

Deconstructing Endogenous Pain Modulation

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Mason, Peggy. Deconstructing endogenous pain modulation. *J Neurophysiol* 94: 1659–1663, 2005; doi:10.1152/jn.00249.2005. A pathway from the midbrain periaqueductal gray (PAG) through the ventromedial medulla (VMM) to the dorsal horn constitutes a putative endogenous nociceptive modulatory system. Yet activation of neurons in both PAG and VMM changes the responses of dorsal horn cells to nonnoxious stimuli and elicits motor and autonomic reactions that are not directly related to nociception. Activation of mu-opioid receptors in VMM and PAG also modifies processes in addition to nociceptive transmission. The descending projections of VMM neurons are not specific to nociception as VMM projects to the spinal superficial dorsal horn where thermoreceptors as well as nociceptors terminate. In addition, experiments with pseudorabies virus demonstrate multisynaptic pathways from VMM to sympathetic and parasympathetic target organs. VMM neurons respond to both noxious and unexpected innocuous stimuli of multiple modalities, and change their discharge during behaviors unrelated to pain such as micturition/continence and sleep/wake. In conclusion, all available evidence argues against the idea that PAG and VMM target nociception alone. Instead these brain stem sites may effect homeostatic adjustments made necessary by salient situations including but not limited to injury.

INTRODUCTION

More than thirty years ago, Reynolds stimulated near the midbrain periaqueductal gray (PAG) and produced a profoundly unreactive state in otherwise untreated rats, allowing him to perform a laparotomy in the absence of any general or local anesthesia (Reynolds 1969). Because the stimulated rats continued to startle to unexpected noises, the reduced reactivity was interpreted as specific to noxious input and therefore analgesia. Anatomical and physiological studies conducted throughout the 1970s elucidated a major pathway from PAG to the raphe magnus and adjacent reticular formation of the ventromedial medulla (VMM) and in turn from VMM to the dorsal horn. The termination zone of many VMM axons within the superficial and deep layers of the dorsal horn matched the region where nociceptors terminated, further suggesting that PAG and VMM specifically modulate nociception. As the descending pathways supporting suppression of nociceptive transmission were being elucidated, opioid receptors and endogenous opioid peptides were discovered (Hughes et al. 1975; Pert and Snyder 1973). The concentration of opioid signaling within PAG, VMM, and the dorsal horn coupled with opioids' well-known analgesic properties reinforced the idea of an endogenous pain modulatory system. In this review I will argue that, whereas the brain stem can powerfully alter nociceptive transmission, it does not do so specifically or exclusively. Moreover, the categorization of the PAG and VMM and opioid signaling therein to endogenous pain modulatory path-

ways obfuscates the true functions of these complex brain stem regions.

Analgesia refers to a specific reduction in pain sensation. By analogy, pain modulation is a modification of the sensitivity to pain alone. Such "pure" pain modulation requires that the sensitivity to other sensory modalities remains unaltered and that changes to motor and autonomic output do not occur. Using these definitions, the notion of the PAG to VMM to dorsal horn being an endogenous pain modulatory system depends critically on several criteria:

- Activation of the PAG or VMM specifically modulates dorsal horn responses and behavioral reactions to noxious but not innocuous stimulation.
- The VMM projection to dorsal horn specifically targets nociceptive neurons.
- Nociceptive modulatory neurons are engaged exclusively by noxious stimuli and manipulations that selectively target nociceptive transmission.

Further, the prevailing view of endogenous pain modulation holds that it is largely opioid mediated. Therefore the specific modulation of nociception by opioids within the PAG and VMM is another feature of the putative endogenous pain modulatory system. Each of these points is considered below in light of a body of work performed primarily in the rat.

In this review, it is not my intention to refute the antinociceptive power of brain stem activation or the importance of PAG, VMM, and opioid-receptor signaling to nociceptive modulation. Nor do I question the clinical interest in endogenous pathways that *can* powerfully alter pain processing. Rather I try to examine the physiological context within which these dramatic processes may occur naturally. Although few of the data referenced below were originally motivated by this issue, the data consistently support the idea that PAG and VMM have multiple and coordinated effector functions, including but not limited to nociceptive modulation.

CAN PAIN BE MODULATED IN ISOLATION?

To determine the specificity of PAG- and VMM-evoked modulation, the effects of PAG and VMM activation on behavioral and physiological reactions as well as neuronal responses have been studied. In sum, these studies reveal that PAG and VMM are capable of altering numerous reactions and responses in addition to those associated with noxious stimulation.

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At a neuronal level, initial reports suggested that stimulation in PAG and VMM preferentially modulates the responses of dorsal horn neurons to noxious stimulation (Belcher et al. 1978; Bennett and Mayer 1979; Fields et al. 1977; Guilbaud et al. 1977). Yet, as was appreciated by the early 1980s, VMM stimulation modulates the responses of low-threshold and convergent dorsal horn cells to innocuous stimulation as well as the responses of nociceptive dorsal horn cells to noxious stimulation in both rat and cat (Chiang et al. 1994; Dostrovsky et al. 1983; Gray and Dostrovsky 1983). Raphe magnus stimulation even modulates the activity of cells in the superficial dorsal horn responsive to innocuous skin cooling and warming (Sato 1993; cf. Dawson et al. 1981).

At a behavioral and physiological level, PAG stimulation evokes effects beyond the specific modulation of nociceptive reactions required by the strict definition of a specific pain modulatory system. Motor acts such as gnawing, vocalizing, and explosive jumps, specific postures such as lordosis, and behaviors such as freezing, occur concurrently with changes in nociceptive sensitivity after PAG stimulation in the awake rat (Fardin et al. 1984). R. Bandler and colleagues have demonstrated two basic patterns resulting from PAG activation in either awake or decerebrate animals (Bandler et al. 2000). After activation of dorsolateral PAG neurons animals become highly active—running, jumping, and moving away or dorsoflexing with piloerection and hissing. A reduction in the blood flow to the viscera and an increase in that to skeletal muscle accompany such active, fight-or-flight defensive behavior. In a second behavioral pattern, the animal stops all ongoing behavior and becomes immobile and unresponsive to another conspecific's approaches. Such quiescent behavior is accompanied by a decrease in heart rate, blood pressure, and respiration rate and redirection of blood flow from skeletal muscle to internal organs (Carrive et al. 1989a,b).

Although only a small number of studies have stimulated VMM in awake animals, it appears that VMM stimulation does not evoke full behavioral packages such as defense as does PAG stimulation. Nonetheless, activation of VMM neurons decreases locomotor activity more consistently than it elicits nociceptive modulatory changes (Morgan and Whitney 2000). Lesions of the rostral medullary raphe in the pigeon not only enhance the tachycardia evoked by a light stimulus associated with foot shock, a conditioned response, but also the elevation in heart rate evoked by an unpaired light stimulus (Cabot et al. 1981). The latter represents an elevation in the heart rate reaction during an orienting response and is independent of any noxious stimulation. In anesthetized animals, VMM activation evokes a panoply of physiological changes including changes in blood pressure, heart rate, respiration, and thermoregulatory status (Adair et al. 1977; Nason and Mason 2004). In sum, neither PAG nor VMM modulates nociceptive transmission in isolation but instead they concurrently influence a number of homeostatic, motor, and complex behavioral functions.

PATHWAYS FROM VMM TO SYMPATHETIC AND PARASYMPATHETIC TARGETS

The projections from VMM to superficial and deep layers of dorsal horn have been emphasized by investigators focused on nociceptive modulation. Yet even the initial reports using anterograde tract-tracing methods in cat and opossum demon-

strated dense termination zones in the intermediate gray and central canal regions after injections into raphe magnus or the adjacent ventral reticular region (Basbaum et al. 1978; Holstege and Kuypers 1982; Martin et al. 1982). A similar projection pattern appears to hold in the rat (Skagerberg and Bjorklund 1985; Zemlan et al. 1984). More recently, transsynaptic retrograde tract tracing has become possible using viruses modified to be lysis incompetent such as "pseudorabies virus" (PRV) (Card et al. 1993). Polysynaptic pathways from the CNS to peripheral autonomic targets have been described by using PRV in combination with lesions and traditional tract-tracing methods (Strack et al. 1989a,b).

PRV injection into all peripheral autonomic targets tested to date results in at least some labeled VMM neurons; to my knowledge there are no exceptions to this statement. Tissues targeted polysynaptically by VMM neurons include the heart, cutaneous blood vessels, adipose tissue, kidney, adrenal medulla, trachea, pancreas, bladder, penis, colon, and urethra (see references in Mason 2001). When two peripheral tissues have been injected, individual VMM neurons that target both autonomic targets have been observed (Jansen et al. 1995; Nadelhaft and Vera 2001; Nadelhaft et al. 2002). Currently it remains unclear whether a subset of VMM neurons projects to multiple targets or whether this is a common feature of all VMM neurons. Finally, it is important to note that the proportions of nonserotonergic and serotonergic cells among PRV-labeled cells (Haxhiu et al. 1996; Nakamura et al. 2004; Strack et al. 1989b) are not dramatically skewed from their overall regional representations (15–20% serotonergic; Leger and Wiklund 1982; Potrebic et al. 1994). Thus these anatomical experiments suggest that similar proportions of serotonergic and nonserotonergic VMM cells target at least one internal organ tissue and that many VMM cells target several tissues.

NEURONS IN VMM ARE ENGAGED DURING CONDITIONS UNRELATED TO PAIN

The discovery of VMM neurons that respond to noxious stimulation and to opioid administration led to the hypothesis that these cells were pain modulatory in function (Barbaro et al. 1986; Fields et al. 1983a,b). VMM neurons that are excited by noxious stimulation are inhibited by opioids and are termed ON cells. A second group of putative pain modulatory neurons are inhibited by noxious stimulation and excited by antinociceptive doses of opioids; these are termed OFF cells. We now know that both ON and OFF cells are nonserotonergic (Gao and Mason 2000; Mason 1997). In addition to ON and OFF cells, VMM contains nonserotonergic neutral cells and a heterogeneous population of serotonergic cells (Bowker et al. 1982; Gao and Mason 2001), cell classes that are unresponsive to both noxious stimulation and opioids (Auerbach et al. 1985; Barbaro et al. 1986).

The physiological characteristics of ON and OFF cells, but not those of NEUTRAL and serotonergic cells, have implicated them in phasic nociceptive modulation. The original model proposed that OFF cell discharge inhibits nociceptive transmission and that reactions such as withdrawals occur only after the cessation of OFF cell firing (Basbaum and Fields 1984). In anesthetized rats, morphine and other mu-opioid receptor agonists increase OFF cell discharge and prevent the pause in OFF cell firing elicited by noxious stimulation, thereby blocking withdrawals. The nociceptive mod-

ulatory role of ON cells is now thought to be facilitatory, not merely permissive, and in fact obligatory for certain types of persistent pain (Bederson et al. 1990; Porreca et al. 2001). Because NEUTRAL and serotonergic cells fail to respond to either noxious stimulation or opioids, they may not contribute to phasic nociceptive modulation; alternatively one or the other of these cell types may play a permissive role (Mason and Gao 1998).

The reciprocal responses of ON and OFF cells to opioids and noxious stimulation formed the basis for the hypothesis that ON and OFF cells modulate nociceptive transmission (Fields et al. 1983a,b). In the anesthetized rat, ON and OFF cells respond to noxious but not innocuous stimulation. However, in the unanesthetized animal, ON and OFF cells respond to innocuous somatosensory stimulation such as brush (Leung and Mason 1999; Oliveras et al. 1990). These same cells do not change their discharge during active movements that provide similar sensory stimulation, such as grooming, suggesting that ON and OFF cells respond only to stimuli that are not self-generated and therefore unexpected. Further, ON and OFF cells respond to noninjurious stimuli of other modalities such as a hand clap or looming (Leung and Mason 1999). Thus these cells appear responsive to unexpected stimuli regardless of modality, perhaps aiding an organism to detect a dangerous situation before actually being injured. For instance, the sound of a predator's footsteps could engage ON and OFF cells before the predator's bite. Such a "danger" or "warning" signal based on unexpected stimuli is of obvious adaptive value. It should be noted that under normal conditions, noxious stimulation, whether caused by an extrinsic force or occurring during active movement (e.g., biting one's cheek during chewing) is always unexpected and thus may access ON and OFF cells regardless of context.

ON and OFF cell discharge is altered during natural behaviors that have no exclusive relationship to nociception. For instance, along with serotonergic cells, ON and OFF cells also change their discharge across sleep-wake cycles. Serotonergic cells and ON cells are more active during waking than sleep, whereas OFF cells discharge with the reverse pattern (Fornal et al. 1985; Leung and Mason 1999). ON and OFF cells also discharge differently during micturition compared with during continence (Baez et al. 2005). These results demonstrate that the stimuli and conditions that alter VMM cell discharge are diverse and are not limited to noxious stimulation and analgesic manipulations. Nevertheless, it remains possible that the effect of changing VMM cell discharge results exclusively in the modulation of nociception. Indeed, nociceptive processing changes across the sleep-wake cycle (Lavigne et al. 2000; Mason et al. 2001) and between voiding and continence states (Baez et al. 2005). Yet, the ability of VMM activation to elicit a myriad of physiological effects and the anatomical pathways from VMM cells to autonomic targets (see above) make it likely that differences in ON and OFF cell discharge impact spinal processes other than nociception. For instance, during continence, ON and OFF cell discharge appears to influence the timing of micturition (Baez et al. 2005; Sugaya et al. 1998).

OPIOID SIGNALING IN VMM AND PAG PARTICIPATES IN FUNCTIONS BESIDES NOCICEPTIVE MODULATION

Because of their unparalleled efficacy and long history of use, opioids have earned distinction as archetypical analgesics.

Although this is indisputable, it is also clear that opioids elicit changes in virtually every physiological process from cardiovascular control to gastrointestinal motility to appetite. Even within PAG and VMM, opioid-receptor-mediated transmission influences processes beyond nociception. Microinjection of the mu-opioid receptor agonist, DAMGO, into the PAG (Matsumoto et al. 2004) or raphe magnus (EA York, MA Baez, and P Mason, unpublished observations) blocks micturition and causes urinary retention. Mu-opioid-receptor-mediated signaling within the PAG also elicits increases in heart rate and blood pressure (Keay et al. 1997) and inhibits feeding evoked by hypothalamic stimulation (Jenck et al. 1987). The suppression of respiratory-related discharge in cells of the nucleus tractus solitarius by raphe magnus stimulation is reversed by naloxone, suggestive of an opioid-receptor-mediated influence of VMM on respiration (Sessle et al. 1981). It has even been reported that morphine microinjection into VMM or PAG elicits locomotor effects (immobility or wild running depending on the site of injection) more reliably than antinociception (Morgan and Whitney 2000; Morgan et al. 1998).

PAIN MODULATION IS NOT A SPECIFIC ENDOGENOUS SYSTEM

The data outlined above argue that nociception is not and cannot be modulated in isolation, even by using pharmacological agents selective for the mu-opioid receptor. Although the lack of specificity in descending modulation has been recognized previously (Dostrovsky et al. 1983; Gray and Dostrovsky 1983; Perl 1984), the existence of a specific endogenous nociceptive modulatory system continues to be widely recognized. Does such ideation mislead and limit our potential understanding of brain stem modulatory systems or is the reification of endogenous pain modulation a simple and harmless semantic choice? To address this question, it is informative to consider that pain is a rarity in the life of an animal under natural circumstances. Certainly, noxious stimuli occupy a minute fraction of a wild animal's life. Thus viewing the PAG to VMM to spinal cord projections as an endogenous system for modulating nociception specifically would leave this pathway largely idle. Perhaps pain is so important that PAG and VMM are designed for and held in a state of readiness for just such a rare but critical occasion. On the other hand, it is hard to reconcile devoting essential brain stem "real estate" to such little effect. More teleologically attractive is the idea that PAG and VMM modulate and control a number of sensory, autonomic, and motor processes in the spinal cord across normal life conditions such as sleep and wake, micturition and continence.

Let us also consider the rare event in an animal's life when noxious stimulation does occur and most particularly those unfortunate circumstances when the activation of nociceptive pathways persists. Although the modulation of nociceptive transmission assumes a more primary importance under such conditions, the PAG and VMM would be expected to have additional modulatory effects, just as they did in the absence of pain. Interactions between VMM modulatory effects on homeostatic functions such as sleep-wake and blood pressure would be expected to influence nociception in turn. A particularly dramatic example of this is the "vicious cycle" that exists between insomnia and persistent pain. Poor sleep exac-

erbates pain report and persistent pain leads to poor sleep (reviewed in Foo and Mason 2003). The connections of VMM neurons and the discharge characteristics of ON and OFF cells reviewed above predict similar but yet unexplored interactions between descending nociceptive modulation and other homeostatic processes.

In summary, decades after Reynold's dramatic demonstration of descending antinociception, it is time to consider afresh the functions of PAG and VMM. The pathways from VMM to sympathetic and parasympathetic neurons, the multitude of effects elicited by VMM and PAG activation, and the engagement of VMM neurons by situations and stimuli unrelated to pain argue against a specific nociceptive modulatory system. Instead PAG and VMM may operate as the funnel into the spinal cord for descending spinal control. By integrating input from forebrain sites such as the amygdala and hypothalamus, the PAG to VMM to spinal cord pathway may serve to execute the homeostatic and behavioral adjustments deemed most salient by higher centers. Because intense pain that accompanies severe injury may be life-threatening, it achieves special significance and trumps other homeostatic challenges. Thus pain is a "curiously imperative" occurrence that coopts descending bulbospinal neurons to make necessary adjustments to sensory, autonomic, and motor functions (Sherrington 1900).

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GRANTS

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