CHAPTER 31

Pain and addiction

31.1. Opioid peptides and other addictive compounds

The opiate systems are a major factor in pain perception and addiction. Moreover, these systems are involved in a wide variety of neural functions, including eating, drinking, reproduction, stress, emotions, learning and homeostasis. The opiate systems are also supposed to be involved in a number of placebo effects (Stefano et al., 2001; Chapter 31.2b). Four different classes of opioid peptides are distinguished: (i) β-endorphins, (ii) dynorphins, (iii) enkephalins, and (iv) the orphanin peptide system. They are synthesized by different genes, with different precursor molecules:

(i) Pro-opiomelanocortin (POMC) is a 267-amino acid peptide. It yields a group of opioid peptides, the β-endorphins, corticotropin (ACTH)- and MSH-like peptides (Fig. 23.21). The maturation and cleavage into its various products are area-specific and post-translational processing plays a crucial role in determining the biological activity of the POMC derivatives. Patients with POMC mutations leading to a lack of ACTH, α-melanotropin (αMSH) and β-endorphin show severe early-onset obesity (Chapter 23.d), but no unusual pain sensation, which points to only a minor role of β-endorphin in the modulation of pain (Krude and Grüters, 2000). Of the three opioid systems, pre-POMC neurons have the most restricted distribution and are the most numerous in the infundibular nucleus and retrochiasmatic area of the mediobasal hypothalamus (Sukhov et al., 1995; Fig. 31.1A-C). In the adult infundibular nucleus, the same neurons stain for β-endorphin ACTH, αMSH, βMSH, α-endorphin and β-lipotropic hormone (LPH) (Bloch et al., 1978).

(ii) The most recently discovered class of endogenous opioid peptides consists of derivates of the 256-amino acid precursor proenkephalin B (PENKB) or prodynorphin (PDYN) and coded for the pre-PDYN gene. Cleavage of PDYN yields three main opioid peptides, i.e., neoeendorphin, dynorphin A, and dynorphin B, all of which contain the sequence leu-enkephalin (Sukhov et al., 1995). Leu-enkephalin regulates the gonadal axis and, in the medial preoptic area infundibular/median eminence region, leu-enkephalin neurons and many leu-enkephalin fibers seem to terminate on luteinizing hormone-releasing hormone (LHRH) neurons (Dudás and Merchenthaler, 2003). Neoeendorphin can exhibit two different forms, α-neoendorphin and β-neoendorphin, which differ by only one amino acid (Sukhov et al., 1995; Hurd, 1996). The best-known cleavage products of dynorphin A are two smaller fragments, DYNA1–8, and DYNA1–17. Processing of dynorphin B (DYNB) can produce the 29-amino acid peptide leumorphin or dymorphin B1–13 (Sukhov et al., 1995). Transcutaneous electrical nerve stimulation (TENS) induces a release of dynorphin and is very effective in ameliorating the withdrawal syndrome in heroin addicts (Wu et al., 1999). Pre-PDYN gene expression is found in neurons of the dorsomedial nucleus, ventromedial nucleus (VMM), tubermamillary nucleus, caudal lateral hypothalamus, retrochiasmatic area and in the bed nucleus of the stria terminals (Fig. 31.2A–F; Sukhov et al., 1995). Abe et al. (1988) have found dynorphin staining neurons mainly in the supraoptic nucleus (SON), paraventricular nucleus (PVN), supramamillary nucleus and

lateral hypothalamus, while a few positive cells have been found in the arcuate nucleus.

(iii) **Enkephalins** are also produced by the 267-amino acid precursor PENK. All cleavage products, including 4 metenkephalins, 2-carboxyl-extended metenkephalins and one leu-enkephalin, exhibit opioid activity. The opioid peptides are concentrated heavily in the hypothalamus (Sukhov et al., 1995). Pre-PDYN neurons are especially abundant in neurons of the tuberal and mamillary regions, with a distinct population of labeled cells in the premamillary nucleus and dorsal posterior hypothalamus (Sukhov et al., 1995). Pre-PENK neurons occur in varying numbers in all hypothalamic nuclei except the mamillary bodies. The chiasmatic area is particularly rich in pre-PENK neurons, with the highest packing density in the sexually dimorphic nucleus of the preoptic area (SDN-POA). Simler et al. (1988) found more enkephalin neurons in the POA of the male rat. Sexual dimorphism in the number of enkephalin neurons in the human SDN-POA has yet to be elucidated. In addition, pre-PENK neurons are found in the dorsal suprachiasmatic nucleus, medial preoptic area and rostral lateral hypothalamic area. Pre-PENK neurons are numerous in the infundibular nucleus, VMN, dorsomedial nucleus, caudal parvicellular neurons of the PVN, tuberomammillary nucleus, lateral hypothalamus and retrochiasmatic area, nucleus basalis of Meynert (NBM), and in the bed nucleus of the stria terminalis (Fig. 31.3A–F) (Sukhov et al., 1995).

(iv) The **orphanin** peptides are structurally related to the endogenous opioid family. The opioid receptor-like receptor (ORL1) binds an endogenous ligand, a heptadecapeptide, referred to as nociceptin or orphanin. Orphanin has an amino acid sequence strikingly similar to the endogenous opioid dynorphin, and may play a role in stress and pain systems. Human ORL1 and orphanin expression are observed in the hypothalamus from 16 weeks of gestation.

Fig. 31.1. A–C: Computer-assisted maps of the distribution of pro-opiomelanocortin (POMC) cells in coronal sections of human hypothalamus arranged rostrocaudally from A to C. Each dot represents a single neuron. Numbers at the lower left correspond to sequential locations of sections from anterior to posterior. Each section is 20 μm thick; hence, the distance between A and C is approx. 4.6 mm. Scale bar 5 mm. (From Sukhov et al., 1995, Fig. 1, with permission.)
Fig. 31.2. A–F: Computer-assisted maps of the distribution of prodynorphin (PDYN) cells in coronal sections of human hypothalamus arranged rostrocaudally from A to F. The most anterior section is A, and the most posterior section is F. Numbers at the lower left correspond to sequential locations of sections from anterior to posterior. Each section is 20 μm thick. Each dot represents a single neuron. Scale bar 5 mm. (From Sukhov et al., 1995, Fig. 4, with permission.)
Fig. 31.3. A–F: Computer-assisted maps of the distribution of proenkephalin (PENK) cells in coronal sections of the human hypothalamus. The most anterior section is A, and the most posterior section is F. Each dot represents a single neuron. Numbers at the lower left correspond to sequential locations of sections from anterior to posterior. Each section is 20 μm thick. Scale bar 5 mm. (From Sukhov et al., 1995, Fig. 7, with permission.)
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CSF = cerebrospinal fluid

onwards. Prepro-orphanin mRNA is present in this fetal stage in the PVN and dorsal hypothalamic area. By 21–22 weeks it is present in the zona incerta, mamillary bodies and subthalamic nucleus. At this stage, expression of ORL1 messenger RNA (mRNA) is found in the dorsomedial and ventromedial hypothalamus, and in the PVN (Neal et al., 2001). The human opioid receptor in present in the postmortem hypothalamus and a number of other brain areas (Becker et al., 2003).

The POMC neurons (Fig. 31.1), located in the mediobasal hypothalamus, have an inhibitory influence on the regulation of gonadotropin secretion (Sukhov et al., 1995). There is a cyclic β-endorphin release into the portal capillaries, and naloxan stimulates LHRH release. It has therefore been postulated that β-endorphin is an important determinant of the menstrual cycle (Ferlin et al., 1984; Gindoff and Ferin, 1987). The observation that in postmenopausal women POMC mRNA decreases in the infundibular nucleus (Abel and Rance, 1999) supports such a tonic inhibitory function of β-endorphin on LHRH release. The effect of opiates on LHRH release from the adult human hypothalamus has been confirmed experimentally, using in vitro perfusion of postmortem mediobasal hypothalamic tissue. Addition of morphine to the medium reduced the frequency of LHRH pulses, whereas subsequent addition of the opioid receptor antagonist naloxone restored the frequency. Furthermore, fetal hypothalamic tissue responded to administration of naloxone with increased release of LHRH and this effect was inhibited by simultaneous administration of β-endorphin (Rasmussen, 1992). Leu-enkephalin neurons are also involved in LHRH regulation, most probably by directly synaptically contacting the latter neurons (Dudás and Merchenthaler, 2003). In addition, POMC-derived peptides containing nerve fibers are found in the neural lobe of the human pituitary. These peptides comprise ACTH, α-MSH, β-endorphin and N-acetyl-β-endorphin, and may be involved in the regulation of oxytocin and vasopressin release (Manning et al., 1993; see Chapter 8d). A large number of neurons in the SON and PVN coexpress dynorphin; these neurosecretory neurons are probably the source of the dynorphin-containing nerve fibers in the neurohypophysis (Abe et al., 1988). The strikingly densely packed PDYN neurons of the premamillary nucleus may be involved in hunger, thirst, dysphoria and reproduction. PENK neurons are distributed throughout the hypothalamus and may participate in numerous homeostatic functions and euphoria (Sukhov et al., 1995). Endogenous opioid peptides inhibit the hypothalamic-pituitary–adrenal (HPA) axis. This system is hyperactive in depression (see Chapter 26.4). Using an intravenous bolus injection of naloxone, a reduced endogenous opioid tone is found that may explain why some depressed patients ‘self-medicate’ with opiates (Burnett et al., 1999).

The hypothalamic opiate systems are presumed to play a central role in addictive behavior (Sukhov et al., 1995; Hurd, 1996). Studies on twins, adopted children and cross-fostering also indicate that, apart from environmental factors, there are also hereditary determinants for alcohol dependency. The observation that individuals from families with a high occurrence of alcohol dependency are more sensitive to naloxone seems to imply that families with a history of alcohol dependency have diminished endogenous hypothalamic opioid activity. In addition, there are differences in the HPA axis dynamics as a function of family history of alcoholism (Wand et al., 1998). At first glance, the older observations of the influence of stereotactic hypothalatomy on alcohol and drug addiction (Dieckmann and Schneider, 1978) seem to be of interest, in connection with the possible involvement of hypothalamic systems in addiction. In a 2- to 3-year follow-up of 13 patients addicted to alcohol and drugs, the VMN was lesioned. The patients regained their self-control and tended toward social stabilization. However, this was an uncontrolled study. In the case of bilateral hypothalatomy (in 6 of 15 patients), the number of side effects was considerable, including one patient who died in a ‘vegetative crisis’. All patients experienced a reduction of their sexual drive. The practical utility of bilateral hypothalatomy is euphemistically judged to be “limited” (Dieckmann and Schneider, 1977). In a totally insufficiently documented study, Nádvorník et al. (1977) have reported that bilateral anterior hypothalactomy is quite effective in the treatment of “hedonic manifestations” such as “toxicomania” and alcoholism. Little attention was paid to the considerable risk of this operation (Sramka and Nádvorník, 1975), and even less to its questionable ethical basis.

Analgesia by electrostimulation, using deep brain electrodes, is presumed to act via the opioid system, since it is associated with elevation of enkephalin and β-endorphin in the CSF of the third ventricle and because the analgesic effect could be blocked by naloxone (see Chapter 31.2). Transcutaneous cranial electric stimulation has been used for the attenuation of drug and alcohol
abstinence syndrome, the suppression of stress, the attenuation of postoperative pain, the potentiation of morphine analgesia for patients with chronic pain, the regulation of biorhythms disturbed by jet lag, and obstetric analgesia. Since transcutaneous cranial electric stimulation increases the level of endorphins in the CSF and plasma, while naloxone antagonizes its effects, it also seems to act via the opioid system (Limoge et al., 1999).

Neuropeptide FF (NPFF) and neuropeptide AF (NPAF) are two amidated peptides, highly concentrated in the posterior pituitary and hypothalamus, but also present in other brain areas. They are derived from one precursor. These peptides may be involved in pain modulation, memory, autonomic and neuroendocrine regulation, i.e. in water balance and prolactin release. In addition, NPFF probably circulates as a hormone. The NPFF receptors are coupled to a G protein. Intracerebroventricular injection of NPFF induces a vigorous abstinence syndrome in morphine-tolerant rats (Boersma et al., 1993; Panula et al., 1996, 1999; Laemmle et al., 2003).

A new hypothalamic peptide that may be involved in drug abuse is cocaine- and amphetamine-regulated transcript (CART; Kuhar and Dall Vechia, 1999). For distribution and its possible role in feeding behavior, see Chapter 23c.

Marijuana (Cannabis sativa) has long been recognized as a centrally acting cannabinoid with complex cognitive, behavioral and endocrine effects. The cannabinoid receptor is found in the hippocampal complex, in the cortex of the frontal lobe, mediodorsal nucleus of the thalamus, globus pallidus and substantia nigra. In the hypothalamus the receptor has been observed in the mamillary body (Glass et al., 1997). The enzyme that degrades the ‘endocannabinoids’ is an integral membrane protein, fatty acid amidohydrolase. Its distribution resembles that of the central cannabinoid receptors. In the hypothalamus it is present in the mamillary bodies, dorsomedial nucleus and posterior hypothalamic area (Romero et al., 2002). Exposure of animals to Δ⁹-tetrahydrocannabinol (Δ⁹-THC), which has effects that are similar to those of the endogenous ligand anandamide, inhibits gonadotropin, prolactin, growth hormone and thyroid-stimulating hormone release, and stimulates the release of ACTH. Therefore, hypothalamic mechanisms of action are presumed (Murphy et al., 1998b). Marijuana and THC affect multiple endocrine systems. A suppressive effect is seen on the reproductive hormones, prolactin, growth hormone and the thyroid axis, while the HPA axis is activated. These effects are mediated through CB1 receptor activation in the hypothalamus. Many of these responses are, however, lost with chronic administration (Brown and Dobs, 2002).

Many epidemiological studies have shown that prenatal exposure to tobacco increases the risk of cognitive deficits, attention deficit disorder, conduct disorder and criminal behavior in adulthood (see Chapter 26.9). In addition, it has been shown that maternal smoking during pregnancy or childhood increases the risk of the children becoming smokers, possibly by a direct effect of nicotine on the developing brain of the child (Hellström-Lindahl and Nordberg, 2002). Polymorphism in the MAO genes influences smoking habits and nicotine dependency (Ito et al., 2002).

The effects of ethanol abuse on the hypothalamus are described in Chapter 29.5. A functional NPY polymorphism (leu7Pro) is a risk factor for alcohol dependency (Lappalainen et al., 2002).

MDMA (3,4-methylenedioxymethamphetamine, or ecstasy) causes a release of vasopressin for at least 4 h and may thus cause hyponatremia – characteristic of the syndrome of inappropriate vasopressin secretion (Henry et al., 1998; Fallon et al., 2002; Chapter 22.6). Hyperthermia, an acute and potentially life-threatening complication associated with the use of ecstasy, results from an interaction between the hypothalamic–pituitary–thyroid axis and the sympathetic nervous system (Sprague et al., 2003).

31.2. Pain and the hypothalamus

Although pain is considered to be a necessary ingredient for survival, life without any pain occurs in a few rare, hereditary disorders, i.e. Riley–Day syndrome or familial dysautonomia (Chapter 30) and in a congenital indifference to pain (Mancini, 1990). Insensitivity to pain has been reported in idiopathic hypothalamic syndrome of childhood (Chapter 32.1), and as a congenital absence of pain in a mentally retarded child. The total CSF opioid activity was raised in this patient, but naloxone failed to reverse the analgesia (Manfredi et al., 1981). Congenital insensitivity to pain with anhidrosis is an autosomal-recessive disorder characterized by recurrent episodes of unexplained fever, absence of sweating and of reaction to noxious stimuli, and by self-mutilating behavior and mental retardation. Most probably this syndrome is based upon defects in the high-affinity neurotrophin receptor tyrosine kinase A (TrkA) (Indo et al., 1996). Since
patients affected by POMC mutations reveal no unusual pain sensation, β-endorphin seems to play only a minor role in pain modulation (Krude and Grüters, 2000). Whether the elevated pain tolerance in patients with anorexia nervosa, bulimia nervosa and binge-eating (Raymond et al., 1999) has a hypothalamic basis should be investigated. A core feature of fibromyalgia is pain, a syndrome that has many neuroendocrine characteristics (Chapter 26.8; Dessein et al., 2000).

(a) The anatomy of pain; hypothalamic structures and systems involved

Pain in the brain: are hormones to blame?  

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage (Chapman, 1996). The distribution of the opiate systems involved in pain regulation is discussed in Chapter 31.1. The many brain structures and extensive pathways involved in pain are discussed elsewhere (Ray, 1981; May et al., 2000). Acute experimental, traumatic pain induction by intracutaneous injection of a minute amount of ethanol prominently activates the hypothalamus, periaqueductal gray, amygdala and a number of other brain areas as shown by PET studies. The circuits involving these structures are responsible for integrating the endocrine, autonomic, aggressive and defensive reactions to pain. The metabolic activation of the hypothalamus by traumatic pain implies that this structure may serve as a bridge between higher cognitive states and physiological/emotional responsivity (Hsieh et al., 1996). Also, in a patient with chronic facial pain, the hypothalamic blood flow was increased, as was the flow in other pain-related brain structures (Kupers et al., 2000). Electrical stimulation, not only of the raphe nucleus and periaqueductal gray, but also of the hypothalamus, produces analgesia in experimental animals (Carstens, 1986), and medial hypothalamic stimulation relieves pain also in humans (see below).

Nociceptive transmission engages both spinoreticular and spinothalamic pathways. A brainstem structure that is important in nociception is the parabrachial nucleus. This structure is seriously affected in Alzheimer's disease (AD) (Parvizi et al., 1998), a disorder in which the experience of affective components of pain in particular is reduced (Scherder et al., 2003). Systems involved in the processing of nociceptive signals are the dorsal noradrenergic bundle, originating in the locus coeruleus, the serotonergic fibers that arise in the dorsal and median raphe nuclei, the dopaminergic pathways of the ventral tegmentum, and the cholinergic neurons of the NBM. The dorsal noradrenergic bundle innervates the hypothalamus; and neurons in the medullary reticular formation project to the PVN of the hypothalamus via the ventral noradrenergic bundle. In the rat it has been shown that nociceptive stimuli do not reach the hypothalamus by indirect multisynaptic pathways only. Thousands of neurons throughout the length of the spinal cord send axons directly into the hypothalamus, and many of these axons carry nociceptive information. Axon collaterals of these fibers terminate in the lateral hypothalamus, VMN, periventricular and posterior nuclei. Evidence for similar connections is present in primates (Giesler et al., 1994).

The long-term antinociceptive effect of massage-like stroking may be attributed, at least partly, to the oxytocinergic system, as shown in the rat; increased oxytocin plasma levels and release of oxytocin in the periaqueductal gray matter takes place. Here, the oxytocinergic fibers interact with the opiate system, where the μ- and κ-receptors especially are involved (Lund et al., 2002).

The hypothalamic-mediated stress response plays a role in pain chronicity. The PVN coordinates the neuroendocrine, autonomic, emotional and behavioral responses to pain. The PVN activates the HPA axis and is responsible for the stress-induced analgesia (Chapman, 1996). Corticotropin-releasing hormone (CRH) may preferentially play a role in prolonged clinical pain (Lariviere and Melzack, 2000). Fibromyalgia is characterized by widespread muscle pain and a hyperactive CRH system (Chapter 26.8b). CRH levels in CSF are increased in chronic pain (Nemeroff, 1996), but the origin of CSF-CRH may be extrahypothalamic (Chapter 26.4). CRH is the central compound in the stress response and is also a mediator in the stress-induced analgesia. It has been shown to produce analgesia by all routes of administration, including local, systemic and central routes. The majority of the studies indicate that the pituitary or endogenous opioids are not necessary for the analgesia that occurs following intracranial or intravenous administration of CRH. In the human fetus, a potentially painful procedure such as prolonged intrauterine needling at 29–34 weeks of gestation is associated with an increase in plasma cortisol and β-endorphin. The hormonal stress response to invasive procedures suggests (but does not prove) that the human fetus may feel pain in utero and may
benefit from analgesia or anesthesia (Giannakoulopoulos et al., 1994).

Chronic pain disorder is characterized by the absence of any relevant organic pathology, and psychological factors have consequently been suggested to have an important role in the etiology of their disorder. There are various peptides that have antinociceptive effects in experimental animals, such as angiotensin II, vasopressin, CRH, calcitonin, neurotensin, somatostatin, and some of the opioid melanocortin family. Nociceptive peptides include substance P and cholecystokinin (Carr and Lipkowski, 1990; Wahlbeck et al., 1996). Substance P effects on blood pressure and heart rate seem to be mediated by oxytocin. This is part of an integrated response to nociceptive stimuli and stress (Maier et al., 1998). In fibromyalgia, CSF levels of substance P are elevated, while met-enkephalin levels are low (Pillemer et al., 1997; see Chapter 26.8b). It has been hypothesized that incomplete degradation of nociceptide peptides might produce the pain experienced in chronic pain disorder. However, so far only higher and not lower plasma vasopressin and serum osmolality, and an increased CRH level in CSF have been observed, possibly reflecting the chronic stress condition of these patients (Nemeroff, 1996; Wahlbeck et al., 1996). Others did not find alterations in plasma or CSF vasopressin levels (Olsson et al., 1987). Patients in a surgical emergency department complaining of pain have increased plasma vasopressin levels (Kendler et al., 1978). In addition, increased vasopressin levels are observed in women with premenstrual pain or primary dysmenorrhea (Åkerlund et al., 1979; Strömberg et al., 1984). A therapeutic effect of an orally active vasopressin V1a receptor antagonist in the prevention of dysmenorrhea has been published (Brouard et al., 2000; Paranjape and Thibonnier, 2001). However, another study has failed to show increased blood levels of vasopressin, finds no effect of a vasopressin antagonist on menstrual pain, and is thus unable to confirm the contention that vasopressin is involved in the etiology of dysmenorrhea (Valentin et al., 2000).

Sex steroids are thought to be involved in pain sensitivity. In general, women are more sensitive to pain than men. Pain sensitivity peaks when estrogens are high (Blackburn-Munro and Blackburn-Munro, 2003).

Melatonin has experimentally been shown to have profound analgesic effects. Hypocretins (Chapter 28.4) may also modulate nociception (Blackburn-Munro and Blackburn-Munro, 2003).

Nerve growth factor causes hyperalgesia and pain when administered either locally or systematically. In this connection it may be highly relevant that high levels of nerve growth factor are found in the CSF of patients with chronic daily headache and a previous history of migraine (Sarchielli et al., 2001). A pilot study on the treatment of Alzheimer patients with nerve growth factor, intracerebroventricularly, had to be stopped because of weight loss and pain as side effects (Chapter 2.5).

Alzheimer patients experience less-intense pain and also suffer less from pain than nondemented elderly people (Scherder and Bouma, 1997, 2001; Scherder et al., 1999; Scherder, 2000; Scherder and Bouma, 2000a, b). The primary sensory areas are relatively preserved in AD (Braak and Braak, 1991). Consequently, AD patients may still be able to perceive the nature of the pain and differentiate between dull and sharp pricking pain (the sensory-discriminative aspects of pain; Treede et al., 2000). The pain threshold does not appear to be affected by AD, a suggestion which is supported by a study in which the pain threshold of AD patients was determined by the application of peripheral electrical nociceptive stimuli (Benedetti et al., 1999). Importantly, in contrast to the pain threshold, Benedetti and co-workers (1999) observed an increase in pain tolerance in the AD patients. Pain tolerance concerns the processing of the affective-motivational aspects of pain (Treede et al., 2000). One can only speculate about the decrease in the processing of the affective aspects of pain in AD. One explanation might be the neuropathology that is present in the hypothalamus, the medial temporal lobe, the anterior cingulate gyrus and the prefrontal cortex (Chapter 29.1; Coleman and Flood, 1987; Braak and Braak, 1991). Interestingly, these areas are involved not only in cognition but also in the processing of the emotional components of pain (Scherder et al., 2003; Treede et al., 2000). An affected functioning of these areas might thus explain the increase in pain tolerance. Alternatively or additionally, a decrease in experience of the affective components of pain in AD patients may also be explained by an increase in the amount of opioid peptides in the CSF (Mühlbauer et al., 1986) and β-endorphin in plasma (Franceschi et al., 1988; Rolandi et al., 1992) of AD patients. The influence of AD on β-endorphin levels is, however, equivocal, since Kaiya et al. (1983) and Heilig et al. (1995) have observed a decreased CSF level of β-endorphin in AD patients.
(b) Placebo analgesia and other placebo effects

...we should learn to maximize the placebo effect inherent in any active drug that we give to the patient...

De La Fuente-Fernández et al., 2002.

The word ‘placebo’ (Latin) means ‘I shall please’ and is the first word of the church vespers sung for those who have died. In 12th century Europe the word ‘placebo’ was shorthand for those vespers. By 1300 the term had been adapted in the secular vernacular to mean ‘false consolidation’, since insincere mourners were paid to sing these placebos. In 1811 ‘placebo’ was defined as an epithet given to any medicine meant to please rather than benefit the patient. The term has kept this negative connotation in medicine as something ‘inactive’. Nevertheless, a placebo response rate of on average 35% is found in the treatment of conditions such as pain, hypertension, migraine, seasickness and mood disturbances. Even higher rates in effectiveness are found in angina pectoris, asthma, herpes simplex and duodenal ulcers. The placebo effect seems to represent an innate protective response, tapping into positive expectations and beliefs of the patient, and into the dopaminergic reward system. The placebo effect has been defined as ‘any effect attributable to a pill, potion, or procedure, but not to its pharmacodynamic or specific properties.’ Whereas the ingredients of a placebo preparation may be totally nonspecific, the effects depend on the information given to the patient and the expectations of the patient and can be very specific. The power of placebos can thus be conceptualized as the mind’s healing power (Stefano et al., 2001; De La Fuente-Fernández et al., 2002).

Placebo analgesia represents a situation where the administration of a substance known to be nonanalgesic produces an analgesic response. When the subject is told that the ineffective substance is a hyperalgesic drug, an increase in pain may occur. Such a negative effect is called a nacebo effect. The effect of a placebo on pain is mediated by endogenous opioids, since naloxone can reverse placebo analgesia. The blockade of cholecystokinin (CCK) receptors potentiate the placebo analgesic response, suggesting an inhibitory role of CCK in placebo analgesia. The sites of action of the endogenous opiates and of interaction of the opiates and CCK are not exactly clear, but naloxone antagonizes analgesia induced by stimulation of the periaqueductal gray as it also antagonizes analgesia induced by TENS or acupuncture and by a placebo (Benedetti and Amanzio, 1997). The possibility that hypothalamic opiate and CCK systems are involved in these analgesic effects still has to be studied.

It has been proposed that placebo effects can be elicited by inducing a ‘relaxation response’. This is the opposite of a ‘stress response’ (see Chapter 8.5), resulting in decreased metabolism, heart rate, blood pressure and rate of breathing. Many different methods can be used to elicit this acquired relaxation response, including progressive muscle relaxation, meditation, autogenic training, yoga and repeated physical exercise (Stefano et al., 2001). Yoga exercise was shown to be accompanied by lower serum cortisol levels (Kamei et al., 2000b); meditation is followed by increased plasma melatonin levels during the night (Tooley et al., 2000). In addition, many forms of prayer can be used to elicit the relaxation response; the method may be secular or religious, performed at rest or during exercise. The opiates and nitric oxide are hypothesized to be involved in this response. Relaxation response-based approaches have been demonstrated to be effective in chronic pain, hypertension, cardiac arrhythmias, insomnia, anxiety, depression, premenstrual syndrome and infertility (Stefano et al., 2001).

It has been estimated that about 75% of the effectiveness of antidepressants derives from the placebo effect (De la Fuente-Fernández et al., 2002). In a PET study in depressed patients, the clinical improvement was comparable in both the placebo and the fluoxetine responder groups. The regions of change in the placebo group strongly overlapped with those seen in responders who were administered fluoxetine, including the decrease in metabolic activity in the hypothalamus and the increase in activity in the prefrontal cortex. This is of considerable interest in relation to the hyperactivity of a number of hypothalamic systems in depression and the hypometabolism found in the prefrontal cortex in this disorder (see Chapter 26.4). However, the fluoxetine response is associated with additional changes, which are proposed to explain the longer period of effectiveness of this compound compared with placebo (Mayberg et al., 2002). In a study using quantitative EEG, ‘effective’ placebo treatment has induced changes in brain function that are distinct from those associated with antidepressant medication (Leuchter et al., 2002). There thus appear to be similarities as well as differences between placebo and antidepressant treatment, as far as the mechanism of action is concerned.

Placebo effects can thus be very specific, and the specificity seems to depend on the information available.
to the recipient. PET studies have indicated that the placebo effect in Parkinson’s disease is related to the release of dopamine in the striatum, and to downregulation of the dopamine transporter. Since the nucleus accumbens is susceptible to placebo-induced dopamine release in Parkinson’s disease, placebos may activate reward mechanisms. Indeed, placebos can also be addictive and can cause withdrawal symptoms when treatment is discontinued (De la Fuente-Fernández and Stoessl, 2002).

(c) Analgesia by deep brain electrostimulation, stereotactic lesions, acupuncture and TENS

Brief periods of stimulation aimed at the fibers of the pro-opiomelanocortin system produces long-lasting analgesia in patients with chronic pain, e.g. from metastases, low-back pain, paraplegia, spinal arachnoiditis, spinal cord injury, thalamic pain, scoliosis, postherpetic neuralgia, phantom limb pain, arthritis and atypical face pain (Richardson and Akil, 1977; Akil et al., 1979; Hosobuchi et al., 1979; Richardson, 1982; Pickel et al., 1988). In approximately 60% of patients who had deep brain electrodes implanted for chronic self-stimulation, this procedure caused significant relief from pain. Analgesic brain stimulation has an ‘opioid’ nature, because it is associated with elevation of enkephalin and β-endorphin in the third-ventricular fluid, while the analgesic stimulation can be blocked by naloxone. However, other neurotransmitter systems might also be involved in this effect. The effects and side effects depend on the stimulation site:

- Stimulation of the basal hypothalamus produces pain relief with side effects that occur at the level of effective stimulation, such as flushing, smothering, dizziness and diplopia. In addition, during stimulation, marked elevation of blood pressure and pulse rate are obtained. Endocrine side effects have not been studied. Stimulation of the inferior septal area produces pain relief with side effects obtained at hypalgesic stimulation levels, i.e. flushing, nystagmus and tingling paresthesias.
- Stimulation of the superior septal area produces pain relief, while side effects, i.e. flushing, tingling, nausea and warmth or heat sensation, occur only at levels well above those producing pain reduction.
- Periventricular gray stimulation in the third ventricle produces significant pain relief with vertigo, tingling, and elevation of pulse and blood pressure at levels of stimulation above those producing pain reduction.
- Superior periaqueductal gray stimulation induces pain relief, while side effects are experienced just above the level of analgesia. Side effects include oscillopsia, warmth, flushing, tingling and strabismus.
- Inferior periaqueductal gray stimulation causes pain relief, with more side effects below pain-reduction levels. The periaqueductal β-endorphin-containing fibers are thought to originate from the basal tuberal hypothalamus. Stimulation proves most efficacious with minimal side effects in the superior septal area and periventricular gray, at the level of the posterior third ventricle adjacent to the posterior commissure (Akil et al., 1979; Richardson, 1982; Pickel et al., 1988). Others have reported that electrical stimulation of the postero medial hypothalamus produces relief of pain, especially in the case of cancer. It also elevates β-endorphins in the third-ventricular CSF (Sano, 1987). A thus-far underreported complication of deep brain stimulation is the development of migraine-like headaches in approximately 20–50% of the patients (Kumar et al., 1997).

Stereotactic lesions of the posterior hypothalamus relieve intractable pain due to malignancies and are claimed to be either not so effective for central pain (Sano, 1987) or, on the contrary, to give a satisfactory relief of pain (Fairman, 1973). A marked increase in appetite is noted as a side effect of such operations (Fairman, 1973). Such an operation was presumed to lesion not only one of the main end-stations of the C-fibers and the slow delta-fibers, but also the portions that exert influences on the specific sensory system and thus decrease the intensity of volleys of impulses and change the pattern of impulses which can be interpreted as pain, especially pain in the case of cancer, and elevate β-endorphins in the third-ventricular cerebrospinal fluid (Sano, 1987). On the other hand, the same author had claimed earlier that stimulation of the postero medial hypothalamus produces an unpleasant feeling of fear and horror. The hypothalamus is, therefore, supposed to be important in the emotional coloring of pain sensation (Sano et al., 1975).

Electroacupuncture and TENS both release dynorphin and induce analgesia at 100 Hz, and even more efficiently by alternating the stimulation between 2 Hz and 100 Hz. Different kinds of opioid peptides and receptors are implicated in these effects under different circumstances (Wu et al., 1999; Han, 2003). A 2-Hz stimulation of a
classical analgesic acupuncture point (LI4, Hegu) on the back of the hand activated the hypothalamus as measured by PET, suggesting that this brain structure may mediate the analgesic efficacy of acupuncture (Hsieh et al., 2001). It is interesting to note that in animal experiments hypothalamic activity is enhanced by electroacupuncture (Du and Chao, 1976). The positive effects of TENS – a technique frequently used to treat chronic pain – and tactile stimulation are hypothesized to result from activation of brainstem areas such as the locus coeruleus and nucleus raphe dorsalis, with subsequent activation of the hypothalamus. In TENS, electrical pulses applied to the skin are transmitted to spinal and supraspinal areas through afferent nerve fibers of the peripheral nervous system (A-β and A-δ fibers) (Scherder et al., 1995a, b, 1996). Histamine, produced in the tuberomamillary nucleus (Chapter 13) plays an important role in antinociception, both by naloxone-sensitive and naloxone-insensitive mechanisms. Histamine is a mediator of the stress-induced release of hormones such as ACTH and β-endorphin, and the release of noradrenaline and serotonin (Brown et al., 2001).

31.3. Headache

Various observations suggest an interplay of chronobiological, neuroendocrine and autonomic nervous systems of the hypothalamus in these disorders. Headache can be a symptom of many processes in the hypothalamic-pituitary region, including crianiopharyngiomas and sometimes even Rathke’s cleft cysts (Chapter 19; Ward et al., 2001).

"Suicide headache" (Dodick et al., 2000)

(a) Cluster headache

Cluster headache is characterized by stereotypic, shortlasting (several minutes to several hours), severe, unilateral ‘trigeminal’ pain attacks with a highly distinctive cyclic recurrence pattern, usually located in the orbitotemporal region. An attack may be triggered by an alcoholic beverage, by increased body heat from the environment, a hot bath, central heating or from exercise (including sexual intercourse) (Peres et al., 2000). The pain is accompanied by homolateral autonomic signs, which include local symptoms such as conjunctivitival injection, lacrimation, rhinorrhea, erythema of the painful area, and occasional miosis and ptosis. In addition, systemic autonomic symptoms such as alteration in blood pressure and heart rate are found. MR images show a marked dilatation of the ophthalmic artery, ipsilateral to the pain (Dodick et al., 2000), while a localized narrowing of the internal carotid artery is found (Goaody, 2002). Cluster headache has been differentiated into an upper and a lower syndrome. It is proposed that changes in hypothalamic activity may lead, postero-inferiorly, to activation of the caudal part of the spinal trigeminal nucleus by way of the hypothalamus, midbrain and trigeminal nerve fibers, and consequently to activation of the trigeminovascular system, with a different location for the two syndromes. There would be a larger and more extensive involvement of the subnucleus caudalis in the lower syndrome, compared with the upper syndrome, where its ventrocaudal portions would be activated (Cademartiri et al., 2002). Cluster headache has been identified as a disorder that occurs mainly in men (male-to-female ratio of 6–7:1), but the clinical characteristics are very similar in both sexes (Rozen et al., 2001). The male-to-female ratio of both episodic and chronic cluster headache depends strongly on age. The sex difference is the largest between 30 and 49 years of age (7:2:1 and 11:0:1) and the lowest after 50 (2.3:1 and 0.6:1, respectively) (Ekberg et al., 2002). In addition, it should be noted that between 1960 and 1990 the male-to-female ratio decreased from 6:2:1 to 2:1:1. These changes in sex ratio are presumed to be related to changes in lifestyle and smoking (Manzoni, 1998; Ekberg et al., 2002). In 4% of patients there is a family history (Dodick et al., 2000). An autosomal dominant gene has a role in some families with cluster headache (Ekberg and Hardebo, 2002).

It has been postulated that the cyclic phenomena would originate from the hypothalamic clock, i.e. the suprachiasmatic nucleus (SCN), with subsequent trigeminovascular reaction (Dodick et al., 2000; Goaody, 2002), but there is only indirect evidence available for this presumption. The most common episodic variety of cluster headache is that 50% of the attacks occur during the night and with a circannual pattern that is similar to seasonal depression, because it increases in July and January and decreases in April and October, suggesting the involvement of the SCN in both disorders (see Chapters 4.1 and 26.4). There are, moreover, various other analogies between cluster headache, seasonal affective disorder, and bipolar mood disorders in addition to common seasonal patterns, i.e. the nature of predisposing or precipitating factors, the peculiar relationship with
sleep, such as the temporal connection between attacks and REM sleep, the neuroendocrine findings and clinical response to current treatments such as lithium and flunarizine (Morales-Asin et al., 1997; Costa et al., 1998). Some patients improve after melatonin or corticosteroid administration (Pepping, 1999; Peres et al., 2000; Peres and Rozen, 2001; Ekborn and Hardebo, 2002; Pringsheim et al., 2002). Support for the idea that the hypothalamus is the central site of origin of the pathogenesis of this disorder has emerged from four other independent observations. In the first place a significant structural difference in gray matter density has been observed by MRI. The difference consisted of an increase in gray matter volume, bilateral in the inferior posterior hypothalamus. In the second place, PET scanning has shown ipsilateral activation during cluster headache in the same hypothalamic area (May et al., 1998, 1999; Goadsby et al., 1999). The third relevant observation is that, in patients with intractable cluster headache, who underwent chronic high-frequency electric stimulation by means of an electrode implanted in the posterior inferior ipsilateral hypothalamic gray matter, the attacks were found to disappear after 48 h and to stay away during the follow-up of 2–33 months (Leone et al., 2001, 2003; Franzini et al., 2003). Lastly, during nitroglycerin-induced cluster headache attacks, the regional cerebral blood flow as measured by PET was activated in the ipsilateral inferior hypothalamic gray matter in the region of the SCN and in a number of brain areas that are involved in pain. Activation in the hypothalamus was seen solely while the patients were still in a state of pain, and not in patients who were recovering from the pain. The activation of the hypothalamus is, therefore, proposed to be the primum movens in the pathophysiology of cluster headache (May et al., 1998, 2000). In addition to the episodic occurrence, there are the neuroendocrine symptoms.

The possible involvement of the circadian timing system (see Chapter 4) in this disorder is supported by the observation that the acrophase of melatonin is moved forward and the night-time peak is blunted and significantly reduced during cluster headache periods (Chazot et al., 1984; Leone and Bussone, 1993; Dodick et al., 2000). Also the growth hormone evening peak is advanced in cluster headache (Chazot et al., 1984; Leone and Bussoni, 1993), while there is an acrophase delay in testosterone release (Facchinetti et al., 1986). Some investigations have reported modifications in the diurnal plasma levels of ACTH and cortisol, consisting of an acrophase delay or advance, or an abnormal afternoon peak of cortisol. Increased plasma levels of cortisol and ACTH are especially found in the morning and in the evening. Hypothalamic dysfunction in cluster headache also appears from changes in hormone levels (Waldenlind and Gustafsson, 1987; Leone and Bussone, 1993). In addition, 24-h cortisol production is increased in the cluster period. The CRH test shows a downregulation of adenral function in cluster headache patients, as is also found in patients receiving prolonged CRH administration. The dexamethasone suppression test results are normal in cluster headache patients, showing that the feedback control of CRH production is not altered. Factors other than pain or sleep disturbances probably explain hypercortisolism in cluster headache, such as an alteration in the circadian rhythm of this hormone (Facchinetti et al., 1986; Leone and Bussone, 1993; Strittmatter et al., 1996b). The diurnal rhythm of prolactin has been reported as normal or altered, as in cluster headache. Blunted night peaks of prolactin are observed in men in clinical remission, suggesting an impaired neuroendocrine regulation of prolactin, also during symptom-free intervals. There are, however, great individual differences. In some patients a loss of release rhythms is found, and attacks of cluster headache are accompanied by prolactin increases, especially when the attacks take place at night. The persistence of hyperprolactinemia during cluster headache remission indicates that these increases occur independent of pain (Ferrari et al., 1983; Waldenlind and Gustafsson, 1987; Leone and Bussone, 1993). Several investigations have reported reduced thyrotropin (TSH) responses to the TRH test during the cluster headache period (Leone and Bussone, 1993). In addition, cluster headache patients demonstrate significantly decreased levels of norepinephrine, homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) in the CSF, which concurs with a central genesis of this disorder (Strittmatter et al., 1996b).

The prevalence of cluster headache in men, and the fact that it is extremely rare in the preadolescent period, indicates that sex hormones might also be involved in the pathogenetic mechanism. Testosterone levels have been reported to be normal or low during the cluster headache period (Leone and Bussoni, 1993). Total, free and carrier protein-bound testosterone levels are significantly diminished only in chronic cluster headache patients whose basal and peak FSH levels are significantly increased (Murialdo et al., 1989). In addition, a significant reduction of the 24-h integrated mean testosterone level (mesor) is found in cluster headache patients. It has been
suggested that the stress of the attack causes elevated cortisol levels and that this, in turn, reduces testosterone levels (Facchinetti et al., 1986). Testosterone administration does not change the course of cluster headache, whereas it does enhance sexual excitement (Nicolodi et al., 1993).

A recognized treatment for intractable chronic cluster headache is to section the trigeminal root proximal to the ganglion. Oxygen and verapamil treatment also work (Goadsby, 2002).

(b) Migraine

Episodes of migraine may occur regularly, indicating the involvement of some internal clock that probably involves the hypothalamus, because premonitory symptoms such as elation, a craving for sweet food, thirst or drowsiness may precede headache by some 24 h. Hypothalamic symptoms are reported by about 25% of patients (Lance, 1992). It has even been proposed that the SCN is the site of initiation of a migraine attack (Zurak, 1997). Patients with migraine are more likely to have headaches during the bright arctic summer season. This distinguishes migraine from other headaches and suggests a role of the circadian/circannual system (Chapter 4) in the pathogenesis of this disorder (Salvesen et al., 2000). In this connection it is also of interest that melatonin secretion is reduced in patients with menstrual migraine (Dodick et al., 1998) and that melatonin may relieve migraines (Gagnier, 2001). Moreover, the circadian rhythmicity of prolactin is often disturbed in migraine (Ferrari et al., 1983). In chronic migraine, hypothalamic dysfunction appears from: (i) a decreased nocturnal prolactin peak, (ii) increased cortisol concentrations, (iii) a delayed nocturnal melatonin peak, and (iv) lower melatonin concentrations in patients with insomnia. On the basis of these findings, a chronobiological dysregulation and a possible hyperdopaminergic state are presumed to be present in patients with chronic migraine (Peres et al., 2001).

Migraine occurs more often in women than in men. However, this sex difference is only present in the reproductive period of life. In children, migraine prevalence is independent of sex. It is presumed that the basis of the sexual dimorphism of migraine should be sought in hypothalamic systems related to LHRH secretion, since LHRH agonists may induce a complete relief of migraine attacks (Facchinetti et al., 2000). The prevalence of migraine headaches in women is influenced strongly by events in the reproductive cycle. With puberty there is a marked increase in the incidence of migraine headaches, with a peak incidence occurring at menarche, and a decrease at menopause. The majority of migrainous women will have some of their attacks linked to the menstrual cycle. Menstrual migraine seems to respond very well to LHRH administration and to “add-back” therapy, i.e. a combination with continuous, transdermal estrogen–progesterone therapy (Murray and Muse, 1997). Clear examples of the periodicity of headache are weekend headaches, migraines that start during nocturnal sleep, and (pre)menstrual migraine. The primary trigger of menstrual migraine thus appears to be the withdrawal of estrogen rather than the maintenance of sustained high or low estrogen levels (Silberstein and Merriam, 1999). In migraine patients, prolactin is excreted excessively in response to stimulation (Dexter and Riley, 1975; Awaki et al., 1989; Lance, 1992). Plasma levels of met-enkephalin are higher in migraine patients, both during the attack and when there is no headache. However, individual patients consistently present with lower met-enkephalin levels during the pain-free period than during the acute headache (Mosnaum et al., 1986).

Vasopressin plasma levels rise during migraine attacks and are followed by a rise in endothelin-1, which exerts vasoconstrictor and vasodilator actions on cerebral vessels via endothelin A and B receptors. The elevated vasopressin levels may attribute in part to the nausea and emesis that accompany the attack (Hassellblatt et al., 1999). Another observation that connects migraine to the hypothalamus is the increased digoxin synthesis and upregulated isoprenoid pathway observed in these patients. Digoxin is an inhibitor of membrane Na–K adenosine triphosphatase (ATP-ase); it is produced by the hypothalamus and synthesized by the isoprenoid pathway (Kumar and Kurup, 2001a). In patients with chronic daily headaches, with a previous history of migraine, increased nerve growth factor levels are found in the CSF. As nerve growth factor is known for hyperalgesia when administered either locally or systemically in many species (Sarchielli et al., 2001), this observation may be of therapeutic relevance.

(c) Hypnic headache syndrome

The hypnic headache syndrome (“alarm clock syndrome”) is a rare, benign disorder of the elderly. It is characterized by recurrent, nocturnal bilateral headaches that awaken the patients from their sleep at a consistent time each
night, usually between 1 and 3 a.m., more than 4 nights a week. The pain is moderate to extremely severe and lasts 20–180 min. The mean age of onset is 61 years. These headaches respond to treatment with lithium carbonate and in some cases to caffeine in a tablet or beverage (Newman et al., 1990; Dodick et al., 1998). One case with a good response to indomethacin has been described (Ivañez et al., 1998). The striking circadian rhythmicity and the effectiveness of lithium carbonate suggest the involvement of the SCN. The involvement of the hypothalamus in the pathogenesis of cluster headache is supported by the reduced 24-h plasma melatonin levels during the cluster period, loss of circadian melatonin secretion in remission and reduced urinary melatonin. In addition, the levels of the melatonin metabolite 6-sulfa-toxymelatonin do not differ during day and night in these patients. The observation that altered excretion of 6-sulfo-toxymelatonin is also present during remission indicates that these anomalies are independent of the pain, and provide further evidence of the involvement of hypothalamic, rhythm-regulating centers in cluster headache (Leone et al., 1998).