Periaqueductal gray : An interface for behavioral control

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The periaqueductal gray (PAG) is an anatomic and functional interface between the forebrain and the lower brainstem and has a major role in integrated behavioral responses to internal (e.g., pain) or external (e.g., threat) stressors. The PAG consists of distinct columns that receive selective inputs from the prefrontal cortex, amygdala, hypothalamus, and nociceptive pathways. Via its connections with different brainstem nuclei, the PAG coordinates specific patterns of cardiovascular, respiratory, motor, and pain modulatory responses. These responses vary according to the type of stress and the subject's perception of the threatening stimulus. The PAG is also involved in vocalization, micturition, and thermoregulation, and contributes to mechanisms of arousal and control of REM sleep. The PAG is affected in neurodegenerative disorders, such as Alzheimer disease (AD) and multiple system atrophy. Stimulation of the PAG has been utilized for management of chronic neuropathic pain and recent evidence suggests that it may also be used to relieve refractory hypertension. The organization of the PAG and its multiple functions have been the subjects of several reviews.[1–11]

FUNCTIONAL ORGANIZATION OF THE PAG

Anatomic subdivisions and neurochemistry. The PAG is continuous with the periventricular gray matter (PVG) and surrounds the midbrain aqueduct except for ventral part, which contains oculomotor-related nuclei rostrally and the dorsal raphe nucleus caudally (figure). Based on cytoarchitecture, chemoarchitecture, and connectivity patterns, the PAG has been subdivided into 4 columns: dorsomedial, dorsolateral, lateral, and ventrolateral.[2–5] The PAG contains different types of neurons that utilize L-glutamate, γ-aminobutyric acid (GABA), opioids (particularly enkephalin), substance P, neurotensin, and other neurotransmitters. The dorsolateral PAG also contains neurons that express NADPH-diaphorase and synthesize nitric oxide (NO)[12]; the ventrolateral PAG contains a group of dopaminergic neurons.[13] There is also abundant expression of NMDA,[14] $GABA_A$,[15] μ-opioid,[16] neurokinin-1,[17] and transient receptor potential vanilloid type 1 (TRPV1) receptors[18] in the PAG.

Inputs and outputs of the PAG. The PAG is a critical component of the so-called "emotional motor system."[19] This distributed network receives input from the medial prefrontal and anterior cingulate cortices and projects to brainstem areas that control behavior-specific patterns of motor and autonomic responses and modulate both dorsal horn excitability to nociceptive inputs and gain of spinal reflexes (figure).[19] The PAG receives afferents from the forebrain, brainstem, and sensory neurons of the dorsal horn and trigeminal nucleus; these inputs have a distinct pattern of termination in the different PAG columns (table 1). The prefrontal cortex provides the major forebrain input to the PAG. The medial wall of the prefrontal cortex targets the dorsolateral column; the anterior cingulate gyrus targets the lateral, ventrolateral, and dorsomedial columns; and the posterior orbitofrontal and anterior insular cortices target the ventrolateral column.[20] The inputs from the amygdala originate in the central nucleus and ventrolateral portion of the basal nucleus; the input from the hypothalamus originates primarily from the medial preoptic, anterior, periventricular, ventromedial, posterior, and supramammillary nuclei and lateral hypothalamic areas.[20] The PAG receives a dense network of noradrenergic and adrenergic fibers originating in the ventrolateral (A1 and C1 groups) and dorsomedial (A2 and C3 groups) medulla.[21] Neurons of lamina I of the superficial dorsal horn and caudal trigeminal nucleus provide nociceptive information to the contralateral PAG. These projections target

GLOSSARY

AD = Alzheimer disease; **DBS** = deep brain stimulation; **GABA** = γ-aminobutyric acid; **NO** = nitric oxide; **PAG** = periaqueductal gray; **PVG** = periventricular gray matter; **RVM** = rostral ventromedial medulla; **TRPV1** = transient receptor potential vanilloid type 1; **VLM** = ventrolateral medulla.

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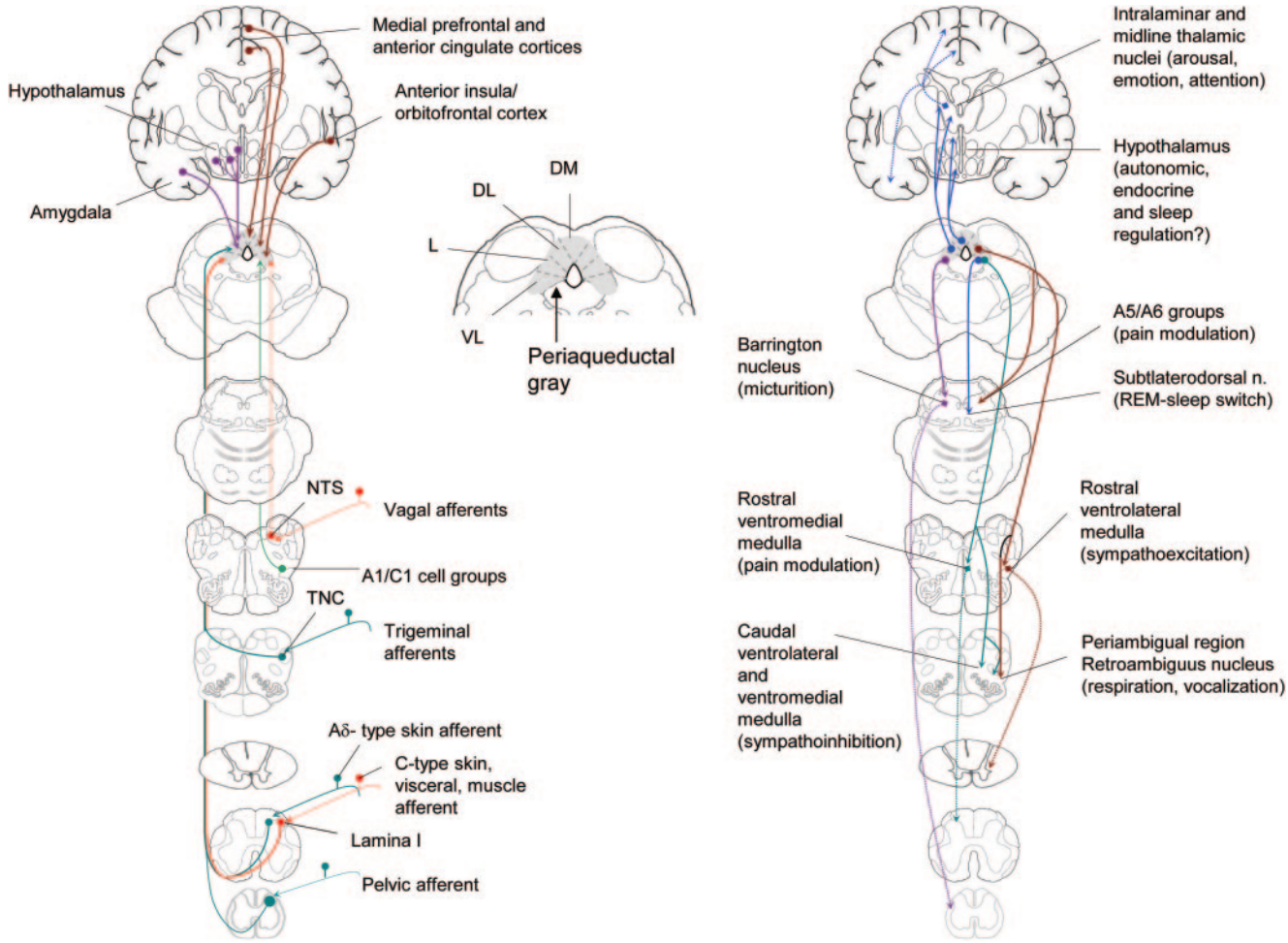
Figure Main connections of the periaqueductal gray (PAG)



The PAG is subdivided into 4 functional columns: dorsomedial (DM), dorsolateral (DL), lateral (L), and ventrolateral (VL), which have distinct connections with the forebrain, brainstem, and nociceptive neurons of lamina I of the spinal cord and trigeminal nucleus. The main forebrain sources of input to the PAG are the medial prefrontal cortex, anterior cingulate, and the posterior orbitofrontal/anterior insular cortex; the central nucleus of the amygdala; and essentially all regions of the hypothalamus. Brainstem input includes vagal inputs relayed via the nucleus of the solitary tract (NTS) and catecholaminergic noradrenergic and adrenergic fibers originating in the A1/C1 groups of the ventrolateral medulla. Neurons of lamina I of the superficial dorsal horn and caudal trigeminal nucleus (TNC) provide nociceptive information to the contralateral PAG. Forebrain projections target the intralaminar and midline nuclei of the thalamus, which serve as a gateway to the prefrontal cortex, amygdala, and basal ganglia, and several regions of the hypothalamus. Most brainstem targets of the PAG projections are premotor centers that in turn project to sensory, motor, or autonomic nuclei of the brainstem and spinal cord. These include the nucleus cuneiformis (not shown), locus ceruleus and pericerulus regions, Barrington nucleus (pontine micturition center), parabrachial nucleus, rostral ventromedial medulla (including the nucleus raphe magnus), rostral and caudal ventrolateral medulla, and nucleus ambiguus and retroambiguus. Via these projections, the PAG participates in micturition, regulation of REM sleep switch, pain modulation, cardiovascular responses to stress, and vocalization.

the lateral and ventrolateral PAG columns and are somatotopically organized; trigeminal projections terminate in the rostral PAG, and cervical and lumbar spinal projections at progressively more caudal levels.[22]

The PAG provides efferents to the forebrain, brainstem, and spinal cord (figure, table 1). Forebrain projections target the thalamus and hypothalamus.[21,22] The PAG projection to the intralaminar and midline nuclei of the thalamus serves as a gateway to the prefrontal cortex, amygdala, and basal ganglia.[23] The PAG projects heavily to the anterior, medial, and posterior hypothalamus and substantia innominata; the main route for PAG-diencephalic projections is through the periventricular bundle.[24] With the exception of the dorsolateral column, all PAG columns project to the lower brainstem. The PAG projects densely to the nucleus cuneiformis; locus ceruleus; Barrington nucleus (pontine micturition center); motor nuclei of the pontomedullary reticular formation; parabrachial nucleus; nucleus ambiguus and retroambiguus, rostral and caudal ventrolateral medulla (VLM); rostral ventromedial medulla (RVM), including the nucleus raphe magnus; and nucleus raphe pallidus.[25] Most of these targets of PAG inputs are premotor centers that in turn project to sensory, motor, or autonomic nuclei of the brainstem and spinal cord.[19]

Table 1 Main connections of the periaqueductal gray

Inputs	Outputs
Medial prefrontal cortex	Thalamus (intralaminar, midline, and reticular nuclei)
Posterior orbitofrontal cortex	Hypothalamus (anterior, dorsomedial, posterior, and lateral regions)
Anterior insular cortex	Superior colliculus
Anterior cingulate	Nucleus cuneiformis
Amygdala (central nucleus)	Locus ceruleus
Hypothalamus (preoptic, anterior, periventricular, ventromedial, posterior, and lateral)	Barrington nucleus (pontine micturition center)
Superior and inferior colliculi	Parabrachial nucleus
Mesencephalic reticular formation	Pontomedullary reticulospinal nuclei; nucleus ambiguus
Cuneiform nucleus	Nucleus retroambiguus
Locus ceruleus	Periambigual region
Parabrachial nucleus	Rostral and caudal ventrolateral medulla
Ventromedial medulla	Rostral ventromedial medulla (including the nucleus raphe magnus)
Ventrolateral medulla	Caudal ventromedial medulla
A1/C1 and A2/C3 groups	Nucleus raphe pallidus
Spinal and trigeminal dorsal horn (lamina I)	

The connections of the PAG in humans have been studied using diffusion fractography.[26–28] A recent study in patients undergoing PAG deep brain stimulation (DBS) for neuropathic pain showed ascending connections of the dorsal PAG with the ventral posterior thalamus and primary somatosensory cortex and connections of the ventral PAG with the ventromedial prefrontal and anterior cingulate cortices, amygdala, and nucleus accumbens; the dorsal and ventral PAG also showed different connections with the ipsilateral dorsomedial medulla and the cerebellum.[26] These findings confirm the different connectivity of the different regions of the PAG but do not fully correlate with anatomic tracing studies in experimental animals.

PAG AND RESPONSES TO STRESS The PAG is a critical component of a network that is activated in response to internal stressors, such as pain, or external threats, such as the presence of a predator. This network includes different areas of the prefrontal cortex, anterior cingulate cortex, amygdala, and hypothalamus that connect with specific columns of the PAG. These connections form parallel circuits that are activated according to the characteristics of the stimulus and initiate different pain modulatory, autonomic, and motor responses[3–5] (table 2). Humans, like other animals, react with distinct emotional coping strategies to "escapable" or "inescapable" stressors.[29] Active strategies, such as fight-or-flight responses, occur in the presence of short lasting, cutaneous pain and other types of escapable stress and are associated with motor and sympathetic activation. Passive emotional coping strategies such as quiescence and vasodepression occur in response to inescapable stress, including deep somatic or visceral pain.[3–5]

PAG activation by threat. The responses to threatening stimuli have been subdivided into defensive avoidance (associated with fear) or defensive approach (associated with anxiety) and vary with the proximity of the stressor.[29–32] Functional magnetic resonance studies show differential activation of components of the fear system according to the threatening stimulus in humans.[33,34] Awareness of a threatening stimulus (i.e., a predator) resulted in activation of the ventromedial prefrontal and anterior cingulate cortices; close proximity of a predator elicited activation of the central amygdala and PAG.[33,34] These findings are consistent with evidence that elec-

Table 2 Active and passive coping strategies orchestrated by the periaqueductal gray

Stimulus	Escapable (e.g., superficial pain)	Inescapable (e.g., deep somatic or visceral pain)
Coping strategy	Active (fight-or-flight)	Passive (hyperactive immobility)
Periaqueductal gray column involved	Dorsolateral and lateral	Ventrolateral
Prefrontal input	Medial prefrontal and anterior cingulate	Posterior orbital/rostral insular
Nociceptive input	Aδ-skin nociceptors, somatotopic	C-skin, deep somatic, and visceral nociceptors
Autonomic response	Sympathoexcitation (hypertension, tachycardia)	Sympathoinhibition and vagal activation (hypotension, bradycardia)
Respiratory response	Hyperventilation	Hypoventilation, apnea
Analgesia	Short-lasting, non-opioid-mediated	Long-lasting, opioid-mediated
Effector mechanisms	Dorsomedial nucleus of the hypothalamus	Rostral and caudal ventromedial medulla
	Rostral ventrolateral medulla	Nucleus retroambiguus
	Nucleus retroambiguus	Nucleus ambiguus

trical stimulation of the human PAG can result in fear and anxiety.[35]

PAG activation by pain. The different PAG columns receive functionally segregated input from nociceptive pathways.[4,5,36–38] The lateral and dorsolateral PAG columns receive somatotopically organized inputs from superficial nociceptors (primarily Aδ type), relayed by the superficial lamina of the spinal and spinal trigeminal nucleus. In contrast, the ventrolateral PAG column receives convergent input from both the superficial and deep dorsal horn relaying nociceptive afferent information from visceral, muscle, and C-fiber skin nociceptors, as well as visceral inputs from the nucleus of the solitary tract and sacral spinal cord.[4,5,36–38] Functional neuroimaging studies in humans indicate that PAG activation by nociceptive inputs is modulated by attention, emotion, expectation of pain, and expectation-related placebo analgesia.[38–45]

Segregated PAG pathways for active vs passive coping strategies. Experimental studies using chemical microstimulation indicate that the different columns of the PAG organize different copying strategies to pain and other stressors.[2–6,35,36,46] The lateral and dorsolateral PAG initiate fight-or-flight responses associated with tachycardia, hypertension, and redistribution of blood flow. The sympathoexcitatory responses elicited by the lateral and dorsolateral PAG are mediated by neurons of the rostral VLM, which activate sympathetic preganglionic neurons controlling cardiovascular effectors.[36,46–48] In contrast, neurons of the ventrolateral PAG column initiate sympathoinhibitory responses (hypotension and bradycardia) that are associated with immobility and hyporeactivity to the environment. These vasodepressor responses are mediated by neurons of the ventromedial medulla and nucleus raphe pallidus,[49] which inhibit the sympathoexcitatory neurons of the rostral VLM.

The different portions of the PAG also elicit site-specific changes in respiratory patterns.[50] Stimulation of the dorsolateral PAG elicits tachypnea, which is associated with sympathoexcitation; stimulation of the ventrolateral PAG elicits respiratory depression. The effects of the PAG on respiration are mediated by projections to premotor interneurons in the brainstem respiratory network, including the nucleus retroambiguus in the ventrolateral medulla.[50]

PAG AND PAIN MODULATION

PAG as a critical component of the pain modulation network. The PAG is a critical component of a descending pain modulatory network that exerts a dual control, inhibitory or excitatory, on nociceptive transmission in the dorsal horn and trigeminal nucleus. This network also includes the prefrontal and anterior cingulate cortex, hypothalamus, amygdala, dorsolateral pontine reticular formation, RVM, and caudal VLM.[6,16,51] Neurons of this network express opioid[16] and TRPV1[18] receptors and mediate opioid-, placebo- and acupuncture-triggered analgesia.[6,16,38,40,45] The balance between inhibition and facilitation of nociception is dynamic, and can be altered in different behavioral, emotional, and pathologic states.[5,6] Stimulation of the PAG typically elicits analgesia, as first shown by Reynolds[52] in the rat and later confirmed in different species, including humans.[35,53,54] Experimental studies show that PAG stimulation strongly inhibits the activity of superficial dorsal horn neurons that relay information carried by C-fibers but does not affect or may even enhance Aδ fiber–mediated nociception.[6,55]

The inhibitory effects of the PAG on nociceptive transmission are a component of the coordinated coping strategies orchestrated by the different columns of the PAG.[2–4,35,36,46] In experimental animals, short-lasting noxious stimulation of the skin activates the lateral and dorsolateral PAG and triggers not only sympathoexcitation but also short-duration, non-opioid-mediated analgesia.[36,37,46] In contrast, deep somatic, visceral, or repetitive superficial pain activates the ventrolateral PAG and elicits long duration, opioid-dependent analgesia associated with vasodepression and immobility.[36,46]

Neurochemical mechanisms of PAG-mediated analgesia. The primary neurotransmitter of afferents and projection neurons of the PAG is L-glutamate; local GABAergic neurons elicit tonic inhibition of these projection neurons.[1] Neuronal activity within the PAG is affected by several neurochemical signals including opioids, endocannabinoids, and neurotensin. [Mu]-opioid agonists produce analgesia by acting via pre- and postsynaptic mechanisms[15]; opioid-induced analgesia is largely due to μ-receptor–mediated inhibition of local GABAergic interneurons.[1,16] In humans, the μ-opioid antagonist naloxone enhances postoperative pain.[56] Endocannabinoids such as anandamide may tonically control nociception via activation of TRPV1 receptors expressed in the ventrolateral PAG; this effect requires glutamate release and activation of NMDA receptors,[18] and may be in part mediated by NO.[57] Neurotensin inhibits GABAergic transmission within the PAG indirectly, via the release of glutamate leading to production of endocannabinoids that activate presynaptic CB1 receptors in GABAergic terminals.[58]

Effector mechanisms for pain modulation by the PAG. The PAG exerts its pain modulatory effects primarily via its descending projection to the RVM, including the

nucleus raphe magnus, and in part via noradrenergic nuclei of the dorsolateral pontine tegmentum.[1,6,16] The RVM exerts a bidirectional control on spinal nociceptive processing via 2 types of cells, off-cells and on-cells: off-cells are activated by opioids and inhibit nociception; on-cells are inhibited by opioids and promote nociceptive responses.[16] Thus, the balance of activity between these 2 neuronal populations determines the threshold for nociception in the dorsal horn. Descending facilitation of spinal (and trigeminal) nociceptive transmission is a major contributor to central sensitization and development of secondary hyperalgesia. Since C-fiber inputs have a major role in sensitization of dorsal horn neurons, descending inhibitory control of those inputs via the PAG-RVM pathway may limit development of a central sensitized state.[6]

OTHER FUNCTIONS OF THE PAG

Vocalization. The PAG has a critical role in vocalization in response to painful stimulus or other stressors.[9] Stimulation studies indicate that the lateral and ventrolateral PAG integrate the expiratory and laryngeal activity required for the generation of vocalization.[50] Voluntary control of vocalization involves the anterior cingulate cortex, which projects to the PAG. The PAG has direct connections with the medullary reticular formation surrounding the nucleus ambiguus; this periambigual region projects to motoneurons in the ventral horn (controlling expiration), nucleus ambiguus (controlling phonation), and trigeminal, facial, and hypoglossal nuclei (controlling articulation). Lesions of the PAG produce mutism both in experimental animals[9] and humans.[59]

Micturition. The PAG acts as an interface between bladder afferent input and forebrain modulatory influences controlling micturition. Normal bladder voiding involves a spinobulbospinal reflex coordinated by the pontine micturition center.[60] The ventrolateral PAG receives Aδ afferents from the bladder and relays this information to the pontine micturition center to trigger micturition.[61] In vivo recordings in experimental animals[62] and functional neuroimaging studies in humans[63] show that the PAG is activated both in response to bladder filling and during micturition. Meta-analysis of functional neuroimaging studies emphasizes the central role of the PAG in normal micturition and leads to a model of possible functional connectivity between the PAG and forebrain areas controlling bladder function.[63] According to this model, the medial prefrontal cortex would exert a tonic inhibition on the PAG during urine storage; withdrawal of this inhibitory control would allow PAG to activate the pontine micturition center when the subject decides to void.[60]

Sleep. The ventrolateral PAG participates in mechanisms of arousal[13] and switch between non-REM and REM sleep.[64,65] Lu et al.[13] identified a group of dopaminergic neurons in the ventrolateral PAG that were active during wakefulness and inactive during sleep and had extensive reciprocal connections with other sleep-wake regulatory neurons in the brainstem and hypothalamus. Fuller et al.[64] described a GABA-mediated REM switching circuitry model; GABAergic REM-off neurons located in the ventrolateral PAG (and lateral pontine tegmentum) inhibit GABAergic REM-on neurons located in the sublaterodorsal tegmental nucleus and are reciprocally inhibited by these REM-on neurons.

CLINICAL CORRELATIONS

PAG stimulation for management of neuropathic pain. Stimulation of the PAG and adjacent periventricular regions (PVG/PAG) in patients with intractable pain produces pain relief that is associated with release of opioids[66] and is blocked by naloxone.[53] PAG stimulation may provide long-term effective pain relief in selected patients.[67,68] A recent study showed that DBS of the PVG/PAG alone was associated with at least 50% reduction of pain in 66% of patients; the best effects were for phantom limb syndromes, head pain, and anesthesia dolorosa.[68] A study correlating the clinical results of chronic PVG/PAG stimulation with the anatomic site of electrode placement as determined at autopsy indicates that the ventrolateral PAG at the level of the posterior commissure is the optimal site for therapeutic electrical brain stimulation for opiate-responsive pain in humans.[54] Placebo-induced analgesia involves the PAG and is reversed by opioid antagonists. A PET study using [(11)C]carfentanil, which measures regional μ-opioid receptor availability in vivo, showed that placebo treatment affected endogenous opioid activity in the PAG and nearby dorsal raphe and nucleus cuneiformis, amygdala, orbitofrontal cortex, insula, rostral anterior cingulate, and lateral prefrontal cortex.[45]

Cardiovascular effects of PAG stimulation in humans. Stimulation of PAG in humans elicits changes in blood pressure and heart rate that are consistent with those observed in experimental animals.[69,70] Dorsal PAG stimulation may elicit increases in sympathetic activity and baroreflex sensitivity and may reduce the severity of orthostatic hypotension in some patients.[71] Stimulation of the ventrolateral PAG, which is the most effective site to induce analgesia, is associated with a decrease in arterial pressure.[70] A recent study showed that ventral PAG stimulation elicited a relative predominance of vagal over sympathetic modulation of the heart rate, which correlated with subjective reporting of analgesic efficacy.[27] Stimula-

tion of the ventrolateral PAG may produce long-standing decrease in blood pressure in patients with refractory hypertension.[72]

Involvement of the PAG in neurodegenerative diseases. The PAG is affected in neurodegenerative disorders such as Alzheimer disease,[73] Parkinson disease,[74] and multiple system atrophy.[75] However, the clinical correlations of PAG involvement in these disorders remain to be established. Parvizi et al.[73] showed the presence of β-amyloid peptide and abnormally phosphorylated tau protein in the PAG; the type and density of pathologic changes were expressed differently in different PAG regions and correlated with gender and the duration of dementia. Presumably, PAG involvement may contribute to behavioral manifestations in AD and autonomic manifestations in multiple system atrophy. Loss of dopaminergic neurons in the ventral PAG in both multiple system atrophy and in dementia with Lewy bodies may contribute to excessive daytime sleepiness in these disorders.[76]

PERSPECTIVE The PAG is a nodal structure within a distributed CNS network that controls and integrates autonomic, motor, and pain modulatory responses to relevant environmental stimuli. Via the PAG, attention and emotion modulate behavior and survival strategies. Functional neuroimaging studies and results of electrical microstimulation have provided further insight into the participation of the PAG in pain modulation and autonomic control in humans. The potential clinical applications of PAG stimulation have been extended from the alleviation of specific subtypes of neuropathic pain to the possible adjuvant management of refractory hypertension. It could be speculated that PAG stimulation may also be used for treatment of hyperactive bladder and, perhaps, some cases of recurrent reflex (neurally mediated) syncope triggered by emotion.

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