

Headache: endocrinological aspects

MARIO FERNANDO PRIETO PERES,^{1*} AND MARCELO MORAES VALENÇA²

¹Hospital Israelita Albert Einstein, São Paulo, Brazil

²Federal University of Pernambuco and Hospital Esperança, Recife, Brazil

INTRODUCTION

Pain is an unpleasant sensorial and emotional experience exerting a major protective function throughout the lifetime of the individual. It is a warning sign indicating the existence of imminent or actual tissue injury that should be avoided or treated. Occasionally a headache can signal a serious condition requiring prompt medical attention (Valença et al., 2002; Aygun and Bildik, 2003). Analogous to other internal organs, a pain system which signals tissue injury is working in the brain (the trigeminovascular system), causing headache to help safeguard the intracranial structure against insults such as hemorrhage, ischemia, toxins, and intrinsic diseases. This system can be compared to the cardiovascular system when an angina pectoris crisis takes place and forces the individual to slow down the exertion of activities in order to protect the heart against ischemia. In the case of secondary headaches, such as thunderclap headache associated with subarachnoid hemorrhage, the pain component of the syndrome indicates a potential danger to the individual's life.

On the other hand, in the context of primary headaches, its role as a warning sign is still unclear. The fact is that stressful situations, in which the individual feels that something may be hazardous, habitually cause headache (Eggers, 2001; Kelman, 2007; Lin et al., 2007; Wober et al., 2007). Farias da Silva and collaborators (2005) described that emotional stress was the principal trigger factor of migraine attacks. In their series of 844 patients, emotional problems were referred to by 43%. In that series of patients the other trigger factors of migraine were: olfactory (17%) and visual (12%) stimuli, lack of sleep (16%), food deprivation/hunger (9%), and chocolate ingestion (9%). Furthermore, essential hypertension, depression, and the metabolic syndrome

in addition to migraine are considered diseases of chronic stress (Eggers, 2007). A number of patients also mention fatigue, lack of sleep, hunger and food deprivation, glaring lights, and excessive noise as pain-triggering events (Farias da Silva et al., 2005; Kelman, 2007). Is a primary headache attack or a change in its frequency/intensity a warning in the sense that something abnormal is happening either inside the body or in the living environment?

The autonomic nervous system and the neuroendocrine system are activated to prepare the body and optimize a reaction of fighting or fleeing during a situation that is different from the day-to-day routine, and mainly during conditions that generate stress. In that case, the hypothalamus immediately initiates a series of events in order to increase blood levels of adrenocorticotrophic hormone (ACTH), beta-endorphin, cortisol, oxytocin, and epinephrine (Negro-Vilar et al., 1987; Lopez-Jimenez et al., 1989). Curiously, some of those stress hormones as well as stress situations may cause pain relief under certain circumstances (Bodnar et al., 1984; Amit and Galina, 1986; Lundeberg et al., 1994; Valença et al., 1999). Along with that line of thinking, the presence of headache or the exacerbation of it could be a way through which the central nervous system signals an alarm whenever the organism is exposed to a potentially harmful situation such as stress. Migraine comorbidity (i.e., psychiatric disorders, epilepsy, sleep disturbances, asthma/allergies, fibromyalgia) (Thompson et al., 2003; Bigal and Lipton, 2006a, b) or some unhealthy associated condition (obesity, hypertension) (Cortelli et al., 2004; Bigal and Lipton, 2006b) may also trigger headache. In addition, hormonal imbalances are associated with headache, e.g., those encountered in hypothyroidism (Moreau et al., 1998).

*Correspondence to: Mario Peres, MD, Hospital Israelita Albert Einstein, São Paulo, Brazil, E-mail: marioperes@yahoo.com, Website: www.cefaleias.com.br

Genetic factors play a pivotal role in the susceptibility to migraine (Pietrobon, 2005). For that reason they are under the influence of forces of natural selection. There is evidence that migraine is an ancient disorder (Friedman, 1972; Isler, 1992; Rose, 1995; Koehler and van de Wiel, 2001; Martin-Araguz et al., 2002) whose prevalence may have been increasing, hence signifying that a migraine-prone nervous system may be associated with reproductive and survival advantages, two things strongly influenced by circulating hormones. Loder (2002), considering an evolutionary perspective on migraine, reviewed five explanations that could be responsible for the persistence of migraine: (1) migraine as a defense mechanism; (2) migraine as a result of conflict with other organisms; (3) migraine as result of novel environmental factors; (4) migraine as a trade-off between genetic harms and benefits; and (5) migraine as a design constraint.

The clinical expression of the primary headaches is under a complex mechanism of hormonal regulation. The influence of physiological hormonal fluctuations on the frequency and intensity of several of the primary headaches is well known, particularly those concerning migraine in women. A bidirectional mechanism of control works between the endocrine system and the nervous system to keep different systems of the body in balance within a constantly changing environment. Most cells are capable of producing one or more molecules that act as signaling molecules to other cells, altering their growth, function, or metabolism. A hormone (from Greek *ὁρμή* – “to set in motion”) is an organic chemical messenger, usually a peptide or steroid, released from one cell population, conveyed by the bloodstream or other fluid spaces, to a distant part of the body to influence the physiological activity of other cell groups, thus promoting growth, metabolism, reproduction, and homeostasis in vertebrates. Therefore, hormones exert a specific effect for the benefit of the body as a whole. The endocrine system is one of two communication systems (the other being the nervous system) used by the body for communication between cells. Accordingly, endocrine glands secrete hormones specialized in serving as regulators at the overall organism level, including the peripheral and central nervous systems. This would explain why headaches are so prejudiced or alleviated by them.

Target cells have specific receptors for that particular hormone. The mode of transmission may be classified as:

1. Epicrine: direct cell to cell contact through gap junctions
2. Paracrine: cell to cell via interstitial fluid (cells do not have to be in direct contact)

3. Endocrine: classical system via bloodstream
4. Autocrine: secreted by the cell to act on itself
5. Neurocrine: secreted by neurons, may affect other neurons or cells in contact with neuron
6. Neuroendocrine: secreted by neurons into specialized bloodstream (e.g., hypophyseal portal blood) and transported to the anterior pituitary gland
7. Exocrine: hormone secreted to the exterior of the body.

Neurohormone is a hormone that is produced by neurosecretory cells and released by nerve impulses (e.g., norepinephrine, oxytocin, vasopressin). Neurohormonal activity is distinguished from that of classical neurotransmitters as it can exert effects on cells distant from the source of the hormone production. Some authors also consider as neurohormones the hormones that act on a part of the nervous system.

We could classify hormones into three chemical classes:

1. Amine-derived: hormones are derivatives of the amino acids tyrosine (dopamine, norepinephrine, epinephrine) and tryptophan (serotonin (5-hydroxytryptamine; 5-HT), melatonin)
2. Peptide: thyrotropin-releasing hormone (TRH), vasopressin, oxytocin, protein (insulin, growth hormone (GH)) or glycoprotein (luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH))
3. Lipid and phospholipid-derived hormones: steroid hormones, testosterone, estrogen, progesterone, and cortisol; sterol hormones, calcitriol; prostaglandins are derived from eicosanoids.

Many hormones and their analogs are used in clinical practice as medications, and headache complaints are not uncommon as adverse effects of their use. The most commonly prescribed hormones are estrogens and progestagens, thyroxine, and insulin. Otolaryngologists often use local preparations containing pharmacological equivalents of epinephrine, while in dermatological practice steroid and vitamin D creams are used extensively. A “pharmacological dose” of a hormone is a medical usage referring to an amount of a hormone far greater than naturally occurs in a healthy body. The effects of pharmacological doses of hormones may be different from responses to naturally occurring amounts and may be therapeutically useful. An example is the ability of pharmacological doses of glucocorticoid to suppress both inflammation and pain. Considering this, primary headaches have been treated with hormones such as oxytocin (Phillips et al., 2006) and melatonin (Peres et al., 2006). Antistress-like effects such as reduction

of blood pressure and of cortisol levels are induced by oxytocin. Besides, oxytocin may also increase the pain threshold and exert anxiolytic-like effects, stimulating a number of positive social interactions (Uvnas-Moberg and Petersson, 2005).

Drug-related headache is a relatively frequent adverse effect of a number of pharmacological agents. Indomethacin, nifedipine, atenolol, trimethoprim-sulfamethoxazole, zimeidine, glyceryl trinitrate, isosorbide dinitrate, zomepirac, cimetidine, and ranitidine are among the most frequent pharmacological agents associated with headache (Askmark et al., 1989). Curiously, some of these drugs are used to treat specific types of primary headache and may alter physiological hormonal secretion. Regarding migraine, oral contraceptives were also among the most implicated drugs. Vasodilation and salt and water retention with subsequent redistribution of intracranial fluid seem to be common mechanisms underlying drug-related headache (Askmark et al., 1989).

Factors such as blood pressure, body temperature, fluid and electrolyte balance, and body weight are under hypothalamic control (mainly through hormonal and autonomic regulation) and hold to a precise value called the set point. The hypothalamic nuclei constitute part of the corticodiencephalic mechanism activating, controlling, and integrating the peripheral autonomic mechanisms, endocrine activity, and many somatic functions, e.g., regulation of water balance, body temperature, sleep, food intake, and the development of secondary sex characteristics. The hypothalamus is wired to the brainstem periaqueductal gray substance, the locus coeruleus, and the median raphe nuclei (all involved in autonomic, sleep, and in the descending control of pain perception mechanisms).

To achieve this, the hypothalamus receives input from several places about the state of the body and initiates compensatory changes. That input comes from: (1) nucleus of the solitary tract (information about blood pressure and gut distension); (2) reticular formation (information about skin temperature); (3) retina (fibers from the optic nerve go directly to the suprachiasmatic nucleus, involved in regulation of circadian rhythms, and couple the rhythms to the light/dark cycles); (4) circumventricular organs, nuclei located along the ventricles, which lack a blood-brain barrier, allowing them to monitor substances in the blood (e.g., organum vasculosum of the lamina terminalis, which is sensitive to changes in osmolarity; area postrema, which is sensitive to toxins in the blood and can induce vomiting); (5) limbic and olfactory systems: structures such as the amygdala, the hippocampus, and the olfactory cortex regulate a broad range of psychological and physiological functions, including

anger, fear, reproduction, learning and memory, drinking, eating, autonomic activity, and pain.

Agitation (cluster headache) and desire to rest (migraine) are some of the behavioral symptoms alluded to in the primary headaches. Migraine is an ictal disorder and patients with this type of headache are more vulnerable to sensory overload (sensory dysmodulation) (Goadsby, 2007), both during and outwith the attack, probably due to widespread neural “dysexcitability” (Ambrosini and Schoenen, 2006). Some of the migraineurs describe that olfactory stimuli might initiate a migraine attack (Blau and Solomon, 1985; Farias da Silva et al., 2005). Moreover, aversion to strong smells (odor phobia) during a migraine attack is another relatively common feature encountered in migraineurs. Additionally, intrinsic hypothalamic receptors (thermoreceptors and osmoreceptors) monitor temperature and ionic balance (Antunes-Rodrigues et al., 2004).

Once the hypothalamus is informed of a problem, to maintain homeostasis regulatory mechanisms are activated by two major outputs:

1. Neural signals to the autonomic nervous system: the lateral hypothalamus projects on to cells that control the autonomic systems located in the medulla. These include the parasympathetic vagal nuclei and a group of cells that descend to the sympathetic system in the spinal cord. Thus, the physiological functions of heart rate and force of contraction; constriction and dilation of blood vessels; contraction and relaxation of smooth muscles in various organs; visual accommodation and pupil size; secretions from exocrine and endocrine glands (i.e., digestion, lacrimation, sweating) are all also under hypothalamic influence.
2. Endocrine signals through the hypothalamic-pituitary axis: large hypothalamic neurons positioned around the third cerebral ventricle send their axons directly to the posterior pituitary where the nerve terminals release oxytocin and vasopressin into the bloodstream. Smaller neurons which exist all over the hypothalamus send their axons to the median eminence in the medial basal hypothalamus where they discharge releasing factors (corticotropin-releasing hormone (CRH), gonadotropin-releasing hormone (GnRH), growth hormone-releasing hormone (GHRH), TRH) and inhibiting factors (dopamine, somatostatin) into the hypophyseal portal capillary (Negro-Vilar et al., 1987; Negro-Vilar, 1988). That specialized system of vessels communicates the base of the hypothalamus with the anterior pituitary gland (Valença et al., 1987a, b; Ching et al., 1988). Releasing factors induce the anterior

pituitary gland to secrete hormones such as ACTH, TSH, LH, FSH, and GH. On the other hand, inhibiting factors, such as dopamine and somatostatin, cause a strong inhibition of prolactin (PRL) and GH secretions, respectively. Hormonal effects, which vary widely, include: stimulation or inhibition of growth; regulating metabolism; preparation for a new activity (e.g., fighting, fleeing, or mating); preparation for a new phase of life (e.g., puberty, caring for offspring, menopause); controlling the reproductive cycle; induction or suppression of apoptosis (programmed cell death); activation or inhibition of the immune system, among others.

The master coordinator of hormonal endocrine activity in mammals is the hypothalamus. Interestingly, the hypothalamus also exerts an important role during the mechanism of headache triggering (Cortelli and Pierangeli, 2007). Therefore, the presence of pain and concomitant changes in the hormonal secretory pattern are expected during a headache attack when hypothalamic structures are involved (Peres et al., 2001a; Benjamin et al., 2004). The hypothalamus, especially in the posterior regions, is activated during attacks of trigeminal autonomic headache, while in the brainstem (e.g., dorsal pontine region) the activity shows up during migraine attacks (Bahra et al., 2001). Therefore, the hypothalamus and the adjacent brainstem both represent a complex interconnected neural region responsible for the chronobiological features of some cephalalgias, in particular the sleep-related attacks typical of the trigeminal autonomic headaches, migraines, and the hypnic headaches (Montagna, 2006).

Furthermore, the clinical manifestation of hemicrania continua overlaps with that of other trigeminal autonomic headaches and migraine in which activations in the hypothalamus and dorsal rostral pons, respectively, have been postulated to play important pathophysiological roles (May et al., 1998; Bahra et al., 2001; Matharu et al., 2004; Matharu and Goadsby, 2005). Functional brain imaging demonstrated significant activation of the ipsilateral dorsal rostral pons in association with the headache attack of hemicrania continua (Matharu et al., 2004; Matharu and Goadsby, 2005). There was also a significant activation of the contralateral posterior hypothalamus and ipsilateral ventrolateral midbrain, which extended over the red nucleus and the substantia nigra, and bilateral pontomedullary junction. In those circumstances, the ipsilateral hypothalamus mediates cluster headache while the contralateral hypothalamus mediates hemicrania continua.

A disruption in the normal function of the hypothalamus is implicated in the genesis of some prodromal symptoms and signs of migraine such as mood

changes, drowsiness, thirst, food cravings, and yawning. Some of those migraine prodromal symptoms are under limbic system control, as emphasized by Raffaelli and Menon (1975). In a study involving 97 patients, premonitory symptoms in 72% of patients predicted migraine headaches (Giffin et al., 2003). The most regular premonitory symptoms were: feeling tired and weary (72% of attacks with warning features), having difficulty concentrating (51%), and a stiff neck (50%). These signs and symptoms may occur several hours, or even as long as 2 days, before headache begins.

PAIN MECHANISMS AND INVOLVEMENT OF NEUROTRANSMITTERS – HOW HORMONES MAY MODULATE PAIN CIRCUITRY

Abundant evidence indicates that in the peripheral and central nervous system there are both nociceptive and -nociceptive pathways, which modulate the perception of pain. During some stress situations, in which the animal should adapt to an excessive environmental demand, the sensation of pain could be an additional factor of failure. Hans Selye (1973) coined the term “stress” as an adaptive response of organisms to stressors to maintain homeostasis. Pani et al. (2000) defined stress as “a general reaction of the mammalian central nervous system which plays a vital role in the way an organism monitors internal conditions, as well as conditions in the world around it, in order to attempt to survive.” Under stressful circumstances an endogenous analgesic system is activated, to suppress pain (Amit and Galina, 1986). Several endogenous substances are involved in the regulatory mechanisms of pain modulation, either facilitating pain or leading to an analgesic state or pain inhibition. Among these substances, endogenous opioid peptides exert a major influence on this pain-alleviating system (Price et al., 1985).

Another putative neurotransmitter is oxytocin. However, the role of oxytocin on endogenous pain control is not yet well known. A few reports evaluated the pharmacological effects of oxytocin and its antagonists on the nociceptive response, using distinct animal models, such as rat, mouse, and dog. In addition, there are reports claiming analgesic properties of oxytocin in humans (Madrado et al., 1987; Yang, 1994). The distinctions between pharmacological and physiological effects, as well as the mechanisms through which oxytocin would increase the pain threshold, are not completely understood. Some authors claim an analgesic property for oxytocin (Lundeberg et al., 1993, 1994; Uvnas-Moberg et al., 1993a, b), whereas others failed

to demonstrate antinociception induced by this nonapeptide (Berkowitz and Sherman, 1982; Witt et al., 1992; Xu and Wiesenfeld-Hallin, 1994). Whether oxytocin increases the pain threshold through activation of endogenous opioid neurons is also a controversy. In a review, Richard and collaborators (1991) concluded that: "in no case does oxytocin-induced analgesia appear to be opiate-dependent."

The oxytocin perikarya are present largely in the magnocellular nuclei, although fibers are widely distributed in the central nervous system, including the spinal cord, where they end particularly in layers I, II, and X of the gray matter. In the spinal cord, the oxytocin fibers may originate from the paraventricular nucleus (Lang et al., 1983) or from dorsal root ganglia C fibers, using oxytocin as neurotransmitter (Kai-Kai et al., 1986).

Under physiological conditions, pain sensation is mediated by two primary afferent neurons: (1) small-diameter non-myelinated C fibers that transmit slow dull pain; and (2) thinly myelinated A δ fibers, transmitters of fast sharp pain. Both are referred to as nociceptors that respond to mechanical, thermal, and chemical forms of energy. In this regard, thermal nociceptors are activated by extreme temperatures ($>45^{\circ}\text{C}$ or $<5^{\circ}\text{C}$). On the other hand, the mechano- and heat-responsive C fibers present heat thresholds ranging from 40°C to 50°C . In humans, rapid immersion of a finger in a hot-water bath (57°C) causes at onset a stinging pain after a time interval of 0.84 s on average. This is followed by a second wave of a burning pain after 2.1 s (Handwerker and Kobal, 1993). The latency between the two forms of pain waves decreases as the stimulus moves up the limbs toward the trunk, and at the trunk level it was not feasible to obtain a double pain sequence. This double pain experience is triggered by fast-rising stimulus (electric shock, pinprick, or heating pulse). Interestingly, opioid substances appear to affect the second pain component more than the first one (Price et al., 1985). In contrast, the first pain component is differentially blocked by compression ischemia (Handwerker and Kobal, 1993).

Previously, we demonstrated that oxytocin caused analgesia in mice (Lins Filho, 2000), an effect abolished by the blockade of opioid receptor with naloxone. The analgesia was evaluated using the tail flick test. The mean latency duration observed, during the tail flick test, in control animals ($n = 80$) before any treatment was 4.8 ± 0.2 s (100%, ranging from 2 to 12 s). Intraperitoneal administration of oxytocin (1 mg/kg; 0.2 ml) induced an analgesic state. It was evident as early as 10 min after oxytocin administration ($81.5 \pm 6.2\%$ in the saline vehicle-treated group (0.9% NaCl; 0.2 ml) versus $130.0 \pm 17.5\%$ in the oxytocin-treated group; $P < 0.01$), which was maximal at

45 min ($93.3 \pm 6.7\%$ in the saline-treated group versus $205.0 \pm 45.3\%$ in the oxytocin-treated group). No significant difference in analgesia was detected after 75 min of oxytocin injection. On the other hand, the previous blockade of opioid receptor by naloxone completely canceled the enhancement in the latencies observed during tail flick test, at all times studied (from 10 to 60 min). This indicates that oxytocin causes analgesia through the involvement of endogenous opioids.

An additional experiment was performed to evaluate the effects of naloxone or the oxytocin antagonist on analgesia induced by immobilization stress (10 min). The mice were treated with the respective receptor blocker 10 min before the beginning of the physical restraint. The analgesia induced by immobilization was amplified by oxytocin administration, which became statistically significant at 40 min. This time is closely correlated with the peak of analgesia occurring at 45 min, when oxytocin was given alone.

The physical restraint stress for a 10-min period caused a strong analgesia, with the latency in the tail flick test increasing from $100.0 \pm 6.2\%$ at time 0 min (before intraperitoneal injection) to $197.5 \pm 23.3\%$ immediately after the end of the 10 min of immobilization ($P < 0.001$). Oxytocin treatment slightly enhanced the analgesia induced by immobilization ($283.2 \pm 39.0\%$ at the end of the 10-min period of restraint; $P < 0.05$), although the treatment with oxytocin only modified significantly the increase in latency induced by this type of stress 40 min after the drug injection (124.5 ± 13.2 in saline vehicle-treated animals versus $182.9 \pm 21.5\%$ in the oxytocin-treated animals; $P < 0.05$). Naloxone significantly inhibited the analgesia induced by immobilization stress. In contrast, the oxytocin antagonist did not modify the increase in the tail flick test latency induced by this kind of stress. The magnitude of the analgesic response was similar between both analgesic inducers, although immobilization induced a rapid analgesic effect, whereas oxytocin administration caused a delayed (45 min) maximal response in terms of antinociception. Hence, analgesia induced by oxytocin, in mice without restraint stress, is blocked by naloxone, which indicates that the effect of oxytocin is mediated by opioids. But when a restraint stress is applied, the analgesic effect does not involve the oxytocin neurons, suggesting that other circuitries are involved. Indeed, the antinociceptive effects produced by immobilization were mediated by the opioid system, since the blockade of opioid receptors inhibited the analgesia.

In 1982, Berkowitz and Sherman reported that peripheral injection of oxytocin does not have any analgesic effects. In contrast, it was demonstrated that injections

of oxytocin intracisternally in mice (Lundeberg et al., 1994) or intrathecally in rats (Yang, 1994) caused analgesia. Lundeberg and collaborators (1993) suggested a central action of oxytocin since intrathecal injection of oxytocin induced a delay in the reaction time in the paw pressure test. Besides, oxytocin levels in plasma and cerebrospinal fluid were found to increase after a 30-min exposure to different non-noxious sensory stimuli, an effect concomitant with the development of analgesia (Uvnas-Moberg et al., 1993b). Immobilization stress also provoked elevation in plasma oxytocin levels (Jezova et al., 1993). The oxytocin antagonist decreased the latency of tail flick test observed after exposure to non-noxious stimuli and reduced the analgesia induced by oxytocin (Uvnas-Moberg et al., 1993a). However, Xu and Wiesenfeld-Hallin (1994) attributed the increase in the latency response in the hot-plate test in rats to the sedative and vasoconstrictive effects of oxytocin, rather than an analgesic phenomenon. Additionally, they also reported that oxytocin antagonist did not influence the latency to heat pain sensitivity in rats.

In humans, acute and chronic low-back pain causes a significant increase of oxytocin concentration within the cerebrospinal fluid and plasma (Yang, 1994). Furthermore, oxytocin administration can alleviate low-back pain (Yang, 1994). In rats, oxytocin had a dose-related analgesic effect. The use of oxytocin antagonists or naloxone can reverse the analgesia induced by oxytocin. It was also shown that oxytocin might increase the levels of endogenous opioid peptides in the spinal cord, whereas oxytocin antagonists caused a decrease (Yang, 1994).

Since during labor the action of oxytocin over the uterus provokes muscle contraction (an event which would trigger pain sensation), it would be expected that the same neuropeptide could exert a dual physiological role – analgesia and uterus contraction during labor. Indeed, parturition and vaginal dilation both cause enhancement in plasma oxytocin concentration and increase in pain threshold (Crowley et al., 1977). Interestingly, vaginal dilation activates oxytocin neurons and induces maternal behavior in ewes, an effect blocked by naltrexone (Kendrick and Keverne, 1989). It was demonstrated that during the first stage of labor the intrathecal administration of sufentanil decreased plasma concentration of oxytocin in women with pain (Stocche et al., 2001). This suggests again a close interaction between endogenous opioid peptides and oxytocin.

The oxytocin present in the systemic blood under physiological conditions does not penetrate into the cerebrospinal fluid or into the brain. In guinea pig, only 2–3% of the intraperitoneally administrated oxytocin was detected in the brain. Hence, the need for high doses of oxytocin, if injected systemically, to

induce analgesia, when considering a central site of action (Annat et al., 1986). Two minutes after administration of 1 g [³H]oxytocin, 0.008%/g was found in the brain (Witt et al., 1992). It was reported that the neurohypophyseal hormones or their fragments are transported under normal conditions from blood to brain (van Bree et al., 1989). Furthermore, under either stress condition or injection of epinephrine there is an increased permeability of the blood–brain barrier to peptides (Banks, 2001).

Modifications of the response latencies to the tail flick test due to different temperatures were found with oxytocin antiserum intracerebroventricular injections: no changes at high temperatures, decrease in the latencies at moderate temperature, and increase in latencies at low temperature (analgesia). Similar results were observed with other antisera, such as against vasopressin, met-enkephalin, and beta-endorphin (Bodnar et al., 1984). On the other hand, it has been shown that naloxone, by itself, does not cause pain, but may enhance the perception of pain (Buchsbbaum et al., 1983).

The concentration of oxytocin in cerebrospinal fluid of dogs with spinal cord compression was higher than in control dogs, suggesting that during painful conditions oxytocin is released in order to attenuate the unpleasant, hurtful situation (Brown and Perkowski, 1998). Furthermore, analgesia may be caused by different types of stress. The restraint stress-induced analgesia is mediated by endogenous opioid peptides; other kinds of stresses, such as surgical stress, are unaffected by previous opioid receptor blockade (Valença et al., 1999).

It seems that individuals prone to migraine have a genetically determined migraine threshold that renders them susceptible to a migraine attack upon exposure to some or any of a range of patient-specific triggers. Hormonal influences, environmental and physiological stressors, hypoglycemia, and fatigue are all thought to influence this threshold. Associated diseases such as temporomandibular disorders, sinusitis, and obesity may also decrease the pain threshold (Valença et al., 2003). Once the threshold is exceeded, trigeminovascular discharge is thought to be responsible for inducing a migraine.

The physiopathogenic mechanisms involved in the primary headaches are still poorly known. A migraine attack may be the result of nociceptive neuronal activation of the trigeminal vascular system, which would involve the meninges and part of the soft structures of the head. Vasoactive neural peptides are released during migraine crisis, indicating that depolarization of primary afferent neurons, with perivascular release of substance P and calcitonin gene-related peptide (CGRP), occurs at the sensitive terminal. This, in turn,

would provoke a sterile neurogenic inflammation. This principle has been used in an attempt to develop animal models utilizing inflammatory mediators in the proximity of the meninges (Ebersberger et al., 1997; Burstein et al., 1998), which are innervated by the trigeminal nerve to a great extent.

The experimental models of headaches are few, and often involve painful, brutal handling of the animal, thus implying the necessity to anesthetize it (Burstein et al., 1998). Among the scarce animal models can be cited the following: (1) intracisternal injection of irritating substances, such as capsaicin, and posterior determination of C-fos expression in brain areas involved in the pain and analgesic mechanism (i.e., trigeminal caudalis nucleus) (Cutrer and Moskowitz, 1996), or responsiveness of neurons in the caudal nucleus of the trigeminal brainstem to inflammatory mediators (Ebersberger et al., 1997); (2) electrical stimulation of the superior sagittal sinus (Zagami et al., 1990; Benjamin et al., 2004); (3) animal models of Leão's spreading depression, a model that attempted to explain the migraine aura on an electrical corticographic basis (Guedes, 1984; Guedes et al., 1996; Bolay and Moskowitz, 2005; Goadsby, 2007); and (4) intracerebral drug microinjections (Levy et al., 2003).

There are a vast number of studies evaluating various forms of pain by applying painful stimuli to different parts of the body other than the head. In those models the animal remains conscious and a particular type of behavior concerning the pain felt is analyzed. This allows the disclosure of possible mechanisms and the neural circuitry involved in both the analgesic and painful phenomena.

A classic model of pain is the use of formalin injection into the animal's paw. Rats, mice, cats, and monkeys were some of the species in which the formalin test was performed (Alreja et al., 1984; Hunskaar et al., 1985). Formalin as an irritating agent stimulates directly nociceptive receptors localized at the neural terminal of the trigeminal nerve and would also trigger a local inflammatory process. Recently, we developed a new experimental model of headache in rats (Valença et al., 2005), deploying the use of formalin as a pain inductor injected in the cephalic segment. The modification of the animal behavioral pattern reveals the intensity of the pain felt over the head (i.e., headache). The behavior related to the pain felt in the head consisted of two phases or peaks of activity: a phasic one (0–10 min) and a tonic one (10–50 min). This response to formalin injection was reduced by previous treatment with acetylsalicylic acid. The pain induced by formalin caused a significant increase of 85% in the tail flick test latency, which was already evident at 5 min after the drug administration. This analgesic

effect, induced by the formalin, persisted for 60 min. Previous administration of the opioid receptor blocker naloxone completely abolished the analgesia observed after the formalin pain induction.

By deploying this animal model (Valença et al., 2005) of headache using conscious animals, our results suggested that: (1) the induced pain in the head activates areas of the central nervous system related to analgesia, since an enhancement in the latency on the tail flick test was observed after the formalin injection in the frontal subcutaneous region; (2) the analgesic phenomenon was mediated by the endogenous opioid system since the opioid receptor blocker naloxone completely canceled the increase observed in the latency after formalin injection during the tail flick test. That antinociceptive response justifies the fact that primary headaches have a self-limiting time course, some of them lasting a few minutes or hours.

It is known that stressful situations may induce analgesia. This analgesia may be mediated by the endogenous opioid peptides or not. In the case of immobilization stress the blockade of opioid receptors nullifies the analgesia. On the other hand, surgical stress, such as laparotomy, induces analgesia through a non-opioid system since the use of opioid receptor blockers does not modify the analgesic effect (Valença et al., 1999). Furthermore, electrical stimulation of specific brain areas can result in analgesia (Gebhart, 2004). Morphine injections into those same areas cause antinociceptive effects as well (Taylor and Basbaum, 2003). During normal situations, it seems that the opioid systems are not activated or exerting a tonic inhibitory effect on the pain threshold, since treatment with opioid receptor blockers, by itself, does not cause pain. Nevertheless, during painful situations, the use of those blockers would enhance the perception of pain by the patient. This indicates that the feeling of pain may activate the endogenous cerebral centers to counteract the painful sensation.

One of the main brain peptides involved in pain regulation is beta-endorphin. It is synthesized by neurons located in the arcuate nuclei in the hypothalamus, which project their axons through the entire central nervous system, particularly to the periaqueductal substance. Other non-opioid brain substances, such as oxytocin and melatonin, may also participate in the analgesic system.

Notwithstanding the great number of studies on the physiopathology of migraine, there is still controversy as to whether migraine is primarily a vascular or a neurological dysfunction. Irrespective of this controversy, levels of 5-HT, a vasoconstrictor and a central neurotransmitter, appear to decrease during a migraine attack (Anthony, 1968; Rydzewski, 1976). An attack of

migraine can be aborted by an intravenous infusion of 5-HT or 5-HT agonists (mainly 5-HT_{1B/1D} agonists) (Spencer et al., 1999). In fact, 5-HT as well as ergotamine, dihydroergotamine, and other antimigraine agents invariably produce vasoconstriction. A new class of drugs, the 5-HT_{1B/1D/1F} receptor agonists – sumatriptan and second-generation triptans (e.g., zolmitriptan, rizatriptan, naratriptan) – also produce vasoconstriction (via 5-HT_{1B} receptors) in addition to a presynaptic inhibition of the trigeminovascular inflammatory responses implicated in migraine (via 5-HT_{1D}/5-HT_{1F} receptors).

Sympathetic fibers, parasympathetic fibers, and sensory fibers of the trigeminovascular system are responsible for the regulation of cerebral vessel caliber (Wahl and Schilling, 1993). The stimulation of sympathetic fibers leads to a modest decrease in cerebral blood flow (Baumbach and Heistad, 1983), whereas stimulation of parasympathetic fibers or trigeminal fibers causes an increase in cerebral blood flow (Suzuki et al., 1990). Trigeminal ganglion stimulation results in increased cerebral blood flow (Lambert et al., 1988), probably mediated by parasympathetic fibers. The parasympathetic nerves that innervate cerebral blood vessels arise from the sphenopalatine ganglion, which is known to be innervated by trigeminal fibers (Suzuki et al., 1989). In this regard, stimulation of the trigeminovascular system results in both head pain and increased cortical blood flow (Ray and Wolff, 1940; Lambert et al., 1984; Suzuki et al., 1989).

Trigeminal fibers containing substance P and CGRP innervate vascular structures within the cranium, including the meningeal arteries and the large arteries forming the circle of Willis (Saito et al., 1987; Suzuki et al., 1989). Those vessels are the main pain-sensitive structures within the cranium (Ray and Wolff, 1940) and are collectively referred to as the trigeminovascular system. It is now generally believed that stimulation of the trigeminovascular system is responsible for the pain associated with vascular headaches (Moskowitz, 1990, 1991).

The vascular endothelium synthesizes vasorelaxant substances, e.g., endothelium-derived relaxing factor (EDRF), acetylcholine (ACh), bradykinin, purines (i.e., adenosine triphosphate (ATP)), histamine, vasopressin, substance P, neurokinin A and B, and prostaglandin F_{2α} (Jansen et al., 1990, 1991; Suzuki et al., 2002). On the other hand, endothelium-derived constricting factors may also be involved in the control of vascular tone, including 5-HT, norepinephrine, prostaglandin E₂, thromboxane A₂, leukotriene C₄, endothelin-1, and endothelin-3. In addition, ACh releases EDRF. Norepinephrine also induces release of EDRF and substance P, which seems to attenuate the vasoconstrictor

response to norepinephrine. EDRF was identified as being nitric oxide (NO), which is produced by neurons, glia, and endothelium. Sympathetic nerve varicosities release norepinephrine and other putative transmitters, such as ATP, neuropeptide Y (constrictor), vasoactive intestinal peptide (dilator), and CGRP (dilator) (Baumbach and Heistad, 1983; Jansen et al., 1991, 1992; Suzuki et al., 2002).

Blood-borne norepinephrine and stimulation of sympathetic nerves do not affect significantly brain circulation (Baumbach and Heistad, 1983). After chronic trigeminal ganglionectomy there was an increase in the constrictor response of pial arteries to norepinephrine (Moskowitz et al., 1988). Also, inhibition of EDRF synthesis or endothelial denudation enhances the vasoconstriction induced by norepinephrine. Likewise, acute hypertension allows the occurrence of important vasoconstrictor effects induced by sympathetic stimulation (Tamaki and Heistad, 1986), indicating that, under certain circumstances, cerebral vessels may respond to noradrenergic stimuli. Interestingly, acute hypertension generates superoxide anion, which, in turn, inactivates EDRF (Wei et al., 1985). This may reverse the ACh-induced cerebral arterial dilatation and augment cerebral vasoconstriction induced by norepinephrine or sympathetic stimulation.

Endothelins are a group of hormones that affect vascular tone and have important implications for the treatment of heart and renal failure, pulmonary hypertension, ischemic strokes, migraine, and other disorders. Endothelin, a 21-amino-acid peptide, has very potent and long-lasting constrictive effects. In isolated human cerebral artery segments, endothelin produced intense and sustained vascular constriction, which was inhibited by sodium nitroprusside or verapamil. The enhanced vascular tone induced by endothelin is resistant to norepinephrine antagonists, 5-HT, isoproterenol, histamine, ACh, and angiotensin II. In canine basilar artery, calcium channel blockers such as nifedipine and papaverine reversed the contraction induced by endothelin-1. The arterial contraction induced by both norepinephrine and 5-HT is amplified by the addition of low concentrations of endothelin-1 (Zimmermann and Seifert, 1998). During experimental subarachnoid hemorrhage the cerebral vessels are hyperreactive to endothelin, indicating that, in a given situation of higher reactivity of a particular segment of the cerebral arterial system, sudden release of norepinephrine, 5-HT, or any other vasoconstrictor into the circulation could precipitate a severe and long-lasting arterial constriction.

NO also inhibits endothelin-1 synthesis. A close interaction between endothelin (a vasoconstrictor) and NO (a vasodilator) appears to take place and to play

a major physiological role in the control of cerebral blood flow and vessel caliber. So, any disturbance that may occur in the equilibrium between constrictor and dilator factors could generate arterial spasm.

Endothelin-1 levels increase during (Gallai et al., 1994; Kallela et al., 1998; Hasselblatt et al., 1999) and between (Kallela et al., 1998) migraine attacks, suggesting that the peptide is implicated in the physiopathogenesis of migraine. Tzourio and collaborators (2001) reported that a variant of the endothelin type A receptor gene modulates the risk for migraine. This may imply that migraineurs with qualitatively or quantitatively altered endothelin type A receptor may present an abnormal response of the arterial tone, resulting in inadequate dilatation or constriction of cerebral vessels in response to different stimuli.

Supporting the hypothesis that NO might also participate in the genesis of pain, nitroglycerine is able to induce, in healthy subjects, an immediate, short-lasting, bilateral frontotemporal and pulsating headache that can be aggravated by routine physical activity (Schmetterer et al., 1997). This happens as a consequence of a vasodilation due to NO formation. Intriguingly, nitroglycerine causes a more severe pain in migraine patients (Olesen et al., 1993; Thomsen et al., 1993). Alteration of intracranial vessel tone and regional instability of the cerebral blood flow was documented in migrainous patients during the headache-free interval (Sakai and Meyer, 1979; Lagreze et al., 1988; Thomas et al., 1990; Totaro et al., 1997). This suggests that cerebral arteries of migraineurs might react differently to diverse stimuli.

Plasma levels of CGRP are associated with the degree of pain in the acute attacks of primary headaches. The treatment with triptans alleviates both the pain and the associated CGRP release, probably via a presynaptic effect on the sensory nerves (Edvinsson, 2006).

Moskowitz (1984) hypothesized that the headache may be the result of the release of vasoactive peptides from trigeminal sensory perivascular fibers. Humoral or cell-mediated interactions occur between blood and cerebral vessel. For example, mast cells control microvasculature and local nerve fiber activity (Dimitriadou et al., 1987). Evidence suggests that central trigeminal sites are involved in the processing of craniovascular pain. Pain stimuli coming from pain-sensitive intracranial structure may cause activation of groups of cells present in the trigeminal nucleus caudalis and dorsal horns of the C1 and C2 cervical spinal cord (Goadsby and Zagami, 1991; Kaube et al., 1993; Hoskin et al., 1996). Quite the reverse, trigeminovascular reflex is mediated via brainstem connections to activate parasympathetic outflow from the seventh cranial nerve,

which regulates regional cerebral blood flow (Goadsby and Duckworth, 1987). So, cerebral blood flow and pain may exert a reciprocal control.

In addition, electrode implantation in the periaqueductal gray region caused pain episodes in humans (Raskin et al., 1987), suggesting that dysfunction in specific brainstem regions may trigger pain experience. Some of the patients reported abrupt, icepick-like, stabbing, rhythmic pounding pain, associated with transient visual symptoms, nausea, or vomiting. In this regard, dysfunction of brainstem nuclei and altered cerebral blood flow in patients with migraine have recently been established (Sliwka et al., 2001), despite the fact that during migraine attacks activation of locus coeruleus and dorsal raphe nuclei was demonstrated by positron emission tomography. The brainstem plays an important role in the regulation of pain and cerebral blood flow, since it contains antinociceptive and trigeminal nociceptive systems, and intracerebral vascular regulatory centers. In a recent report (Valença et al., 2007) it was suggested that hemicranial pain and autonomic symptomatology may occur ipsilateral to a brainstem dysfunction in a case of hemicrania continua associated with pontine vascular lesion. The concept that migraine is related to microcirculatory disturbances mediated by fibers projecting from the locus coeruleus may also suggest another possible explanation for the vascular constriction (Lance, 1985).

Tricyclic antidepressants (e.g., amitriptyline), potent inhibitors of the neuronal uptake of norepinephrine, systemically administered to humans caused a reduction of the whole-body norepinephrine spillover to plasma, due to the reduction in nerve firing rates. Propranolol had a similar effect on norepinephrine overflow (Esler et al., 1990). Propranolol, by blocking vascular beta-receptors, could impair the anticipated vasodilation induced by activating β -adrenergic receptors. Hence, propranolol could facilitate a predominance of the vasoconstrictor effect. Non-selective beta-blockers can also have the adverse effect of increasing platelet aggregability (Silberstein et al., 1998). In this regard, the association of propranolol with stroke in migraineurs has been mentioned previously (Bardwell and Trott, 1987; Mendizabal et al., 1997). Lance and Goadsby (1998) advise avoiding the use of beta-blockers in migraineurs with prolonged aura or severe focal neurological symptoms.

Prostaglandins, 5-HT, and histamine, which are neurochemical activators, may under certain situations stimulate the trigeminal nerve. Migraine triggers may also work directly through these chemical mediators. For example, estrogen levels alter prostaglandins during menses. Additionally, migraine triggers can also provoke an indirect attack through neural mediators,

similarly to the example of the decrease in 5-HT release from the dorsal raphe nucleus induced by rapid eye movement sleep. In the genesis of a migraine attack it seems that the trigeminal nerve releases substance P and CGRP into dural and cerebral blood vessels. The release of substance P provokes the degranulation of mast cells and the attraction of polymorphonuclear leukocytes. The mast cell releases histamine, and platelet releases 5-HT, and these cause vasodilation and exudation of plasma into the tissues. Sterile arteritis is the result of the inflammation and swelling of the blood vessels. The neurogenic inflammation and release of substance P cause distension of cranial arteries and, consequently, headache. It is likely that NO mediates the vasodilation and may also act as a nociceptive neurotransmitter. Tyramine contained in certain foods may trigger a migraine attack by a direct action on vasomotor tone or by mediating neurochemical release. Platelet changes, neurochemical mediators, and ischemia can all activate the trigemino-vascular system.

Increases in platelet activity and catecholamine levels and in 5-HT release from the dorsal raphe nucleus occur in the early morning. This would trigger the trigemino-vascular system, explaining the circadian rhythm of some of the primary headaches. In migraineurs a circadian variation in migraine onset was demonstrated, with a marked increase in attacks between 6:00 and 8:00 a.m., peak frequency of migraine onset between 8:00 and 10:00 a.m., and a dramatic decrease in frequency between 8:00 p.m. and 4:00 a.m. (Solomon, 1992). The circadian rhythm of migraine onset is similar to the circadian rhythm observed in myocardial infarction, ischemic stroke, platelet aggregability, plasma cortisol, and plasma catecholamines. This suggests that pain threshold and vasomotor tone may be involved in the initiation of migraine attacks (Solomon, 1992).

A few theories on the pathogenesis of migraine are briefly discussed below: the vascular theory; the cortical spreading depression of Leão theory; the neurovascular hypothesis; the serotonergic abnormalities hypothesis; and the integrated hypothesis.

During the 1940s and 1950s Harold Wolff hypothesized the vascular theory of migraine pathogenesis (Blau, 2004). Nonetheless, over the preceding three centuries, from William Harvey's concept, various hypotheses concerning migraine pathogenesis had been considered, a few bearing reasonably strong resemblances to Wolff's thoughts. Many of these earlier hypotheses regarded migraine primarily as either a vascular (e.g., Willis, Wepfer, Latham) or a neural (e.g., Harvey, Lieving and his "nerve storms") illness (Spierings, 2004; Eadie, 2005). In accordance with the vascular theory, migraine is a vasospastic disorder that

is initiated by vasoconstriction in the cranial arteries. Following the initial vasoconstrictive period, intracranial and extracranial blood vessels dilate (Bartolini et al., 2005). The vasoconstriction stage appears to be associated with migraine aura. Whereas most of the brain is insensitive to pain, meningeal blood vessels show a high level of innervation. Thus, blood vessel dilation activates the trigeminal sensory nerves that surround the meningeal blood vessels, causing pain. Activation of trigeminal nerves also causes the release of vasoactive neuropeptides that further contribute to dilation and worsen pain. The occurrence of "spreading oligemia" during the aura phase of a migraine, and an increase in cerebral blood flow during the headache phase, supports the vascular theory (Olesen, 1982; Lance, 1985, 1993; Olsen et al., 1990; Prodan et al., 2002; Bartolini et al., 2005). Besides, the use of a vasodilator, such as a nitrate, intensifies the headache, whereas when a vasoconstrictor is used in the course of a headache attack, such as a 5-HT agonist, the pain component of the syndrome is lightened.

Cortical spreading depression is a relatively short-lasting wave of depolarization that spreads across the surface of the brain cortex, generally moving at a speed of about 2–5 mm/min from the occipital region toward the front, resulting in brain ion dysfunction and secondary vasoconstrictor vascular events (Guedes et al., 2002; Costa-Cruz et al., 2006). This electrocortical phenomenon can be induced in animals with noxious stimuli, although it was not demonstrated to occur in humans under normal conditions. However, transient electrocorticogram suppressions (i.e., spreading depression) were registered in patients with an acutely injured brain (Strong et al., 2002), indicating that under certain circumstances spreading depression might occur in humans.

Fibers from the trigeminal nerve innervate blood vessels in the meninges, the extracranial arteries, and the circle of Willis. These nerve fibers contain nociceptors that are capable of generating pain impulses. The neurovascular hypothesis proposes that either migraine triggers or cortical spreading depression-like phenomena (oligemia in humans) (Diener and May, 1996) can activate trigeminal nerve axons. This, in turn, provokes release of inflammatory neuropeptides (i.e., substance P, neurokinin A, and CGRP) from axon terminals near the meningeal and other blood vessels. Substance P and neurokinin A cause vasodilation and promote the extravasation of plasma proteins and fluid from nearby meningeal blood vessels. Although CGRP does not promote plasma extravasation, it is a potent vasodilator. Together, these neuropeptides produce an inflammatory response in the area around the innervated blood

vessels, a tissue response termed sterile neurogenic perivascular inflammation. Furthermore, the neuropeptides may also sensitize nerve endings, providing a mechanism for sustaining the headache. When activated, the trigeminal nerve also transmits pain impulses to the trigeminal nucleus caudalis, which relays pain impulses to higher centers of the brain.

According to the neurovascular theory, vasodilation is not the cause of migraine headaches but is an accompanying phenomenon attributable to trigeminal nerve activation. Although the cause of this activation is not known, it may be due to ionic and metabolic disturbances in brain function, such as those associated with cortical spreading depression. Abnormal activity in brainstem sensory nuclei may also set off antidromic activation of trigeminal sensory pathways.

The integrated hypothesis of migraine pathogenesis is an attempt to consider the different theories and explain several facts related to migraine. Thus, triggers such as stress, glare, noise, the patient's internal clock, dilation of the internal or external carotid arteries, or other factors may activate specific centers in the brainstem. The locus coeruleus, once activated, would cause changes in epinephrine concentration, and the dorsal raphe nucleus would have an effect on brain 5-HT levels. In that way, cerebral vasoconstriction would cause a localized decrease in blood flow (the equivalent to spreading depression), which, in turn, would stimulate trigeminovascular fibers. Neurogenic inflammation and headache would then occur. The locus coeruleus also sends descending projections interacting with the body's pain control mechanisms. The dorsal raphe nucleus sends fibers to blood vessels and upward towards the cerebral cortex. These 5-HT-secreting fibers also regulate sleep and neuroendocrine functions.

The concept of a central sensitization and a peripheral sensitization as part of migraine pathogenesis is a recent theory that supports the fact of a temporal progression and symptomatic expression of migraine attacks (Dodick and Silberstein, 2006). This theory tries to explain the symptom of cutaneous allodynia and the development of chronic forms of migraine.

WOMEN – MENSTRUAL CYCLE, LACTATION, PREGNANCY, POSTMENOPAUSE, HORMONAL CONTRACEPTION

Gender may influence the establishment of migraine by at least two mechanisms: (1) pre-existent sexual brain dimorphism that makes the female brain more susceptible; and (2) direct effects of the sex steroids on neuronal cells.

The development of sexual brain dimorphism is influenced in a strong way by sex steroids. Distinct differences between the sexes in brain morphology occur and are believed to be responsible for a number of the observed behavioral differences between men and women. The morphological and behavioral differences observed between the genders are the result of the different circulating levels of gonadal steroid hormones, which reach brain cells during early critical periods of brain development. Testosterone is secreted at much higher concentrations by the testes than by the ovaries. Testosterone and its two primary derivatives, dihydrotestosterone and estradiol, are carried into the brain in the blood. Gene expression is thus either up- or down regulated (enhanced or diminished) by them. The proteins that are synthesized lead to the formation of specific neural circuits within the male brain. The absence of these androgen hormones during critical periods of early central nervous system development (*intra* uterus in human beings) leads to the formation of different neural circuits within the female brain. Sex differences in circulating androgens that occur shortly after conception in humans are thought to be responsible for sex differences in programmed cell death. Thus, the establishment of sex differences in neuron number within these brain regions may result from hormonal influences on mitotic activity or the migratory routes that neuroblasts take (Garcia-Segura et al., 1994; Davis et al., 1996; Cooke et al., 1998; Rhodes and Rubin, 1999; Hagiwara et al., 2007).

Sexual dimorphisms in brain regions involved in the neural control of gonadotropin secretion and sexual/maternal behavior were identified in humans in post-mortem studies (Allen et al., 1989; Allen and Gorski, 1990; Highley et al., 1999). A study with neuroimaging showed that sexual dimorphisms of adult brain volumes were more evident in the cortex, with women having larger volumes, relative to cerebrum size, particularly in frontal and medial paralimbic cortices. Men had larger volumes, relative to cerebrum size, in fronto-medial cortex, the amygdala, and the hypothalamus (Goldstein et al., 2001). Thus, gender exerts an important influence in brain development and organization, and such influences may persist until later in life.

Considering the direct effects of gonadal steroids on neuronal cells which happens from moment to moment, a few remarks must be made. Around the time of the menarche, there is a rapid rise in the incidence of migraine in young women. Migraine occurs more often in women than in men. In a study from Denmark, the incidence of migraine was 8.1 per 1000 person-years (male-to-female ratio, 1:6), compared to the frequent tension-type headache that was 14.2 per 1000 person-years (male-to-female ratio, 1:3)

(Lyngberg et al., 2005). Although migraine headaches are equally common in young girls and boys, the number of girls affected increases sharply after the beginning of menstruation. This indicates that certain hormonal changes that occur during puberty in girls, and remain throughout adulthood, are implicated in the triggering and frequency of migraine attacks in women. Headache is also a frequent complaint reported by women during the perimenopausal and postmenopausal years.

A large amount of evidence suggests that migraine attacks can be influenced by oral contraceptive use, pregnancy, and the menstrual period. It is believed that, when a sudden withdrawal of estrogen occurs, a migraine attack may be facilitated. In various studies, hormonal therapy has been shown to improve, exacerbate, or have no effect on headache frequency in women sufferers. Estrogen and progestin, through effects on vascular tone and biochemical mediators, might exacerbate migraine, in addition to estrogen withdrawal as a migraine trigger.

In women, two-thirds of migraineurs relate attacks to their menstrual period. This supports a link between female hormone fluctuation and migraine headaches. Attacks may occur several days before or during the woman's menstrual cycle. There are women who also get the headache mid-cycle at the time of ovulation. As we know, estrogen levels fluctuate throughout the menstrual cycle. The headaches typically occur in association with drops in the estrogen level. A small number of women (less than 10%) have headaches exclusively during menstruation. In a series of 422 women with migraine only 5% reported headache during the menstrual period or 2 days before menses (Farias da Silva et al., 2005). Furthermore, in 77% of women the migraine attacks were more frequent and more severe during the menstrual period (Farias da Silva et al., 2005).

Oral contraceptives may also affect the incidence of migraine (Martin and Behbehani, 2006a; Silberstein, 1993). Because of the higher estrogen content in birth control pills, this was more common a decade or more ago. Some of the current triphasic pill products might exacerbate migraine as well. There are variable effects today with the availability of contraceptive pills, transdermal patches, or vaginal rings (Swica, 2007). Some women benefit, some do not, and others have worsening of their migraine. For some women the use of the pill, patch, or ring for three or four consecutive cycles, without taking any days off, may help to reduce the number of menstrual migraines.

Migraine attacks are also influenced during the months of pregnancy. Migraine may worsen during the first trimester, but usually improves during later pregnancy (Silberstein, 1993). Some women confirmed that their attacks disappeared completely, occurred less

often, or were milder during pregnancy (40–80%) (Farias da Silva et al., 2005). Attacks either worsen (10.2%) or remain unchanged (21.9%) in others (Farias da Silva et al., 2005). In a few women migraine attacks begin during pregnancy (2.9%) (Farias da Silva et al., 2005). Regardless, attacks of migraine with and without aura seem to respond differently to changes in ovarian hormones (Martin and Behbehani, 2006b).

Near menopause the estrogen levels may fluctuate more and trigger an increase in migraine frequency in about one-third of women. Daily preventive therapy may again be necessary if the headaches are frequent and the periods are unpredictable. Women who go through natural menopause may have fewer headache problems than women having hysterectomies. In menopause, the use of continuous estrogen replacement, without any days off, helps to minimize migraine for many women. The dose should be the lowest effective dose. Progesterone agents rarely have an effect on migraine.

Migraine and epilepsy are diseases with neuronal hyperexcitability and may have similar pathogenesis. Gonadal steroid hormones may also exert an important role in seizure susceptibility (Schwartz-Giblin et al., 1989; Velisek et al., 1998). Proconvulsant effects of estrogen have also been reported (Klein and Herzog, 1998), and menstrual cycle effects on cortical excitability suggest a close interrelationship between sex hormone and migraine/epilepsy in women (Smith et al., 2002). Estrogen may induce synaptic and dendritic remodeling (Naftolin et al., 1990), and increase the density of *N*-methyl-D-aspartate (NMDA) receptors in neural cells (Woolley et al., 1997) as well as glial activation (Garcia-Segura et al., 1999). Progesterone is a natural anticonvulsant that acts by increasing chloride conductance at GABA-A receptors and attenuates glutamate excitatory response (Rabe and Fromter, 2000). It also alters messenger RNA for glutamic acid decarboxylase (GAD) and GABA-A receptor subunits (Agis-Balboa et al., 2006; Mostallino et al., 2006). On the other hand, estrogen acts as a proconvulsant by reducing chloride conductance and acting as an agonist at NMDA (Mukai et al., 2006).

In 1989, Askmark and Lundberg described the case of a 26-year-old woman suffering from brief attacks of headache that happened on every occasion of nursing. At the onset of the attacks, serum prolactin increased during nursing, as expected. Simultaneously, plasma vasopressin concentration was elevated before each headache attack. The headache disappeared after lactation had ceased. A few cases of such headaches are attributed to oxytocin surges associated with the milk ejection reflex. Thorley (1997) reported a case in which the apparent trigger was breast overfulness, rather than an oxytocin surge. The mild accumulation occurred when the infant began sleeping through the

night or after a missed, delayed, or partial feed, events associated with the beginning of the headache. Afterward, the headaches were relieved by putting the baby to the breast.

Low levels of thyroid hormones (triiodothyronine and thyroxine, hypothyroidism) are the second cause of frequent headaches associated with endocrinological disturbance, after menstrual cephalgia. Hypothyroidism is very commonly present in people complaining of migraine and tension headaches. Many endocrinological conditions can cause headache, but hypothyroidism should be at the top of the list when evaluating chronic headaches – especially in those patients complaining of fatigue. [Moreau and collaborators \(1998\)](#), studying 102 patients with hypothyroidism, found that 31 (30%) presented with headache 1–2 months after the first symptoms of hypothyroidism. The headache was slight, non-pulsatile, continuous, bilateral, and salicylate-responsive and disappeared with thyroid hormone therapy. They concluded that there is a prevalence of non-specific headache in hypothyroidism and that it has a particular response to thyroid hormone therapy.

As discussed above, headache is one of the neurological manifestations of hypothyroidism but it is unknown whether there is a relationship between hyperthyroidism and chronic headache. In one study, a series of 30 individuals with chronic headache were evaluated in relation to their thyroid function. Six were found to have hyperthyroidism and none had hypothyroidism. The authors concluded that thyroid testing may be beneficial for differential diagnosis of chronic headache, and indicate that headache could be caused by hyperthyroidism ([Iwasaki et al., 1991](#)). Recently, an observational study of thyroid function tests performed in patients with headache prior to referral to a neurological clinic found no headache cases attributable to either hypothyroidism or hyperthyroidism. The role of thyroid dysfunction in the etiology of headache remains uncertain ([Larner, 2006](#)).

Regarding prolactin influence on headache neurobiology, [Strebel et al. \(1986\)](#) demonstrated that hyperprolactinemia was associated with headache only if a prolactinoma was present and not in the absence of a prolactinoma, in women with non-puerperal hyperprolactinemia. Thus, in women with secondary amenorrhea or galactorrhea, or both, headache may be a practical indicator of the presence of an occult prolactinoma.

MELATONIN AND HEADACHE DISORDERS

Life on Earth is under 24-h rhythmicity, due to the rotation of Earth on its axis. The nervous system evolved over the millennia to meet the demands of

environmental conditions, including the light–dark cycle, in order to ensure survival and reproduction of living organisms. A synchronization system to adapt the internal to the external environment is one of the key elements of the central nervous system to maintain life.

The main elements for synchronization between internal biological events and the environment are the pineal gland and its main secretory product, melatonin. Melatonin is absent during the day in humans and its nocturnal secretion is the main biological event signaling what is night to the organism.

Melatonin is a derivative of the essential amino acid tryptophan. The pinealocyte is the principal location for melatonin biosynthesis. After its uptake into cells, tryptophan is first hydroxylated and then decarboxylated, resulting in the formation of 5-HT ([Reiter et al., 2000](#)). 5-HT is *N*-acetylated, with the resulting formation of *N*-acetyl-serotonin, which is subsequently *O*-methylated to form melatonin ([Reiter et al., 2000](#)). Once melatonin is synthesized in the pineal, it is quickly released, generating a blood melatonin rhythm reminiscent of that seen in the gland.

At present, indications for therapeutic applications for melatonin include sleep disorders, circadian rhythm disorders, insomnia in blind people, insomnia in elderly patients, aging, Alzheimer's disease, and as an adjuvant in cancer therapy ([Bubenik et al., 1998](#)). Melatonin has been proposed to be an important element in migraine ([Peres, 2005](#)). Its role in headache disorders may have also treatment implications. A potential therapeutic use of melatonin has been considered in several headache disorders, including cluster headaches (the first to be studied), migraines, and indomethacin-responsive headache syndromes.

Sleep is well known to play an important role as a restorative function. In human beings, it has a circadian rhythm, normally occurring at night, usually together with the nocturnal melatonin secretion ([Rodenbeck et al., 1999](#)). This has led to the idea that melatonin is an internal sleep facilitator in humans, and therefore useful in the treatment of insomnia and the readjustment of circadian rhythms. There is evidence that administration of melatonin is able to induce sleep when the drive to sleep is insufficient; to inhibit the drive for wakefulness from the suprachiasmatic nucleus; and to induce phase shifts in the circadian clock such that the circadian phase of increased sleep propensity occurs at a new, desired time ([Cajochen et al., 2003](#)).

Many neurological disorders occur with a marked rhythmicity, dependent either on the 24-h or the seasonal cycle, thus probably linked to the pineal function and melatonin secretion, including stroke, multiple

sclerosis, facial paralysis, and seasonal affective disorder (Checkley et al., 1993; Turek et al., 2001).

The pineal gland is a photoneuroendocrine organ, converting external luminous stimuli into a hormone secretion, being responsible for synchronization between internal homeostasis and the environment; therefore, an altered synchronization system may interfere with all neurological diseases. Sleep and circadian rhythms are often disrupted in people with neurological disorders (Turek et al., 2001). The symptoms associated with neurological diseases may be due in part to disruption of the sleep–wake cycle. In addition, various neurological disorders may themselves disrupt the sleep–wake cycle, resulting in a positive-feedback loop whereby disrupted sleep and wake exacerbate the neurological disorders while the disease itself has a negative effect on the sleep–wake states (Turek et al., 2001).

Symptoms associated with those disorders may fluctuate according to a specific rhythm (circannual, circamensual, circadian) and are often related to either sleep or wake periods. Epilepsy, dementia, movement disorders, multiple sclerosis, cerebrovascular disorders, neuromuscular disorders, and brain tumors have all been linked to an altered chronobiology, melatonin dysfunction, or benefit from melatonin treatment (Turek et al., 2001). Primary headaches also follow this rule. Migraines, cluster headaches, indomethacin-responsive headaches, and hypnic headaches have been related to melatonin.

Melatonin may play a role in headache pathophysiology via several mechanisms. Melatonin has been shown to possess anti-inflammatory effects, among a number of actions. By virtue of its ability to scavenge directly toxic free radicals (Reiter et al., 2000), it reduces macromolecular damage in all organs. Melatonin inhibits the production of adhesion molecules that promote the sticking of leukocytes to endothelial cells, attenuating transendothelial cell migration and edema (Shaikh et al., 1997). Melatonin inhibits the activity of NO synthase (Bettahi et al., 1996), besides acting in membrane stabilization (Garcia et al., 1997).

Inhibition of dopamine release by melatonin has been demonstrated in specific areas of the mammalian central nervous system (hypothalamus, hippocampus, medulla pons, and retina) (Zisapel, 2001). A growing body of biological, pharmacological, and genetic data supports a role for dopamine in the pathophysiology of migraine (Peroutka, 1997).

Melatonin has been related to dopamine, GABA, and glutamate neurotransmission, and to headache pathophysiology (Ramadan, 2003). Melatonin is also involved in cerebrovascular regulation (Ebadi et al., 1998), and modulation of 5-HT neurotransmission (spontaneous efflux and evoked release) (Monnet, 2002).

Melatonin and migraine are linked in several ways. Clinical symptoms may fluctuate; some patients report their headaches predominantly or specifically in a certain period of the day.

Melatonin was first studied in migraine patients by [Claustrat and collaborators, in 1989](#), showing lower plasma levels in patients compared to controls. Migraine patients without depression had lower levels than controls, but migraineurs with superimposed depression exhibited the greatest melatonin deficiency. [Murialdo and collaborators \(1994\)](#) also found nocturnal urinary melatonin to be significantly decreased throughout the ovarian cycle of patients with migraine without aura compared to controls. During the luteal phase, when melatonin levels should normally increase, migraine patients showed a less pronounced change when compared to controls. Melatonin excretion was further decreased when patients suffered a migraine attack.

[Brun and collaborators \(1995\)](#) studied urinary melatonin in women with migraine without aura attacks associated with menses and controls. Melatonin levels throughout the cycle were significantly lower in the migraine patients than in controls. [Peres and collaborators \(2001a\)](#) studied plasma melatonin nocturnal profile, observing lowered melatonin levels in patients with insomnia, suggesting a chronobiological dysfunction in chronic migraineurs.

Some studies showed a benefit in migraine patients from melatonin treatment ([Claustrat et al., 1989, 1997](#); [Nagtegaal et al., 1998](#)). An open-label trial has been performed using melatonin 3 mg for migraine prevention ([Peres et al., 2004](#)). Thirty-four patients (27 women, 5 men) were included and a significant headache relief was found in 64.7%. Headache response was observed already in the first month of treatment. Complete response was found in 25% of patients. Headache frequency, duration, intensity, and analgesic consumption significantly decreased when baseline was compared to the last month of treatment ($P < 0.001$). The medication was well tolerated; only 2 patients dropped out the study.

It has been suspected that melatonin may be involved in cluster headache genesis, primarily because melatonin is a sensitive marker of endogenous rhythms, which are disrupted in cluster headache ([May et al., 1998](#)).

In 1984, Chazot and collaborators identified a decrease in nocturnal melatonin secretion and abolished melatonin rhythm in cluster headache patients. [Waldenlind and collaborators \(1987\)](#) also showed lowered nocturnal melatonin levels during cluster periods than remissions. Determining urinary levels of 6-sulfatoxymelatonin throughout the year, [Waldenlind](#)

and collaborators (1994) found higher melatonin levels in women than men. Swedes had higher melatonin levels than Italians, and smokers lower levels than non-smoking cluster headache patients. Leone and collaborators (1995) observed that melatonin and cortisol acrophases were significantly correlated in controls but not in cluster headache patients, indicating a chronobiological disorder in these patients.

Blau and Engel (1999) found that increases in body temperature from exercise, a hot bath, or elevated environmental temperature triggered cluster headaches in 75 of 200 cluster headache patients. This finding can be explained by a decrease in melatonin secretion caused by an increase in temperature (Peres et al., 2000). Melatonin for cluster headache prevention was then studied in a double-blind, placebo-controlled trial by Leone and collaborators (1996), with a significant decrease in cluster headache attacks in the melatonin-treated group compared with placebo. Twenty patients (2 primary chronic, 18 episodic) received oral melatonin 10 mg ($n = 10$) or placebo ($n = 10$) for 14 days taken in a single evening dose. Five of the 10 treated patients were responders whose attack frequency declined 3–5 days after treatment, and they experienced no further attacks until melatonin was discontinued. No side-effects were observed in either group.

Two patients with chronic cluster headache in Leone and collaborators' (1996) trial did not respond to melatonin therapy, but Peres and Rozen (2001) described 2 chronic cluster headache patients who responded to melatonin 9 mg at bedtime. Melatonin prevented not only nocturnal cluster attacks, but daytime attacks as well. Nagtegaal and collaborators (1998), studying melatonin treatment in delayed-sleep-phase syndrome, identified a patient with episodic cluster headache in whom both disorders improved after melatonin treatment. Melatonin plays an important role in the pathophysiology and treatment of cluster headaches.

Other headache disorders have been linked to melatonin secretion, such as hypnic headaches (Peres et al., 2006), and other trigeminal autonomic cephalalgias. Peres and collaborators (2001b) described a patient with hemicrania continua with seasonal variation, proposing that the chemical structure similarity between melatonin and indomethacin, could be one of the possible mechanisms of action involved in indomethacin-responsive headaches. Rozen (2003) reported a patient with hemicrania continua who responded to melatonin 9 mg, and described 3 idiopathic stabbing headache patients treated with melatonin with excellent clinical response and side-effect profile. A recent study showed hypothalamic activation in paroxysmal hemicranias, a similar mechanism found in cluster headache, which could make the paroxysmal hemicranias potential candidates for melatonin treatment.

FINAL CONSIDERATIONS

We have reviewed the current understanding of how hormones, neurohormones, and neurotransmitters participate in the pain modulation of primary headaches. Stressful conditions and hormones are intimately implicated in the headache neurobiology. With the recent progress in neuroimaging techniques and the development of animal models to study headache mechanisms, the physiopathology of several of the primary headaches is starting to become more evident. Various clinical characteristics of the primary headaches, such as pain, autonomic disturbances, and behavioral changes, are linked to hypothalamic activation and hormonal influence. In summary, primary headaches are under a strong influence of physiological hormonal fluctuation, when nociceptive and non-nociceptive pathways are differentially activated to modulate the perception of pain.

REFERENCES

- Agis-Balboa RC, Pinna G, Zhubi A et al. (2006). Characterization of brain neurons that express enzymes mediating neurosteroid biosynthesis. *Proc Natl Acad Sci U S A* 103: 14602–14607.
- Allen LS, Gorski RA (1990). Sex difference in the bed nucleus of the stria terminalis of the human brain. *J Comp Neurol* 302: 697–706.
- Allen LS, Hines M, Shryne JE et al. (1989). Two sexually dimorphic cell groups in the human brain. *J Neurosci* 9: 497–506.
- Alreja M, Mutalik P, Nayar U et al. (1984). The formalin test: a tonic pain model in the primate. *Pain* 20: 97–105.
- Ambrosini A, Schoenen J (2006). Electrophysiological response patterns of primary sensory cortices in migraine. *J Headache Pain* 7: 377–388.
- Amit Z, Galina ZH (1986). Stress-induced analgesia: adaptive pain suppression. *Physiol Rev* 66: 1091–1120.
- Annat G, Guell A, Gauquelin G et al. (1986). Plasma vasopressin, neurophysin, renin and aldosterone during a 4-day head-down bed rest with and without exercise. *Eur J Appl Physiol Occup Physiol* 55: 59–63.
- Anthony M (1968). Plasma serotonin levels in migraine. *Adv Pharmacol* 6: 203.
- Antunes-Rodrigues J, de Castro M, Elias LL et al. (2004). Neuroendocrine control of body fluid metabolism. *Physiol Rev* 84: 169–208.
- Askmark H, Lundberg PO (1989). Lactation headache – a new form of headache? *Cephalalgia* 9: 119–122.
- Askmark H, Lundberg PO, Olsson S (1989). Drug-related headache. *Headache* 29: 441–444.
- Aygun D, Bildik F (2003). Clinical warning criteria in evaluation by computed tomography the secondary neurological headaches in adults. *Eur J Neurol* 10: 437–442.
- Bahra A, Matharu MS, Buchel C et al. (2001). Brainstem activation specific to migraine headache. *Lancet* 357: 1016–1017.

- Banks WA (2001). Enhanced leptin transport across the blood-brain barrier by alpha 1-adrenergic agents. *Brain Res* 899: 209–217.
- Bardwell A, Trott JA (1987). Stroke in migraine as a consequence of propranolol. *Headache* 27: 381–383.
- Bartolini M, Baruffaldi R, Paolino I et al. (2005). Cerebral blood flow changes in the different phases of migraine. *Funct Neurol* 20: 209–211.
- Baumbach GL, Heistad DD (1983). Effects of sympathetic stimulation and changes in arterial pressure on segmental resistance of cerebral vessels in rabbits and cats. *Circ Res* 52: 527–533.
- Benjamin L, Levy MJ, Lasalandra MP et al. (2004). Hypothalamic activation after stimulation of the superior sagittal sinus in the cat: a Fos study. *Neurobiol Dis* 16: 500–505.
- Berkowitz BA, Sherman S (1982). Characterization of vasopressin analgesia. *J Pharmacol Exp Ther* 220: 329–334.
- Bettahi I, Pozo D, Osuna C et al. (1996). Melatonin reduces nitric oxide synthase activity in rat hypothalamus. *J Pineal Res* 20: 205–210.
- Bigal ME, Lipton RB (2006a). Modifiable risk factors for migraine progression. *Headache* 46: 1334–1343.
- Bigal ME, Lipton RB (2006b). Obesity is a risk factor for transformed migraine but not chronic tension-type headache. *Neurology* 67: 252–257.
- Blau J (2004). Harold G Wolff: the man and his migraine. *Cephalalgia* 24: 215–222.
- Blau JN, Engel HO (1999). A new cluster headache precipitant: increased body heat. *Lancet* 354: 1001–1002.
- Blau JN, Solomon F (1985). Smell and other sensory disturbances in migraine. *J Neurol* 232: 275–276.
- Bodnar RJ, Nilaver G, Wallace MM et al. (1984). Pain threshold changes in rats following central injection of beta-endorphin, met-enkephalin, vasopressin or oxytocin antisera. *Int J Neurosci* 24: 149–160.
- Bolay H, Moskowitz MA (2005). The emerging importance of cortical spreading depression in migraine headache. *Rev Neurol (Paris)* 161: 655–657.
- Brown DC, Perkowski S (1998). Oxytocin content of the cerebrospinal fluid of dogs and its relationship to pain induced by spinal cord compression. *Vet Surg* 27: 607–611.
- Brun J, Claustrat B, Sadiet P et al. (1995). Nocturnal melatonin excretion is decreased in patients with migraine without aura attacks associated with menses. *Cephalalgia* 15: 136–139; discussion 179.
- Bubenik GA, Blask DE, Brown GM et al. (1998). Prospects of the clinical utilization of melatonin. *Biol Signals Recept* 7: 195–219.
- Buchsbaum MS, Davis GC, Naber D et al. (1983). Pain enhances naloxone-induced hyperalgesia in humans as assessed by somatosensory evoked potentials. *Psychopharmacology (Berl)* 79: 99–103.
- Burstein R, Yamamura H, Malick A et al. (1998). Chemical stimulation of the intracranial dura induces enhanced responses to facial stimulation in brain stem trigeminal neurons. *J Neurophysiol* 79: 964–982.
- Cajochen C, Krauchi K, Wirz-Justice A (2003). Role of melatonin in the regulation of human circadian rhythms and sleep. *J Neuroendocrinol* 15: 432–437.
- Chazot G, Claustrat B, Brun J et al. (1984). A chronobiological study of melatonin, cortisol growth hormone and prolactin secretion in cluster headache. *Cephalalgia* 4: 213–220.
- Checkley SA, Murphy DG, Abbas M et al. (1993). Melatonin rhythms in seasonal affective disorder. *Br J Psychiatry* 163: 332–337.
- Ching M, Valença M, Negro-Vilar A (1988). Acute ethanol treatment lowers hypophyseal portal plasma luteinizing hormone-releasing hormone (LH-RH) and systemic plasma LH levels in orchidectomized rats. *Brain Res* 443: 325–328.
- Claustrat B, Loisy C, Brun J et al. (1989). Nocturnal plasma melatonin levels in migraine: a preliminary report. *Headache* 29: 242–245.
- Claustrat B, Brun J, Geoffriau M et al. (1997). Nocturnal plasma melatonin profile and melatonin kinetics during infusion in status migrainosus. *Cephalalgia* 17: 511–517; discussion 487.
- Cooke B, Hegstrom CD, Villeneuve LS et al. (1998). Sexual differentiation of the vertebrate brain: principles and mechanisms. *Front Neuroendocrinol* 19: 323–362.
- Cortelli P, Pierangeli G (2007). Hypothalamus and headaches. *Neurol Sci* 28 (Suppl. 2): S198–S202.
- Cortelli P, Grimaldi D, Guaraldi P et al. (2004). Headache and hypertension. *Neurol Sci* 25 (Suppl. 3): S132–S134.
- Costa-Cruz RR, Amancio-dos-Santos A, Guedes RC (2006). Characterization of cortical spreading depression in adult well-nourished and malnourished rats submitted to the association of pilocarpine-induced epilepsy plus streptozotocin-induced hyperglycemia. *Neurosci Lett* 401: 271–275.
- Crowley WR, Rodriguez-Sierra JF, Komisaruk BR (1977). Analgesia induced by vaginal stimulation in rats is apparently independent of a morphine-sensitive process. *Psychopharmacology (Berl)* 54: 223–225.
- Cutrer FM, Moskowitz MA (1996). Wolff Award 1996. The actions of valproate and neurosteroids in a model of trigeminal pain. *Headache* 36: 579–585.
- Davis EC, Popper P, Gorski RA (1996). The role of apoptosis in sexual differentiation of the rat sexually dimorphic nucleus of the preoptic area. *Brain Res* 734: 10–18.
- Diener HC, May A (1996). New aspects of migraine pathophysiology: lessons learned from positron emission tomography. *Curr Opin Neurol* 9: 199–201.
- Dimitriadou V, Aubineau P, Taxi J et al. (1987). Ultrastructural evidence for a functional unit between nerve fibers and type II cerebral mast cells in the cerebral vascular wall. *Neuroscience* 22: 621–630.
- Dodick D, Silberstein S (2006). Central sensitization theory of migraine: clinical implications. *Headache* 46 (Suppl. 4): S182–S191.
- Eadie MJ (2005). The pathogenesis of migraine – 17th to early 20th century understandings. *J Clin Neurosci* 12: 383–388.

- Ebadi M, Govitrapong P, Phansuwan-Pujito P et al. (1998). Pineal opioid receptors and analgesic action of melatonin. *J Pineal Res* 24: 193–200.
- Ebersberger A, Ringkamp M, Reeh PW et al. (1997). Recordings from brain stem neurons responding to chemical stimulation of the subarachnoid space. *J Neurophysiol* 77: 3122–3133.
- Edvinsson L (2006). Neuronal signal substances as biomarkers of migraine. *Headache* 46: 1088–1094.
- Eggers AE (2001). New neural theory of migraine. *Med Hypotheses* 56: 360–363.
- Eggers AE (2007). Redrawing Papez' circuit: a theory about how acute stress becomes chronic and causes disease. *Med Hypotheses* 69: 852–857.
- Esler M, Jennings G, Lambert G et al. (1990). Overflow of catecholamine neurotransmitters to the circulation: source, fate, and functions. *Physiol Rev* 70: 963–985.
- Farias da Silva W, Sampaio M, Costa Neto J et al. (2005). Migrânea. Sociedade Brasileira de Cefaléia, Rio de Janeiro.
- Friedman AP (1972). The headache in history, literature, and legend. *Bull N Y Acad Med* 48: 661–681.
- Gallai V, Sarchielli P, Firenze C et al. (1994). Endothelin I in migraine and tension-type headache. *Acta Neurol Scand* 89: 47–55.
- Garcia JJ, Reiter RJ, Guerrero JM et al. (1997). Melatonin prevents changes in microsomal membrane fluidity during induced lipid peroxidation. *FEBS Lett* 408: 297–300.
- Garcia-Segura LM, Chowen JA, Parducz A et al. (1994). Gonadal hormones as promoters of structural synaptic plasticity: cellular mechanisms. *Prog Neurobiol* 44: 279–307.
- Garcia-Segura LM, Naftolin F, Hutchison JB et al. (1999). Role of astroglia in estrogen regulation of synaptic plasticity and brain repair. *J Neurobiol* 40: 574–584.
- Gebhart GF (2004). Descending modulation of pain. *Neurosci Biobehav Rev* 27: 729–737.
- Giffin NJ, Ruggiero L, Lipton RB et al. (2003). Premonitory symptoms in migraine: an electronic diary study. *Neurology* 60: 935–940.
- Goadsby PJ (2007). Recent advances in understanding migraine mechanisms, molecules and therapeutics. *Trends Mol Med* 13: 39–44.
- Goadsby PJ, Duckworth JW (1987). Effect of stimulation of trigeminal ganglion on regional cerebral blood flow in cats. *Am J Physiol* 253: R270–274.
- Goadsby PJ, Zagami AS (1991). Stimulation of the superior sagittal sinus increases metabolic activity and blood flow in certain regions of the brainstem and upper cervical spinal cord of the cat. *Brain* 114: 1001–1011.
- Goldstein JM, Seidman LJ, Horton NJ et al. (2001). Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. *Cereb Cortex* 11: 490–497.
- Guedes RC (1984). On some conditions that influence cortical spreading depression. *An Acad Bras Cienc* 56: 445–455.
- Guedes RC, Amorim LF, Teodosio NR (1996). Effect of aging on cortical spreading depression. *Braz J Med Biol Res* 29: 1407–1412.
- Guedes RC, Amancio-Dos-Santos A, Manhaes-De-Castro R et al. (2002). Citalopram has an antagonistic action on cortical spreading depression in well-nourished and early-malnourished adult rats. *Nutr Neurosci* 5: 115–123.
- Hagiwara H, Funabashi T, Mitsushima D et al. (2007). Effects of neonatal testosterone treatment on sex differences in formalin-induced nociceptive behavior in rats. *Neurosci Lett* 412: 264–267.
- Handwerker HO, Kobal G (1993). Psychophysiology of experimentally induced pain. *Physiol Rev* 73: 639–671.
- Hasselblatt M, Kohler J, Volles E et al. (1999). Simultaneous monitoring of endothelin-1 and vasopressin plasma levels in migraine. *Neuroreport* 10: 423–425.
- Highley JR, Esiri MM, McDonald B et al. (1999). The size and fibre composition of the corpus callosum with respect to gender and schizophrenia: a post-mortem study. *Brain* 122: 99–110.
- Hoskin KL, Kaube H, Goadsby PJ (1996). Central activation of the trigeminovascular pathway in the cat is inhibited by dihydroergotamine. A c-Fos and electrophysiological study. *Brain* 119: 249–256.
- Hunnskaar S, Fasmer OB, Hole K (1985). Formalin test in mice, a useful technique for evaluating mild analgesics. *J Neurosci Methods* 14: 69–76.
- Isler H (1992). The Galenic tradition and migraine. *J Hist Neurosci* 1: 227–233.
- Iwasaki Y, Kinoshita M, Ikeda K et al. (1991). Thyroid function in patients with chronic headache. *Int J Neurosci* 57: 263–267.
- Jansen I, Alafaci C, Uddman R et al. (1990). Evidence that calcitonin gene-related peptide contributes to the capsaicin-induced relaxation of guinea pig cerebral arteries. *Regul Pept* 31: 167–178.
- Jansen I, Alafaci C, McCulloch J et al. (1991). Tachykinins (substance P, neurokinin A, neuropeptide K, and neurokinin B) in the cerebral circulation: vasomotor responses in vitro and in situ. *J Cereb Blood Flow Metab* 11: 567–575.
- Jansen I, Uddman R, Ekman R et al. (1992). Distribution and effects of neuropeptide Y, vasoactive intestinal peptide, substance P, and calcitonin gene-related peptide in human middle meningeal arteries: comparison with cerebral and temporal arteries. *Peptides* 13: 527–536.
- Jezova D, Michajlovskij N, Kvetnansky R et al. (1993). Paraventricular and supraoptic nuclei of the hypothalamus are not equally important for oxytocin release during stress. *Neuroendocrinology* 57: 776–781.
- Kai-Kai MA, Anderton BH, Keen P (1986). A quantitative analysis of the interrelationships between subpopulations of rat sensory neurons containing arginine vasopressin or oxytocin and those containing substance P, fluoride-resistant acid phosphatase or neurofilament protein. *Neuroscience* 18: 475–486.
- Kallela M, Farkkila M, Saijonmaa O et al. (1998). Endothelin in migraine patients. *Cephalalgia* 18: 329–332.
- Kaube H, Keay KA, Hoskin KL et al. (1993). Expression of c-Fos-like immunoreactivity in the caudal medulla and upper cervical spinal cord following stimulation of the superior sagittal sinus in the cat. *Brain Res* 629: 95–102.
- Kelman L (2007). The triggers or precipitants of the acute migraine attack. *Cephalalgia* 27: 394–402.

- Kendrick KM, Keverne EB (1989). Effects of intracerebroventricular infusions of naltrexone and phentolamine on central and peripheral oxytocin release and on maternal behaviour induced by vaginocervical stimulation in the ewe. *Brain Res* 505: 329–332.
- Klein P, Herzog AG (1998). Hormonal effects on epilepsy in women. *Epilepsia* 39 (Suppl. 8): S9–S16.
- Koehler PJ, van de Wiel TW (2001). Aretaeus on migraine and headache. *J Hist Neurosci* 10: 253–261.
- Lagreze HL, Dettmers C, Hartmann A (1988). Abnormalities of interictal cerebral perfusion in classic but not common migraine. *Stroke* 19: 1108–1111.
- Lambert GA, Bogduk N, Goadsby PJ et al. (1984). Decreased carotid arterial resistance in cats in response to trigeminal stimulation. *J Neurosurg* 61: 307–315.
- Lambert GA, Goadsby PJ, Zagami AS et al. (1988). Comparative effects of stimulation of the trigeminal ganglion and the superior sagittal sinus on cerebral blood flow and evoked potentials in the cat. *Brain Res* 453: 143–149.
- Lance JW (1985). The pathophysiology of migraine. *Ann Acad Med Singapore* 14: 4–11.
- Lance JW (1993). Current concepts of migraine pathogenesis. *Neurology* 43: S11–S15.
- Lance JW, Goadsby PJ (1998). *Mechanism and Management of Headache*. 6th edn. Butterworth-Heinemann, Oxford.
- Lang RE, Heil J, Ganten D et al. (1983). Effects of lesions in the paraventricular nucleus of the hypothalamus on vasopressin and oxytocin contents in brainstem and spinal cord of rat. *Brain Res* 260: 326–329.
- Larner AJ (2006). Thyroid dysfunction and headache. *J Headache Pain* 7: 51–52.
- Leone M, Lucini V, D'Amico D et al. (1995). Twenty-four-hour melatonin and cortisol plasma levels in relation to timing of cluster headache. *Cephalalgia* 15: 224–229.
- Leone M, D'Amico D, Moschiano F et al. (1996). Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. *Cephalalgia* 16: 494–496.
- Levy MJ, Knight YE, O'Shaughnessy CT et al. (2003). Effect of IL-1beta microinjection into the posterior hypothalamic area on trigeminal nociception in the rat. *J Neural Transm* 110: 1349–1358.
- Lin KC, Huang CC, Wu CC (2007). Association between stress at work and primary headache among nursing staff in Taiwan. *Headache* 47: 576–584.
- Lins Filho R (2000). [Analgesic actions of oxytocin.] In: *Physiology*, Federal University of Pernambuco, Recife, Brazil, p. 56. MSc thesis.
- Loder E (2002). What is the evolutionary advantage of migraine? *Cephalalgia* 22: 624–632.
- Lopez-Jimenez M, Valenca MM, Moreira AC et al. (1989). Ether and immobilization stress effects on pituitary adrenal function in hemidecorticate rats. *Braz J Med Biol Res* 22: 779–782.
- Lundeberg T, Meister B, Bjorkstrand E et al. (1993). Oxytocin modulates the effects of galanin in carrageenan-induced hyperalgesia in rats. *Brain Res* 608: 181–185.
- Lundeberg T, Uvnas-Moberg K, Agren G et al. (1994). Antinociceptive effects of oxytocin in rats and mice. *Neurosci Lett* 170: 153–157.
- Lyngberg AC, Rasmussen BK, Jorgensen T et al. (2005). Incidence of primary headache: a Danish epidemiologic follow-up study. *Am J Epidemiol* 161: 1066–1073.
- Madrazo I, Franco-Bourland RE, Leon-Meza VM et al. (1987). Intraventricular somatostatin-14, arginine vasopressin, and oxytocin: analgesic effect in a patient with intractable cancer pain. *Appl Neurophysiol* 50: 427–431.
- Martin-Araguz A, Bustamante-Martinez C, Emam-Mansour MT et al. (2002). [Neuroscience in ancient Egypt and in the school of Alexandria.] *Rev Neurol* 34: 1183–1194.
- Martin VT, Behbehani M (2006a). Ovarian hormones and migraine headache: understanding mechanisms and pathogenesis – part 2. *Headache* 46: 365–386.
- Martin VT, Behbehani M (2006b). Ovarian hormones and migraine headache: understanding mechanisms and pathogenesis – part I. *Headache* 46: 3–23.
- Matharu MS, Goadsby PJ (2005). Functional brain imaging in hemispheric continua: implications for nosology and pathophysiology. *Curr Pain Headache Rep* 9: 281–288.
- Matharu MS, Cohen AS, McGonigle DJ et al. (2004). Posterior hypothalamic and brainstem activation in hemispheric continua. *Headache* 44: 747–761.
- May A, Bahra A, Buchel C et al. (1998). Hypothalamic activation in cluster headache attacks. *Lancet* 352: 275–278.
- Mendizabal JE, Greiner F, Hamilton WJ et al. (1997). Migrainous stroke causing thalamic infarction and amnesia during treatment with propranolol. *Headache* 37: 594–596.
- Monnet FP (2002). Melatonin modulates [³H]serotonin release in the rat hippocampus: effects of circadian rhythm. *J Neuroendocrinol* 14: 194–199.
- Montagna P (2006). Hypothalamus, sleep and headaches. *Neurol Sci* 27 (Suppl. 2): S138–S143.
- Moreau T, Manceau E, Giroud-Baleyrier F et al. (1998). Headache in hypothyroidism. Prevalence and outcome under thyroid hormone therapy. *Cephalalgia* 18: 687–689.
- Moskowitz MA (1984). The neurobiology of vascular head pain. *Ann Neurol* 16: 157–168.
- Moskowitz MA (1990). Basic mechanisms in vascular headache. *Neurol Clin* 8: 801–815.
- Moskowitz MA (1991). The visceral organ brain: implications for the pathophysiology of vascular head pain. *Neurology* 41: 182–186.
- Moskowitz MA, Wei EP, Saito K et al. (1988). Trigeminallectomy modifies pial arteriolar responses to hypertension or norepinephrine. *Am J Physiol* 255: H1–H6.
- Mostallino MC, Mura ML, Maciocco E et al. (2006). Changes in expression of the delta subunit of the GABA (A) receptor and in receptor function induced by progesterone exposure and withdrawal. *J Neurochem* 99: 321–332.

- Mukai H, Takata N, Ishii HT et al. (2006). Hippocampal synthesis of estrogens and androgens which are paracrine modulators of synaptic plasticity: synaptocrinology. *Neuroscience* 138: 757–764.
- Murialdo G, Fonzi S, Costelli P et al. (1994). Urinary melatonin excretion throughout the ovarian cycle in menstrually related migraine. *Cephalalgia* 14: 205–209.
- Naftolin F, Garcia-Segura LM, Keefe D et al. (1990). Estrogen effects on the synaptology and neural membranes of the rat hypothalamic arcuate nucleus. *Biol Reprod* 42: 21–28.
- Nagtegaal JE, Smits MG, Swart AC et al. (1998). Melatonin-responsive headache in delayed sleep phase syndrome: preliminary observations. *Headache* 38: 303–307.
- Negro-Vilar A, Valença MM (1988). Male neuroendocrinology and endocrine evaluation of reproductive disorders. In: JC Lamb 4th, PM Foster (Eds.), *Physiology and Toxicology of Male Reproduction*. Academic Press, Orlando, pp. 103–136.
- Negro-Vilar A, Johnston C, Spinedi E et al. (1987). Physiological role of peptides and amines on the regulation of ACTH secretion. *Ann N Y Acad Sci* 512: 218–236.
- Olesen J (1982). Is ischemia involved in the pathogenesis of migraine? *Pathol Biol (Paris)* 30: 318–324.
- Olesen J, Iversen HK, Thomsen LL (1993). Nitric oxide supersensitivity: a possible molecular mechanism of migraine pain. *Neuroreport* 4: 1027–1030.
- Olsen TS, Friberg L, Lassen NA (1990). [Migraine aura – vascular or neuronal disease?] *Ugeskr Laeger* 152: 1507–1509.
- Pani L, Porcella A, Gessa GL (2000). The role of stress in the pathophysiology of the dopaminergic system. *Mol Psychiatry* 5: 14–21.
- Peres MF (2005). Melatonin, the pineal gland and their implications for headache disorders. *Cephalalgia* 25: 403–411.
- Peres MF, Rozen TD (2001). Melatonin in the preventive treatment of chronic cluster headache. *Cephalalgia* 21: 993–995.
- Peres MF, Seabra ML, Zukerman E et al. (2000). Cluster headache and melatonin. *Lancet* 355: 147.
- Peres MF, Sanchez del Rio M, Seabra ML et al. (2001a). Hypothalamic involvement in chronic migraine. *J Neurol Neurosurg Psychiatry* 71: 747–751.
- Peres MF, Stiles MA, Oshinsky M et al. (2001b). Remitting form of hemicrania continua with seasonal pattern. *Headache* 41: 592–594.
- Peres M, Zukerman E, da Cunha TF et al. (2004). Melatonin, 3 mg, is effective for migraine prevention. *Neurology* 63: 757.
- Peres MF, Masruha MR, Zukerman E et al. (2006). Potential therapeutic use of melatonin in migraine and other headache disorders. *Exp Opin Invest Drugs* 15: 367–375.
- Peroutka SJ (1997). Dopamine and migraine. *Neurology* 49: 650–656.
- Phillips WJ, Ostrovsky O, Galli RL et al. (2006). Relief of acute migraine headache with intravenous oxytocin: report of two cases. *J Pain Palliat Care Pharmacother* 20: 25–28.
- Pietrobon D (2005). Migraine: new molecular mechanisms. *Neuroscientist* 11: 373–386.
- Price DD, Von der Gruen A, Miller J et al. (1985). A psychophysical analysis of morphine analgesia. *Pain* 22: 261–269.
- Prodan CI, Holland NR, Lenaerts ME et al. (2002). Magnetic resonance angiogram evidence of vasospasm in familial hemiplegic migraine. *J Child Neurol* 17: 470–472.
- Rabe A, Fromter E (2000). Micromolar concentrations of steroids and of aldosterone antagonists inhibit the outwardly rectifying chloride channel with different kinetics. *Pflugers Arch* 439: 559–566.
- Raffaelli EJr, Menon AD (1975). Migraine and the limbic system. *Headache* 15: 69–78.
- Ramadan NM (2003). The link between glutamate and migraine. *CNS Spectr* 8: 446–449.
- Raskin NH, Hosobuchi Y, Lamb S (1987). Headache may arise from perturbation of brain. *Headache* 27: 416–420.
- Ray B, Wolff HG (1940). Experimental studies on migraine: pain sensitive structures of the head and their significance in headache. *Arch Surg* 41: 813–885.
- Reiter RJ, Calvo JR, Karbownik M et al. (2000). Melatonin and its relation to the immune system and inflammation. *Ann N Y Acad Sci* 917: 376–386.
- Rhodes ME, Rubin RT (1999). Functional sex differences ('sexual diergism') of central nervous system cholinergic systems, vasopressin, and hypothalamic–pituitary–adrenal axis activity in mammals: a selective review. *Brain Res Brain Res Rev* 30: 135–152.
- Richard P, Moos F, Freund-Mercier MJ (1991). Central effects of oxytocin. *Physiol Rev* 71: 331–370.
- Rodenbeck A, Huether G, Ruther E et al. (1999). Nocturnal melatonin secretion and its modification by treatment in patients with sleep disorders. *Adv Exp Med Biol* 467: 89–93.
- Rose FC (1995). The history of migraine from Mesopotamian to Medieval times. *Cephalalgia* 15 (Suppl. 15): 1–3.
- Rozen TD (2003). Melatonin as treatment for idiopathic stabbing headache. *Neurology* 61: 865–866.
- Rydzewski W (1976). Serotonin (5HT) in migraine: levels in whole blood in and between attacks. *Headache* 16: 16–19.
- Saito K, Liu-Chen LY, Moskowitz MA (1987). Substance P-like immunoreactivity in rat forebrain leptomeninges and cerebral vessels originates from the trigeminal but not sympathetic ganglia. *Brain Res* 403: 66–71.
- Sakai F, Meyer JS (1979). Abnormal cerebrovascular reactivity in patients with migraine and cluster headache. *Headache* 19: 257–266.
- Schmitterer L, Wolzt M, Graselli U et al. (1997). Nitric oxide synthase inhibition in the histamine headache model. *Cephalalgia* 17: 175–182.
- Schwartz-Giblin S, Korotzer A, Pfaff DW (1989). Steroid hormone effects on picrotoxin-induced seizures in female and male rats. *Brain Res* 476: 240–247.
- Selye H (1973). The evolution of the stress concept. *Am Sci* 61: 692–699.
- Shaikh AY, Xu J, Wu Y et al. (1997). Melatonin protects bovine cerebral endothelial cells from hyperoxia-induced DNA damage and death. *Neurosci Lett* 229: 193–197.

- Silberstein SD (1993). Headaches and women: treatment of the pregnant and lactating migraineur. *Headache* 33: 533–540.
- Silberstein SD, Lipton RB, Goadsby PJ (1998). *Headache in Clinical Practice*. ISIS Medical Media, Oxford.
- Sliwka U, Harscher S, Diehl RR et al. (2001). Spontaneous oscillations in cerebral blood flow velocity give evidence of different autonomic dysfunctions in various types of headache. *Headache* 41: 157–163.
- Smith MJ, Adams LF, Schmidt PJ et al. (2002). Effects of ovarian hormones on human cortical excitability. *Ann Neurol* 51: 599–603.
- Solomon GD (1992). Circadian rhythms and migraine. *Cleve Clin J Med* 59: 326–329.
- Spencer CM, Gunasekara NS, Hills C (1999). Zolmitriptan: a review of its use in migraine. *Drugs* 58: 347–374.
- Spierings EL (2004). The aura-headache connection in migraine: a historical analysis. *Arch Neurol* 61: 794–799.
- Stocche RM, Klamt JG, Antunes-Rodrigues J et al. (2001). Effects of intrathecal sufentanil on plasma oxytocin and cortisol concentrations in women during the first stage of labor. *Reg Anesth Pain Med* 26: 545–550.
- Strebel PM, Zacur HA, Gold EB (1986). Headache, hyperprolactinemia, and prolactinomas. *Obstet Gynecol* 68: 195–199.
- Strong AJ, Fabricius M, Boutelle MG et al. (2002). Spreading and synchronous depressions of cortical activity in acutely injured human brain. *Stroke* 33: 2738–2743.
- Suzuki N, Hardebo JE, Owman C (1989). Origins and pathways of cerebrovascular nerves storing substance P and calcitonin gene-related peptide in rat. *Neuroscience* 31: 427–438.
- Suzuki N, Hardebo JE, Kahrstrom J et al. (1990). Selective electrical stimulation of postganglionic cerebrovascular parasympathetic nerve fibers originating from the sphenopalatine ganglion enhances cortical blood flow in the rat. *J Cereb Blood Flow Metab* 10: 383–391.
- Suzuki N, Shimizu T, Takao M et al. (2002). Neurokinin-1 receptors in the cerebrovascular vasoactive intestinal polypeptide-containing nerves in the rat. *Auton Neurosci* 95: 103–111.
- Swica Y (2007). The transdermal patch and the vaginal ring: two novel methods of combined hormonal contraception. *Obstet Gynecol Clin North Am* 34: 31–42, viii.
- Tamaki K, Heistad DD (1986). Response of cerebral arteries to sympathetic stimulation during acute hypertension. *Hypertension* 8: 911–917.
- Taylor BK, Basbaum AI (2003). Systemic morphine-induced release of serotonin in the rostroventral medulla is not mimicked by morphine microinjection into the periaqueductal gray. *J Neurochem* 86: 1129–1141.
- Thomas TD, Harpold GJ, Troost BT (1990). Cerebrovascular reactivity in migraineurs as measured by transcranial Doppler. *Cephalalgia* 10: 95–99.
- Thompson D, Lettich L, Takeshita J (2003). Fibromyalgia: an overview. *Curr Psychiatry Rep* 5: 211–217.
- Thomsen LL, Iversen HK, Brinck TA et al. (1993). Arterial supersensitivity to nitric oxide (nitroglycerin) in migraine sufferers. *Cephalalgia* 13: 395–399; discussion 376.
- Thorley V (1997). Lactational headache: a lactation consultant's diary. *J Hum Lact* 13: 51–53.
- Totaro R, Marini C, De Matteis G et al. (1997). Cerebrovascular reactivity in migraine during headache-free intervals. *Cephalalgia* 17: 191–194.
- Turek FW, Dugovic C, Zee PC (2001). Current understanding of the circadian clock and the clinical implications for neurological disorders. *Arch Neurol* 58: 1781–1787.
- Tzourio C, El Amrani M, Poirier O et al. (2001). Association between migraine and endothelin type A receptor (ETA-231 A/G) gene polymorphism. *Neurology* 56: 1273–1277.
- Uvnas-Moberg K, Petersson M (2005). [Oxytocin, a mediator of anti-stress, well-being, social interaction, growth and healing.] *Z Psychosom Med Psychother* 51: 57–80.
- Uvnas-Moberg K, Bruzelius G, Alster P et al. (1993a). The antinociceptive effect of non-noxious sensory stimulation is mediated partly through oxytocinergic mechanisms. *Acta Physiol Scand* 149: 199–204.
- Uvnas-Moberg K, Lundeberg T, Bruzelius G et al. (1993b). Low doses of ethanol may induce anti-nociceptive effects via an oxytocinergic mechanism. *Acta Physiol Scand* 149: 117–118.
- Valença MM, Ching M, Masotto C et al. (1987a). How does the gonad affect LHRH secretion? Effects of gonadectomy on LHRH release from median eminence nerve terminals incubated in vitro and on LHRH concentration in hypophyseal portal blood. *Adv Exp Med Biol* 219: 617–621.
- Valença MM, Johnston CA, Ching M et al. (1987b). Evidence for a negative ultrashort loop feedback mechanism operating on the luteinizing hormone-releasing hormone neuronal system. *Endocrinology* 121: 2256–2259.
- Valença MM, Dias MH, Araújo AMB et al. (1999). [Analgesia induced by immobilization and surgical stress: participation of the endogenous opioid system.] *An Fac de Med UFPE* 44: 97–102.
- Valença MM, Valença LP, Menezes TL (2002). Computed tomography scan of the head in patients with migraine or tension-type headache. *Arq Neuropsiquiatr* 60: 542–547.
- Valença MM, Valença LPAA, Bordini CA et al. (2003). [Poor control headache.] *Migrãneas Cefaléias* 6: 117–120.
- Valença MM, Ferreira AV, Betti KCM et al. (2005). [A new experimental model of headache in rat: evidence of the activation of the analgesic endogenous system by the headache.] *Rev Dor* 6: 688–695.
- Valença MM, Andrade-Valença LP, da Silva WF et al. (2007). Hemicrania continua secondary to an ipsilateral brainstem lesion. *Headache* 47: 438–441.
- van Bree JB, de Boer AG, Verhoef JC et al. (1989). Transport of vasopressin fragments across the blood–brain barrier: in vitro studies using monolayer cultures of bovine brain endothelial cells. *J Pharmacol Exp Ther* 249: 901–905.
- Velisek L, Veliskova J, Moshe SL et al. (1998). Prenatal morphine exposure alters ovarian steroid hormonal regulation of seizure susceptibility. *Brain Res* 796: 247–256.

- Wahl M, Schilling L (1993). Regulation of cerebral blood flow – a brief review. *Acta Neurochir Suppl* 59: 3–10.
- Waldenlind E, Gustafsson SA, Ekbom K et al. (1987). Circadian secretion of cortisol and melatonin in cluster headache during active cluster periods and remission. *J Neurol Neurosurg Psychiatry* 50: 207–213.
- Waldenlind E, Ekbom K, Wetterberg L et al. (1994). Lowered circannual urinary melatonin concentrations in episodic cluster headache. *Cephalalgia* 14: 199–204.
- Wei EP, Kontos HA, Christman CW et al. (1985). Superoxide generation and reversal of acetylcholine-induced cerebral arteriolar dilation after acute hypertension. *Circ Res* 57: 781–787.
- Witt DM, Winslow JT, Insel TR (1992). Enhanced social interactions in rats following chronic, centrally infused oxytocin. *Pharmacol Biochem Behav* 43: 855–861.
- Wober C, Brannath W, Schmidt K et al. (2007). Prospective analysis of factors related to migraine attacks: the PAMINA study. *Cephalalgia* 27: 304–314.
- Woolley CS, Weiland NG, McEwen BS et al. (1997). Estradiol increases the sensitivity of hippocampal CA1 pyramidal cells to NMDA receptor-mediated synaptic input: correlation with dendritic spine density. *J Neurosci* 17: 1848–1859.
- Xu XJ, Wiesenfeld-Hallin Z (1994). Is systemically administered oxytocin an analgesic in rats? *Pain* 57: 193–196.
- Yang J (1994). Intrathecal administration of oxytocin induces analgesia in low back pain involving the endogenous opiate peptide system. *Spine* 19: 867–871.
- Zagami AS, Goadsby PJ, Edvinsson L (1990). Stimulation of the superior sagittal sinus in the cat causes release of vasoactive peptides. *Neuropeptides* 16: 69–75.
- Zimmermann M, Seifert V (1998). Endothelin and subarachnoid hemorrhage: an overview. *Neurosurgery* 43: 863–875; discussion 875–866.
- Zisapel N (2001). Melatonin–dopamine interactions: from basic neurochemistry to a clinical setting. *Cell Mol Neurobiol* 21: 605–616.