THE JOURNAL OF COMPARATIVE NEUROLOGY 493:9–14 (2005)

Unitary Hypothesis for Multiple Triggers of the Pain and Strain of Migraine

RAMI BURSTEIN* **AND MOSHE JAKUBOWSKI**
Departments of Anesthesia and Critical Care, Beth Israel Deaconess Medical Center; Department of Neurobiology and the Program in Neuroscience, Harvard Medical School, Boston, Massachusetts 02115

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. Is there a common descending pathway accounting for the activation of meningeal nociceptors by different migraine triggers? 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 perfume, stress, or awakening 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. Are there ascending pathways through which the trigeminovascular system can induce the wide variety of migraine symptoms? We propose that trigeminovascular projections from the medullary dorsal horn to selective areas in the midbrain, hypothalamus, amygdala, and basal forebrain are functionally positioned to produce migraine symptoms such as irritability, loss of appetite, fatigue, depression, or the quest for solitude. 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 network of perpetual feedback that drives a migraine attack for many hours and even days. J. Comp. Neurol. 493:9–14, 2005.

Indexing terms: headache; PAG; nociception; trigeminal; stress; sleep; olfaction

ANATOMY OF THE PAIN

Migraine is a recurring neurological disorder commonly described as unilateral throbbing headache, readily aggravated by routine activities. The sensory discriminative aspect of migraine pain is mediated by activation and modulation of nociceptive trigeminothalamic tract neurons 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 (Penfield and McNaughton, 1940; Ray and Wolff, 1940). Evidence for descending modulation comes from studies that examined the effects of electrical stimulation of the periaqueductal gray (PAG) and rostral ventromedial medulla (RVM) 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 (Porreca et al., 2002).

The initiation of migraine headache is commonly associated with a wide variety of circumstances, such as hor-

Grant sponsor: National Institutes of Health; Grant number: DE13347; Grant number: NS051484; Grant number: NS35611 (to R.B.).

*Correspondence to: Rami Burstein, Department of Anesthesia and Critical Care, Harvard Institutes of Medicine, Room 830, 77 Avenue Louis Pasteur, Boston, MA 02115. E-mail: rburstei@caregroup.harvard.edu

Received 27 April 2005; Accepted 3 June 2005

DOI 10.1002/cne.20688

Published online in Wiley InterScience (www.interscience.wiley.com).

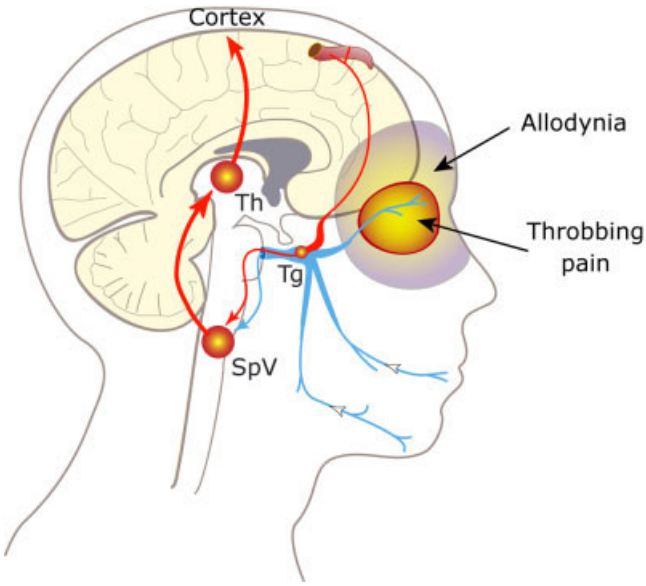

Fig. 1. The trigeminovascular pathway subserving migraine pain. Neurons in the trigeminal ganglion (Tg) that innervate the meninges (i.e., meningeal nociceptors) carry pain signals to trigeminovascular neurons in the spinal trigeminal nucleus (SpV). From there the pain signals are conveyed to several thalamic nuclei (Th) en route to the somatosensory cortex, where the perception of pain is formed.

monal milieu, periods of stress, poststress periods, skipping a meal, lack of sleep, olfactory stimulation, and several types of aura (Liveing, 1873; Zagami and Rasmussen, 2000). These associations raise the possibility that a migraine attack originates in brain areas that are not directly involved in nociception, but are wired 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 (Fig. 1).

ANATOMY OF THE STRAIN: 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. In the wake of cortical spreading depression, the blood–brain barrier becomes more permeable (Moskowitz and Cutrer, 1993; Gursoy-Ozdemir et al., 2004), allowing potassium and hydrogen ions to diffuse from the surface of the cortex to the pia where they activate C-fiber meningeal nociceptors (Moskowitz and Macfarlane, 1993). 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 (Ebersberger et al., 1999) from their peripheral branches, resulting in neurogenic inflammation in the dura (Goadsby and Edvinsson, 1993).

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, menstrual cycle, sleep, food intake, or responses to olfactory stimuli 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 neurons 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 extravasation, and local release of inflammatory molecules that activate adjacent terminals of meningeal nociceptors.

Several lines of evidence support this parasympathetic hypothesis: 1) meningeal blood vessels are densely innervated by parasympathetic fibers (Larsson et al., 1976; Nozaki et al., 1993; Suzuki and Hardebo, 1993); 2) preganglionic parasympathetic neurons in the superior salivatory nucleus increase their activity after activation of meningeal nociceptors (Knight et al., 2005); 3) ongoing activity in meningeal nociceptors appears to depend on enhanced activity in the SPG (Bolay et al., 2002); 4) parasympathetic tone is enhanced during migraine, as evidenced by lacrimation, teary eyes, nasal congestion (Liveing, 1873); and 5) blockade of the sphenopalatine ganglion provides partial or complete relief of migraine pain (Sluder, 1908; Dalessio, 1980; Kudrow, 1980; Diamond and Dalessio, 1982; Waldman, 1990, 1993; Reutens et al., 1991; Kudrow et al., 1995; Maizels et al., 1996; Yarnitsky et al., 2003).

The SSN receives extensive input from more than 50 brain areas distributed throughout the forebrain, diencephalon, midbrain, pons, and medulla (Spencer et al., 1990). 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 olfactory perception, physiological functions, emotional responses, and hormonal secretions (Fig. 2A). The neuroanatomy of a few examples is illustrated in Figure 2B. The piriform cortex processes olfactory information (Wilson, 2001) and may therefore be positioned to mediate the action of migraine-triggering odorants, such as perfume or fried food. The lateral hypothalamus and perifornical area contain hypocretinergic neurons that become active during food deprivation (Qu et al., 1996; Sakurai et al., 1998; Elmquist et al., 1999; Diano et al., 2003) and sleep deprivation (Yoshida et al., 2001; Zeitzer et al., 2003); such hypocretinergic neurons may mediate the triggering of a migraine attack when the patient skips a meal or when the patient is mildly sleep-deprived. The tuberomammillary nucleus (TMN) contains histaminergic neurons that

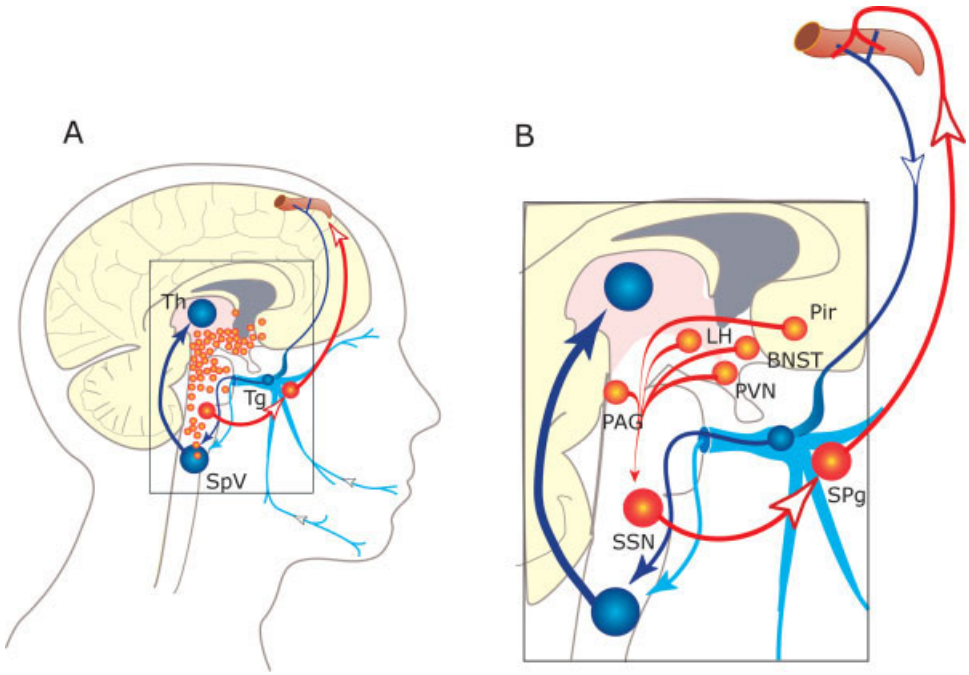

Fig. 2. A proposed parasympathetic pathway for the activation of meningeal nociceptors. Preganglionic parasympathetic neurons in the superior salivatory nucleus (SSN) can trigger intracranial vasodilation and the release of nitric oxide in the meninges through postganglionic parasympathetic neurons in 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 or poststress (PVN, BNST, PAG). BNST, bed nucleus stria terminalis; LH, lateral hypothalamus; PAG, periaqueductal gray; Pir, piriform cortex; PVN, paraventricular hypothalamic nucleus.

begin to fire at the end of the sleep period and have been implicated in cortical arousal and the process of waking up (Schwartz et al., 1991; Lin et al., 1996; Steininger et al., 1999); such arousal neurons may also be involved in the triggering of early-morning migraine. 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 the hypothalamic–pituitary–adrenal axis, appear to mediate long-lasting behavioral responses during sustained stress, which persist long after the termination of stress (Walker et al., 2003; Forray and Gysling, 2004); 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 (Swanson and Sawchenko, 1980; Coote, 2005), which includes localized cerebrovascular vasodilation in the early phase of the migraine attack (Olesen, 1998). Ventrolateral PAG neurons involved in passive emotional coping with inescapable stressors such as repeated defeat in social encounters (Bandler et al., 2000; Keay and Bandler, 2001) may mediate the onset of increased migraine frequency associated with a long period of social stress such as divorce.

ANATOMY OF THE STRAIN: 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 (Norgren, 1970; Panksepp, 1971; Kruk et al., 1983; Swanson, 1987; Lin et al., 1989; Bernardis and Bellinger, 1993, 1998; Roeling et al., 1993; Scammell et al., 1993; Simerly, 1995; Saper, 1995; Sherin et al., 1996; Peyron et al., 1998). 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. 3A)—an area containing the majority of second-order trigeminovascular neurons (Burstein and Giesler, 1989; Burstein et al., 1990; Keay and Bandler, 1992; Burstein and Potrebic, 1993; Strassman et al., 1994; Bernard et al., 1995; Bester et al., 1995; Vanderhorst et al., 1996; Malick and Burstein, 1998; Malick et al., 2000).

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. 3B). 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 (Lin et al., 1989; Peyron et al., 1998; Chemelli et al., 1999) through widespread projections to the cerebral cortex, brainstem, and spinal cord (Bittencourt et al., 1992; Bittencourt and Elias, 1993; Sakurai et al., 1998; van den Pol, 1999; Elmquist et al., 1999). Migraine-associated stress may be mediated by trigeminovascular projections to the paraventricular nucleus of the hypothalamus; this nucleus con-

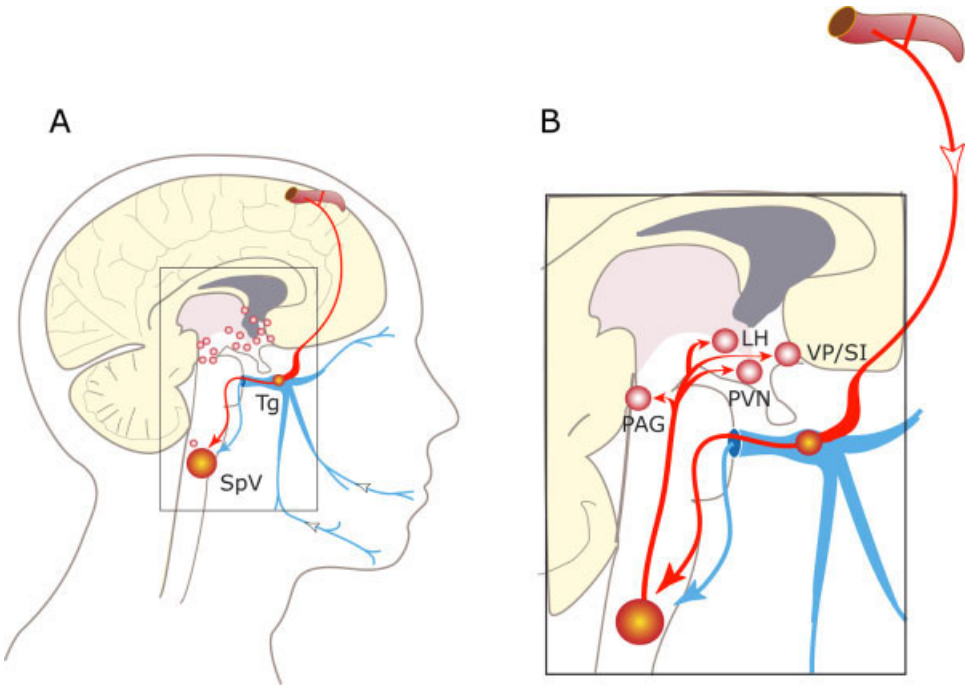

Fig. 3. Proposed mechanism for the initiation of symptoms commonly associated with migraine headache by ascending trigeminovascular pathways to the brainstem, hypothalamus, and basal ganglia. **A:** Trigeminovascular neurons in the spinal trigeminal nucleus (SpV) project to multiple limbic and hypothalamic 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.

tains neurons expressing corticotrophin-releasing hormone and oxytocin which regulate stress responses (Armstrong, 1995). 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 (Heimer et al., 1997).

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 (Keay and Bandler, 1992, 2001; Vanderhorst et al., 1996). The input to the ventrolateral PAG originates mainly in visceral and deep somatic tissues (Keay et al., 1994; Clement et al., 2000). Trigeminovascular projections to the ventrolateral PAG can activate neurons that mediate responses to deep, inescapable pain, such migraine pain (Depaulis et al., 1994; Keay and Bandler, 2001).

SUMMARY

The same hypothalamic, limbic, and cortical areas that project to the SSN also appear to receive extensive afferent connections from the trigeminovascular pathway. This provides a neuroanatomical roadmap by which the trigeminovascular pathway can activate the same brain areas that have triggered its own activity in the first place. Such a network of bidirectional trafficking provides an attractive mechanism of perpetual feedback that drives a migraine attack for many hours and even days. Therefore, enhanced activity of any structure in this network during a migraine attack, as shown by functional MRI, cannot be simply interpreted as "migraine generators" because it is also likely to be driven by the migraine pain itself.

LITERATURE CITED

Armstrong WE. 1995. Hypothalamic supraoptic and paraventricular nuclei. In: Paxinos G, editor. The rat nervous system, 2nd ed. San Diego: Academic Press. p 377–390.

Bandler R, Keay KA, Floyd N, Price J. 2000. Central circuits mediating patterned autonomic activity during active vs. passive emotional coping. Brain Res Bull 53:95–104.

Bernard JF, Dallel R, Raboisson P, Villanueva L, Le Bars D. 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 353:480–505.

Bernardis LL, Bellinger LL. 1993. The lateral hypothalamic area revisited: neuroanatomy, body weight regulation, neuroendocrinology and metabolism. Neurosci Biobehav Rev 17:141–193.

Bernardis LL, Bellinger LL. 1998. The dorsomedial hypothalamic nucleus revisited: 1998 update. Proc Soc Exp Biol Med 218:284–306.

Bester H, Menendez L, Besson JM, Bernard JF. 1995. Spino (trigemino) parabrachiohypothalamic pathway: electrophysiological evidence for an involvement in pain processes. J Neurophysiol 73:568–585.

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.

Bittencourt JC, Presse F, Arias C, Peto C, Vaughan J, Nahon JL, Vale W, Sawchenko PE. 1992. The melanin-concentrating hormone system of the rat brain: an immuno- and hybridization histochemical characterization. J Comp Neurol 319:218–245.

Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA. 2002. Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. Nat Med 8:136–142.

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.

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 335:469–485.

Burstein R, Cliffer KD, Giesler GJ Jr. 1990. Cells of origin of the spinohypothalamic tract in the rat. J Comp Neurol 291:329–344.

Chemelli RM, Willie JT, Sinton CM, Elmquist JK, Scammell T, Lee C, Richardson JA, Williams SC, Xiong Y, Kisanuki Y, Fitch TE, Nakazato

M, Hammer RE, Saper CB, Yanagisawa M. 1999. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. Cell 98:437–451.

Clement CI, Keay KA, Podzebenko K, Gordon BD, Bandler R. 2000. Spinal sources of noxious visceral and noxious deep somatic afferent drive onto the ventrolateral periaqueductal gray of the rat. J Comp Neurol 425:323–344.

Coote JH. 2005. A role for the paraventricular nucleus of the hypothalamus in the autonomic control of heart and kidney. Exp Physiol 90:169–173.

Dalessio DJ. 1980. The major neuralgias, postinfections neuritis, intractable pain, and atypical facial pain. In: Delessio DJ, editor. Wolff's headache, 4th ed. New York: Oxford Press. p 247–248.

Depaulis A, Keay KA, Bandler R. 1994. Quiescence and hyporeactivity evoked by activation of cell bodies in the ventrolateral midbrain periaqueductal gray of the rat. Exp Brain Res 99:75–83.

Diamond S, Dalessio DJ. 1982. The practicing physicians approach to headaches. Baltimore: Williams & Wilkins.

Diano S, Horvath B, Urbanski HF, Sotonyi P, Horvath TL. 2003. Fasting activates the nonhuman primate hypocretin (orexin) system and its postsynaptic targets. Endocrinology 144:3774–3778.

Ebersberger A, Averbeck B, Messlinger K, Reeh PW. 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 89:901–907.

Elmquist JK, Elias CF, Saper CB. 1999. From lesions to leptin: hypothalamic control of food intake and body weight. Neuron 22:221–232.

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 47:145–160.

Goadsby PJ, Edvinsson L. 1993. The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. Ann Neurol 33:48–56.

Gursoy-Ozdemir Y, Qiu J, Matsuoka N, Bolay H, Bermpohl D, Jin H, Wang X, Rosenberg GA, Lo EH, Moskowitz MA. 2004. Cortical spreading depression activates and upregulates MMP-9. J Clin Invest 113:1447–1455.

Heimer L, Harlan RE, Alheid GF, Garcia MM, de Olmos J. 1997. Substantia innominata: a notion which impedes clinical-anatomical correlations in neuropsychiatric disorders. Neuroscience 76:957–1006.

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 139:143–148.

Keay KA, Bandler R. 2001. Parallel circuits mediating distinct emotional coping reactions to different types of stress. Neurosci Biobehav Rev 25:669–678.

Keay KA, Clement CI, Owler B, Depaulis A, Bandler R. 1994. Convergence of deep somatic and visceral nociceptive information onto a discrete ventrolateral midbrain periaqueductal gray region. Neuroscience 61: 727–732.

Knight YE, Classey JD, Lasalandra MP, Akerman S, Kowacs F, Hoskin KL, Goadsby PJ. 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 1045:1–11.

Kruk MR, Van der Poel AM, Meelis W, Hermans J, Mostert PG, Mos J, Lohman AH. 1983. Discriminant analysis of the localization of aggression-inducing electrode placements in the hypothalamus of male rats. Brain Res 260:61–79.

Kudrow L. 1980. Cluster headache: mechanism and management. London: Oxford Press. p 114–116.

Kudrow L, Kudrow DB, Sandweiss JH. 1995. Rapid and sustained relief of migraine attacks with intranasal lidocaine: preliminary findings. Headache 35:79–82.

Larsson LI, Edvinsson L, Fahrenkrug J, Hakanson R, Owman C, Schaffalitzky de Muckadell O, Sundler F. 1976. Immunohistochemical localization of a vasodilatory polypeptide (VIP) in cerebrovascular nerves. Brain Res 113:400–404.

Lin JS, Sakai K, Vanni-Mercier G, Jouvet M. 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: 225–240.

Lin JS, Hou Y, Sakai K, Jouvet M. 1996. Histaminergic descending inputs to the mesopontine tegmentum and their role in the control of cortical activation and wakefulness in the cat. J Neurosci 16:1523–1537.

Liveing E. 1873. On megrim, sick headache. Nijmegen: Arts & Boeve.

Maizels M, Scott B, Cohen W, Chen W. 1996. Intranasal lidocaine for treatment of migraine: a randomized, double- blind, controlled trial [see Comments]. JAMA 276:319–321.

Malick A, Burstein R. 1998. Cells of origin of the trigeminohypothalamic tract in the rat. J Comp Neurol 400:125–144.

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 84:2078–2112.

Moskowitz MA, Cutrer FM. 1993. SUMATRIPTAN: a receptor-targeted treatment for migraine. Annu Rev Med 44:145–154.

Moskowitz MA, Macfarlane R. 1993. Neurovascular and molecular mechanisms in migraine headaches. Cerebrovasc Brain Metab Rev 5:159–177.

Norgren R. 1970. Gustatory responses in the hypothalamus. Brain Res 21:63–77.

Nozaki K, Moskowitz MA, Maynard KI, Koketsu N, Dawson TM, Bredt DS, Snyder SH. 1993. Possible origins and distribution of immunoreactive nitric oxide synthase-containing nerve fibers in cerebral arteries. J Cereb Blood Flow Metab 13:70–79.

Olesen J. 1998. Regional cerebral blood flow and oxygen metabolism during migraine with and without aura. Cephalalgia 18:2–4.

Panksepp J. 1971. Aggression elicited by electrical stimulation of the hypothalamus in albino rats. Physiol Behav 6:321–329.

Penfield W, McNaughton F. 1940. Dural headache and innervation of the dura mater. Arch Neurol Psychiatry 44:43–75.

Peyron C, Tighe DK, van den Pol AN, de Lecea L, Heller HC, Sutcliffe JG, Kilduff TS. 1998. Neurons containing hypocretin (orexin) project to multiple neuronal systems. J Neurosci 18:9996–10015.

Porreca F, Ossipov MH, Gebhart GF. 2002. Chronic pain and medullary descending facilitation. Trends Neurosci 25:319–325.

Qu D, Ludwig DS, Gammeltoft S, Piper M, Pelleymounter MA, Cullen MJ, Mathes WF, Przypek R, Kanarek R, Maratos-Flier E. 1996. A role for melanin-concentrating hormone in the central regulation of feeding behaviour. Nature 380:243–247.

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.

Reutens DC, Fatovich DM, Stewart-Wynne EG, Prentice DA. 1991. Is intravenous lidocaine clinically effective in acute migraine? Cephalalgia 11:245–247.

Roeling TA, Kruk MR, Schuurmans R, Veening JG. 1993. Behavioural responses of bicucculline methiodide injections into the ventral hypothalamus of freely moving, socially interacting rats. Brain Res 615: 121–127.

Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, Williams SC, Richardson JA, Kozlowski GP, Wilson S, Arch JR, Buckingham RE, Haynes AC, Carr SA, Annan RS, McNulty DE, Liu WS, Terrett JA, Elshourbagy NA, Bergsma DJ, Yanagisawa M. 1998. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell 92:573–585.

Saper CB. 1995. Central autonomic system. In: Paxinos G, editor. The rat nervous system, 2nd ed. San Diego: Academic Press. p 107–136.

Scammell TE, Price KJ, Sagar SM. 1993. Hyperthermia induces c-fos expression in the preoptic area. Brain Res 618:303–307.

Schwartz JC, Arrang JM, Garbarg M, Pollard H, Ruat M. 1991. Histaminergic transmission in the mammalian brain. Physiol Rev 71:1–51.

Sherin JE, Shiromani PJ, McCarley RW, Saper CB. 1996. Activation of ventrolateral preoptic neurons during sleep. Science 271:216–219.

Simerly RB. 1995. Anatomical substrates of hypothalamic integration. In: Paxinos G, editor. The rat nervous system, 2nd ed. San Diego: Academic Press. p 353–376.

Sluder G. 1908. The role of the sphenopalatine ganglion in nasal headaches. N Y State J Med 27:8–13.

Spencer SE, Sawyer WB, Wada H, Platt KB, Loewy AD. 1990. CNS projections to the pterygopalatine parasympathetic preganglionic neurons in the rat: a retrograde transneuronal viral cell body labeling study. Brain Res 534:149–169.

Steininger TL, Alam MN, Gong H, Szymusiak R, McGinty D. 1999. Sleep-waking discharge of neurons in the posterior lateral hypothalamus of the albino rat. Brain Res 840:138–147.

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 14:3725–3735.

Suzuki N, Hardebo JE. 1993. The cerebrovascular parasympathetic innervation. Cerebrovasc Brain Metab Rev 5:33–46.

Swanson LW. 1987. Integrated systems of the CNS, part I. In: Bjorklund A, Hokfelt T, Swanson LW, editors. The hypothalmus. Amsterdam: Elsevier. p 1–124.

Swanson LW, Sawchenko PE. 1980. Paraventricular nucleus: a site for the integration of neuroendocrine and autonomic mechanisms. Neuroendocrinology 31:410–417.

van den Pol AN. 1999. Hypothalamic hypocretin (Orexin): robust innervation of the spinal cord. J Neurosci 19:3171–3182.

Vanderhorst VG, Mouton LJ, Blok BF, Holstege G. 1996. Distinct cell groups in the lumbosacral cord of the cat project to different areas in the periaqueductal gray. J Comp Neurol 376:361–385.

Waldman SD. 1990. The role of neural blockade in the management of common pain syndromes. In: Weiner RS, editor. Innovations in pain management. Orlando, FL: Deutch Press. p 4–14.

Waldman SD. 1993. Sphenopalatine ganglion block—80 years later. Reg Anesth 18:274–276.

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 463:199–216.

Wilson DA. 2001. Receptive fields in the rat piriform cortex. Chem Senses 26:577–584.

Yarnitsky D, Goor-Aryeh I, Bajwa ZH, Ransil BI, Cutrer FM, Sottile A, Burstein R. 2003. 2003 Wolff Award: possible parasympathetic contributions to peripheral and central sensitization during migraine. Headache 43:704–714.

Yoshida Y, Fujiki N, Nakajima T, Ripley B, Matsumura H, Yoneda H, Mignot E, Nishino S. 2001. Fluctuation of extracellular hypocretin-1 (orexin A) levels in the rat in relation to the light-dark cycle and sleep-wake activities. Eur J Neurosci 14:1075–1081.

Zagami AS, Rasmussen BK. 2000. Symptomology of migraine without aura. In: Olesen J, Tfelt-hansen P, Welch MA, editors. The headaches. New York: Raven Press. p 337–343.

Zeitzer JM, Buckmaster CL, Parker KJ, Hauck CM, Lyons DM, Mignot E. 2003. Circadian and homeostatic regulation of hypocretin in a primate model: implications for the consolidation of wakefulness. J Neurosci 23:3555–3560.