

# Neural substrate of depression during migraine

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**Abstract** Migraine headache is triggered by and associated with a variety of hormonal, emotional, nutritional and physiological changes. The perception of migraine headache is formed when nociceptive signals originating in the meninges are conveyed to the somatosensory cortex through the trigeminal ganglion, medullary dorsal horn and thalamus. We propose that different migraine triggers activate a wide variety of brain areas that impinge on parasympathetic neurons innervating the meninges. According to this hypothesis, migraine triggers such as stress activate multiple hypothalamic, limbic and cortical areas, all of which contain neurons that project to the preganglionic parasympathetic neurons in the superior salivatory nucleus (SSN). The SSN, in turn, activates postganglionic parasympathetic neurons in the sphenopalatine ganglion, resulting in vasodilation and local release of inflammatory molecules that activate meningeal nociceptors. We propose that trigeminovascular projections from the medullary dorsal horn to selective areas in the mid-brain, hypothalamus, amygdala and basal forebrain are functionally positioned to produce migraine symptoms such as irritability, loss of appetite, fatigue, depression and the quest for solitude. The network of bidirectional trafficking by which the trigeminovascular system can activate the same brain areas that have triggered its own activity in the first place provides an attractive mechanism of perpetual feedback that drives a migraine attack for many hours and even days.

**Keywords** Headache · Nociception · Trigeminal · Stress · Sleep

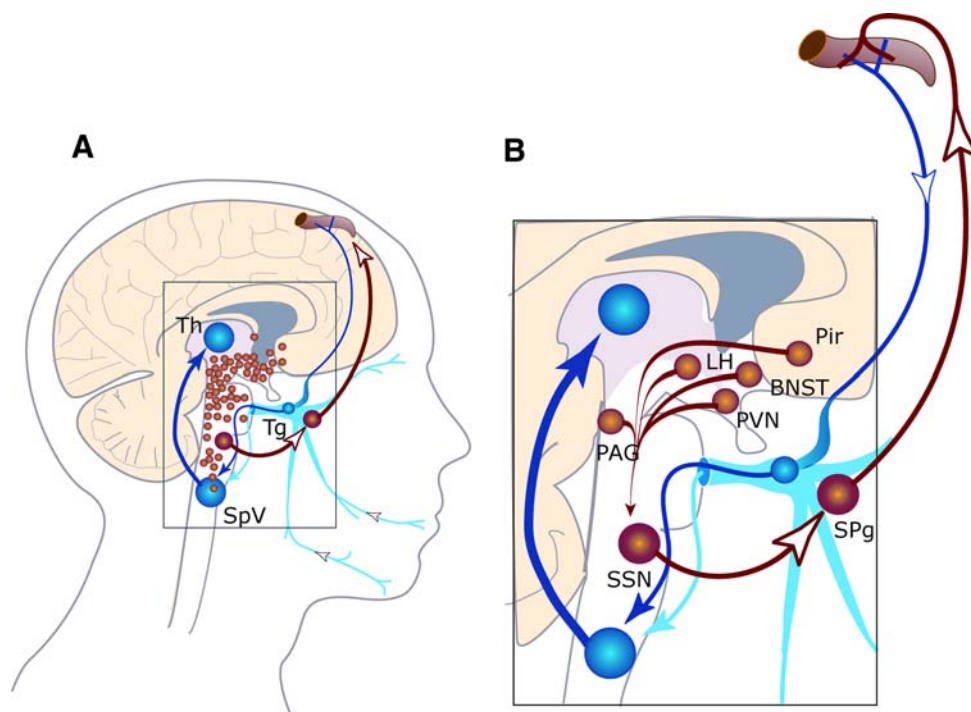
## Introduction

Migraine is a recurring neurological disorder commonly described as unilateral throbbing headache, readily aggravated by routine activities. Similar to other pain pathways, the sensory discriminative aspect of migraine pain is believed to be mediated by activation and modulation of nociceptive trigeminothalamic tract by peripheral drivers and central modulators, respectively. In the case of the trigeminothalamic tract, the role of driver is played by meningeal nociceptors, whereas modulation is provided by inhibitory and facilitatory neurons in the brainstem. Evidence for the driving role of meningeal nociceptors comes from studies in which awake patients experienced headache in response to electrical stimulation of their dura [1, 2]. Evidence for descending modulation comes from studies that examined the effects of electrical stimulation of the periaqueductal gray (PAG) and rostral ventromedial medulla on nociceptive spinal neurons. Whereas electrical brainstem stimulation per se did not induce any activity in the spinal nociceptive neurons when they were quiet, it clearly increased or decreased their response magnitude to noxious and innocuous stimulation of their cutaneous and visceral receptive fields [3].

The initiation of migraine headache is commonly associated with a wide variety of circumstances, such as hormonal milieu, periods of stress, post-stress periods, skipping a meal, lack of sleep, olfactory stimulation and several types of aura [4, 5]. These associations raise the possibility that a migraine attack originates in brain areas that are not directly involved in nociception, but are wired

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**Fig. 1** A proposed parasympathetic pathway for the activation of meningeal nociceptors. Preganglionic parasympathetic neurons in the superior salivatory nucleus (SSN) can trigger intracranial vasodilation and the release of nitric oxide in the meninges through postganglionic parasympathetic neurons in the sphenopalatine ganglion (SPG). **a** The SSN receives input from over 50 limbic and hypothalamic brain areas (red dots) whose activity may be influenced by common migraine

triggers. **b** Examples of SSN afferents proposed to be involved in migraine triggering by olfactory stimuli (Pir), food and sleep deprivation (LH), stress and post stress (PVN, BNST, PAG). *BNST* bed nucleus stria terminalis, *LH* lateral hypothalamus, *PAG* periaqueductal gray, *Pir* piriform cortex, *PVN* paraventricular hypothalamic nucleus

to activate the trigeminovascular pathway. The trigeminovascular pathway consists of first-order nociceptors in the trigeminal ganglion that innervate the meninges; second-order trigeminothalamic tract neurons that receive sensory inputs from the meninges, periorbital skin and neck muscles; third-order thalamocortical neurons that process incoming pain signals from the trigeminal nerve, including the meninges; and cortical neurons located in the first somatosensory cortex.

#### Activation of the trigeminovascular pathway by the limbic system and hypothalamus

The observation that visual aura precedes the onset of headache by several minutes promoted extensive research on the neural substrate by which cortical spreading depression can result in activation of meningeal nociceptors. Evidence suggests that in the wake of cortical spreading, depression the blood brain barrier becomes more permeable [6, 7], allowing potassium and hydrogen ions to diffuse from the surface of the cortex to the pia where they activate C-fiber meningeal nociceptors [8]. This activation appears to involve direct depolarization by

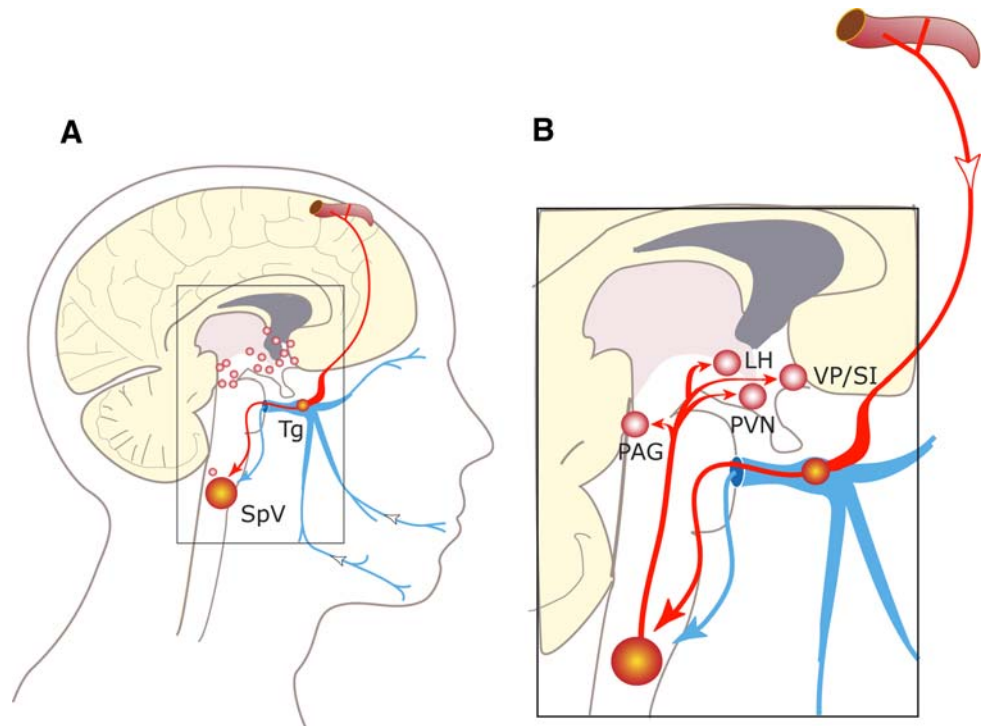
potassium ions, and action of hydrogen ions through the vallinoid receptor (Caterina et al. 1997) or the acid-sensitive ion channel receptor (Waldmann et al. 1997). Consequently, the activated meningeal nociceptors release calcitonin-gene-related peptide [9] from their peripheral branches, resulting in neurogenic inflammation in the dura [10].

In contrast to the ongoing effort, to understand how aura triggers activity in meningeal nociceptors, little attention was given to the mechanisms by which brain areas involved in regulation of stress could activate meningeal nociceptors and trigger the headache. Is there a common pathway that activates meningeal nociceptors for a variety of migraine triggers? We are proposing that such a pathway involves pre- and postganglionic parasympathetic neuron in the superior salivatory nucleus (SSN) and sphenopalatine ganglion (SPG), respectively. According to our hypothesis, migraine triggers either activate or originate in a number of brain areas whose projections converge on the SSN. The SSN, in turn, stimulates the release of acetyl choline, vasopressin intestinal peptide and nitric oxide from meningeal terminals of SPG neurons, resulting (directly or indirectly) in a cascade of events that include the dilation of intracranial blood vessels, plasma protein

**Fig. 2** Proposed mechanism for the initiation of symptoms commonly associated with migraine headache by ascending trigeminovascular pathways to the brainstem, hypothalamus and basal ganglia.

**a** Trigemino-vascular neurons in the spinal trigeminal nucleus (SpV) project to multiple limbic and hypothalamic brain areas (red dots) whose activity may underlie common migraine symptoms. **b** Examples of SpV projections proposed to be involved in stress (PVN), decreased motivational state (VP/SI), pursuit of solitude (PAG), sleepiness, irritability and loss of appetite (LH).

*LH* lateral hypothalamus, *PAG* periaqueductal gray, *PVN* paraventricular hypothalamic nucleus, *VP/SI* ventral pallidum/substantia innominata



extravasation, and local release of inflammatory molecules that activate adjacent terminals of meningeal nociceptors (Fig. 1).

Several lines of evidence support this parasympathetic hypothesis: (1) meningeal blood vessels are densely innervated by parasympathetic fibers [11–13]; (2) preganglionic parasympathetic neurons in the SSN increase their activity after activation of meningeal nociceptors [14]; (3) ongoing activity in meningeal nociceptors appears to depend on enhanced activity in the SPG [15]; (4) parasympathetic tone is enhanced during migraine, as evidenced by lacrimation, teary eyes, nasal congestion [5]; (5) blockade of the SPG provides partial or complete relief of migraine pain [16–25].

The SSN receives extensive input from more than 50 brain areas distributed throughout the forebrain, diencephalon, midbrain, pons and medulla [26]. SSN-projecting neurons located in some of these brain areas are theoretically positioned to mediate the onset of a migraine by means of their involvement in emotional responses (Fig. 1a). The bed nucleus of stria terminalis (BNST), the paraventricular hypothalamic nucleus (PVN) and the PAG are all involved in the circuitry that regulates “stress response”. BNST neurons, which regulate hypothalamic-pituitary-adrenal axis, appear to mediate long-lasting behavioral responses during sustained stress, which persist long after the termination of stress [27, 28]; such neurons may be involved in stress-induced migraine and also in migraine triggered after the termination of stress.

Parvocellular PVN neurons that project to sympathetic and parasympathetic preganglionic neurons in the brainstem and spinal cord promote the autonomic part of the stress response [29, 30], which includes localized cerebrovascular vasodilation in the early phase of the migraine attack [31]. Ventrolateral PAG neurons involved in passive emotional coping with inescapable stressors such as repeated defeat in social encounters [32, 33] may mediate onset of increase migraine frequency associated with a long period of social stress such as divorce.

#### Activation of the hypothalamus and limbic system by the trigeminovascular pathway

The most frequently reported symptoms associated with migraine are depression, stress, irritability, fatigue, sleepiness, exaggerated emotional responses, nausea and loss of appetite. To elicit these symptoms, pain signals that originate in the trigeminovascular pathway during migraine must reach and alter the activity of hypothalamic and limbic structures that integrate sensory, physiological and cognitive signals that drive behavioral, affective and autonomic responses. Brain areas involved in the execution of such responses include the parabrachial complex, PAG, hypothalamus, amygdala, septum, nucleus accumbens, bed nucleus of the stria terminalis and basal ganglia [34–46]. Many of these brain areas receive direct inputs from laminae I–II and V neurons located in the ventrolateral area of

the upper cervical and medullary dorsal horn (Fig. 2)—an area containing the majority of second-order trigemino-vascular neurons [47–56].

We propose that these ascending pathways are functionally positioned to produce irritability, loss of appetite, sleepiness, fatigue, chill, stress, depression, emotional arousal, decreased motivation, the quest for solitude and lethargy during migraine (Fig. 2b). For example, loss of appetite, sleepiness and irritability during migraine may be mediated by trigeminovascular projections to the lateral hypothalamus; in this area, neurons expressing melanin-concentrating hormone or hypocretin regulate food and water intake, sleep and arousal [36, 37, 57] through widespread projections to the cerebral cortex, brainstem and spinal cord [58–62]. Migraine-associated stress may be mediated by trigeminovascular projections to the paraventricular nucleus of the hypothalamus; this nucleus contains neurons expressing corticotrophin-releasing hormone and oxytocin which regulate stress responses [63]. Emotional arousal and decreased motivation during migraine may be mediated by trigeminovascular projections to forebrain nuclei such as the ventral pallidum and substantia innominata; these areas can alter endocrine, autonomic and somatomotor functions to match different emotional and motivational states [64].

The pursuit of solitude during migraine may be mediated by the ventrolateral PAG; this area receives more input from trigeminal neurons located in C1-3 and nucleus caudalis than from the entire spinal cord [32, 54, 55]. The input to the ventrolateral PAG originates mainly in visceral and deep somatic tissues [65, 66]. Trigemino-vascular projections to the ventrolateral PAG can activate neurons that mediate responses to deep, inescapable pain, such as migraine pain [32, 67].

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## References

1. Penfield W, McNaughton F (1940) Dural headache and innervation of the dura mater. *Arch Neurol Psychiat* 44:43–75
2. Ray BS, Wolff HG (1940) Experimental studies on headache. Pain-sensitive structures of the head and their significance in headache. *Arch Surg* 41:813–856
3. Porreca F, Ossipov MH, Gebhart GF (2002) Chronic pain and medullary descending facilitation. *Trends Neurosci* 25(6):319–325
4. Zagami AS, Rasmussen BK (2000) Symptomology of migraine without aura. In: Olesen J, Tfelt-hansen P, Welch MA (eds) *The headaches*. Raven Press, New York, pp 337–343
5. Liveing E (1873) *On megrim, sick headache*. Arts & Boeve Publishers, Nijmegen
6. Gursoy-Ozdemir Y et al (2004) Cortical spreading depression activates and upregulates MMP-9. *J Clin Invest* 113(10):1447–1455
7. Moskowitz MA, Macfarlane R (1993) Neurovascular and molecular mechanisms in migraine headaches. *Cerebrovasc Brain Metab Rev* 5(3):159–177
8. Moskowitz MA, Cutrer FM (1993) SUMATRIPTAN: a receptor-targeted treatment for migraine [Review] [44 refs]. *Annu Rev Med* 44:145–154
9. Ebersberger A et al (1999) Release of substance P, calcitonin gene-related peptide and prostaglandin E2 from rat dura mater encephali following electrical and chemical stimulation in vitro. *Neuroscience* 89(3):901–907
10. Goadsby PJ, Edvinsson L (1993) The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. *Ann Neurol* 33(1):48–56
11. Suzuki N, Hardebo JE (1993) The cerebrovascular parasympathetic innervation. *Cerebrovasc Brain Metab Rev* 5(1):33–46
12. Larsson LI et al (1976) Immunohistochemical localization of a vasodilatory polypeptide (VIP) in cerebrovascular nerves. *Brain Res* 113(2):400–404
13. Nozaki K et al (1993) Possible origins and distribution of immunoreactive nitric oxide synthase-containing nerve fibers in cerebral arteries. *J Cereb Blood Flow Metab* 13(1):70–79
14. Knight YE et al (2005) Patterns of fos expression in the rostral medulla and caudal pons evoked by noxious craniovascular stimulation and periaqueductal gray stimulation in the cat. *Brain Res* 1045(1–2):1–11
15. Bolay H et al (2002) Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. *Nat Med* 8(2):136–142
16. Yarnitsky D et al (2003) 2003 Wolff Award: possible parasympathetic contributions to peripheral and central sensitization during migraine. *Headache* 43(7):704–714
17. Sluder G (1908) The role of the sphenopalatine ganglion in nasal headaches. *N Y State J Med* 27:8–13
18. Waldman SD (1990) The role of neural blockade in the management of common pain syndromes. In: Weiner RS (ed) *Innovations in pain management*. Deutch press, Orlando, pp 4–14
19. Waldman SD (1993) Sphenopalatine ganglion block—80 years later. *Reg Anesth* 18(5):274–276
20. Diamond S, Dalessio DJ (1982) *The practicing physicians approach to headaches*, 3rd edn. Williams & Wilkins, Baltimore
21. Dalessio DJ (1980) The major neuralgias, postinfections neuritis, intractable pain, and atypical facial pain. In: Delessio DJ (ed) *Wolff's headache*. Oxford Press, New York, pp 247–248
22. Kudrow L (1980) *Cluster headache: mechanism and management*. Oxford Press, London, pp 114–116
23. Kudrow L, Kudrow DB, Sandweiss JH (1995) Rapid and sustained relief of migraine attacks with intranasal lidocaine: preliminary findings. *Headache* 35(2):79–82
24. Reutens DC et al (1991) Is intravenous lidocaine clinically effective in acute migraine? *Cephalalgia* 11(6):245–247
25. Maizels M et al (1996) Intranasal lidocaine for treatment of migraine: a randomized, double-blind, controlled trial [see comments]. *JAMA* 276(4):319–321
26. Spencer SE et al (1990) CNS projections to the pterygopalatine parasympathetic preganglionic neurons in the rat: a retrograde transneuronal viral cell body labeling study. *Brain Res* 534(1–2):149–169
27. Forray MI, Gysling K (2004) Role of noradrenergic projections to the bed nucleus of the stria terminalis in the regulation of the hypothalamic-pituitary-adrenal axis. *Brain Res Brain Res Rev* 47(1–3):145–160

28. Walker DL, Toufexis DJ, Davis M (2003) Role of the bed nucleus of the stria terminalis versus the amygdala in fear, stress, and anxiety. *Eur J Pharmacol* 463(1–3):199–216
29. Swanson LW, Sawchenko PE (1980) Paraventricular nucleus: a site for the integration of neuroendocrine and autonomic mechanisms. *Neuroendocrinology* 31(6):410–417
30. Coote JH (2005) A role for the paraventricular nucleus of the hypothalamus in the autonomic control of heart and kidney. *Exp Physiol* 90(2):169–173
31. Olesen J (1998) Regional cerebral blood flow and oxygen metabolism during migraine with and without aura. *Cephalalgia* 18(1):2–4
32. Keay KA, Bandler R (2001) Parallel circuits mediating distinct emotional coping reactions to different types of stress. *Neurosci Biobehav Rev* 25(7–8):669–678
33. Bandler R et al (2000) Central circuits mediating patterned autonomic activity during active vs. passive emotional coping. *Brain Res Bull* 53(1):95–104
34. Bernardis LL, Bellinger LL (1993) The lateral hypothalamic area revisited: neuroanatomy, body weight regulation, neuroendocrinology and metabolism. *Neurosci Biobehav Rev* 17(2):141–193
35. Bernardis LL, Bellinger LL (1998) The dorsomedial hypothalamic nucleus revisited: 1998 update. *Proc Soc Exp Biol Med* 218(4):284–306
36. Lin JS et al (1989) A critical role of the posterior hypothalamus in the mechanisms of wakefulness determined by microinjection of muscimol in freely moving cats. *Brain Res* 479(2):225–240
37. Peyron C et al (1998) Neurons containing hypocretin (orexin) project to multiple neuronal systems. *J Neurosci* 18(23):9996–10015
38. Panksepp J (1971) Aggression elicited by electrical stimulation of the hypothalamus in albino rats. *Physiol Behav* 6(4):321–329
39. Kruk MR et al (1983) Discriminant analysis of the localization of aggression-inducing electrode placements in the hypothalamus of male rats. *Brain Res* 260(1):61–79
40. Norgren R (1970) Gustatory responses in the hypothalamus. *Brain Res* 21(1):63–77
41. Roeling TA et al (1993) Behavioural responses of bicuculline methiodide injections into the ventral hypothalamus of freely moving, socially interacting rats. *Brain Res* 615(1):121–127
42. Saper CB (1995) Central autonomic system. In: Paxinos G (ed) *The rat nervous system*. Academic Press, San Diego, pp 107–136
43. Sherin JE et al (1996) Activation of ventrolateral preoptic neurons during sleep. *Science* 271(5246):216–219
44. Simerly RB (1995) Anatomical substrates of hypothalamic integration. In: Paxinos G (ed) *The rat nervous system*. Academic Press, San Diego, pp 353–376 of 1136
45. Swanson LW (1987) The hypothalamus. In: Bjorklund A, Hokfelt T, Swanson LW (eds) *Integrated systems of the CNS, part I*. Elsevier, Amsterdam, pp 1–124
46. Scammell TE, Price KJ, Sagar SM (1993) Hyperthermia induces c-fos expression in the preoptic area. *Brain Res* 618(2):303–307
47. Burstein R, Giesler GJ Jr (1989) Retrograde labeling of neurons in the spinal cord that project directly to nucleus accumbens or the septal nuclei in the rat. *Brain Res* 497:149–154
48. Burstein R, Cliffer KD, Giesler GJ Jr (1990) Cells of origin of the spinohypothalamic tract in the rat. *J Comp Neurol* 291(3):329–344
49. Burstein R, Potrebic S (1993) Retrograde labeling of neurons in the spinal cord that project directly to the amygdala or the orbital cortex in the rat. *J Comp Neurol* 335(4):469–485
50. Malick A, Burstein R (1998) Cells of origin of the trigeminohypothalamic tract in the rat. *J Comp Neurol* 400:125–144
51. Malick A, Strassman RM, Burstein R (2000) Trigeminohypothalamic and reticulohypothalamic tract neurons in the upper cervical spinal cord and caudal medulla of the rat. *J Neurophysiol* 84(4):2078–2112
52. Bernard JF et al (1995) Organization of the efferent projections from the spinal cervical enlargement to the parabrachial area and periaqueductal gray: a PHA-L study in the rat. *J Comp Neurol* 353(4):480–505
53. Bester H et al (1995) Spino (trigemino) parabrachiohypothalamic pathway: electrophysiological evidence for an involvement in pain processes. *J Neurophysiol* 73(2):568–585
54. Keay KA, Bandler R (1992) Anatomical evidence for segregated input from the upper cervical spinal cord to functionally distinct regions of the periaqueductal gray region of the cat. *Neurosci Lett* 139(2):143–148
55. Vanderhorst VG et al (1996) Distinct cell groups in the lumbosacral cord of the cat project to different areas in the periaqueductal gray. *J Comp Neurol* 376(3):361–385
56. Strassman AM, Mineta Y, Vos BP (1994) Distribution of fos-like immunoreactivity in the medullary and upper cervical dorsal horn produced by stimulation of dural blood vessels in the rat. *J Neurosci* 14(6):3725–3735
57. Chemelli RM et al (1999) Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. *Cell* 98(4):437–451
58. van den Pol AN (1999) Hypothalamic hypocretin (Orexin): robust innervation of the spinal cord. *J Neurosci* 19(8):3171–3182
59. Bittencourt JC et al (1992) The melanin-concentrating hormone system of the rat brain: an immun- and hybridization histochemical characterization. *J Comp Neurol* 319(2):218–245
60. Bittencourt JC, Elias CF (1993) Diencephalic origins of melanin-concentrating hormone immunoreactive projections to medial septum/diagonal band complex and spinal cord using two retrograde fluorescent tracers. *Ann N Y Acad Sci* 680:462–465
61. Sakurai T et al (1998) Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell* 92(4):573–585
62. Elmquist JK, Elias CF, Saper CB (1999) From lesions to leptin: hypothalamic control of food intake and body weight. *Neuron* 22(2):221–232
63. Armstrong WE (1995) Hypothalamic supraoptic and paraventricular nuclei. In: Paxinos G (ed) *The rat nervous system*. Academic Press, San Diego, pp 377–390
64. Heimer L et al (1997) Substantia innominata: a notion which impedes clinical-anatomical correlations in neuropsychiatric disorders. *Neuroscience* 76(4):957–1006
65. Keay KA et al (1994) Convergence of deep somatic and visceral nociceptive information onto a discrete ventrolateral midbrain periaqueductal gray region. *Neuroscience* 61(4):727–732
66. Clement CI et al (2000) Spinal sources of noxious visceral and noxious deep somatic afferent drive onto the ventrolateral periaqueductal gray of the rat. *J Comp Neurol* 425(3):323–344
67. Depaulis A, Keay KA, Bandler R (1994) Quiescence and hypoactivity evoked by activation of cell bodies in the ventrolateral midbrain periaqueductal gray of the rat. *Exp Brain Res* 99(1):75–83

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