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# Primary Headaches and their Relationship with the Autonomic Nervous System

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Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/65737>

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## Abstract

Headache disorders, described as early as 3000 BC, represent both a treatment challenge and a serious public health concern, with impact on the individual and society. Existing research in primary headache syndromes (not being caused by any underlying problem) focuses mainly on pain mechanisms. However, the painful symptomatology is the main encounter for the decreased quality of life and discomfort, the vegetative manifestations that frequently accompany the cephalalgic syndromes represent an important source of distress. Despite the advancement of the understanding of the molecular basis of headache disorders and neurovascular complex interactions, there is still lack of a cohesive understanding of the neurovegetative modulation in different types of primary cephalalgic syndromes. The aim of this chapter is to present an overview of the neurochemical mechanisms and pathways, which subtend dysautonomic manifestations in headache.

**Keywords:** headache, autonomic dysfunction, neurovascular system, heart rate variability, sympathetic nervous system

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## 1. Introduction

The foundation of our current understanding of the mechanisms of headache dates back to seventeenth century, when Thomas Willis, one of the great figures in medicine, proposed that the source of pain was not the brain itself, but nerve fibers being pulled by the distended vessels. He therefore postulated the vascular theory of headache. It is known today that the

autonomic manifestations of the vascular headaches are provoked by the tight connections between the pain receptors located at the head level and the autonomic structures of the central nervous system. The primary cephalgic syndromes with vascular implications (migraine, cluster headache, SUNCT, and paroxysmal hemicrania) present intricate pathogenic mechanisms, involving autonomic centers of the brain stem. Therefore, headache's complex manifestations must be understood based on anatomical and physiological correlations with pain sensitive structures of the cranium.

Primary headaches define “idiopathic” types of cephalgia, which are not the result of an underlying disease or process. However, these conditions seem to be the result of a complex interaction among genetic, developmental, and environmental risk factors. The World Health Organisation (WHO) considers headache disorders as a major public-health concern, given the individual and social impact and financial costs to society [1]. Migraine—one of the most common primary headaches—is now ranked by the WHO as number 19 among all diseases worldwide causing disability.

During the last years, the classification of headaches has undergone a dynamic process of restructuration, more detailed specifications to each entity being gradually added, due to the advancement in the understanding of the pathophysiological mechanisms. The International Headache Society (IHS) classifies primary headaches into four main categories: migraine (with its subtypes), tension-type headache, cluster headache and other trigeminal autonomic cephalgias, and other primary headaches [2].

Migraine is characterized by attacks of moderate to severe unilateral and pulsatile headache lasting for 4–72 h, which is often associated with photophobia, phonophobia, nausea, and vomiting. In migraine with aura, the headache may be preceded by transient focal neurological symptoms. Trigeminal autonomic cephalgias (TACs) are a group of primary headaches characterized by lateralized headache and ipsilateral cranial autonomic features such as conjunctive injection, lacrimation, and rhinorrhea. The main subtypes are represented by cluster headache, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)/short-lasting unilateral neuralgiform headache attacks with cranial autonomic features (SUNA), and hemicrania continua [2]. The TACs are distinguished from each other by their attack length, duration, and frequency of occurrence [2].

Preclinical studies in primary headaches highlighted the complex and intricate mechanisms involving the anatomy and physiology of trigeminovascular and cranial autonomic systems responsible for a variety of symptoms [3–5]. The nociceptive innervation of intracranial vessels and the meninges is based on unmyelinated (C-fibers) and thinly myelinated (A $\delta$  fibers) axons containing vasoactive neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP) [6]. Besides the trigeminal fibers originating in the ipsilateral trigeminal ganglion, neurovegetative fibers formed mainly by sympathetic tracts arising mainly from the superior cervical ganglion and a rather sparse innervation by parasympathetic fibers originating in the sphenopalatine and otic ganglia have been described [7, 8]. The innervation of intracerebral (pial) blood vessels has also an autonomic component, represented mainly by

parasympathetic fibers coming principally from the internal carotid and sphenopalatine ganglia [9].

However, despite an increasing body of data concerning the morphofunctional organization of the pain system in headache, the episodic and rather unpredictable manifestations of most primary headaches still represent a clinical and therapeutic challenge. There are numerous hypotheses at different levels, from molecular signaling to brain networks, with more and more data defining the “pain matrix” as a top-down system, implying both central and peripheral structures, from impairment in the functional connectivity during resting state (default mode network) to neurogenic inflammation mediating vasodilatation and increased permeability of blood vessels [10, 11].

## **2. Complex neurovascular interactions in primary headaches: migraine as a pathophysiological model**

Primary headaches share many similarities, primarily trigeminovascular activation. While migraine is the most studied of all primary headaches, from both a clinical and a preclinical perspective, there have been advances in our understanding of the pathophysiology of tension-type headache and the trigeminal autonomic cephalalgias, through a combination of clinical studies and preclinical animal models.

Migraine is a complex primary brain disorder that involves a cascade of events that lead to recurrent inappropriate activations of the trigeminocervical pain system. As any other pain, it is perceived differently by each patient. Conceived as an alarm system of the body, the pain may become, at some point, an aggressor factor of the own body by the reflex reactions that it can trigger. It is well known that the pain perception is dependent not only on the intensity of the stimulus, but also on a multitude of genetic, psychological associated factors (emotional state and attention), on anterior experiences, memories, associations with facts of life, and comorbidities. The stimulation of the nociceptors in teguments, vessels, and joints leads the stimulus on known sensitive paths toward the parietal cortex, but a series of regulating neural mechanisms intervene both at the cortical level and on the route of the stimulus, trying to adapt the perception of the pain sensation to the individual body homeostasis. Which are those structures and whether they can be influenced represent the concern of scientists for decades.

The meningeal vessels have a motor and sensitive innervation by the trigeminal terminations (ophthalmic branches for the anterior and posterior compartment, the cervical C2, C3 nerve roots, with sympathetic fibers from the paravertebral sympathetic chain-contributing for the posterior part), which, in the end, establish connections with the secondary trigeminal neurons from the caudal trigeminal nucleus. Trigeminal nucleus is made up of the spinal portion in the converging information about pain and temperature and the pontine region with tactile information. The dendrites of the bipolar neurons from Gasser ganglia receive input from the pain receptors of dura mater and craniofacial structures, but also from the vascular wall and they direct it to trigeminal nucleus, thalamus, and contralateral parietal cortex (and in the same time collateral projections also target mesencephalic nuclei), including the dorsal reticular

nucleus (DRt), the rostral ventral medulla (RVM), and the midbrain periaqueductal gray (PAG) [12–14].

The motor component of the cerebrovascular system implies an extrinsic innervation of the meningeal vessels, from the cervical (sympathetical), otic, sphenopalatin, and trigeminal ganglia (parasympathetical) and an intrinsic innervation for the small intraparenchymatous vessels, derived from brain stem nuclei such as locus coeruleus [15].

Cerebral blood flow (CBF) is regulated by vasomotor, chemical, metabolic, and neurogenic mechanisms, but under normal physiological conditions neurogenic control has little influence on cerebral autoregulation as other methods of control are dominant [16].

There is considerable experimental literature to document that stimulation of trigeminal afferents can result in cranial autonomic outflow, the trigeminal–autonomic reflex.

From the time of the stimulation of the nociceptive endings until the perception of the pain sensation, the transmission of the signal is modified by a series of mechanisms with the final aim of improving the painful sensation.

### 3. Nociceptive system modulation in primary headaches

Known in a great measure, the endogenous antinociceptive system is organized on three levels: first, supraspinal descending inhibition; second, segmental spinal inhibition (inhibitor complex of the pain in the posterior horn of the spine), and third, propriospinal, heterosegmental inhibition-supraspinal descending inhibition system.

The experimental studies, using pharmacological techniques, inhibitors, electrical stimulators, and functional neuroimaging techniques, revealed the existence of a complex system of pain modulation, a real neuronal matrix that is highly activated at the arrival of a nociceptive stimulus. This network is a dynamic and plastic connection between different neuronal relays and it is also involved in other higher nervous activities: cognition, emotion, and motivation. The pain network, with an anatomical basis still partially known, involves a series of neuro-modulators and receptors and may be influenced both pharmacologically (including opiates, cannabinoids, NSAIDs, and serotonin/norepinephrine reuptake blockers) and mentally and emotionally, ultimately determining the sensation of pain [17].

Anatomically, the parietal cortex 1 and 2, insular lobe, thalamus, hypothalamus, amygdala, and the rostral anterior cingulate cortex (rACC) send messages to the periaqueductal gray matter (PAG) from where the descending inhibitor stimulus is transmitted to the trunk (sensory trigeminal core) and rostral bone marrow, with descending inhibitory projection on the medullar posterior horn.

The periaqueductal gray matter is a real center for holistic integration of the painful sensation because it has connections with the prefrontal cortex and amygdala, which, in turn, have a recognized role in the integration of emotions, anxiety, and risk assessment with avoidance [18].

Fields et al. [19] have identified in the rostral cervical region the existence of two neuronal populations with different functional roles: population “on” which increases its discharges before initiating the nociceptive reflex, and the population “off” which reduces its discharges when responding to the pain and whose activation produces analgesia. The population “on” is represented by the  $\mu$ -opioid receptors whose activation inhibits the discharges of these neurons. Opioids and cannabinoids inhibit pain by enhancing the baseline firing rate of “off”-cells and eliminating the “off”-cells pause in response to nociceptive stimuli [20]. In these interdependent connections, a series of neuromediators may have multiple actions, such as serotonin and norepinephrine, but also other aminergic systems.

The PAG and RVM stimulation determine the release of serotonin, as the nucleus raphe magnus located near the trigeminal nucleus, in the bilateral inferior arch, releases serotonin with a possible role in the process of endogenous analgesia. The functional neuroimaging using BOLD technique revealed the activation of the nucleus as answer to the trigeminal painful stimulation suggesting its role [14, 21, 22].

Conversely, the implication of serotonin in stimulating the PAG and RVM neurons is not fully understood, but it is obvious that other nonserotonergic systems are involved in modulating the pain. Serotonin could be both inhibitory and facilitating the pain depending on the subtype of receptors excited. That GABAergic and glycinergic projections from the RVM mediate antinociception [23].

Norepinephrine released by the locus coeruleus and Kölliker-Füse nuclei under the impulses arrived from PAG and RVM seem to have a strong antinociceptive role by blocking the pre- and postsynaptic receptors of the spinal neurons involved in transmitting the pain or by stimulating the alpha-2-adrenergic receptors and indirectly by stimulating the alpha-1-receptors, which will cause the depolarization of inhibitory GABAergic neurons [23].

### **3.1. Segmental spinal inhibition**

At the posterior horn of the spine, the endogenous antinociceptive system is represented by interneurons and the supramedullary descending endings. The opioids act on  $\mu$  receptors located on the presynaptic endings of the related fibers where it blocks the calcium channels and open the potassium channels producing a hyperpolarization by inhibiting the release of neurotransmitter and thus analgesia. The endogenous analgesic system that is usually inactive and whose center is PAG projects from it axons (enkephalin conductors) to the raphe magnus nucleus, and from here to the interneurons from the posterior horn where they can secrete serotonin facilitating the release of enkephalins from the spinal interneurons. The interneurons receive external nociceptive fibers and the enkephalins from the two sources are blocking presynaptically the nociceptive signal. The stimulation of the opioid receptors from the related nociceptive fibers by enkephalin will determine the same blockage of the calcium channels whose activation is also necessary for releasing the substance P [24]. Supraspinal descending inhibition may not only depress mean discharge rates of nociceptive spinal dorsal horn neurons, but also may modify harmonic oscillations and nonlinear dynamics (dimensionality) of discharges [25].



### 3.2. Propriospinal, heterosegmental inhibition

Besides the classical, local, segmental, and supraspinal descending systems, it seems that there is a third endogenous antinociceptive system: propriospinal, intersegmental system inhibiting the nociceptive neurons in the dorsal horn. It seems to modulate partially the descending pathways and it is activated by conditioning (stimulating) the heterosegmental painful stimuli causing a neuronal contrastimulation (counterirritation) [25].

This multistage organization of the endogenous antinociceptive system can be influenced with beneficial results or it can be demodulated resulting in pain exacerbation.

The new functional neuroimaging techniques have showed the influence of the placebo-type psychogenic factor that cause the activation of the descending inhibitory network with the stimulation of the  $\mu$ -opioids in rostral anterior cingulate cortex (rACC), the posterior cingulate cortex (PCC), the dorsolateral prefrontal cortex, and the anterior insular cortex with the increase of the blood flow in PAG also. Similarly, the reverse reaction of waiting, anticipation of a painful sensation determines a tendency to inhibition similar to that of an intense stimulation (nocebo effect) [26].

In patients with migraine, interictal, the functional MRI studies revealed an increase in the nociceptive diffuse activity mediated in different ways [27]. Another way of modulating pain is represented by “the nociceptive diffuse control of the pain.” The concept, issued by Le Bars since the 8th decade of the last century refers to the wide dynamic range inhibition of neurons from the dorsal horn responsive to a painful stimulation by a nociceptive stimulus applied elsewhere in the body. The inhibition mechanism seems to be central and its loss is involved in the chronic painful syndromes, but also in the becoming chronic and of medication-overuse headache [28, 29]. This system is integrated in the dorsal reticular nucleus which receives nociceptive information from the marrow and communicates with PAG and RVM, amygdala, thalamus, and finally inhibiting the marrow by descending projections. The neurons in dorsal reticular nucleus (DRt) establish connections with the cortex and multiple central nervous system areas involved in modulating the pain—the spino-supraspinatus loop [30].

Perrotta et al. [31] found the existence of a process of central sensitizing of the pain pathways, with the abnormal and facilitating processing of the stimuli in the trigeminal nucleus both in crisis and interictally, suggesting a chronic hyperexcitability possibly conditioned genetically with dysfunctional consequences on the antinociceptive modulating system [32].

It is possible that this demodulation of the nociceptive stimulus processing to be due to a defect of the default mode network, claim supported by the neuroimaging morphofunctional studies which revealed metabolic changes in the brain areas involved in processing the pain. The default mode network consists of a series of relays (part of the medial temporal lobe, part of the medial prefrontal cortex, and the posterior cingulate cortex, along with the adjacent ventral precuneus and the medial, lateral, and inferior parietal cortex) whose anatomical bases are intertwined with the pain processing pathways. The current data suggest that the network is active when the individual is not focused on the outside world and the brain is at wakeful rest and it is possible that it participates in the basic settings of the main brain functions [33].

The hypothalamus, the vegetative brain, establish direct anatomical connections with the trigeminal structures and it is involved in a variety of cerebral functions with vegetative component including regulating the vasomotricity and processing of pain, maintaining the homeostasis. The recent studies have found that there is a disorder of its functional connectivity with the vegetative structures, in the sense of its increasing or decreasing, all being able to disorder the processing of exteroceptive stimuli, especially those painful [34–37].

The hypothalamus is also connected with the sympathetic cerebral structures, such as the parahippocampal gyrus and cerebellar peduncle. The accentuation of connectivity with these centers, found in patients with migraine could prevail in the cortical answer to external nociceptive stimuli. The finding was made by BOLD neuroimaging studies, by increasing the activity in these structures both in sympathetic stimulation and at rest. Similarly, there have been found hyperexcitable connections (enhanced functional connectivity) with parasympathetic structures (temporal pole, superior temporal gyrus, and cerebellar lobules V and VI) ultimately determining a disorder of the processing of internal stimuli in patients with migraine, explaining some features of reaction of the patient to external stimuli [38].

Locus coeruleus, the largest noradrenergic nucleus in the brain is connected by anatomical structures with the hypothalamus, with which it establishes hyperfunctional connections. Involved in modulating the neuronal discharges from thalamus and prefrontal cortex as response to the nociceptive stimuli and in the inhibition of the nociceptive reflexes, it may have an important role in processing the pain in patients with migraine [39]. The caudate nucleus recently involved in processing the pain has also hyperfunctional connectivity with the hypothalamus suggesting an involvement in the chronobiology of migraine [40].

On the other hand, a decrease in the functional connectivity with various cerebral structures (cortical regions in the frontal and occipital regions) was found where hypofunctions were found. No one can say for now that hypothalamus plays in migraine a role similar to vascular face algias, but it certainly interferes with the processing of the pain and it is responsible for a part of the vegetative manifestations in the migraine and their relationship with the human psyche. The disorder could be due to the large amount of information received from the neurons of the spinal trigeminal nucleus, repeated activation during the attacks, and a phenomenon of central sensitizing of the hypothalamic and autonomic connections [41].

In addition to the fast synaptic transmission mediated by classic neurotransmitters, the extra synaptic transmission of chemical signals such as neuropeptides could act a key role for long-term effects following intense noxious stimulation. These extra synaptic peptides, among their intrinsic vascular activity, also increase the excitability of neurons in the dorsal horn and trigger the expression of the immediate-early genes, thus changing the underlying chronicity of the pain.

The transmission of the nerve signal to the trigeminal neurons also involves the presence of some peptides with strong vasodilatory action of the cerebral vessels, the essential link in the pathogenesis of the primary cephalalgias. These peptides (calcitonin gene-related peptide—CGRP, substance P (SP), and neurokinin A—NKA) are often secreted by the same neuron, in



different quantities and combinations giving them a remarkable functional diversity. Calcitonin gene-related peptide is the most potent vasodilator transmitter identified in the cerebral circulation, and its action is endothelium independent and associated with an increase in vessel wall cyclic AMP [42–44].

Substance P is a nondecapeptide involved in nociceptive transmission. In many vascular beds, including the cerebral bed, substance P is a potent vasodilator and it also dilates both arteries and veins *in situ* [45]. Substance P can induce protein extravasation in the periphery and a similar response is seen in the dura with protein extravasation and mast cell degranulation [46]. Neurokinin A can relax cerebral vessels both *in vitro* and *in vivo*, although it is only one-tenth as potent as substance P [47]. Both substance P and NKA coexist in perivascular nerve fibers in peripheral and cerebral vessels [48].

It is possible that the antinociceptive system to be activated not only by direct stimulation, but also by disinhibition in PAG. By researching the expression of the protein c-FOS in the activated neurons, patterns different from the neuronal activity in the structures involved in controlling analgesia were found. The existence of these patterns different from the neuronal discharge especially in the spine and finding a background noise have suggested the existence of a tonic activity of the most nociceptive neurons in the posterior horn of the marrow determined by the supraspinal continuous discharges of the endogenous antinociceptive system defining the hypothesis of “prophylactic antinociceptive system” [49].

#### 4. Autonomic system dysfunction in primary headaches

The precise involvement of autonomous nervous system (ANS) in different types of primary headaches is still a subject of debate, as there is still not a clear-cut explanation of the differences found across various studies, both in humans and in animals, concerning the modulation of sympathetic and parasympathetic nervous system. The different results on dysautonomic mechanisms in headache patients can be partially explained by the numerous methods used to quantify the ANS activity, therefore generating specific results for different systems, such as cardiac (e.g., heart rate variability), cardiovascular (e.g., hypotension), pupillary response, and also by the different time-related variations with impact on the vegetative system dynamics [50, 51].

Autonomic dysfunction of different primary headache types have been investigated in several studies, most of them analyzing cardiovascular reflex mechanisms or biochemical changes [52–54]. It is known today that different subtypes of primary headaches share common autonomic mechanisms implying different endogenous molecules and dysfunctional interactions between vegetative pathways and brain-vessel system [55]. Findings indicate as central mechanisms both sympathetic hyperfunction and parasympathetic hypofunction in autonomic manifestations of headache patients [56, 57].

#### 4.1. Sympathetic nervous system and headache

The sympathetic tracts involved in the vascular regulation in headache arise mainly from the ipsilateral superior cervical ganglion, while some nerve fibers that supply the vertebral and basilar arteries originate from the inferior cervical ganglion and the stellate ganglion [58, 59].

The vascular dynamics and regulation of the intracranial pressure are mediated by noradrenaline (NA) and neuropeptide Y (NPY) [60, 61]. Neuropeptide Y is widely distributed throughout sympathetic nerve endings together with NA and it is considered a marker of noradrenergic function. It has been shown that both mediators may be externally influenced, for instance, by sympathectomize, which in turns, stimulates the expression of parasympathetic fibers [62]. NPY participates in the autonomic control of cerebral circulation and can be involved in disorders characterized by neurogenically mediated changes in the cerebral blood flow, such as migraine, cluster headache, and stroke. Decreased NPY concentrations during symptoms-free periods bring further evidence of the dysregulation of the sympathetic function in the course of migraine. The levels of NPY increase during attacks in migraine patients [63]. Microscopic and functional studies have revealed that NPY expression becomes prominent with the increase of sympathetic activity [64]. Furthermore, it has been proven that NA modulates the response of the small pial vessels on the cortical surface and that sympathetic fibers arise from central sources such as locus coeruleus (LC) or the hypothalamus [65–67]. Therefore, via direct influence, destruction of the LC induces a reduction in the number of noradrenergic nerve fibers in intracerebral vessels [59], while on contrary that stimulation of NA neurons in the hypothalamus is associated with an increase in hypothalamic blood flow which is not influenced by superior cervical ganglionectomy or by the  $\beta$ -adrenoceptor antagonist propranolol [68]. These anatomic and physiological features showing central control may represent possible therapeutic targets in primary headaches.

#### 4.2. Parasympathetic nervous system

As it is well known, cerebral blood vessels display perivascular nerves presenting parasympathetic activity (mediated by acetylcholine and acetylcholinesterase activity [69, 70]). The vast majority of parasympathetic nerve fibers to cerebral vessels implied sphenopalatine and otic ganglia [71]. Interesting enough, it has been shown that parasympathetic nerves may interact with sympathetic terminals in the close vicinity of the cerebrovascular smooth muscle effector [71]. Activation of trigeminal nerves and subsequent nociceptive signaling mediates a parasympathetic reflex leading to the release of vasoactive neuropeptides [9, 72, 73]. Vasodilatation of the cranial vessels seems a common property of cranial neurovascular dynamics involving sensory and parasympathetic mechanisms [44, 74].

Along with acetylcholine, there are other neuro messengers that mediate neurogenic vasodilatation, such as vasoactive intestinal peptide (VIP), pituitary adenylate cyclase activating polypeptide (PACAP), and nitric oxide (NO), as demonstrated both by experimental responses of isolated cerebral arteries and by hemodynamic measurements *in vivo* [75–77]. VIP is one of the parasympathetic signaling transmitters contributing to cranial parasympathetic outflow mediated through the sphenopalatine ganglia. It has been shown that VIP coexists with Ach in the perivascular nerve fibers around brain vessels [78]. Although, the VIP-immunoreactive

nerve supply is sparse in cerebral arteries or veins, it is considered that VIP concentrations are a marker of parasympathetic activation in migraine [79–81].

### 4.3. Pathogenic autonomic mechanisms in headache

Large body of data suggests a central role for sensory and parasympathetic mechanisms in the pathophysiology of primary headaches. Studies have provided support for a dysbalance between parasympathetic and sympathetic nervous system, which trigger the pathogenic mechanisms and contribute to the clinical presentation in primary headaches. The activation of the parasympathetic cranial outflow during migraine and cluster headache (CH) attacks seems to be due to the activation of the trigeminovascular system, which was described previously. This implies the release of specific neuromediators, such as the neuropeptide calcitonin gene-related peptide (CGRP) [82].

Some studies used transcranial Doppler sonography to assess vascular oscillations corresponding to myogenic cerebrovascular regulation in migraine and tension-headache patients [55, 83]. Most of the data focus on migraine, a chronic neurovascular disorder, which is classically considered the result of the sympathetic system unbalance, generally meaning increased sympathetic activity, although some studies showed decreased sympathetic activity [53, 57]. Both in the prodromal phase and in the headache phase of a migrainous episode, there are vegetative symptoms, such as hunger, sleepiness, and orthostatic hypotension initially, and later, in the headache phase, vomiting and nausea, pointing out a close relationship between the ANS and this type of headache [2]. The autonomic manifestations imply decreased plasma noradrenaline levels and increased adrenergic receptor sensitivity [53]. There are still contradictory data on the exact involvement of sympathetic system in migraine. Some studies investigated cardiac and cardiovascular reactions during vagal and sympathetic activation [84]. An increased basal sympathetic tone is also suggested by a frequent association of hypertension with migraine [85]. However, the association of migraine with blood pressure variations is still unclear, as there are studies showing an increased diastolic blood pressure in migraine and also an association of migraine with lower blood pressure [85]. Sympathetic hypofunction has been reported for migraine in studies of pupil diameter [82, 86], cardiovascular reflex responses, and heart rate recovery [87]. The heart rate variability in migraine patients across a longer time period was different compared to healthy controls during normal daily activity, which pointed out parasympathetic hypofunction in migraine patients [88].

Sympathetic skin responses [89] and salivary amylase levels as marker of sympathoadrenal medullary activity [90] seem decreased during migraine attacks, suggesting the dynamic involvement of the sympathetic system in this pathology.

Gass and Glaros [91] examined different vegetative biomarkers such as the heart rate variability, skin temperature, skin conductance, and respiration in patients with migraine and compared to healthy controls, and found in migraine patients a decreased variability of the consecutive R-to-R intervals, therefore pleading for a sympathetic hyperfunction and decreased parasympathetic tone in migraine patients [91]. Yerdelen et al. [87] examined heart rate recovery after physical exercise as an index for vagal parasympathetic activity in migraine

and tension-type headache patients (TTH) and controls and showed that even though parasympathetic function has not been affected in migraine and TTH patients, sympathetic tone in migraine patients is elevated compared to patients with episodic tension-type headache [87].

In an interesting study, Tomé-Pires and Miró [92] measured skin conductance responses (SCRs) in migraine versus control subjects while presenting pain descriptors, emotional negative words, and neutral words [92]. The authors showed no differences in the skin conductance responses in the two groups, but migraineurs recalled more emotional words than controls, thus suggesting possible new avenues to modulate migraine pain perception and autonomic responses.

#### **4.4. Cluster headache**

This type of headache implies the ophthalmic division of the trigeminal nerve responsible for the pain manifestations. In addition, there are signs of parasympathetic over activity acting on the facial and cranial vasculature, such as lacrimation, nasal congestion, and injection of the eyes [2]. Cranial parasympathetic systems may be involved in mediating these dysfunctions, with the release of the VIP stimulating vasomotor facial symptoms [93]. Furthermore, it has been shown that noxious chemical stimulation of rat facial mucosa increases intracranial blood flow through a trigemino-parasympathetic reflex, which may explain the involvement of autonomic pathway [94]. Animal models used superior salivatory nucleus as a model to measure cranial autonomic symptoms and changes in blood flow in the lacrimal gland/duct as a measure of cranial autonomic activation [95]. The superior salivatory nucleus projects to the cranial vessels through the sphenopalatine ganglion, via the greater petrosal nerve of the facial nerve. Electrophysiological methods measured neural activity in response to superior salivatory nucleus stimulation. There were two populations of neurons with differential latencies in action. The longer latency neuronal response was mediated by activation of the parasympathetic outflow and that the action of oxygen—as the therapeutic approach, is likely via this pathway. The shorter latency response seemed most likely via antidromic activation of the trigeminal autonomic reflex [96]. Moreover, it has been shown also that posterior hypothalamus may play a central role in the CH, thus explaining the circadian and circannual periodicity of the symptoms [97].

#### **4.5. Tension-type headache (TTH)**

Although very frequent, the relationship between the tension-type headache and ANS activity is less documented [87]. It seems that chronic TTH along with migraine may be associated with increased sympathetic tonus, expressed by elevated resting heart rate, compared to episodic TTH [93]. TTH patients may also have a delayed adaptation in heart-rate to stress and a reduced pain control system inhibition [97].

Even though the dynamics of ANS intervention in primary headaches is not yet fully understood, the emergence of translational research models and also the development of new

techniques to measure the vegetative biomarkers in headaches provide a robust basis for new and more efficient therapeutic strategies.

## **5. Heart rate variability as a measure of autonomic nervous system in migraine**

The autonomic nervous system (ANS) has important functions in maintaining homeostasis by adjustment of the body to internal and environmental demands. Beside key functions controlled by the ANS such as respiration, blood pressure, heart rate, hormonal regulation, etc., ANS is also involved in regulating emotional behavior and cognitive functions.

The sympathetic nervous system (SNS) controls of the heart coming from the upper thoracic region of the spinal cord. Preganglionic fibers synapse with postganglionic sympathetic fibers and release acetylcholine, which binds to nicotinic receptors on the postganglionic fibers. Through sympathetic adrenergic efferent fibers extend to the sinoatrial and atrioventricular nodes in the heart where they release norepinephrine at synapses with beta-adrenergic receptors [98]. Stimulation of the SNS increases heart rate (positive chronotropy), ventricular contraction (positive inotropy), conduction velocity (positive dromotropy), and rate of relaxation (positive lusitropy). The parasympathetic nervous system (PNS) control of the heart coming from vagal nuclei within the medulla oblongata in the brainstem, and efferent nervous outflow occurs via the 10th cranial nerve (vagus nerve). The long preganglionic efferent nerve fibers extent to the heart and synapse with a ganglia located near the sinoatrial and atrioventricular nodes. Acetylcholine is released, binds to nicotinic receptors, and activates short postganglionic efferent nerve fibers. These postganglionic fibers synapses with muscarinic receptors in the sinoatrial and atrioventricular nodes, and is activated by acetylcholine. For heart PNS decreases heart rate (negative chronotropy), force of atrial contraction (negative inotropy), rate of relaxation (negative lusitropy), and negative dromotropy [98].

The actions of the SNS and PNS are often opposing in their effects and normally the SNS and PNS activities are in dynamic balance thus indicating a healthy and flexible physiological system [99]. The autonomic imbalance described by increased SNS activity and suppressed PNS activity is associated with an increased risk of diseases [99]. The central control of cardiovascular system involved several areas throughout spinal, bulbopontine, pontomesencephalic, and forebrain. The medullary centers work through reflex cardiovascular mechanisms such as baroreflex, chemoreflex, and cardiopulmonary reflex [100]. The afferent fibers of the cardiovascular reflexes are terminated in the nucleus tractus solitarii [100]. The reticular formation of the ventrolateral medulla (VLM) is the primary central site that regulates sympathetic outflow, thus contributing to the regulation of BP and heart rate (HR). In the rostral VLM part are excitatory neurons which synapse in the intermediolateral gray column of the spinal cord, and in the caudal VLM are inhibitory neurons that sent projections to the rostral VLM. The preganglionic parasympathetic neurons located in the nucleus ambiguous and the dorsal motor nucleus of vagus are involved in the parasympathetic regulation of the cardiac



reflexes [101]. Also parabrachial nucleus, Kolliker-Fuse nucleus, the cluster of A5 cells are the brainstem centers involved in the control of the cardiovascular system.

The upper brainstem level includes the periaqueductal gray matter (PAG), which integrates the autonomic control with pain modulation and behavioral responses to stress [102]. The forebrain level includes the paraventricular and related nuclei of the hypothalamus, thalamus, amygdala, and anterior cingulate cortex, the insular and medial prefrontal cortex that integrates autonomic and endocrine responses [102]. The anterior limbic circuit (insula, the anterior cingulate cortex, and amygdala) assures integration of specific sensations with emotional and goal-related autonomic responses [102]. Electrical stimulation of the prefrontal and cingulate cortex, left insula, lateral nucleus of hypothalamus decreased heart rate and blood pressure, whereas electrical stimulation of right insula, ventromedial nucleus of hypothalamus increased heart rate and blood pressure [103]. Stimulation of the basolateral nucleus of amygdala increases blood pressure and decreases heart rate; stimulation of the rostral nucleus of amygdala results in depressor effects and variable changes in heart rate [103].

The normal sympathovagal regulation induces an increase in heart rate during inspiration and decrease during expiration, and this physiological phenomenon is known as respiratory arrhythmia. The intrinsic heart rate is 105 beats/minute while resting heart rate is only 60–80 beats/minute, indicating that the heart is under “vagal dominance” [104].

The electrical signal produced by the heart can be measured with an electrocardiogram. Electrocardiogram registers depolarization of the atria (P-wave), depolarization of the ventricles (the QRS complex), and repolarization of the ventricles (T-wave). Using these points we can measure heart period or inter beat interval which measure the time between two consecutive heart beats in milliseconds [105]. Heart rate (HR) measures the numbers of consecutive heart beats in 1 min (beats per min). The analysis of consecutive sinus rhythm R-R intervals is known as heart rate variability (HRV), a noninvasive electrocardiographic marker reflecting the activity of the ANS on sinus node function.

HRV parameters can be calculated in time domain (statistical and geometrical), frequency domain (power spectral density), and nonlinear measures. In time domain methods HRV parameters are standard deviation between normal intervals during recording—SDNN (ms), standard deviation of the average values of NN intervals calculated from all 5-min segments of the entire recording—SDANN (ms), square root of the mean of the sum of the squares of differences between adjacent NN intervals—RMSSD (ms), percentage of differences between adjacent NN intervals differing more than 50 ms—pNN50% [105]. A lot of studies indicate that SDNN, RMSSD, and pNN50%, time domain indicators of the HRV, represent the activity of the vagal nerve.

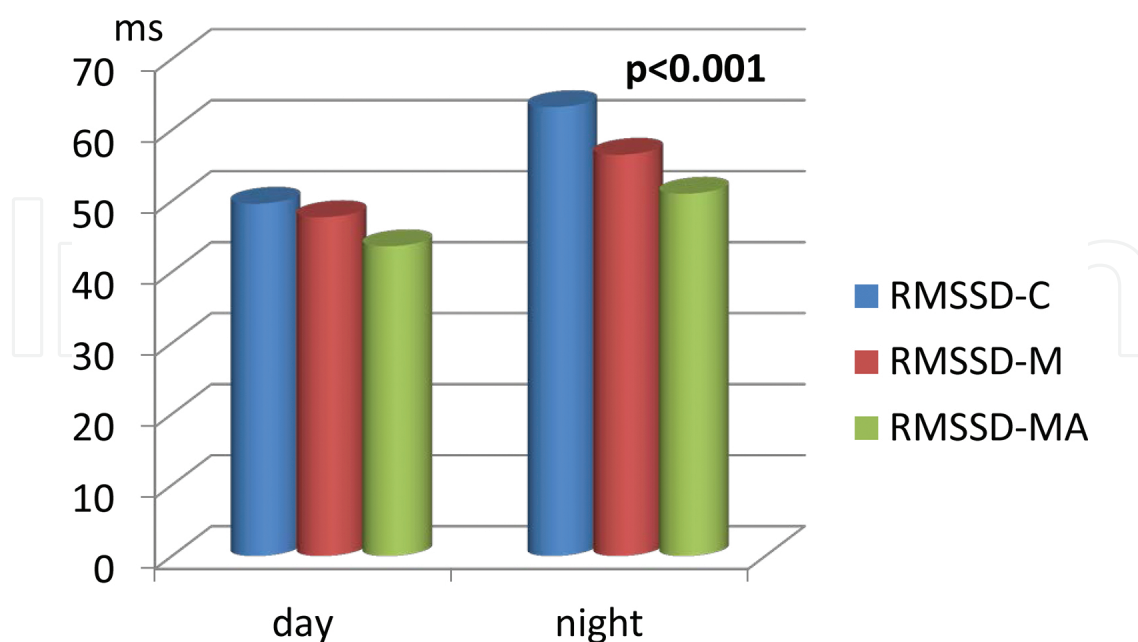
Using simultaneously the Fast Fourier transform method and parametric– autoregressive method (AR), HRV can be analyzed in frequency domain (power spectral analyses of HRV) in which can be measured low-frequency component (LF < 0.15 Hz) taken as an indicator of both vagal and sympathetic functions, high-frequency component (HF ≥ 0.15 Hz) as an indicator of parasympathetic function, very low-frequency component (VLF—the frequency band in the range 0.003–0.04 Hz), ultra-low-frequency (ULF—the frequency band below 0.003 Hz), and



the total power (TP) [105, 106]. VLF is related to the thermoregulatory sympathetic vascular activity and to oscillations in the renin-angiotensin system [107]. The ratio of LF/HF is considered as an index of cardiac sympathetic/parasympathetic tone balance.

Abnormalities in the SNS or PNS have been found in migraine patients during the headache-free phase [108, 109]. Some researchers revealed sympathetic hypofunction and parasympathetic hyper-function in migraine patients during the same period [83, 110]. Other study found that older patients with migraine may have sympathetic hyper-function and a parasympathetic hypofunction during headache-free intervals [111]. Martin et al. [112] found a reduction of HR during deep breathing, and after 2 min of tilting. Appel et al. [113] revealed increase of the low-frequency band of HRV analysis in migraineurs, suggesting an increase in sympathetic activity.

We tried to analyze the ANS involvement in migraine using the HRV on long-term 24-h ECG. We investigated 27 subjects with migraine (10 with migraine with aura and 17 without aura) during headache-free periods and 10 age-matched healthy control subjects. We found a significant decrease in SDNN, RMSSD, and HF indicating parasympathetic dysfunction in migraine groups during night headache-free periods, and the most affected were migraine with aura patients (**Figures 1 and 2**). LF and LF/HF ratio were increased during the night in migraine with aura patients (**Figures 3 and 4**). In both groups of migraine patients, we discovered an autonomic nervous system dysfunction. The most marked ANS impairment being present in the group of migraine with aura sufferers where we found sympathetic hyperfunction associated with parasympathetic hypofunction especially at night with loss of circadian rhythms [114].



**Figure 1.** Square root of the mean of the sum of the squares of differences between adjacent NN intervals—RMSSD (ms) in study groups (C, control group; M, migraine without aura group, MA, migraine with aura group).

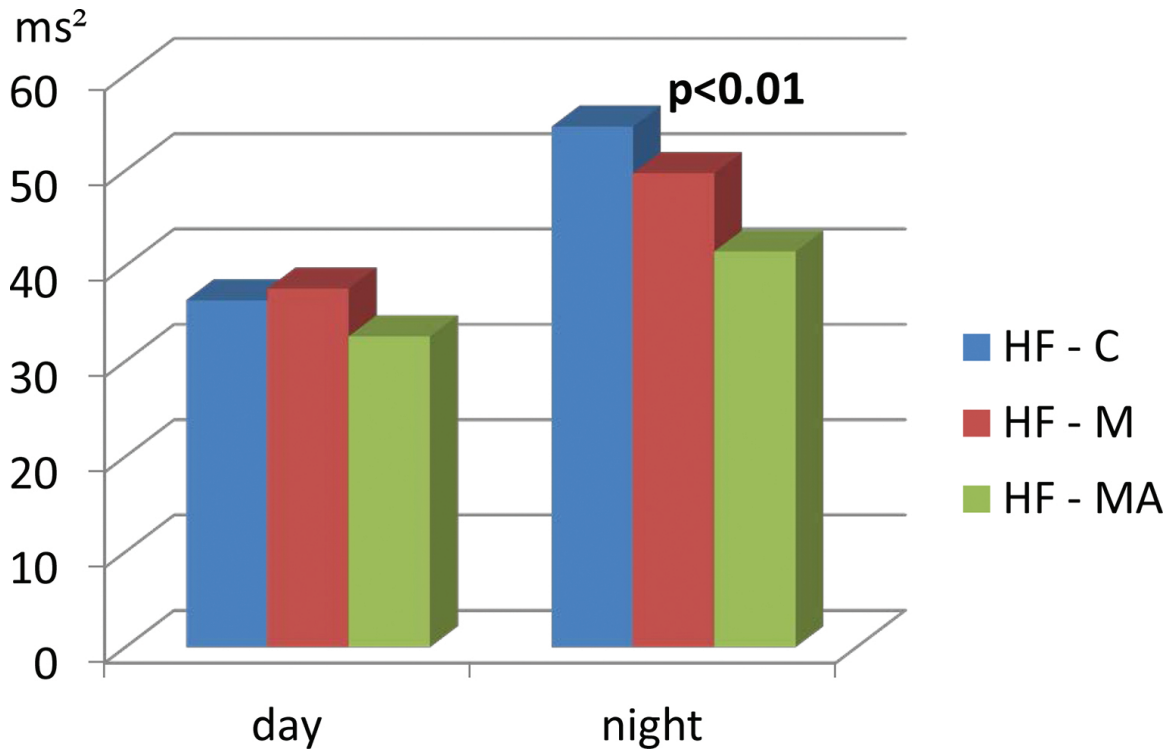


Figure 2. High-frequency component of power spectral analyses of HRV in study groups.

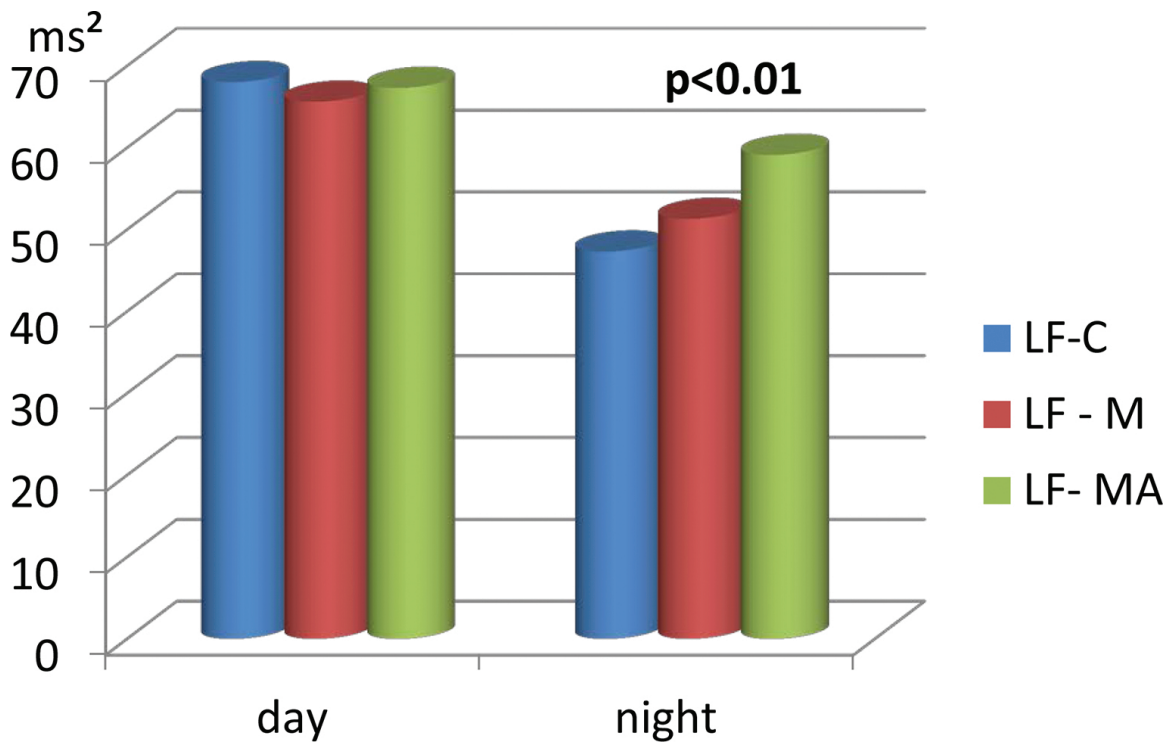
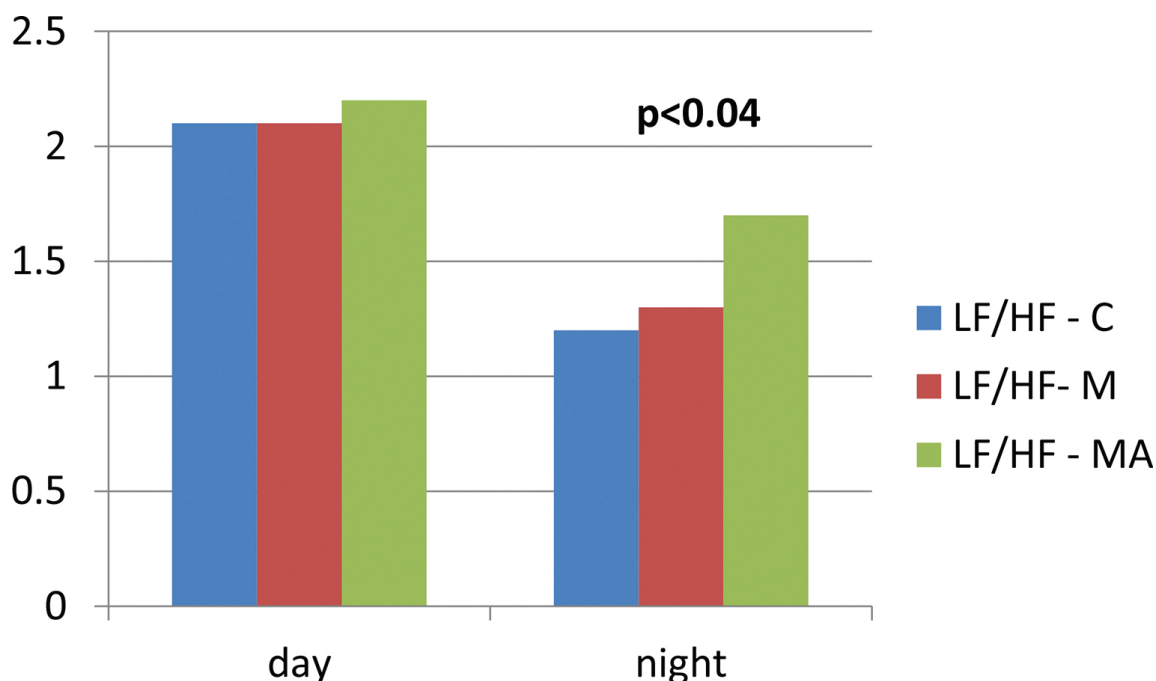


Figure 3. Low-frequency component of power spectral analyses of HRV in study groups.



**Figure 4.** LF/HF ratio in study groups.

HRV is associated with highly functional prefrontal cortex inhibitory activity over subcortical structures that make the body to well adapt to the environment. Low HRV is associated with reduced prefrontal inhibitory control over subcortical structures and failure to recognize safety signals [104]. Failure of inhibition leads to continue to process fear information and is linked with anxiety and depression [115]. Chronic psychological stress and depressed mood have been shown to be associated with SNS dominance and vagal withdrawal, highlighted by decreased HRV [115, 116]. In our study, we found an increased frequency of anxiety and depressive symptoms in migraine patients, especially in migraine with aura group [114]. Individuals with high level of stress, anxiety, and depression display an imbalance between PNS and SNS activities. Prolonged stress may influence health via several different pathways, i.e., alterations in autonomic nervous system (increased SNS and decrease PNS), neuroendocrine activity, immune, behavioral, and cognitive functions.

Many other factors such as alcohol, nicotine, physical exercise, age, gender, diabetes, hypertension, cardiovascular disease, sleep apnea, chronic respiratory disease, or medications (sex steroid hormones, antidepressants,  $\mu$ -blockers, etc.) may influence the autonomic nervous system [117–121]. Moreover, the ANS exhibits a circadian variation [122].

The ANS involvement during the premonitory phase of a migraine attack is suggested by many symptoms and signs with potential involvement of the hypothalamus (depression, irritability, fatigue, food cravings, and increase yawning), brainstem (neck stiffness), and cortex (abnormal sensitivity to light, sound, and smell) [123]. Nausea, vomiting, dizziness, cutaneous vasoconstriction or vasodilation, conjunctival injection, lacrimation, nasal congestion, rhinorrhea, eyelid edema, piloerection, and diaphoresis can occur during pain phase [108, 109]. Also accompanying psychological and cognitive symptoms can appear—inability to organize

thoughts and plans, physical exhaustion, confusion, agitation, aggressiveness, depression, and anxiety.

Migraine can be initiated by diverse triggers including bright lights, sounds, hunger, and mental exertion; poor sleep quality, menses, excess consumption of alcohol, chocolate, and fermented cheese. Sleep usually calms the pain.

In our study when we asked patients about sleep quality and dreaming, they complained about bad sleep quality. The majority experience negative sensations such as anxiety, fear, or terror and contents such as perception of fall and unsuccessful efforts to do various things [114]. These observations suggest that there is some malfunction in the prefrontal cortex, limbic system, amygdala, and hypothalamus, elements involved in dream and migraine pathophysiology [124]. Activation of the limbic system, amygdala, and anterior cingulate cortex observed in rapid eye movement sleep are involved in cardiovascular regulation and could reflect responses to intense emotions such as fear and anxiety found in migraine patients during night [125].

When physiological stressors, such as migraine attacks, are frequent and persistent allostatic responses can become maladaptive, resulting in changes of the body system. Migraine patients were found to have elevated plasma levels of cortisol in headache-free periods [126] and during pain period [127]. Increased chronic levels of cortisol can induce atrophy in the PFC, decrease dopamine in the brain pleasure circuits, deplete the norepinephrine from the LC, and reduce frontal lobe serotonin receptors levels, thus contributing to flatness of emotion, concentration weakening, mood dysfunctions, and bad quality of sleep [128]. Neurogenesis and apoptosis in hippocampus are suppressed [129] and also dysregulation of the autonomic nervous system and hypothalamic-pituitary-adrenal axis with alterations in hormone regulation are revealed during chronic stress. Chronic migraineurs show decreased amygdala volume [130] that can be related to the high levels of anxiety or fear in these patients [131]. In chronic migraine, beside cortisol, other dysfunction in hormone secretion has been reported for prolactin, and melatonin [132]. Sleep deprivation and circadian disruption can have negative consequences for body functions including increased appetite, increased levels of proinflammatory cytokines, decreased parasympathetic and increased sympathetic tone, increased blood pressure, and elevated insulin and blood glucose [133]. Hormonal dysfunctions in estrogen and progesterone regulation are frequent in migraine patients, and migraine improves after menopause or with hormonal therapies [134].

The cumulative effects of migraine over the body, as well as its treatment represents allostatic load [135]. Early interruption of a feed-forward vicious cycle with different techniques (medication and stress reduction) is important to diminish allostatic load [135].

## **6. New directions in the treatment of primary headaches**

It is classically accepted that migraine may respond to few different pharmacological agents such as pain-relieving medications (like triptans) in acute phase and preventive medication

like antiepileptics (like topiramate), CH responds to oxygen and parenteral triptans, while verapamil has the most success for prevention. Paroxysmal hemicrania responds to indomethacin. SUNCT/SUNA responds to lamotrigine and topiramate. Hemicrania continua respond to indomethacin [136].

### 6.1. Neurostimulation

A promising and rather new venue in headache treatment seems to be represented by neuromodulation of pain central system and autonomic pathways. These noninvasive methods may provide relief in patients with chronic and pharmacoresistant forms of headache. Therefore, it was reported that transcutaneous stimulation of the parasympathetic nerve system via the vagus nerve can abort migraine attacks [137]. Vagal nerve stimulation represents a well-established nonpharmacological strategy in epileptic patients with intractable seizures and also in depressed patients. Some cohorts of epileptic patients with implanted VNS have shown improvement in their migraine symptoms, but the eventual causality with seizure frequency reduction still needs to be debated also [138]. Similarly, patients known with migraine and treated with VNS for depression experienced an improvement in the migraine attacks [139]. Yet, further studies need to clarify the exact correlation between VNS effects and migraine mechanisms.

Recently, it has been shown that patients with CH seem also to benefit from noninvasive VNS, with improvement of their initial condition of approximately 50% [140]. On the other hand, occipital nerve stimulation (ONS) has proved favorable clinical results in the treatment of refractory chronic CH in well-documented cases, but there are still limited studies in this direction. The hypothalamic activation during cluster attacks led to the introduction of deep brain stimulation (DBS) technique for refractory CH, with rather positive effects. Still, there is need of further confirmation of this method in CH, in terms of targeted anatomic-functional centers and patients selection in order to have a good risk/benefit outcome [141, 142].

### 6.2. Modulation of signaling molecules

Migraine is considered as a syndrome of chronically low central serotonin system with consequent 5-HT receptor hypersensitivity, with migraine attacks triggered by a sudden increase in 5-HT release [143]. Therefore, medication targeting specific serotonergic pathways showed its efficiency in migraine acute treatment. Triptans are selective serotonin agonists, specifically acting at 5-hydroxytryptamine 1B/1D/1F (5-HT<sub>1B/1D/1F</sub>) receptors on intracranial blood vessels and sensory nerve endings. The first combination product of a triptan and a nonsteroid anti-inflammatory drug (naproxen) was approved by the U.S. Food and Drug Administration in April 2008. It has been proven that migraineurs who experienced poor response to a short-acting triptan, the combination of sumatriptan/naproxen sodium reported more effective results in pain reduction and migraine-associated symptoms of photophobia and phonophobia [144].

New prevention strategy via biochemical signaling in migraine prevention is based on monoclonal calcitonin gene-related peptide (CGRP) antibodies to CGRP are effective in



migraine prophylaxis [145]. As shown previously, robust data showed that neuropeptides present in the perivascular space of cranial vessels are important mediators of nociceptive input during migraine attacks. Pituitary adenylate cyclase-activating polypeptide (PACAP) is present in sensory trigeminal neurons and may modulate nociception at different levels of the nervous system. It has been proposed that the PAC(1) receptor represents a possible signaling pathway implicated in migraine and may be a future pharmacological target in migraine treatment [146].

The precise implication of the hypothalamus in premonitory phases of migraine and also during migraine attacks is discussed. Therefore, novel targets may include hypothalamic peptides such as orexine, which interferes with trigeminal nociceptive activity and cortical spreading depression—the well-known neural phenomena in the prodromal phase of migraine [147]. Interestingly, Botulinum toxin A was associated with a small or modest benefit for chronic daily headaches and chronic migraines, reducing headache episodes per month [148].

### **6.3. Genetic therapies**

Genetic studies have highlighted a potential role in the etiopathogenesis of primary headaches for several genes related to vascular, neuronal, and neuroendocrine mechanisms. Therefore, recent data showed the implication of new genes, like methylenetetrahydrofolate reductase (MTHFR), potassium channel, subfamily K member 18 (KCNK18), transient related potential vanilloid type 1 (TRPV1), transient related potential vanilloid type 3 (TRPV3), hypocretin (orexin) receptor 1 (HCRTR1), and hypocretin (orexin) receptor 2 (HCRTR2), both in migraine and cluster headache. Of course, further preclinical and clinical data need to confirm the precise place and indication of genetic intervention when addressing primary headaches, thus promoting the multifactorial determination of this pathology [149].

### **6.4. Multidisciplinary nonpharmacological interventions**

Behavioral and psychological coaching in chronic headache patients in a multidisciplinary setting may foster treatment adherence and improve the quality of life in these patients. It is considered that behavioral therapy combined with pharmacological intervention (for example, beta blocker alone) renders more effective treatment [150].

The above-mentioned directions of treatment in primary headache highlight the complexity of the pathogenic mechanisms of this pathology and the need for further studies to address therapeutic strategies adapted to individual condition.

## **7. Conclusions**

Headache disorders represent both a treatment challenge and a serious public health concern, with major impact on the individual and society. Although the painful symptomatology is the main encounter for the decreased quality of life and discomfort, the vegetative



manifestations which frequently accompany the cephalalgic syndromes, cause an important amount of distress. Despite the advancement of the understanding of the molecular basis of headache disorders and neurovascular complex interactions, both at central and peripheral levels, especially concerning migraine, there is still lack of an integrated view of the neurovegetative modulation in different types of primary cephalalgic syndromes, translating from animal pathophysiologic “models” to clinical data. As shown in this chapter, the neurochemical mechanisms which subtend dysautonomic manifestations in different types of headache share common pathways, yet there is need to specifically address the various vegetative biomarkers in each type of headache, in order to provide more efficient and individualized therapeutic strategies, combining multimodal pharmacological and nonpharmacological approaches.

Without pretending exhaustively, this chapter highlights the need for a better and a more accurate characterization and classification of primary headaches, taking into consideration the whole spectrum of clinical manifestations, including the dysautonomic activity. Despite locally derived, population-based data describing the burden of primary headache disorders, there is still need of a global perspective on disease impact, through both preclinical and clinical data, in both developed and developing countries, in order to maximize efforts for a better understanding and management of the disease.

## Acknowledgements

This work was supported by “Grigore T. Popa” University of Medicine and Pharmacy Iasi. Authors contributed equally to this work.

### conflict of interest

The authors confirm that this chapter contents have no conflict of interest.

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