer shocks (Lewis et al., 1980; MacLennan et al., 1982; Terman et al., 1984). But how might adrenal hormones sensitize descending antinociceptive mechanisms? One possibility is that the effects are produced by an action of corticosteroids at GABA<sub>A</sub> receptors in the dorsal raphe nucleus. First, corticosteroids have been shown to act as non-competitive GABA antagonists at the GABA<sub>A</sub> receptor complex (Majewska, 1987). Further, there is evidence that an endogenous GABA<sub>A</sub> receptor antagonist, acting in the dorsal raphe nucleus, is responsible for the persistent increase in serotonergic output that appears to underlie anxiety responses including the behavioural changes produced by inescapable shock (Maier, 1993; Maier et al., 1993b, 1994). Finally, the demonstration that the antinociception produced by morphine microinjected into the PAG is reduced by microinjection of methysergide into the same site (Schul and Fenk, 1991) indicates that serotonergic input, quite possibly from the dorsal raphe nucleus to the PAG (Beitz et al., 1986; Kwiat and Basbaum, 1990), is agonistic to opioid-mediated antinociceptive mechanisms in the PAG. Given that the direct cellular effects of serotonin in the PAG are almost entirely inhibitory (Behbehani et al., 1993), serotonergic projections from the dorsal raphe may increase activity in PAG opioid antinociceptive mechanisms by inhibiting local GABAergic neurons. Therefore, corticosteroids released from the adrenal medulla during exposure to inescapable shock may act at GABA<sub>A</sub> receptors in the dorsal raphe nucleus to produce a prolonged up-regulation of serotonergic output from that nucleus. The resultant increase in serotonergic input to the PAG may facilitate activity in descending,
opioid-mediated, antinociceptive mechanisms by inhibiting local GABAAergic neurons (see fig 1).

**Pronociceptive as well as antinociceptive mechanisms in the PAG and RVM**

The foregoing has concentrated on evidence that antinociceptive responses displayed by animals tested in the presence of learned or innate danger signals are mediated by circuits in the PAG and RVM. However, this discussion has not taken account of evidence that both these structures also contain circuits which serve to facilitate spinal nociceptive transmission. For example, electrical stimulation of the RVM has been reported to produce an increase in activity of some nociceptive neurons in the spinal cord (Rivot et al, 1980; Light et al, 1986). Moreover, electrophysiological investigations by Fields and colleagues have revealed the existence of putatively pro-nociceptive neurons (‘on cells’) as well as antinociceptive neurons (‘off cells’).

**Fig 1.** Descending antinociceptive mechanisms and their activation by environmental sources of danger. Intraspinal antinociceptive mechanisms consisting of local GABAAergic neurons and μ, δ and κ opioid receptors are activated directly by intense nociceptive input. Intense noxious stimulation can also activate these spinal antinociceptive circuits via serotonergic (5HT) and noradrenergic (NA) projections descending from nuclei in the rostral ventro-medial medulla (RVM). These descending projections from RVM are also activated by excitatory amino acid (EAA) containing projections from the periaqueductal grey (PAG). The excitatory projections from the PAG are under tonic inhibitory influence of local GABAAergic neurons. Exposure to learned or innate danger signals engages fear and defensive systems in the amygdala, and these activate PAG antinociceptive mechanisms via direct, possibly enkephalin-ergic (Enk), projections that inhibit the local GABAAergic neurons in the PAG. The PAG GABAAergic neurons may also receive inhibitory input from serotonergic projections originating in the dorsal raphe nucleus (DR). Thus, the potentiation of antinociceptive responses observed following prolonged exposure to intense stressors such as inescapable shock may be mediated by a persistent increase in serotonergic output from the DR which would facilitate activity in PAG antinociceptive mechanisms.
in both the RVM and PAG (see Fields et al, 1991 for a review). Further, the firing patterns of on-cells and off-cells indicate that excitatory links exist between cells of the same class, and mutually inhibitory links connect cells of one class with cells of the other (Barbaro et al, 1989). Thus, it appears that the RVM and PAG modulate spinal nociceptive transmission by both inhibitory and facilitatory means.

How can this be reconciled with the claim that the PAG and RVM function as part of the animal's defensive system by inhibiting nociceptive transmission during danger? A likely answer may be found in recent studies into the neural basis of certain pro nociceptive responses. Specifically, the RVM has been shown to mediate the 'anti-analgesic' responses elicited by a learned safety signal (that is, a cue which signals that an otherwise-expected aversive event will not occur), as well as the 'hyperalgesia' provoked by illness-inducing agents such as lithium chloride or lipopolysaccharide (Watkins et al, 1993b, 1994). The complementary nature of the relationship between danger and learned safety is obvious enough. Thus, it should not be surprising that the antinociceptive and 'anti-analgesic' responses that they elicit might be mediated by interconnected neural systems located within the same structures. In other words, if circuits within the PAG and RVM function to inhibit nociception during danger, then it is reasonable that complementary circuits in those same structures should function to turn off that antinociception during safety (Maier et al, 1992).

The relationship between danger and illness is less clear, although the distinction between external (skin) and internal (gut) defense systems (Garcia and Garcia y Robertson, 1985; Garcia et al, 1985) may provide some grounds for supposing that responses to danger and illness would be modulated by interconnected but opposing mechanisms. On more functional grounds, it has been suggested that illness favours an increase in nociceptive sensitivity as a means of promoting recuperative behaviour (Maier et al, 1992; Wiertelak et al, 1994). In either case, it appears that both the PAG and RVM do not purely inhibit nociceptive transmission as part of the animal's defensive system, but rather, they modulate nociception as part of a joint defensive/recuperative system.

Conclusions

Based on the research reviewed above, it is clear that the descending antinociceptive mechanisms in the PAG and RVM function to render the animal antinociceptive during exposure to danger, thereby permitting the threatened animal to engage in defensive behaviours rather than recuperative ones. It is also clear that there are differences in the neural substrates of the antinociceptive responses elicited by different types of danger signals. Nonetheless, it is possible to integrate many of these findings into a single hierarchical antinociceptive system (see fig 1), in which caudal antinociceptive mechanisms are engaged by more rostral ones that have evolved to enable earlier detection of potential danger and to provide more sophisticated ways for dealing with sources of threat (cf Fanselow, 1989, 1991b). For example, it appears that antinociceptive mechanisms contained within the spinal cord are directly activated by intensely noxious stimuli, whereas less intense and thus less threatening noxious stimuli can only activate spinal antinociceptive mechanisms by activating descending projections from the RVM. These RVM descending pathways are also activated by mechanisms in the midbrain PAG, which function to coordinate other defensive responses directed at dealing with sources of threat (cf Bandler and Shipley, 1993; Carriere, 1993; Kim et al, 1993). Finally, the antinociceptive mechanisms in the PAG are, themselves, engaged by projections from forebrain structures, in particular from the amygdala, which function to enable the animal to learn about relationships between environmental events and, thus, to recognize potential sources of danger before being in physical contact with them.

It should be noted that the descending antinociceptive mechanisms other than those in the PAG and RVM may serve functions that are quite different from those described here. For example, the system of 'diffuse noxious inhibitory controls' identified by Le Bars and coworkers (Le Bars et al, 1979a,b) are mediated by circuits that are actually antagonized by the PAG/RVM antinociceptive mechanisms (Bouhassira et al, 1988a, b, 1990, 1992a, b, 1993; Dickenson and Le Bars, 1987).

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