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Review Article

Headaches, Pathogenesis and Therapies

Giorgia Andrisani[1,2]* and Giovanni Andrisani[2]

[1]*Private Practice Tandzorg Delft Centrum, Sintsebastiaansbrug, Delft, Netherland*

[2]*Private Practice Studio Andrisani, Matera, Italy*

***Corresponding Author**: Giorgia Andrisani, Private Practice Tandzorg Delft Centrum, Sintsebastiaansbrug, Delft, Netherland and Private practice Studio Andrisani, Matera, Italy.

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Abstract

We would like to propose a Headaches Etiopathogenesis model and, in particular, of migraine (M), based on cortical hyperexcitability determined by an increase in unspecific activation (UA) caused by ARAS nuclei, activated, specially, by the mesencephalic nucleus of the trigeminal nerve (Me5). This model wants to demonstrate how at a certain time in the migraine disease, the unspecific activity become so strong to generate an unspecific cortical decode, non-sense, regarding different functions related to the neurotransmitter in excess such as the Orexin (OX), hunger, thirst, yawns and so on; also regarding sensorial functions such as the eyesight, the vestibule apparatus (vertigos) or the sense of smell (olfactory hallucination).

This "nonsense" decoding activate a sort of defence mechanism that is the cause, across "the Cortical Spreading Depression "(CSD), of the Cortical Activity Decrease throughout the unspecific activity, therefore the ARAS, with an sudden "resetting" of the neurotransmitter production, mainly the OX, with intense vasoconstriction, at the postero-lateral area of the Hypothalamus, where the OX is produced. So, the Gasser nerve endings reflex is activated, leaving a substance P, Neurokinin A, Calcitonin Gene-Related Peptide (CGRP) and VIP (Vasoactive Intestinal Peptide etc), a protective antidromic way, with protective intent, causing intense vasodilatation and activation of trigeminal nociceptive fibers exaggerated by an excessively activated Trigeminal Caudal nucleus (NTC): the Migraine (M).

Keywords: *Headache; Cortical Hyperactivation Pathology; Migraine*

Introduction

According to lots of authors the predisposition to the migraine attack is based on an excess of cortical excitability (and there are many evidence suggesting that the migraine attack may originate at the level of a hyperexcited cerebral cortex). The concept of migraine cortical hyperexcitability is predominantly the result of studies conducted with non-invasive cerebral stimulation techniques. In particular, transcranial magnetic stimulation (TMS). Neurophysiological studies have shown that cortical excitability variations can precede the beginning of Migraine attack [1-3], factors that can modify cortical excitability (e.g. menstrual cycle) may develop migraine [4] and prodromal symptoms such as irritability, photophobia, phonophobia and osmophobia suggest a widespread increase in cortical responsiveness precedes the pain phase [5,6].

This hypothesis is supported, besides neurophysiological and neuroimaging studies, by other experimental evidence:

1) An excessive activation of glutammatergic excitation circuits is at the basis of the trigger and propagation of the waves of corti cal spreading depression [7,8];
2) Levels of glutamate in plasma, cerebrospinal fluid, platelets and erythrocytes of patients with migraine with and without aura increased compared to those of healthy subjects, both during interictal period and during attacks [9,10];
3) Anti-epileptic drugs acting on the glutamate system play a role in migraine prophylaxis therapy [11];
4) Animal models of Familial Hemiplegic Migraine (FHM) show that an increased release of glutamate represents a common moment whit several genetic alterations at the base of the disorder [12,13].

In the central nervous system (SNC) find out ample space the diffused and scarcely differentiated projection systems commonly associated with the name of ascending activating reticular system (ARAS), whose task is to ensure an adequate level of activation in all SNC structures and the cerebral cortex, which is able to work properly only when is activated by the reticular system.

The increasing of the general level of responsiveness of the central nervous system (arousal) produced by the ARAS, it makes an easier action, on the perceptual elaboration of primary sensory areas, raising the UA level of the cerebral cortex and lowering the threshold for detecting stimuli.

Arousal fluctuations strongly affect the accuracy and speed of sensory analysis and, reciprocally, sensory stimulation condition the level of vigilance. Indeed, any sensory stimulation, in addition to activating a specific path of conscious perception of information, also causes the UA of the entire SNC through its connections with the reticular system, the UA of the entire SNC.

An extreme and little-known case of this mechanism is that of Me5 which is constituted by ganglion cells located within the RF mesencephalic, and which performs the function of UA of the bark, by activating the nuclei of ARAS, as a prevalent activity [14].

Background

The role of the trigeminal-vascular system and in particular of the caudal nucleus of the Trigemino (NTC) remains central in the pathogenesis of E, in which, during the migraine crisis, the increase of C-fos is observed, as well as in the periaqueductal gray (PAG), Locus Coeruleus (LC) and Hypothalamus, as shown by PET images. In addition, given by its pharmacological (Triptans and Ergotamine are efficient vasoconstrictors) and functional features (the RM shows vasodilatation), we can state that it is a vasomotor-like disease, which, by itself, is not a painful fact in the strict sense and, therefore, we must think that there is also a problem related to the structures responsible for the perception and processing of pain: still PAG, Hypothalamus, LC and NTC, also because the headaches are often associated with other disorders of altered perception of pain, such as fibromyalgia [15,16] or temporomandibular joint disorders [17,18].

In the Hypothalamus seems to be involved the postero-lateral area, where Orexina (OX) is produced, which is also affected by pain processing disorders and incorporated in the ARAS: a small nucleus made by few cells (about 20.000) but with a large number of functions.

A particular association is between headaches and sleep [19-23].

However, we have a structure that, during sleep, makes us cyclically more sensitive to stimuli and, therefore, able to process them, external stimuli (environmental), and internal (physiological, such as ejecting liquids or excessive solids): this structure is the mesencephalic nucleus of the trigeminal nerve (Me5), whose activity is stimulated by the GABA of the VLPO/MnPO. Me5 consists of pseudo-unipolar cells of the ganglion type, its peripheral branches arrive at chewing muscles and at periodontal while the central branches stimulate, by releasing glutamate (GLU), some nuclei of ARAS, particularly that of OREXINE (OX) but also the Trigeminal Caudal Nucleus (TCN), not ARAS.

The Me5 crosses all the midbrain. It has a caudal part (Me5c), consisting of small GABAergic cells positioned just in front of the trigeminal motor nucleus (Mo5), and inhibits it [14,25,101]. Upon arrival of the hypothalamic GABA, during sleep, Me5c is inhibited by that GABA and does not inhibit the Mo5, which is activates and leads to activation of chewing muscles and to the dental contact, with the activation of the Me5, thus of ARAS nuclei and, in particular, of the nucleus that produces OX, the so-called "center of appetite" [24].

The Me5, which cannot be inhibited by GABA because its cells are devoid of dendrites, also activates the Me5c, which begins again to inhibit the Mo5 and interrupts the Me5 action. This creates a situation where as sleep becomes more deep, hypothalamic GABA increases and, cyclically, activates the Me5 (we can see it at EEG in the form of a Cyclic Alternating Pattern or PAC) [14,25].

Unspecific activation (UA) also continues during sleep and, thanks to Me5, causes the cortical neurons to have a large number of unspecific synapses (due to Long Term Potentiation) making the cerebral cortex of these subjects hyperexcitability.

The Etiopathogenesis

The cerebral cortex of these patients is hyperexcitable in particular because of the action of Me5 on the nuclei of ARAS and that of the OX.

The intense muscular activity of bruxism, causes muscular and dental pain and consequent further specific cortical activation (due both to muscular contraction and to dental pain) and, together with the mechanisms described above, cause typical pain of tense type headaches (TTH).

Is not a coincidence that both events (Bruxism and cortical hyperactivity) are linked each other being the first, bruxism, the cause of the second, cortical hyperexcitability. Cortical hyperactivation consists of a large number of glutamatergic synapses activated for each neuron, AMPA, Kainato, and especially NMDA. This results in a large influx of Na^+ and Ca^{++} ions in their cytoplasm and a large outflow of K^+, H^+ and ATP into the intercellular matrix. The excess of K^+, H^+ and extracellular ATP is able, physiologically, to activate, in the microglia's cells, a group of so-called pattern recognition receptors (PRRs) capable of recognizing such substances and considering them as a sign of suffering [26-28].

The activation of these receptors will in various ways lead to the formation of specific proteins called NLRP3, which can be assembled in a molecular platform called Inflammasome. The Inflammasome combines many pro-caspase-1 molecules called p45, causing their self-catalytic disintegration into the subunits. p20 and p10 which then assembles into its active form, the Caspasi-1, consisting of two heterodimers with a P20 and P10 subunits each. Once activated, Caspasi-1 can perform a variety of processes in response to the initial "inflammatory" signal. These include the cleavage of pro-IL-18 in IL-18 and, above all, the proteolytic segmentation of pro-IL-1β in IL1β; this is a pluripotent cytokine, able to perform and regulate many immune functions with direct involvement in the activation of inflammatory responses including that of: to promote inflammatory processes and vasodilation, through the production of prostaglandins and NO, - determine an increase in vascular permeability by stimulating the production of: Bradykinin; Leukotrienes C4, D4 and E4; PAF (a potent stimulator of platelet aggregation that stimulates serotonin secretion); Substance P; Calcitonin-related peptide (CGRP); Somatostatin; Vasoactive intestinal peptide (VIP); Neurochinin A; Neurochinin B:

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- Stimulates the production of other cytokines such as IL-2 and the activation and recruitment of other immune system cells in synthesis: the TTH. Obviously, the microglial reaction is aimed at the elimination of excess of glutamate of K^+, of ATP and H^+ [29-35].

Migraine's Etiopathogenesis

In the pathogenesis of headaches the Orexins (OX) plays an important role. The OX derived from a common precursor, the prepro-orexin, whose mRNA is specifically expressed in the postero-lateral hypothalamus and adjacent cerebral areas called "appetite center". The OX plays a key role in promoting and stabilizing the state of vigilance: a deficiency of this peptide leads to narcolepsy [36-39]. Orexinergic neurons have connections with all nodes involved in the sleep-wake cycle and are actively inhibited during the NREM sleep stage by GABAergic neurons of the hypothalamic preoptic region [40]. The Orexinergic nuclei excite the cerebral cortex, both directly both indirectly, through a widespread projection towards aminergic systems, particularly towards the Locus Coeruleus (LC) [41,42] and towards the cholinergic nuclei of the basal forebrain (Meynert nucleus) [43-45]. The OX activates LDT, PPT; DR; LC; VTA; PAG; TMN and ARC nuclei and it is inhibited by VLPO, DR, Leptin and increase of the glycemia. Ox cells send extra-hypothalamic extended projections to the forebrain, to cerebral cortex, hippocampus, amygdale, thalamic medial nuclei, area postrema, nucleus of the solitary tract and bone marrow [46]. Furthermore The OX stimulate: the release of glucocorticoids, the autonomous functions, the behaviour, the appetite, the metabolic rate, the gastric acid secretion (the OX stimulates the dorsal Vagus nucleus and the stomach motility [47] increasing the duodenum and ileum contractibility [48,49].

All we have said about TTH is also valid for migraine but the migraines characteristic is to affect mid-skull and especially the deep ocular region of the sore side. This means that the inflammatory reaction of the microglia manifests itself only in one half of the head and, therefore, that the hyperexcitability of the cerebral cortex is present only in that half of the head. Since this hyperexcitability is mainly due to the action of the OX we must assume that only one of the two nuclei of OX has been hyperactivated and in dental malocclusions the contacts rarely occurs simultaneously, with all the teeth of both dental arches, more often dental contacts occurs between the teeth of only one side (but with the same muscular strength): perhaps the Me5 on that side will be more activated and will activate more the orexinergic nucleus of the that side [50,51].

What happens, sometimes, in headaches: at some point the cortical UA of the corresponding emi-skull becomes so high that it blocks normal nervous transmission or generates a cortical decodification, nonspecific, sometimes "no sense", or that may relate to a variety of commonly associated functions to the neurotransmitter in excess and therefore to the OX, the so-called prodromes: hunger, thirst and, among them, yawns (the origin of which seems to be the paraventricular nucleus, one of OX targets) [52] but it may also relate to sensory functions such as vision (Aura) or vestibular (dizziness) or smell (olfactory hallucinations) or paresthesia. The no-sense decoding may activate protective mechanisms that stop UA by stopping neuronal transmission: the Cortical Spreading Depression (CSD) which can be defined as the reaction that is able to develop the cerebral cortex when its patterns are not the pre-established ones [53,54].

CSD causes a reduction of cortical activity by reducing the AA, and thus the ARAS (probably activating the VLPO/MnPO nuclei that release GABA on the ARAS nuclei, in this case from awake), reducing production of OX from the hypothalamus of that side, with vasoconstriction, which activates the nervous reflexes of Gasser's nervous endings which, stimulated by the NTC, antidromic release of P substance, neurokinin A, calcitonin gene-related peptide (CGRP) and VIP (vasoactive intestinal peptide), causing intense vasodilation, extravasation, activation of nociceptive fibers etc: the Migraine (M) [32].

Both TTH and M share the same mechanisms, being involved in the same pathogenesis (UA surplus). Maybe, "pure" types of TTH or Migraines do not. In support of our thesis we have the following data: In Polysomnograms of many patients with Migraine disorders PAC rate is relatively low than non-cephalic controls [55-62] (and it takes more GABA to sleep an hyper-excited patient), but inside each PACs there is an increase of type A phases to the detriment of B phases [59], sometimes causing an increase in Arousal that can to cause insomnia [63-65] with a decrease in time total sleep [59]. In people affected by M, generally considered to be so excited, we have a deep sleep (low CAP rate, decreased REM and low Arousal) that often breaks [60-62]. Really, to better understand the PSG data, we should consider awakening as A-phase, indeed A3, even several minutes lung or hours, with great excitement due to the action of the Me5 that it activates just when the GABA is high (the patient with E often show bruxism) [66,67], and symptomatology can be improved with the use of oral devices (bits) [51,68-70]. These patients exhibit large UA excursions due to the large amount of GABA (CAP low and low UA) and UA peaks due to the intense activation of the Me5 (which lead to frequent night-time awakening and generally less sleep). Often these patients wake up with headaches, even during the night. During E, the fRMI shows vasodilatation in the areas of the hypothalamus [71], and the deep stimulation of the posterior Hypothalamus is effective in CH [72]. Since vasodilatation is not, in itself, an pain event, the role of PAG modulation and excessive vasodilation due to excessive activation of the NCT are both prevalent in the migraines caused by the Me5 hyperactivity.

Before talking about the therapies we would like to make a reference to the diagnosis: in general we speak of primitive and secondary headaches and sometimes the differential diagnosis is difficult. We think that since the primitive headaches are due to the cortical hyperactivation whereas the secondary ones, generally not, we could make a differential diagnosis through the PSG, because in the primitive headaches we will find the low CAP rate (very GABA to turn off the very active ARAS nuclei), in the secondary ones the CAP rate should be normal (depending on the agent cause).

Another aspect not addressed in this article is the importance of activation of pain pathways: we know that even non-headache patients may develop pain similar to that of migraine when stimulated with electrodes implanted in PAG and that PET images in the course of a migraine attack and in the intercritical period in these patients show the activation of PAG, DR and LC. All of these nuclei are targets of Me5 and participate in the Migraine's mechanisms both by determining IC and vasomotor control, and by modulating pain pathways. Their continuous stimulation (in sleep, through bruxism) can lead to structured functional modifications, with chronic IC, easier vasomotor alterations and lowering of the pain threshold with consequent chronicization of the same.

The headaches have been classified into various types, probably because according to the brain areas affected by the IC the specific headaches may present just with specific symptoms. Among the various headaches, the cluster headache (CH) is particularly interesting, both because it is particularly serious (its pain has been classified as one of the worst that man can try) and because of its clinical characteristics. CH affects mostly males and testosterone levels are low in CH subjects [80].

During the crisis the patient is very agitated and his OX/Hypo levels in the cerebro- spinal fluid are low [81].

We know that CH responds very well to the administration of high-dose O_2 (minimum 12L / min) and we know that OXergic neurons are very sensitive to hypercapnia [82,83].

In addition, OX modulates cardiovascular, respiratory and sympathetic nervous activity [84-86], the "clusters" of CH are very similar to the cyclic activity promoted by Me5 during sleep, moreover Me5 has circadian genes that could determine the typical periodicity of this headache [85].

The set of these data suggests a hypothalamic difficulty to producing Ox, especially when Me5 tries to activate OXergic cells, and in the presence of low levels of Testosterone. It seems that in some periods of the year, when the Me5 is more active, as the cortical activation requests increase, the OXergic cells are exhausted and do not produce enough OX, especially at night, in the NREM, when the hypothalamic GABA increases and activates the Me5 which tries to activate the OXergic cells. OXergic cells fail to meet the demands and decreases the OXergic stimulation of cardiovascular, respiratory and sympathetic nervous activity. Parasympathetic activity related to the Trigeminal prevails, the ganglion sfeno-palatino is activated and the symptoms related to it are manifested (rhinorrhea, lacrimation, palpebral ptosis, etc.), moreover the intense activity of Me5 creates intense activation of the Caudal nucleus of the Trigeminal and, as in Migraine, we have hypothalamic vasoconstriction due to the inactivity of OXergic cells, antidromic release of CGRP which causes great reflex vasodilation, always greater and with great pain: CH.

Therapies

This model of headache's etiopathogenesis clarifies many your characteristics , prodromes, aura, CSD, PSG data, but its true strength is that it allows us to understand the therapies we administer to our patients, both because it clarifies the mechanisms through which the individual drugs act, both because it allows us to set new therapies, with the awareness of what we do, at last. In the acute phase we use:

- Anti-inflammatory drugs, steroids and non-steroids, acting on the mechanisms of inflammation activated by the microglia
- Vasoconstrictors drugs, acting on reflected vasodilatation, induced by antidromic release of CGRP, etc., from the nerve endi ngs of the ophthalmic nerve on meningeal vessels (e.g. Triptans).

In the prevention we use:

- Ca^{++} antagonists drugs, which inhibit the entry of Ca^{++} into the neurons through the NMDA receptor, opposing to the UA increase;
- Also Magnesium favors the closure of the NMDA receptor;
- Antiepileptic drugs (Lamotrigine, Topiramate, Gabapentin, etc.) that counteract many GLU synapses or activate GABAergic synapses, non-specific, related to cortical hyperactivation;
- We also use the antagonists of the major neurotransmitters to lower the UA (e.g. Pizotifen, serotonin antagonist; Propranolol, beta blocker; Cinnarizine, antihistamines; but are also used drugs that increase the amount of certain neurotransmitters, the so-called inhibitors of the reuptake, especially, because serotonin (of DR) inhibits OX but, in our opinion, it's a mistake to use these drugs, for headaches.
- Resection interventions on various nerves in the cranio-cervical area (e.g. N. Occipital) may have a positive feedback (the contribution of ARAS to the nerves of this district is always considerable and their abolition decreases sensibly the UA).
- Some methods such as massages, acupuncture, relaxation techniques and feedback can help, because they decreases the UA.
- This model explains why many migraine patients are graduates, excellent professionals or craftsmen or, in any case, very intelligent people (there is high UA).
- I'm often overweight (high UA requires a lot of glucose).
- Explains why a hypoglycemic diet, almost ketogenic [73]; it can work in the prevention (GLU is produced by Glucose, through the Krebs cycle and if the Glucose is a few cannot be large UA and our SNC is very sensitive to blood glucose). We like to point out that the Me5 activates the center of the vomit, in the posterior area [74], vomiting induces fasting, lowering blood glucose and then UA.
- Also explains why an oral appliance can work in headache care (properly adjusted, can modulate the action of Me5 on orexinergic cells) [24,51,68,69,75,76]; as we have already said, the intense muscular activity of bruxism, causes muscular and dental pain and consequent further specific cortical activation, furthermore, bruxism causes great activation of the Me5, which activates the ARAS nuclei and, above all the one of the OX, increasing the non-specific activation of the cortex. We can intervene on bruxism in a real way, changing dental contacts, increasing or decreasing the their number them according to the case or in a virtual way: using oral devices (bites) through which to manage dental contacts and, therefore, bruxism.
- Explains why deep brain stimulation (DBS) [65] and also less invasive methods such as transcranial magnetic stimulation (TMS) works: DBS interferes with OX production, directly in the Hypothalamus while TMS interferes with the electromagnetic fields generated by the remarkable AA of the cerebral cortex.
- Explains the great activation of the hypothalamus shown by fRMI [60,77].

- Explains why the amount of sleep is important (little sleep means giving to ARAS little GABA and therefore having high UA, vice versa too much sleep means to activate too much the Me5 and, hence, high UA).

- Explains why OX is also responsible for the "headache of the weekend": his levels constantly high in these individuals: allow them to carry out many activities, engage the mind and body and activating many brain areas, "consuming" during the working period, all the GLU available. During pauses (e.g. weekend) excess of GLU does not activate many brain areas and may result in non-sense activation, CSD, etc: the migraine.

In the treatment of migraine, of course, we can't give drugs for all life. However, we can keep UA levels lower through an appropriate lifestyle: low glycemia with an appropriate diet, we can also fight excessive UA by exploiting its main antagonist, the GABA of the VLPO/MnPO, whose excesses are due to a number of factors (Adenosine, IL1β, Prostaglandins etc) on which we can sometimes act in different ways (e.g. trying not to go to bed too tired, cure any other illness, etc). These patients should implement a lifestyle appropriate to their characteristics: always work seven days a week, eat little, eliminate carbohydrates and spirits before go to bed (alcohol stimulates GABAA receptor and makes sleep more profound) , to sleep always the same amount of time (try to go to bed more or less at the same time and wake up at the same time, take good care of health of oneself, both from a general both dental point of view, and, if needed, put an oral appliance [72,75,76,78].

Conclusion

The etiopathogenesis model presented here is based on the idea, not only ours but most of the researchers who deal with this topic, that at the basis of primitive headaches there is an excessive excitability of the cerebral cortex, in our opinion caused by excessive OX production that, directly or indirectly, stimulates the cerebral cortex, in this case excessively (there are also headaches where the hyperactivation is due to genetic alterations such as familial hemiplegic migraine or FHM). The effect of this excessive excitability is the activation of the microglia which, in turn, activates the mechanisms of natural inflammation by producing substances (IL1β and prostaglandins) that cause CTT and migraine. The strength of this model is its ability to explain many features, symptoms and therapies of this pathology.

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