Chapter 17

Sex Hormones

Nancy E. J. Berman and Michael M. Behbehani

Millions of women suffer migraine headaches around the time of their menstrual cycles, a phenomenon known as *menstrual migraine*. Clinical studies completed over 25 years ago established strong links between falling blood estrogen levels and triggering of these attacks (126,127). This chapter addresses current knowledge of likely mechanisms linking hormones to migraine in both the peripheral and central nervous systems.

Migraine and other pain disorders, including fibromyalgia and temporomandibular disorders, are at least twice as prevalent in women as in men (34,73,76,128,156). In these conditions, severity of pain varies with the menstrual cycle, peaking around the time of menstruation when both estrogen and progesterone are lowest (54). Onset of migraine in girls usually occurs around time of menarche (128), and the frequency and severity of migraine attacks often increases during menopause, when hormone levels fluctuate. After menopause, when hormone levels are low, many migraineurs experience improvement (38). The constant high hormone levels of pregnancy are also associated with a decrease in migraine frequency (143). Thus, migraine improves during pregnancy, when estrogen levels are constantly high, and after menopause, when estrogen levels are constantly low. All of these observations indicate a strong link between ovarian steroids and migraine, and they suggest that rapid changes in estrogen and progesterone levels are a trigger for attacks. Ovarian steroids act via classical nuclear receptors such as ERα and ERβ, which regulate transcription by activating or repressing estrogen-responsive genes. Estrogen also activates elements of the MAP kinase pathway including extracellular-signaling related kinases (ERKs) (90). Other, more rapid effects of estrogen may be mediated via membrane estrogen receptors (70). Progesterone has two nuclear receptors, PR-A and PR-B, which are identical except for an additional 164 amino acids at the N-terminal end of PR-B (42). Progesterone also acts via membrane effects (144).

Hormones could affect pain processing at all levels, including peripheral and central mechanisms. Figure 17-1 diagrams regions where hormones could influence transmission of pain information from the peripheral into the central nervous system.

Peripheral Tissue

Meningeal Inflammation

Throbbing pain suggests an origin in arteries, and it has been known for many years that meningeal and large cerebral arteries are capable of transmitting painful sensations. Thus, studies of migraine pathogenesis have focused on meninges and meningeal vessels, and it is thought that migraine involves meningeal inflammation (95). There are at least four potential mechanisms whereby ovarian steroids could modulate meningeal inflammation. First, meningeal vessels are a potential site of estrogen effects, as they express estrogen receptor-α, which increases after estrogen treatment (129). Second, hormones may alter responses of meningeal mast cells. Estrogen receptors in dural mast cells modulate histamine release (109), and histamine excites nociceptive terminals. Third, estrogen may modulate expression of proinflammatory cytokines by macrophages present on the meningeal linings of the subarachnoid space (87) and in the dura, where they are aligned along blood vessels, especially near the superior sagittal sinus (85). Proinflammatory cytokines also excite nociceptive terminals (153). Estrogen modulates expression of proinflammatory cytokines in macrophages (68) and reduces leukocyte migration into injured vessels (153). Fourth, ovarian steroids may regulate sensory sensitization by modulating expression of nerve growth factor (NGF). Retrograde transport of receptor-bound NGF stimulates synthesis of CGRP, substance P, and PACAP (71,72,96). Blocking the high-affinity NGF receptor trkA prevents sensory sensitization following inflammation (14,64). Dural tissue expresses NGF (134), and estrogen treatment alters NGF expression in some tissues (16). Effects of NGF on meninges are unknown.

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-17 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:48

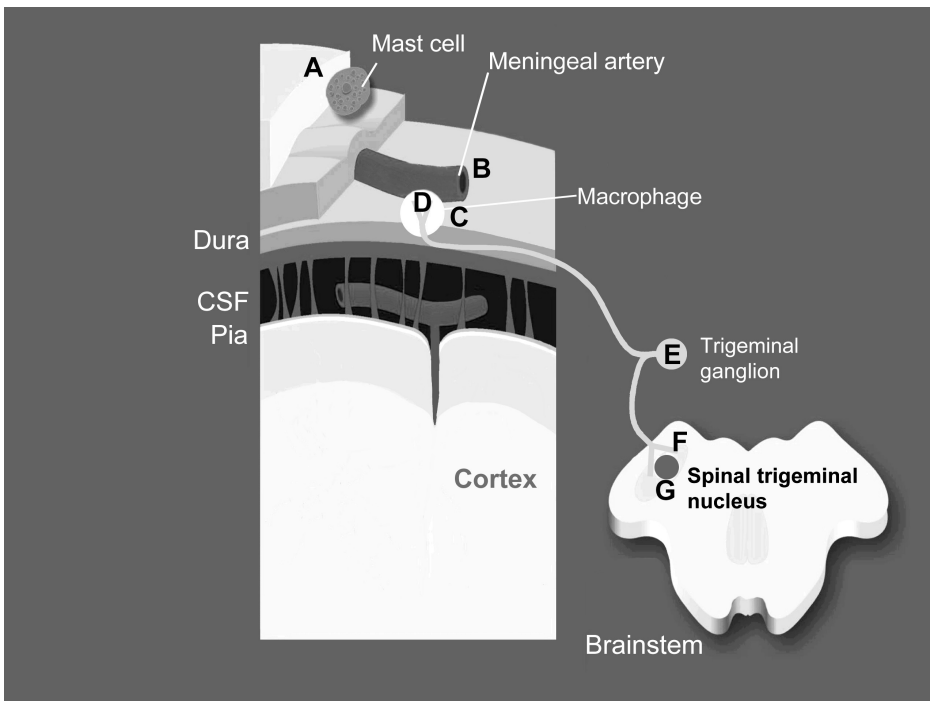

FIGURE 17-1. This figure diagrams trigeminal neurons, which have their cell bodies in the trigeminal ganglion **(E)**, peripheral processes in meninges and orofacial tissue **(D)**, and central processes **(F)** that synapse on cells in the spinal trigeminal nucleus of the brainstem **(G)**. These neurons, like other sensory neurons, secrete neuropeptides at both their peripheral and central axon terminals. Secretion of neuropeptides in the periphery affects blood flow and inflammatory responses, and secretion of neuropeptides at the central terminal affects transmission of nociceptive signals. Hormones could affect this system at all three locations. In the periphery, hormones could alter responses of peripheral tissue to inflammation or injury by regulating responses of mast cells **(A)**, meningeal arteries **(B)**, or meningeal macrophages **(C)**. At the neuronal cell bodies **(E)**, hormones may regulate expression of neuropeptides and other genes that control excitability. Alteration of neuropeptide gene expression may change the mix of neuropeptides secreted at either the peripheral or central terminals, or both. At the central synapse **(F,G)**, hormones may alter synaptic transmission by regulating neuropeptides present in central processes or by altering gene expression in the brainstem target cells. Hormone receptors are located in cells at all of these sites, and there is compelling evidence for hormonal influences at many of these sites.

Trigeminal Neurons

Trigeminal Peripheral Processes

CGRP Innervation of Meninges

The dura is innervated by trigeminal axons containing substance P and CGRP. Migraine attacks involve selective release of CGRP from trigeminal axons (43), which causes plasma extravasation and meningeal edema (23,24,81). CGRP also functions as a potent vasodilator (101,138), stimulates mast cell histamine release (101), is highly chemotactic to macrophages (33), and increases cytokine release from macrophages (133). Estrogen increases CGRP innervation of mammary gland tissue, associated primarily with blood vessels (17). It is not known whether hormones have similar effects on CGRP innervation of meningeal vessels.

Trigeminal Neuronal Cell Bodies, Neuropeptides, and Hormone Receptors

The trigeminal ganglion contains several populations of neurons (see review by Lazarov [69]) that express neuropeptides such as substance P and CGRP, but also other peptides potentially relevant to migraine including PACAP, atrial natiuretic peptide, neurokinin A, endothelin-1, enkephalin, dynorphin cholecystokinin, bombesin, somatostatin, vasoactive intestinal peptide, and galanin (see review by Lazarov [69]). Trigeminal neurons express ERα, which is likely to regulate expression of many of these peptides.

Progesterone receptors are present in dorsal root ganglia (DRG) of female rats. Ovariectomy reduces expression of these receptors and increases behavioral

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-17 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:48

hypersensitivity to heat (93), suggesting a link between low progesterone levels and increased pain sensitivity. Progesterone may also regulate trigeminal function indirectly via effects on CGRP and the NGF-trkA system (41). Very little information is available about the potential role of progesterone or its receptors in trigeminal neurons.

Hormones May Alter Responses to Peripheral Inflammation or Nerve Injury (Phenotypic Plasticity)

Numerous studies have shown that phenotypic changes in sensory neurons accompany changes in response to painful stimuli from temporary to severe and chronic. Cutaneous allodynia occurs in certain well-defined regions of the skin during migraine, suggesting hyperexcitability of pain pathways (22), and migraineurs have significantly lower thresholds for the blink reflex and an increased sensitivity to tactile and painful stimuli, even during the interictal period (115). These increased responses indicate sensitization of trigeminal neurons.

Phenotypic plasticity of nociceptive sensory neurons is regulated by the NGF-trkA system (88). Small DRG neurons that are positive for CGRP transport NGF from the periphery (1,152). During inflammation, NGF levels increase (110) resulting in inflammatory hyperalgesia (84,150–151,152). Inflammation of orofacial tissue results in increased CGRP and substance P in the trigeminal ganglion (53). In addition, motifs that mimic a classical estrogen response element are found in the promoter and 5′-flanking regions of the genes for human trkA (125,135).

Sensory sensitization is associated with altered expression of neuropeptides (NP) such as NPY and galanin in trigeminal neurons in males (35,40). In females, NPY and galanin are regulated by ovarian steroids. NPY is a vasoconstrictive peptide usually associated with the parasympathetic nervous system. NPY-immunoreactive nerve fibers and receptors are expressed around cerebral vessels (12), and NPY inhibits dural plasma protein extravasation after trigeminal stimulation (155). Increased levels of NPY are present in cerebral spinal fluid after a migraine attack (139). Both Y1 and Y2 NPY receptors are located in trigeminal ganglia (131). NPY mRNA levels vary with the phase of the estrous cycle in female mice, with highest levels present at early estrus (104). Galanin increases markedly after nerve injury (49), when it regulates nociceptive signaling (50,62,63,75). In male mice, injury increases the galanin content of dorsal root ganglion cells 120-fold and the number of galanin positive neurons increases from 5% to more than 50% (2). Galanin injections into inflamed knee joints in rats cause a significant reduction in responses to noxious movements, suggesting that galanin is a critical component of the tonic inhibitory system for inflammatory pain (47). In the pituitary, estrogen upregulates galanin mRNA expression up to 4000-fold and immunoreactivity up to 50-fold (59). In mice, galanin expression in trigeminal neurons is highest at proestrus, the stage of the estrous cycle when estrogen levels are highest (104). Galanin has several G-protein–coupled receptors including GalR1, GalR2, and GalR3 (20). GalR1, which has antinociceptive functions (52,61,74), is expressed in trigeminal ganglia and in peripheral targets of trigeminal neurons (130). GalR1 expression in the hypothalamus is modulated by ovarian steroids and is highest at proestrus (37). It is not known if ovarian steroids regulate GalR1 expression in the trigeminal system.

Intracellular Signaling Pathway

Inflammatory mediators produce hyperalgesia via activation of intracellular signaling pathways including members of the MAP kinase pathway ERKs (55). Activation of nociceptive fibers induces phosphoERK (pERK) in sensory neurons in an intensity-dependent manner, and ERK antagonists inhibit capsaicin-induced hyperalgesia (31). Ovarian steroids can modulate the activity of the ERK pathway (67).

Potential Effects of Ovarian Steroids on Trigeminal Central Processes and Postsynaptic Cells

Inflammation increases in the number of substance P and CGRP immunoreactive axons in the dorsal horn, whereas nerve injury increases galanin and NPY (51). The extent of neuroplasticity of trigeminal central terminals and potential effects of ovarian steroids on these responses have received little attention. Ovarian steroids may also regulate activity of postsynaptic cells directly, as neurons in lamina II of trigeminal nucleus caudalis (TNC) express ERα, and the number of these cells increases after ovariectomy (102). ERα is also present in nucleus caudalis (123). Changes in excitability of brainstem trigeminal neurons may underlie the increases in receptive field sizes in the spinal trigeminal nucleus observed when estrogen levels are high (9,10).

INTERACTIONS OF SEX HORMONES WITH BRAIN PAIN PROCESSING NETWORKS

Overall Network

The information regarding the peripheral action of sex hormones has been obtained from experimental animals. This is because there are no noninvasive techniques that can provide this type of information using human subjects. More data on the role of sex hormones in the

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-17 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:48

central processing of trigeminal pain processing in human are known because of the advances in imaging techniques. The currently available information from human studies correlates well with the animal studies of the role of sex hormones.

Information related to activation of sensory terminals innervating the dura and meninges are transmitted to neurons within the nucleus caudalis of the trigeminal complex. Functionally, this region, and its caudal extent into the cervical spinal cord, integrate nociceptive information arriving from the periphery and the descending systems and transmits this information to the medullary, pontine thalamic, and hypothalamic regions (11,26,118). Anatomic studies using injection of retrograde tracers into the TNC have identified four major sites as targets of TNC projections (26,32,46,78–80,94,99,107,108,119,148). These sites are the periaqueductal gray (PAG), the parabrachial nucleus (PBN), medial preoptic nucleus of the hypothalamus, and the ventrobasal nucleus of the thalamus. Further, injections of anterograde tracers into each of these sites indicate site-specific afferents from the TNC neurons that in turn receive afferents from the meninges and dura. The sites that receive afferents from TNC contain a dense population of sex hormone receptors and terminals. Therefore, changes in the level of these hormones can modulate signal processing within the TNC and propagation of these signals to the forebrain. The functions related to sex hormones in each of these sites are discussed next.

Parabrachial Nucleus

The PBN is a major integration site for cardiovascular control and pain modulation. The PBN is a part of the central autonomic circuitry that governs the autonomic response to changes in visceral functions (136). The PBN receives inputs from the nucleus of solitary tract and projects to the PAG, hypothalamus, and amygdala (13). There are reciprocal connections between PBN and it major outputs. The PBN receives nociceptive information from both the spinal and the trigeminal dorsal horns. Inputs from the trigeminal dorsal horn terminate predominantly in three regions of the PBN: the external lateral, the external medial, and the Kolliker-Fuse subnuclei, with sparser labeling present in the dorsal and superior lateral subnuclei and in the medial PBN. The anatomic organization of the PBN supports the hypothesis that this region is involved in autonomic symptoms associated with headache and migraine. Although this issue remains controversial, there is substantial evidence that the autonomic nervous system function is altered in migraine patients (103). Among the components of the changes in this system, a decrease in the basal level of norepinephrine (44,82), increased sensitivity to α-adrenergic agonists (44), increased sensitivity to cold pressor test (132), and increased sensitivity of the pupil to pharmacologic stimulation (36) have been documented. Based on these findings, Peroutka (103) has proposed that the initial vasoconstriction produced by norepinephrine is replaced by vasodilatation produced by dopamine, prostaglandin, and adenosine that are coreleased with norepinephrine from the sympathetic terminals.

In addition to its role in the central autonomic control network, the PBN has profound inhibitory effects on the spinal and trigeminal dorsal horn neurons in both the marginal zone and substantia gelatinosa regions (27,58, 86,146,149,154). The mechanisms that activate this descending system are not fully understood. However, the PBN is a part of the stress-induced analgesic system that includes the PAG, central nucleus of amygdala, and several hypothalamic regions (92).

Considering the properties of the PBN, changes in the activity of this region can have a profound effect on pain processing through the trigeminal system. Of significant interest is the fact that all subregions of the PBN that are involved in autonomic and pain modulation contain estrogen receptors and terminals (113,114,117). Functionally, the effect of estrogen injected into the PBN has been investigated. Studies by Saleh et al. have shown that injection of estrogen into the PBN significantly increases parasympathetic tone and decreases sympathetic tone, reflected as a significant decrease in blood pressure and heart rate. These effects of estrogen can be reversed by NMDA receptor antagonist and GABA receptor antagonist, indicating involvement of these receptors in the effects of estrogen on the autonomic system modulated by PBN (111,112). In addition, single unit recording from PBN neurons have shown that estrogen has an inhibitory effect by potentiation of GABAergic and reduction of glutamatergic tone (113).

Periaqueductal Gray

The PAG is a major site for integration of nociceptive, autonomic and reproductive behavior (6,91). Anatomically, the PAG has been divided in four subregions: dorsal, dorsolateral, lateral, and ventrolateral (4,8). Stimulation of different regions of the PAG produces a number of distinctly different behavioral and physiologic responses including vocalization, autonomic changes, sexual behavior, fear and rage reactions, and anxiety. Only stimulation of the ventrolateral and the dorsomedial parts of dorsal raphe produces relatively pure analgesia.

The PAG areas that receive afferents from the TNC and the areas that project to the TNC contain estrogen receptors and terminals (18,25,97,98,100,106,122,140,141). Estrogen has a significant effect on the synaptic morphology of the PAG neurons. Studies by Chung et al. (28) have shown that ovariectomized adult female rats treated with daily subcutaneous injections of estradiol benzoate for

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-17 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:48

20 days showed significant changes in the synaptic morphology including an increase in the number of synapses, the length of postsynaptic densities (PSDs), the number of PSDs showing perforations, synapses with positive synaptic curvature, dense-cored vesicles, and mean number of terminals that contained dense-cored vesicles. Functionally, the effects of gonadectomy and ovariectomy on the analgesic effect of morphine have been studied (65,66). These studies indicated that central morphine analgesia is significantly greater in male than in female rats. In addition, using a selective μ-opioid receptor agonist and a δ-opioid receptor agonist, Kepler et al. (60) have shown that sham-operated male rats displayed significantly greater magnitudes of peak and total analgesia than sham-operated female rats on the tail-flick test. In addition to a direct effect on opioids, the effects of sex hormones on two types of stress-induced analgesia have been examined. Using continuous cold water swim and intermittent cold water swim, studies by Bodnar have shown that female rats display significantly less analgesia than males, and gonadectomized rats display significantly less analgesia than sham-operated controls (19).

The anxiety circuitry of the PAG also depends on sex hormones. In behavioral studies, mice show maximal anxiety levels in diestrus. The minimal anxiety level is found at metestrus. As a related processes, the ability to acquire conditional response is the highest in female rats during proestrus (29,121). In general, progesterone has an anxiolytic effect (15).

Considering the literature cited, changes in both estrogen and progesterone can have significant effects on ascending pain transmission through the PAG as well as on PAG-mediated analgesia.

Medial Proptic Nucleus of Hypothalamus

Nociceptive information from the trigeminal sensory system is propagated to the hypothalamus by a direct projection from the TNC (21,77,94). The major site of termination of these afferents is the medial preoptic nucleus. This nucleus is involved in modulation of pain and analgesia (7,30), response to stress (120), temperature regulation (3,116), reproductive behavior (5), sleep–wakefulness (57), and autonomic control (145).

The medial preoptic nucleus plays an important role in integration and coordination of autonomic information relayed through the solitary nucleus and PBN and with the sensory information relayed through the dorsal horn and the reticular formation (91). Medial preoptic nucleus forms reciprocal connections with the prefrontal cortex, amygdala, PAG, nucleus tractus solitarii (NTS), and rostral ventral medulla and through these connections it is involved in cognitive and motivational aspects of pain. The pain inhibitory influence of the medial preoptic nucleus is relayed through the PAG (45) and the rostral ventral medulla (56).

The medial preoptic nucleus contains estrogen- and progesterone-containing neurons and their receptors (122,124). Physiologic studies of the effects of estrogen on the preoptic area have indicated that estrogen has a significant effect on opioidergic and GABAergic transmission. Micevych et al. (89) have shown that estrogen treatment induced an internalization of μ-opioid receptors in the medial preoptic nucleus of ovariectomized wild-type mice that is mediated through estrogen receptor-α. This effect of estrogen may in part explain observations that in rodents and humans the analgesic effect of morphine is altered by stages of the estrous cycle (39). Estrogen potentiates the GABAergic transmission within the hypothalamic nuclei including the medial preoptic nucleus (48,105). As mentioned, the medial preoptic nucleus has a strong interaction with the limbic areas and brainstem pain modulatory networks. Considering these interactive networks, changes produced by sex hormones on the medial preoptic nucleus neurons suggest strong involvement of this region on hormone-related pain modulation.

Locus Coeruleus

Studies by Weiller et al. (142) using PET imaging have indicated an increase in regional cerebral blood flow in the brainstem at or near the locus coeruleus/subcoeruleus (LC/SC) region during spontaneous migraine attacks in migraine without aura. These studies also showed that the changes in blood flow persisted despite relief of symptoms following subcutaneous injection of sumatriptan. They concluded that in migraine without aura, brainstem activation during spontaneous migraine may be inherent to migraine and not simply its consequence. The mechanisms that relate to the involvement of LC/SC in headache are not totally clear. Anatomic studies have shown that LC/SC innervates all subnuclei of the trigeminal sensory nuclear complex (83,123,147). Electrophysiologic studies have shown that stimulation of LC/SC inhibits the response of the TNC to noxious stimulation (137). There is substantial evidence that neurons in the LC/SC respond to noxious stimulation (91); therefore, the pathway between LC and TNC may form a feedback system through which the pain produced by noxious stimulation of inflammation is reduced. In this regard, the basal activity of the LC/SC neurons can be of significant importance in pain modulation. Recent studies have shown that estrogen increases mRNA levels of tyrosine hydroxylase (TH) in the LC. Because the LC has an inhibitory role in pain transmission through the trigeminal system, an increase in the level of TH may lead to enhanced inhibitory tone on the trigeminal neurons when the estrogen level is high. This processes may be a contributing factor to “estrogen

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-17 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:48

withdrawal" migraine that develops when estrogen level falls.

SUMMARY

In summary, nociceptive information arising from the head, the dura, and meninges is processed within the TNC. There is substantial integration within the TNC, and sex hormones can modulate these activities at the local circuits in this nucleus. Following integration, the information is propagated to the higher centers through a highly interconnected parallel system to the midbrain, thalamus and hypothalamus. The areas that receive afferents from TNC are interconnected and communicate with major limbic systems of the brain. Sex hormones have modulatory roles in all of these regions. The symptoms associated with the effects of changes in sex hormone levels can be explained by the effects of these hormones at each of these sites.

REFERENCES

1. Averill S, McMahon SB, Clary DO, et al, eds. Immunocytochemical localization of trkA receptors in chemically identified subgroups of adult rat sensory neurons. *Eur J Neurosci*. 1995;7:1484–1494.
2. Bacon A, Holmes FE, Small CJ, et al. Transgenic over-expression of galanin in injured primary sensory neurons. *Neuroreport*. 2002: 2129–2132.
3. Baffi JS, Palkovits M. Fine topography of brain areas activated by cold stress. a fos immunohistochemical study in rats. *Neuroendocrinology*. 2000;72:102–113.
4. Bandler R, Shipley MT. Columnar organization in the midbrain periaqueductal gray: modules for emotional expression? [published erratum appears in *Trends Neurosci*. 1994;17(11):445] [see comments]. *Trends Neurosci.* 1994;17:379–389.
5. Bazzett T, Lumley L, Bitran D, et al. Male rat copulation following 6-OHDA lesions of the medial preoptic area: resistance to repeated administration and rapid behavioral recovery. *Brain Res*. 1992;580:164–170.
6. Behbehani MM. Functional characteristics of the midbrain periaqueductal gray. *Prog Neurobiol*. 1995;46:575–605.
7. Behbehani MM, Da Costa Gomez TM. Properties of a projection pathway from the medial preoptic nucleus to the midbrain periaqueductal gray of the rat and its role in the regulation of cardiovascular function. *Brain Res*. 1996;740:141–150.
8. Beitz AJ, Shepard RD. The midbrain periaqueductal gray in the rat. II. A Golgi analysis. *J Comp Neurol*. 1985;237:460–475.
9. Bereiter DA, Barker DJ. Facial receptive fields of trigeminal neurons: increased size following estrogen treatment in female rats. *Neuroendocrinology*. 1975:115–124.
10. Bereiter DA, Barker DJ. Hormone-induced enlargement of receptive fields in trigeminal mechanoreceptive neurons. I. Time course, hormone, sex and modality specificity. *Brain Res*. 1980:395–410.
11. Bereiter DA, Hirata H, Hu JW. Trigeminal subnucleus caudalis: beyond homologies with the spinal dorsal horn. *Pain*. 2000;88:221–224.
12. Berman NE, Fredrickson E. Morphology and laminar distribution of neuropeptide Y immunoreactive neurons in the human striate cortex. *Synapse*. 1992:20–27.
13. Bernard JF, Alden M, Besson JM. The organization of the efferent projections from the pontine parabrachial area to the amygdaloid complex: a *Phaseolus vulgaris* leucoagglutinin (PHA-L) study in the rat. *J Comp Neurol*. 1993;329:201–229.
14. Bevan S, Winter J. Nerve growth factor (NGF) differentially regulates the chemosensitivity of adult rat cultured sensory neurons. *J Neurosci*. 1995:4918–4926.
15. Bitran D, Purdy RH, Kellogg CK. Anxiolytic effect of progesterone is associated with increases in cortical allopregnanolone and GABAA receptor function. *Pharmacol Biochem Behav*. 1993;45:423–428.
16. Bjorling DE, Beckman M, Clayton MK, et al. Modulation of nerve growth factor in peripheral organs by estrogen and progesterone. *Neuroscience* 2002;110(1):155–167.
17. Blacklock AD, Smith PG. Estrogen increases calcitonin gene-related peptide-immunoreactive sensory innervation of rat mammary gland. *J Neurobiol*. 2004:192–204.
18. Blurton-Jones MM, Roberts JA, Tuszynski MH. Estrogen receptor immunoreactivity in the adult primate brain: neuronal distribution and association with p75, trkA, and choline acetyltransferase. *J Comp Neurol*. 1999;405:529–542.
19. Bodnar RJ, Glusman M, Brutus M, et al. Analgesia induced by cold-water stress: attenuation following hypophysectomy. *Physiol Behav*. 1979;23:53–62.
20. Branchek TA, Smith KE, Gerald C, et al. Galanin receptor subtypes. *Trends Pharmacol Sci*. 2000:109–117.
21. Burstein R, Cliffer KD, Giesler GJ Jr. Cells of origin of the spinohypothalamic tract in the rat. *J Comp Neurol*. 1990;291:329–344.
22. Burstein R, Cutrer MF, Yarnitsky D. The development of cutaneous allodynia during a migraine attack clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. *Brain*. 2000:1703–1709.
23. Buzzi MG, Bonamini M, Moskowitz MA. Neurogenic model of migraine. *Cephalalgia*. 1995:277–280.
24. Buzzi MG, Moskowitz MA. The antimigraine drug, sumatriptan (GR43175), selectively blocks neurogenic plasma extravasation from blood vessels in dura mater. *Br J Pharmacol*. 1990:202–206.
25. Calizo LH, Flanagan-Cato LM. Estrogen-induced dendritic spine elimination on female rat ventromedial hypothalamic neurons that project to the periaqueductal gray. *J Comp Neurol*. 2002;447:234–248.
26. Carstens E, Leah J, Lechner J, et al. Demonstration of extensive brainstem projections to medial and lateral thalamus and hypothalamus in the rat. *Neuroscience*. 1990;35:609–626.
27. Chiang CY, Hu JW, Sessle BJ. Parabrachial area and nucleus raphe magnus-induced modulation of nociceptive and nonnociceptive trigeminal subnucleus caudalis neurons activated by cutaneous or deep inputs. *J Neurophysiol*. 1994;71:2430–2445.
28. Chung SK, Pfaff DW, Cohen RS. Estrogen-induced alterations in synaptic morphology in the midbrain central gray. *Exp Brain Res*. 1988;69:522–530.
29. Clement Y, Chapouthier G. Biological bases of anxiety. *Neurosci Biobehav Rev*. 1998;22:623–633.
30. Cunningham PM, Goldsmith GE, Hellon RF. Medial hypothalamic stimulation produces analgesia to facial heating in unrestrained rats. *Neurosci Lett*. 1986;68:107–111.
31. Dai Y, Iwata K, Fukuoka T, et al. Phosphorylation of extracellular signal-regulated kinase in primary afferent neurons by noxious stimuli and its involvement in peripheral sensitization. *J Neurosci*. 2002:7737–7745.
32. Dostrovsky JO. Raphe and periaqueductal gray induced suppression of non-nociceptive neuronal responses in the dorsal column nuclei and trigeminal sub-nucleus caudalis. *Brain Res*. 1980;200:184–189.
33. Dunzendorfer S, Kaser A, Meierhofer C, et al. Cutting edge: peripheral neuropeptides attract immature and arrest mature blood-derived dendritic cells. *J Immunol*. 2001:2167–2172.
34. Dworkin SF, Huggins KH, LeResche L, et al. Epidemiology of signs and symptoms in temporomandibular disorders: clinical signs in cases and controls. *J Am Dent Assoc*. 1990:273–281.
35. Elcock C, Boissonade FM, Robinson PP. Neuropeptide expression in the ferret trigeminal ganglion following ligation of the inferior alveolar nerve. *Arch Oral Biol*. 2001:729–743.
36. Fanciullacci M, Pietrini U, Boccuni M. Disruption of iris adrenergic transmission as an index of poor endorphin modulation in headache. *Adv Neurol*. 1982;33:365–374.
37. Faure-Virelizier C, Croix D, Bouret S, et al. Effects of estrous cyclicity on the expression of the galanin receptor Gal-R1 in the rat preoptic area: a comparison with the male. *Endocrinology*. 1998:4127–4139.
38. Fettes I. Migraine in the menopause. *Neurology*. 1999:S29–S33.

39. Fillingim RB, Ness TJ. Sex-related hormonal influences on pain and analgesic responses. *Neurosci Biobehav Rev*. 2000;24:485–501.
40. Fristad I, Heyeraas KJ, Kvinnsland IH. Neuropeptide Y expression in the trigeminal ganglion and mandibular division of the trigeminal nerve after inferior alveolar nerve axotomy in young rats. *Exp Neurol*. 1996:276–286.
41. Gangula PR, Lanlua P, Wimalawansa S, et al. Regulation of calcitonin gene-related peptide expression in dorsal root ganglia of rats by female sex steroid hormones. *Biol Reprod*. 2000:1033–1039.
42. Giangrande PH, McDonnell DP. The A and B isoforms of the human progesterone receptor: two functionally different transcription factors encoded by a single gene. *Recent Prog Horm Res*. 1999:291–313; discussion 314.
43. Goadsby PJ, Edvinsson L, Ekman R. Release of vasoactive peptides in the extracerebral circulation of humans and the cat during activation of the trigeminovascular system. *Ann Neurol*. 1988:193–196.
44. Gotoh F, Komatsumoto S, Araki N, et al. Noradrenergic nervous activity in migraine. *Arch Neurol*. 1984;41:951–955.
45. Hall CW, Behbehani MM. The medial preoptic nucleus of the hypothalamus modulates activity of nitric oxide sensitive neurons in the midbrain periaqueductal gray. *Brain Res*. 1997;765:208–217.
46. Hayashi H, Tabata T. Physiological properties of sensory trigeminal neurons projecting to mesencephalic parabrachial area in the cat. *J Neurophysiol*. 1989;61:1153–1160.
47. Heppelmann B, Just S, Pawlak M. Galanin influences the mechanosensitivity of sensory endings in the rat knee joint. *Eur J Neurosci*. 2000:1567–1572.
48. Herbison AE. Estrogen regulation of GABA transmission in rat preoptic area. *Brain Res Bull*. 1997;44:321–326.
49. Hokfelt T, Wiesenfeld-Hallin Z, Villar M, et al. Increase of galanin-like immunoreactivity in rat dorsal root ganglion cells after peripheral axotomy. *Neurosci Lett*. 1987:217–220.
50. Holmes FE, Bacon A, Pope RJ, et al. Transgenic overexpression of galanin in the dorsal root ganglia modulates pain-related behavior. *Proc Natl Acad Sci U S A*. 2003:6180–6185.
51. Honore P, Rogers SD, Schwei MJ, et al. Murine models of inflammatory, neuropathic and cancer pain each generates a unique set of neurochemical changes in the spinal cord and sensory neurons. *Neuroscience*. 2000:585–598.
52. Hua XY, Hayes CS, Hofer A, et al. Galanin acts at GalR1 receptors in spinal antinociception: synergy with morphine and AP-5. *J Pharmacol Exp Ther*. 2004:574–582.
53. Hutchins B, Spears R, Hinton RJ, et al. Calcitonin gene-related peptide and substance P immunoreactivity in rat trigeminal ganglia and brainstem following adjuvant-induced inflammation of the temporomandibular joint. *Arch Oral Biol*. 2000:335–345.
54. Isselee H, De Laat A, De Mot B, et al. Pressure-pain threshold variation in temporomandibular disorder myalgia over the course of the menstrual cycle. *J Orofac Pain*. 2002:105–117.
55. Ji RR, Befort K, Brenner GJ, et al. ERK MAP kinase activation in superficial spinal cord neurons induces prodynorphin and NK-1 upregulation and contributes to persistent inflammatory pain hypersensitivity. *J Neurosci*. 2002:478–485.
56. Jiang M, Behbehani MM. Physiological characteristics of the projection pathway from the medial preoptic to the nucleus raphe magnus of the rat and its modulation by the periaqueductal gray. *Pain*. 2001;94:139–147.
57. John J, Kumar VM, Gopinath G, et al. Changes in sleep-wakefulness after kainic acid lesion of the preoptic area in rats. *Jpn J Physiol*. 1994;44:231–242.
58. Jones SL. Descending noradrenergic influences on pain. *Prog Brain Res*. 1991;88:381–394.
59. Kaplan LM, Gabriel SM, Koenig JI, et al. Galanin is an estrogen-inducible, secretory product of the rat anterior pituitary. *Proc Natl Acad Sci U S A*. 1988:7408–7412.
60. Kepler KL, Standifer KM, Paul D, et al. Gender effects and central opioid analgesia. *Pain*. 1991;45:87–94.
61. Kerekes N, Mennicken F, O'Donnell D, et al. Galanin increases membrane excitability and enhances Ca(2+) currents in adult, acutely dissociated dorsal root ganglion neurons. *Eur J Neurosci*. 2003: 2957–2966.
62. Kerr BJ, Thompson SW, Wynick D, et al. Endogenous galanin is required for the full expression of central sensitization following peripheral nerve injury. *Neuroreport*. 2001:3331–3334.
63. Kerr BJ, Wynick D, Thompson SW, et al. The biological role of galanin in normal and neuropathic states. *Prog Brain Res*. 2000: 219–230.
64. Koltzenburg M, Bennett DL, Shelton DL, et al. Neutralization of endogenous NGF prevents the sensitization of nociceptors supplying inflamed skin. *Eur J Neurosci*. 1999:1698–1704.
65. Krzanowska EK, Bodnar RJ. Analysis of sex and gonadectomy differences in beta-endorphin antinociception elicited from the ventrolateral periaqueductal gray in rats. *Eur J Pharmacol*. 2000;392:157–161.
66. Krzanowska EK, Ogawa S, Pfaff DW, et al. Reversal of sex differences in morphine analgesia elicited from the ventrolateral periaqueductal gray in rats by neonatal hormone manipulations. *Brain Res*. 2002;929:1–9.
67. Kuroki Y, Fukushima K, Kanda Y, et al. Neuroprotection by estrogen via extracellular signal-regulated kinase against quinolinic acid-induced cell death in the rat hippocampus. *Eur J Neurosci*. 2001:472–476.
68. Lambert KC, Curran EM, Judy BM, et al. Estrogen receptor-α deficiency promotes increased TNF-α secretion and bacterial killing by murine macrophages in response to microbial stimuli in vitro. *J Leukoc Biol*. 2004:1166–1172.
69. Lazarov NE. Comparative analysis of the chemical neuroanatomy of the mammalian trigeminal ganglion and mesencephalic trigeminal nucleus. *Prog Neurobiol*. 2002:19–59.
70. Levin ER. Cellular functions of plasma membrane estrogen receptors. *Steroids*. 2002:471–475.
71. Lewin GR, Barde YA. Physiology of the neurotrophins. *Annu Rev Neurosci*. 1996:289–317.
72. Lindsay RM, Harmar AJ. Nerve growth factor regulates expression of neuropeptide genes in adult sensory neurons. *Nature*. 1989: 362–364.
73. Lipton JA, Ship JA, Larach-Robinson D. Estimated prevalence and distribution of reported orofacial pain in the United States. *J Am Dent Assoc*. 1993:115–121.
74. Liu HX, Brumovsky P, Schmidt R, et al. Receptor subtype-specific pronociceptive and analgesic actions of galanin in the spinal cord: selective actions via GalR1 and GalR2 receptors. *Proc Natl Acad Sci USA*. 2001:9960–9964.
75. Liu HX, Hokfelt T. The participation of galanin in pain processing at the spinal level. *Trends Pharmacol Sci*. 2002:468–474.
76. Locker D, Slade G. Prevalence of symptoms associated with temporomandibular disorders in a Canadian population. *Community Dent Oral Epidemiol*. 1988:310–313.
77. Malick A, Strassman RM, Burstein R. Trigeminohypothalamic and reticulohypothalamic tract neurons in the upper cervical spinal cord and caudal medulla of the rat. *J Neurophysiol*. 2000;84:2078–2112.
78. Mantyh PW. The ascending input to the midbrain periaqueductal gray of the primate. *J Comp Neurol*. 1982;211:50–64.
79. Mantyh PW. Connections of midbrain periaqueductal gray in the monkey. II. Descending efferent projections. *J Neurophysiol*. 1983; 49:582–594.
80. Marchand JE, Hagino N. Afferents to the periaqueductal gray in the rat. A horseradish peroxidase study. *Neuroscience*. 1983;9: 95–106.
81. Markowitz S, Saito K, Moskowitz MA. Neurogenically mediated plasma extravasation in dura mater: effect of ergot alkaloids. A possible mechanism of action in vascular headache. *Cephalalgia*. 1988:83–91.
82. Martinez F, Castillo J, Pardo J, et al. Catecholamine levels in plasma and CSF in migraine. *J Neurol Neurosurg Psychiatry*. 1993;56:1119–1121.
83. Matsutani K, Tsuruoka M, Shinya A, et al. Stimulation of the locus coeruleus suppresses trigeminal sensorimotor function in the rat. *Brain Res Bull*. 2000;53:827–832.
84. McMahon SB, Bennett DL, Priestley JV, et al. The biological effects of endogenous nerve growth factor on adult sensory neurons revealed by a trkA-IgG fusion molecule. *Nat Med*. 1995:774–780.
85. McMenamin PG. Distribution and phenotype of dendritic cells and resident tissue macrophages in the dura mater, leptomeninges, and

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-17 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:48

choroid plexus of the rat brain as demonstrated in wholemount preparations. *J Comp Neurol*. 1999:553–562.
86. Meng ID, Hu JW, Bereiter DA. Parabrachial area and nucleus raphe magnus inhibition of corneal units in rostral and caudal portions of trigeminal subnucleus caudalis in the rat. *Pain*. 2000;87: 241–251.
87. Merchant RE, Low FN. Scanning electron microscopy of the subarachnoid space in the dog. V. Macrophages challenged by bacillus Calmette-Guerin. *J Comp Neurol*. 1977:381–407.
88. Merighi A, Carmignoto G, Gobbo S, et al. Neurotrophins in spinal cord nociceptive pathways. *Prog Brain Res*. 2004:291–321.
89. Micevych PE, Rissman EF, Gustafsson JA, et al. Estrogen receptor-alpha is required for estrogen-induced mu-opioid receptor internalization. *J Neurosci Res*. 2003;71:802–810.
90. Migliaccio A, Di Domenico M, Castoria G, et al. Tyrosine kinase/p21ras/MAP-kinase pathway activation by estradiol-receptor complex in MCF-7 cells. *Embo J*. 1996:1292–1300.
91. Millan MJ. The induction of pain: an integrative review. *Prog Neurobiol*. 1999;57:1–164.
92. Millan MJ. Descending control of pain. *Prog Neurobiol*. 2002;66: 355–474.
93. Mizushima T, Yamanaka H, Hashimoto N, et al. Noguchi. Program No. 2003 Abstract Viewer/Itinerary Planner. Washington, D.C.: Expression of progesterone receptor in dorsal root ganglion of ovariectomized rat and the effect of progesterone. Society for Neuroscience Online; 2003.
94. Mokha SS, Goldsmith GE, Hellon RF, et al. Hypothalamic control of nocireceptive and other neurons in the marginal layer of the dorsal horn of the medulla (trigeminal nucleus caudalis) in the rat. *Exp Brain Res*. 1987;65:427–436.
95. Moskowitz MA. Neurogenic versus vascular mechanisms of sumatriptan and ergot alkaloids in migraine. *Trends Pharmacol Sci*. 1992: 307–311.
96. Mulderry PK. Neuropeptide expression by newborn and adult rat sensory neurons in culture: effects of nerve growth factor and other neurotrophic factors. *Neuroscience*. 1994:673–688.
97. Murphy AZ, Hoffman GE. Distribution of gonadal steroid receptor-containing neurons in the preoptic-periaqueductal gray-brainstem pathway: a potential circuit for the initiation of male sexual behavior. *J Comp Neurol*. 2001;438:191–212.
98. Murphy AZ, Shupnik MA, Hoffman GE. Androgen and estrogen (alpha) receptor distribution in the periaqueductal gray of the male Rat. *Horm Behav*. 1999;36:98–108.
99. Nakano K, Kohno M, Hasegawa Y, et al. Cortical and brain stem afferents to the ventral thalamic nuclei of the cat demonstrated by retrograde axonal transport of horseradish peroxidase. *J Comp Neurol*. 1985;231:102–120.
100. Ogawa S, Kow LM, Pfaff DW. In vitro electrophysiological characterization of midbrain periaqueductal gray neurons in female rats: responses to GABA- and Met-enkephalin-related agents. *Brain Res*. 1994;666:239–249.
101. Ottosson A, Edvinsson L. Release of histamine from dural mast cells by substance P and calcitonin gene-related peptide. *Cephalalgia*. 1997:166–174.
102. Pajot J, Ressot C, Ngom I, et al. Gonadectomy induces site-specific differences in nociception in rats. *Pain*. 2003:367–373.
103. Peroutka SJ. Migraine: a chronic sympathetic nervous system disorder. *Headache*. 2004;44:53–64.
104. Puri V, Cui L, Liverman CS, et al. Ovarian steroids regulate neuropeptides in the trigeminal ganglion. *Neuropeptides* (in press).
105. Qiu J, Bosch MA, Tobias SC, et al. Rapid signaling of estrogen in hypothalamic neurons involves a novel G-protein-coupled estrogen receptor that activates protein kinase C. *J Neurosci*. 2003;23:9529–9540.
106. Rees HD, Switz GM, Michael RP. The estrogen-sensitive neural system in the brain of female cats. *J Comp Neurol*. 1980;193:789–804.
107. Ring G, Ganchrow D. Projections of nucleus caudalis and spinal cord to brainstem and diencephalon in the hedgehog (*Erinaceus europaeus* and *Paraechinus aethiopicus*): a degeneration study. *J Comp Neurol*. 1983;216:132–151.
108. Royce GJ, Bromley S, Gracco C. Subcortical projections to the centromedian and parafascicular thalamic nuclei in the cat. *J Comp Neurol*. 1991;306:129–155.
109. Rozniecki JJ, Dimitriadou V, Lambracht-Hall M, et al. Morphological and functional demonstration of rat dura mater mast cell-neuron interactions in vitro and in vivo. *Brain Res*. 1999:1–15.
110. Safieh-Garabedian B, Poole S, Allchorne A, et al. Contribution of interleukin-1 beta to the inflammation-induced increase in nerve growth factor levels and inflammatory hyperalgesia. *Br J Pharmacol*. 1995:1265–1275.
111. Saleh MC, Connell BJ, Saleh TM. Autonomic and cardiovascular reflex responses to central estrogen injection in ovariectomized female rats. *Brain Res*. 2000;879:105–14.
112. Saleh TM, Connell BJ. Estrogen-induced autonomic effects are mediated by NMDA and GABAA receptors in the parabrachial nucleus. *Brain Res*. 2003:161–170.
113. Saleh TM, Connell BJ, McQuaid T, et al. Estrogen-induced neurochemical and electrophysiological changes in the parabrachial nucleus of the male rat. *Brain Res*. 2003;990:58–65.
114. Saleh TM, Saleh MC, Deacon CL, et al. 17beta-Estradiol release in the parabrachial nucleus of the rat evoked by visceral afferent activation. *Mol Cell Endocrinol*. 2002;186:101–110.
115. Sandrini G, Proietti Cecchini A, Milanov I, et al. Electrophysiological evidence for trigeminal neuron sensitization in patients with migraine. *Neurosci Lett*. 2002:135–138.
116. Scammell TE, Price KJ, Sagar SM. Hyperthermia induces c-fos expression in the preoptic area. *Brain Res*. 1993;618:303–307.
117. Scott CJ, Rawson JA, Pereira AM, et al. Oestrogen receptors in the brainstem of the female sheep: relationship to noradrenergic cells and cells projecting to the medial preoptic area. *J Neuroendocrinol*. 1999;11:745–755.
118. Sessle BJ. Acute and chronic craniofacial pain: brainstem mechanisms of nociceptive transmission and neuroplasticity, and their clinical correlates. *Crit Rev Oral Biol Med*. 2000;11:57–91.
119. Sessle BJ, Hu JW, Dubner R, et al. Functional properties of neurons in cat trigeminal subnucleus caudalis (medullary dorsal horn). II. Modulation of responses to noxious and nonnoxious stimuli by periaqueductal gray, nucleus raphe magnus, cerebral cortex, and afferent influences, and effect of naloxone. *J Neurophysiol*. 1981;45: 193–207.
120. Seta KA, Jansen HT, Kreitel KD, et al. Cold water swim stress increases the expression of neurotensin mRNA in the lateral hypothalamus and medial preoptic regions of the rat brain. *Brain Res Mol Brain Res*. 2001;86:145–152.
121. Shors TJ, Lewczyk C, Pacynski M, et al. Stages of estrous mediate the stress-induced impairment of associative learning in the female rat. *Neuroreport*. 1998;9:419–423.
122. Shughrue PJ, Lane MV, Merchenthaler I. Comparative distribution of estrogen receptor-alpha and -beta mRNA in the rat central nervous system. *J Comp Neurol*. 1997;388:507–525.
123. Shughrue PJ, Merchenthaler I. Distribution of estrogen receptor beta immunoreactivity in the rat central nervous system. *J Comp Neurol*. 2001:64–81.
124. Simerly RB, Chang C, Muramatsu M, et al. Distribution of androgen and estrogen receptor mRNA-containing cells in the rat brain: an in situ hybridization study. *J Comp Neurol*. 1990;294:76–95.
125. Sohrabji F, Miranda RC, Toran-Allerand CD. Estrogen differentially regulates estrogen and nerve growth factor receptor mRNAs in adult sensory neurons. *J Neurosci*. 1994:459–471.
126. Somerville B. Estrogen-withdrawal migraine. I. Duration of exposure required and attempted prophylaxis by premenstrual estrogen administration. *Neurology*. 1975:239–244.
127. Somerville B. Estrogen-withdrawal migraine. II. Attempted prophylaxis by continuous estradiol administration. *Neurology*. 1975: 245–250.
128. Stewart WF, Shechter A, Rasmussen BK. Migraine prevalence. A review of population-based studies. Neurology. 1994:S17–S23.
129. Stirone C, Duckles SP, Krause DN. Multiple forms of estrogen receptor-alpha in cerebral blood vessels: regulation by estrogen. *Am J Physiol Endocrinol Metab*. 2003:E184–E192.
130. Suzuki H, Iwanaga T, Yoshie H, et al. Expression of galanin receptor-1 (GALR1) in the rat trigeminal ganglia and molar teeth. *Neurosci Res*. 2002:197–207.
131. Tajti J, Uddman R, Moller S, et al. Messenger molecules and receptor mRNA in the human trigeminal ganglion. *J Auton Nerv Syst*. 1999: 176–183.

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-17 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:48

132. Takeshima T, Takao Y, Urakami K, et al. Muscle contraction headache and migraine. Platelet activation and plasma norepinephrine during the cold pressor test. *Cephalalgia*. 1989;9:7–13.
133. Tang Y, Feng Y, Wang X. Calcitonin gene-related peptide potentiates LPS-induced IL-6 release from mouse peritoneal macrophages. *J Neuroimmunol*. 1998:207–212.
134. Timmusk T, Mudo G, Metsis M, et al. Expression of mRNAs for neurotrophins and their receptors in the rat choroid plexus and dura mater. *Neuroreport*. 1995:1997–2000.
135. Toran-Allerand CD. Mechanisms of estrogen action during neural development: mediation by interactions with the neurotrophins and their receptors? *J Steroid Biochem Mol Biol*. 1996:169–178.
136. Traub RJ, Silva E, Gebhart GF, et al. Noxious colorectal distention induced-c-Fos protein in limbic brain structures in the rat. *Neurosci Lett*. 1996;215:165–168.
137. Tsuruoka M, Matsutani K, Maeda M, et al. Coeruleotrigeminal inhibition of nociceptive processing in the rat trigeminal subnucleus caudalis. *Brain Res*. 2003;993:146–153.
138. Uddman R, Hara H, Edvinsson L. Neuronal pathways to the rat middle meningeal artery revealed by retrograde tracing and immunocytochemistry. *J Auton Nerv Syst*. 1989:69–75.
139. Valenzuela RF, Donoso MV, Mellado PA, et al. Migraine, but not subarachnoid hemorrhage, is associated with differentially increased NPY-like immunoreactivity in the CSF. *J Neurol Sci*. 2000:140–146.
140. VanderHorst VG, Schasfoort FC, Meijer E, et al. Estrogen receptor-alpha-immunoreactive neurons in the periaqueductal gray of the adult ovariectomized female cat. *Neurosci Lett*. 1998;240:13–16.
141. VanderHorst VG, Terasawa E, Ralston HJ, 3rd. Projections from estrogen receptor-alpha immunoreactive neurons in the periaqueductal gray to the lateral medulla oblongata in the rhesus monkey. *Neuroscience*. 2004;125:243–253.
142. Weiller C, May A, Limmroth V, et al. Brain stem activation in spontaneous human migraine attacks. *Nat Med*. 1995;1:658–660.
143. Weitzel KW, Strickland JM, Smith KM, et al. Gender-specific issues in the treatment of migraine. *J Gend Specif Med*. 2001:64–74.
144. Welter BH, Hansen EL, Saner KJ, et al. Membrane-bound progesterone receptor expression in human aortic endothelial cells. *J Histochem Cytochem*. 2003:1049–1055.
145. Westerhaus MJ, Loewy AD. Sympathetic-related neurons in the preoptic region of the rat identified by viral transneuronal labeling. *J Comp Neurol*. 1999;414:361–378.
146. Westlund KN, Bowker RM, Ziegler MG, et al. Noradrenergic projections to the spinal cord of the rat. *Brain Res*. 1983;263: 15–31.
147. Westlund KN, Coulter JD. Descending projections of the locus coeruleus and subcoeruleus/medial parabrachial nuclei in monkey: axonal transport studies and dopamine-beta-hydroxylase immunocytochemistry. *Brain Res*. 1980;2:235–264.
148. Wiberg M, Westman J, Blomqvist A. The projection to the mesencephalon from the sensory trigeminal nuclei. An anatomical study in the cat. *Brain Res*. 1986;399:51–68.
149. Willis WD, Westlund KN. Neuroanatomy of the pain system and of the pathways that modulate pain. *J Clin Neurophysiol*. 1997;14: 2–31.
150. Woolf CJ. Phenotypic modification of primary sensory neurons: the role of nerve growth factor in the production of persistent pain. *Philos Trans R Soc Lond B Biol Sci*. 1996:441–448.
151. Woolf CJ, Allchorne A, Safieh-Garabedian B, et al. Cytokines, nerve growth factor and inflammatory hyperalgesia: the contribution of tumour necrosis factor alpha. *Br J Pharmacol*. 1997:417–424.
152. Woolf CJ, Safieh-Garabedian B, Ma QP, et al. Nerve growth factor contributes to the generation of inflammatory sensory hypersensitivity. *Neuroscience*. 1994:327–331.
153. Xing D, Miller A, Novak L, et al. Estradiol and progestins differentially modulate leukocyte infiltration after vascular injury. *Circulation*. 2004:234–241.
154. Yoshida A, Chen K, Moritani M, et al. Organization of the descending projections from the parabrachial nucleus to the trigeminal sensory nuclear complex and spinal dorsal horn in the rat. *J Comp Neurol*. 1997;383:94–111.
155. Yu XJ, Moskowitz MA. Neuropeptide Y Y2 receptor-mediated attenuation of neurogenic plasma extravasation acting through pertussis toxin-sensitive mechanisms. *Br J Pharmacol*. 1996:229–232.
156. Yunus MB. Gender differences in fibromyalgia and other related syndromes. *J Gend Specif Med*. 2002:42–47.