

## REVIEWS AND COMMENTARIES

## Receptors in the pathophysiology of migraine: Facing a highly promising anti-migraine target.

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**ABSTRACT:** Migraine is a severe neurological recurring type of headache with high socioeconomical impact. The pathophysiological mechanisms behind migraine involve a range of interactions within the CNS that seem to be induced by environmental and psychological stimuli. It has been observed that an abnormal excitation begins followed by a cascade of responses including transmission of pain signals by TNC neurones, release of vasoactive neuropeptides, meningeal vasodilation, neurogenic inflammation and the appearance of autonomic symptoms. Under the supervision of extensive research, at both molecular and pharmacological level, cell receptors emerge among the most significant participants in the etiologic basis of migraine. Serotonin, dopamine, CGRP, vanilloid, glutamate and opioid receptors are discussed thoroughly in this article. Some of them are already approved as treatment targets while others still remain under the spectrum of clinical studies despite the fact that they are considered a highly promising section of antimigraine strategies. Scientists are focusing now on revealing all the aspects behind these biomolecular components and move forward on discovering novel therapies for neurological conditions such as migraine.

*Key Words: Migraine, Pharmacology, Therapeutics, Serotonin receptors, Dopamine receptors, Cannabinoid receptors, CGRP receptors, Vanilloid receptors, Glutamate receptors, Opioid receptors.*

### INTRODUCTION

21<sup>st</sup> century is a promising century, after the explosion of biosciences and medicine. The impact of new fields of medicine such as molecular medicine and molecular pharmacology is associated with the technological improvement. Novel techniques borrowed by molecular biology's «wisdom» encouraged scientists to find the correlations between membrane receptors and diseases. Molecular pharmacology research in the field of diseases associated with receptors abnormalities is still going on. This new area in the field of molecular pharmacology and therapeutics is under the name «channelopathies».

The question that arises whether migraine is another channelopathy or an ion channel abnormality. Migraine is a heterogeneous neurovascular disorder that has a strong genetic and molecular background. It is a global disorder that attacks mostly women and affects approximately the 12% of the general population

with a peak in reproductive years (22<sup>nd</sup> until 55<sup>th</sup> year of life)<sup>1-4</sup>. The International Headache Society (IHS) classifies migraine into two subtypes: migraine without aura (MO) characterized by photophobia and/or phonophobia, emesis, nausea and migraine with aura (MA) with additional neurological symptoms including visual disturbances (blurring, spots)<sup>1,4-7</sup>. In order to diagnose MO, five attacks are needed (in 4-72 hours) to be reported. MA is divided into typical aura, sporadic aura, familiar hemiplegic migraine (FHM) and basilar-type migraine<sup>4</sup>.

The management of migraine can be divided into two axes: pharmacological and non pharmacological intervention<sup>8,9</sup>. Research in laboratory animal models (knockout mice) and patients suffering especially from MA (associated with migraine family history background) resulted in the concept that migraine is closely related to receptor abnormalities. Consequently, pharmacological intervention must be focused on

receptors in order to find the right treatment scheme. However, much has to be done in order to clarify the molecular mechanisms behind the drug - receptor interaction and the therapeutic value of each drug for migraine. Recent studies revealed a large number of important receptors that are involved in the pathophysiology of migraine. The list of potential new drug targets for migraine therapy is continuously updated and the need to identify the molecular mechanisms behind migraine is vital.

### **PATHOPHYSIOLOGY OF MIGRAINE**

Migraine is a form of sensory processing disturbance with wide interactions within the CNS<sup>10</sup>. The trigeminal system - the sensory system of the brain - is a pain transmitting link from the cranial vasculature to the CNS<sup>11</sup>. Changes in the environmental and the psychological state seem to initiate an abnormal excitation of the primary intracranial pain fibres or -in a different version- a cortical spreading depression<sup>10,11</sup>.

The action potential created by the abnormal excitation causes the release of glutamate and CGRP (calcitonin gene-related peptide) which results in the activation of second-order neurones in the trigeminal nucleus caudalis (TNC) and the upper two dimensions of the cervical spinal cord. TNC neurones relay the pain signals to central pain processing structures. Together with CGRP there is also secretion of other vasoactive neuropeptides [e.g. substance P (SP), vasoactive intestinal peptide (VIP)] from the peripheral nerve endings. As a consequence of the release of CGRP mainly there is meningeal vasodilation, plasma extravasation and mast cell degranulation with secretion of other proinflammatory substances in the dura matter causing neurogenic inflammation<sup>10,12</sup>. This type of inflammation sensitizes neurones in the dorsal horn resulting in an increased response to mechanical stimulation of receptive fields and to mechanical and thermal stimulation of cutaneous receptive fields. Their response thresholds decrease and their response magnitude increases. This may explain the intracranial and extracranial sensory hypersensitivity reported by the patients<sup>11</sup>. CGRP enhances and maintains the activation of second-order neurones and is the main cause of the pain symptoms<sup>10</sup>. Nausea and diarrhoea that often accompany migraine must be due to the release of VIP whose secretion initiates these autonomic symptoms<sup>13</sup>.

Cortical spreading depression (CSD) is characterised by a wave of depolarisation and causes hypoaemia. Scientists have found that CSD may lie behind the genesis of migraine's aura but there is no verification yet that the same thing happens in common migraine<sup>13</sup>. Laboratory investigation indicates reduced threshold and increased velocity of CSD resulting in higher susceptibility, in cortical hyperexcitability and link spreading depression and aura in migraine<sup>11</sup>.

### **THE SEROTONIN (5-HT) RECEPTORS: THE KEY-PLAYER IN MIGRAINE**

The significant role of 5-HT receptors in the pathogenesis of migraine was first revealed with the use of triptans for the treatment of acute migraine<sup>3</sup>. Serotonin, their neurotransmitter is localized both in CNS and peripheral nervous system thus implicating their involvement in various physiological conditions such as nociception, circadian rhythm, thermoregulation, memory, sexual behaviour and pathological such as psychiatric diseases (e.g. depression, anxiety) and migraine<sup>7</sup>.

With the aid of molecular and functional criteria, scientists have divided 5-HT receptors in seven classes with the subtypes 5-HT<sub>1A, 1B, 1D, 1E, 1F</sub> being present in humans<sup>4</sup>. 5-HT<sub>1</sub> receptors are coupled to a G-protein through which they negatively regulate the activity of adenylate cyclase<sup>7</sup>. Among these receptors firstly 5-HT<sub>1B</sub> and secondly 5-HT<sub>1D</sub> and 5-HT<sub>1F</sub> seem to have a central role in the pathogenesis of migraine possibly due to their distribution<sup>14</sup>. 5-HT<sub>1B</sub> receptors are located on intracranial blood vessels and CNS neurones, 5-HT<sub>1D</sub> on CNS neurones and trigeminal nerve endings and 5-HT<sub>1F</sub> on trigeminal nerve endings<sup>4</sup>.

With the method of autoradiography scientists have described the distribution of the binding sites of 5-HT receptors in the basal ganglia. 5-HT<sub>1B</sub> receptors are found both in serotonergic and non-serotonergic neurones and they may function as auto- and hetero-receptors, respectively. When they act as auto-receptors they mediate the release of serotonin. When they act as hetero-receptors they mediate the release of other neuropeptides, such as acetylcholine. They have also been characterised as terminal receptors controlling the release of neurotransmitters presynaptically<sup>14</sup>.

Neuropharmacological studies suggest that serotonin and its receptors are involved at different levels in the pathogenesis of migraine<sup>15</sup>. Firstly, 5-HT me-

tabolism is disturbed in migraine patients. Clinical evidence has shown a significant reduction of urinary and platelet 5-HT during migraine attacks<sup>14</sup>. The deficiency of 5-HT reported in migraine attacks results in increased 5-HT synthesis and in central 5-HT receptor hypersensitivity, probably as a self-response<sup>1,14</sup>.

Triptans is a class of agents that are agonists of 5-HT<sub>1B, 1D, 1F</sub> receptors. They oppose their vasodilatory effects in cranial blood vessels during migraine attacks by causing vasoconstriction<sup>1,15</sup>. Triptans are used for the treatment of moderate to severe attacks of migraine<sup>13</sup>. Sumatriptan was the prototype drug of this class but it was soon replaced by second generation triptans including naratriptan and rizatriptan<sup>7</sup>. Even though sumatriptan acts selectively on 5-HT<sub>1</sub> receptors in cranial blood vessels, it also acts on 5-HT<sub>1</sub> receptors located in the peripheral blood vessels<sup>1</sup>. In addition, it was shown through clinical trials that it was only slightly more effective than non-steroidal anti-inflammatory drugs which are frequently used for the treatment of mild migraine attacks<sup>13</sup>. The second generation triptans maintain their efficacy for a longer period of time in comparison to sumatriptan under continuous use<sup>3</sup>. Even though they have similar pharmacodynamic properties with sumatriptan, pharmacokinetics and oral bioavailability are improved. Some times they present longer plasma half-life. Their mode of action depends upon the receptor they stimulate. When they stimulate the vascular 5-HT<sub>1B</sub> receptor, vasoconstriction of cranial blood vessels is caused. When they act on 5-HT<sub>1D</sub> and/or 5-HT<sub>1F</sub> presynaptically they may inhibit dural neurogenic inflammation<sup>1</sup>. Triptans may also modulate the activity of trigemino-vascular nociceptive neurones and inhibit central pain transmission possibly through their combined effect on 5-HT<sub>1B, 1D, 1F</sub> receptors<sup>1,7</sup>.

The dilemma that arises with triptans is that their mechanism of action which is important in migraine treatment, vasoconstriction, can be at the same time a main drawback. This is due to the risk of cardiovascular side effects such as uncontrolled hypertension, that can be fatal, to a certain category of patients<sup>3,13</sup>. Furthermore triptans have contradictions which include uncontrolled hypertension, coronary heart disease and pregnancy<sup>3</sup>.

## **DOPAMINE (DA) RECEPTORS: BEYOND MIGRAINE?**

There have been recognized five different types of DA receptors in the human nervous system so far<sup>16</sup>. They are involved in various physiological functions such as vasoregulation, nociception and autonomic responses<sup>17</sup>. They exert their function through G-proteins to which they are closely connected<sup>16</sup>. DA<sub>2</sub> receptors that are widely expressed in CNS and DA<sub>1</sub> receptors the most abundant DA receptors in humans have an important role in the aetiology of migraine as well as in many psychiatric diseases. DA<sub>1</sub> and DA<sub>2</sub> receptors are also distributed in the cardiovascular system and kidneys as radioligand binding and autoradiographic studies have shown. Migraine sufferers show deficiency of presynaptic dopamine and compensatory hypersensitivity of DA postsynaptic receptors. The hypersensitivity results in a lower threshold for DA receptor activation. This may explain clinical features of migraine such as nausea, vomiting, irritability and yawning<sup>18</sup>.

The significant role of DA receptors in migraine is also supported by the fact that DA antagonists such as droperidol are effectively used in migraine and associated symptoms treatment and that DA agonists contribute to the prophylactic treatment of the disorder<sup>17</sup>. Droperidol is an *in vivo* antagonist of DA receptors and an effective antimigraine agent as a randomized controlled trial performed on more than 300 migraineurs has indicated<sup>9</sup>. Side effects though include anxiety and akathisia and it is not recommended suitable for patients with Parkinson's disease<sup>9,19</sup>.

## **A NEW ERA IN MIGRAINE THERAPY: THE SIGNIFICANT BUT CONTROVERSIAL ROLE OF CALCITONIN GENE-RELATED PEPTIDE (CGRP) RECEPTOR**

The release of the neurotransmitter CGRP and its interaction with the CGRP receptors seem to play a key role in the pathophysiology of migraine. CGRP and its receptors are extensively present in the central and peripheral nervous system<sup>15</sup>. More specifically, they are widely expressed in the trigeminovascular system, a region which is closely associated with the migraine headache<sup>1,15</sup>.

CGRP receptors are involved in various pathophysiological functions such as modulation of motor, sensory, pain pathways and tone regulation of the cranial blood vessels<sup>15,20</sup>. Under the guidance of molecular criteria it has been observed that there are two types of CGRP receptors, CGRP<sub>1</sub> and CGRP<sub>2</sub>. CGRP<sub>1</sub> receptors appear to be highly abundant in humans. Only three of the components comprising the CGRP<sub>1</sub> receptor complex are till now recognized. Each one possesses a different role: (a) the calcitonin-like receptor component (CLR), (b) the receptor activity-modifying protein-1 component (RAMP-1) and (c) the receptor component protein (RCP)<sup>20,21</sup>. Further studies need to be carried out regarding the complete molecular structure of CGRP<sub>1</sub> receptor in order to reveal all its essential components and thus to understand how they interact each other and exert their function. CGRP<sub>2</sub> receptors haven't been described in humans yet<sup>21</sup>.

The presence of CGRP<sub>1</sub> receptors in humans was first discovered in 2002 using its antagonist BIB-N4096BS (olcegepant)<sup>21</sup>. The preclinical studies that followed concerning migraine began to change direction. Further evidence was obtained in regard with intravenously administrated olcegepant and its antimigraine effect based on experiments performed on migraine patients. The reported relief of headache marked at that point the quest for the aetiopathological mechanisms in migraine<sup>9</sup>.

During migraine attacks there are increased plasma concentrations of CGRP as studies *in vivo* and *in vitro* have shown<sup>11,15</sup>. This observation has been described both in migraine with and without aura<sup>11</sup>. CGRP release seems to induce dilation of cranial blood vessels in migraine<sup>11,15</sup>. CGRP also enhances and maintains activation of second-order neurones which cause the pain symptoms<sup>10</sup>. Furthermore the level of CGRP plasma concentration seems to be closely related to the severity of pain<sup>11</sup>.

CGRP antagonist (olcegepant) surpasses other antimigraine agents such as triptans in many aspects. Experiments performed on animals have shown that they inhibit the action of stimulated trigeminovascular neurones by avoiding interference with the cardiovascular system that could cause vasoconstriction. This indicates that vasoconstriction isn't probably the «correct» target for a novel antimigraine agent. In addition the CGRP antagonist acts postsynaptically implicating

that their possible combination with triptans which act presynaptically can be very beneficial<sup>10</sup>. It 's observed that CGRP<sub>1</sub> receptors represent highly promising therapeutic targets. Pharmacological studies are in search for the development of an orally active CGRP<sub>1</sub> antagonist as it appears to be one of the most effective antimigraine emerging therapies.

#### AN ENIGMA IN MIGRAINE: VANILLOID (VR-1 OR TRPV-1) RECEPTORS

During the last decade TRPV-1 receptor drew the attention as a possible effective therapeutic target in migraine. It belongs to the family of «thermo TRP» channels and experiments in knock-out mice revealed the phenomenon of post-inflammatory thermal hyperalgesia that it causes<sup>22</sup>. A lot of trials still remain to be performed in order to light its mechanism of action and to determine the efficacy and side effects of possible antagonists in the treatment of migraine.

There are six subfamilies of TRPV receptors. Among them, TRPV-1 receptor is an intramembranous protein which is present in small and medium sized neurones in dorsal root gaglia, trigeminal gaglia in brainstem and in several non-neuronal tissues<sup>9</sup>. It is involved in the integration of painful stimuli by taking part in the transmission of nociceptive signals in neurogenic inflammation<sup>22</sup>. TRPV-2 receptor is present in CNS and expressed in aortic myocytes, TRPV-3 receptor is found in keratinocytes and seems to act as a heat sensor, TRPV-4 receptor functions as an osmotic receptor and TRPV-5,6 receptors seem to be involved in vitamin D-dependent calcium uptake in kidneys and intestine<sup>11,22</sup>.

TRPV-1 receptor is directly activated by external and internal stimuli such as high temperatures, low pH, capsaicin analogs and indirectly by liberating the receptor from PIP<sub>2</sub> (phosphatidylinositol bisphosphate) which has an inhibitory effect<sup>9,11,22</sup>. The TRPV-1 receptor is connected with sodium and calcium channels of cellular membrane through which it exerts its function<sup>9</sup>. It is suggested that it may promote release of CGRP from trigeminal neurones in pathological conditions such as migraine<sup>22</sup>.

Capsaicin is considered to be the best known vanilloid<sup>9</sup>. It is a compound substance extracted from chilli pepper and stimulates the TRPV-1 receptor in primary sensory neurones<sup>22</sup>. Following stimulation,



pro-inflammatory neuropeptides such as CGRP are released from the sensory terminals which induce the neurogenic inflammation<sup>9,22</sup>. The activation of TRPV-1 receptor is followed rapidly by a period of desensitization during which anti-inflammatory and analgesic effects take place<sup>9,11,22</sup>. At this stage the TRPV-1 receptor leaves its position on the cell membrane and moves to intracellular compartments where it is recycled. The phenomenon of desensitization is of great advantage in the therapeutic strategies against migraine. Molecular and pharmacological studies are now focusing on the development of TRPV-1 antagonists that will make them capable of being administered systematically in contrast to capsaicin<sup>22</sup>.

### OPIOID RECEPTORS AND MIGRAINE

Opioids exist in natural and synthetic form and act via opioid receptors that are located in CNS as well as in the peripheral nerve terminals and digestive system. There are four families of opioid receptors ( $\mu$ ,  $\kappa$ ,  $\delta$ ,  $\sigma$ ). All opioid receptors, through their connection with inhibitory G-proteins, inhibit adenylate cyclase. They also exert their function through ion channels resulting in hyperpolarization and neurotransmitter release. Opioids bind to a specific site on the receptor promoting analgesic and anti-stress effects that mimic the ones generated by the action of endogenous neuropeptides, the opiopeptides<sup>19,23</sup>.

Opioids can be effective in the treatment of pain in migraine patients<sup>15</sup>. They are considered as rescue drugs and are administered when all other therapeutic strategies lose their efficacy. They are also chosen among other antimigraine drugs for pain relief in pregnant migraine patients in the absence of controlled data<sup>4</sup>. Their adverse effects (respiratory suppression, addiction, urinary retention, nausea, vomiting, constipation) mostly arise from their overuse which is a very frequent phenomenon due to their euphoric properties. Opioid antagonists have an important clinical role in managing opioid overdose<sup>19,23</sup>.

### GLUTAMATE RECEPTORS AND MIGRAINE

Glutamate is an amino acid that acts upon NMDA (N-methyl-D-aspartic acid) and non-NMDA receptors such as the AMPA (α-amino-3-hydroxy-5-methylisoxazole) receptors and the kainate receptor. Glutamate is probably the most significant neurotransmitter in the

thalamocortical projections and cells of pyramid system<sup>16,23</sup>. Glutamate receptors are also widely distributed in the trigeminal system. They have an excitatory effect in human brain and seem to cause hyperirritability<sup>15</sup>. More specifically, noxious stimulation of trigeminal neurones increases the cellular concentration of glutamate and excites the neurones in the trigeminal nucleus caudalis resulting in cortical hyperexcitability, typical of migraine<sup>9,15</sup>.

Glutamate and its receptors are being studied as possible antimigraine targets<sup>15</sup>. Genetic evidence seems to support the participation of glutamate and its receptors in migraine pathophysiology. A specific mutation of the excitatory amino acid transporter appears to cause postsynaptic hyperexcitation due to accumulation of glutamate in the synaptic cleft<sup>9</sup>. Recent pharmacological data support that GluR5 (a subunit of kainate receptor) selective antagonists are clinically effective in certain forms of allodynia and hyperalgesia, as well as acute migraine. This brings to the scene the contribution of kainate receptors in the pathogenesis of migraine. Kainate receptors, possibly located presynaptically, are future pharmacological targets for novel drugs because they seem to regulate GABA and glutamate release in bidirectional way<sup>24</sup>.

### CANNABINOID RECEPTORS

There haven't been yet clinical studies that support the use of cannabinoids in the treatment of migraine. Cannabinoids are considered as important blood pressure lowering agents. This pharmacological property brings forward the idea of using them in decreasing the risk or/and the severity of migraine crisis. Although studies conflict about the clinical use of cannabinoids in cardiovascular function, they remain a new prospect of migraine therapeutics<sup>25</sup>.

### CONCLUSION

Through the progress achieved in the understanding of migraine mechanisms, the biomolecular receptors seem to provide new insights into migraine treatment, as they are involved in migraine pathogenesis extensively. Molecular and genetic studies regarding migraine are focusing now on the development of effective antimigraine agents that will be able to act not only at a clinicopathological stage but also at a pre-clinical stage prophylactically.

## Οι υποδοχείς στην παθοφυσιολογία της ημικρανίας: Ένας πολλά υποσχόμενος θεραπευτικός στόχος.

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**ΠΕΡΙΛΗΨΗ:** Η ημικρανία αποτελεί μία από τις συχνότερες αιτίες κεφαλαλγίας με σοβαρές κοινωνικοοικονομικές επιπτώσεις. Σε ότι αφορά τους παθοφυσιολογικούς μηχανισμούς, η ανώμαλη διέγερση, προκύπτει από περιβαλλοντικά και ψυχολογικά ερεθίσματα, συνοδεύεται δε από ένα καταρράκτη αντιδράσεων στο επίπεδο του κεντρικού νευρικού συστήματος. Περιλαμβάνει τη μεταφορά των αλγινών ερεθισμάτων από τους τριδυμικούς νευρώνες, την απελευθέρωση αγγειοδραστικών νευροπεπτιδίων, τη διαστολή των μηνιγγικών αγγείων, τη νευρογενή φλεγμονή και την εκδήλωση αυτόνομων νευρικών συμπτωμάτων. Μελέτες σε μοριακό και φαρμακολογικό επίπεδο, έδειξαν τη συμμετοχή των κυτταρικών υποδοχέων (σεροτονινεργικών, ντοπαμινεργικών, βανιλιοειδών, γλουταμινικών, οπιοειδών, CGRP υποδοχέων και υποδοχέων κανναβινοειδών) στην αιτιοπαθογένεια της ημικρανίας. Ορισμένοι από αυτούς αποτελούν ήδη αναγνωρισμένους θεραπευτικούς στόχους, ενώ άλλοι βρίσκονται ακόμη σε στάδιο έρευνας. Στην παρούσα εργασία διερευνάται η λειτουργία των κυτταρικών αυτών υποδοχέων σε σχέση με την ημικρανία, με σκοπό να αναδυθούν νέες θεραπευτικές στρατηγικές.

*Λέξεις Κλειδιά:* Ημικρανία, Φάρμακα, Θεραπεία, Σεροτονινεργικοί υποδοχείς, Ντοπαμινεργικοί υποδοχείς, Υποδοχείς κανναβινοειδών, Υποδοχείς CGRP, Βανιλιοειδείς υποδοχείς, Γλουταμινικοί υποδοχείς, Υποδοχείς οπιοειδών.

### REFERENCES

1. Arulmozhi DK, Veeranjanyulu A, Bodhankar SL. Migraine: current concepts and emerging therapies. *Vasc Pharm* 2005; 43:176-187.
2. Carasso LR. Migraines - a feminine disease. *Gender Medicine* 2006; 3(Suppl1):S18.
3. Sabuda JT. Innonative approach to migraine headache and other neurologic conditions. *Semin in Integr Med* 2005; 3(3):93-100.
4. Silberstein DS. Migraine. *Lancet* 2004; 363:381-391.
5. Curtain R, Lea RA, Quinlan S, Bellis C, Tajouri L, Hughes R, MacMillan J, Griffiths LR. Investigation of the low-density lipoprotein receptor gene and cholesterol as a risk factor of migraine. *J Neurol Sci* 2004; 227:95-100.
6. Kaushik R, Kaushik MR, Mahajan KS, Rajesh V. Biofeedback assisted diaphragmatic breathing and systematic relaxation versus propranolol in long term prophylaxis of migraine. *Compl Ther Med* 2005; 13:165-174.
7. Shields GK, Goadsby JP. Serotonin receptors modulate trigeminovascular responses in ventroposteromedial nucleus of thalamus: a migraine target? *Neurobiology Disease* 2006; 23:491-501.
8. Kostoudi S, Koutousi C, Mironidou-Tzouveleki M. Coping with pain without medication. *Epitheorese Klinikes Farmakologias kai Farmakokinetikes* 2003; 21:111-126.
9. Ramadan MN, Buchanan MT. New and future migraine therapies. *Pharm & Therap* 2006; 112:199-212.
10. Striessnig J. Pathophysiology of migraine headache: insight from pharmacology and genetics. *DDT: Disease Mechanisms* 2005; 2(4):453-461.
11. Edvinsson L, Uddman R. Neurobiology in primary headaches. *Brain Res Rev* 2005; 48:438-456.
12. Basbaum IA, Julius D. Toward better pain control. *Sci Am* 2006; 294(6):50-57.
13. Just S, Arndt K, Weiser T, Doods H. Pathophysiology of migraine: a role for neuropeptides. *DDT: Dis Mechan* 2006; 3(3):327-333.
14. Sari Y. Serotonin<sub>1B</sub> receptors: from protein to physiological function and behaviour. *Neurosc Biobehav Rev* 2004; 28:565-582.
15. Gupta S, Mehrotra S, Villalon MC, Perusquia M, Saxena RP, MaassenVanDenBrink A. Potential role of female sex hormones in the pathophysiology of migraine. *Pharm & Therap* 2007; 113(2):321-340.

16. Page PC, Curtis JM, Sutter CM, Walker JAM, Hoffman BB. *Integrated Pharmacology*, Mosby, Barcelona, Spain, 1997.
17. Chen CS. Epilepsy and migraine: the dopamine hypotheses. *Med Hyp* 2006; 66:466-472.
18. Emilien G, Maloteaux JM, Geurts M, Hoogenberg K, Cragg S. Dopamine receptors - physiological understanding to therapeutic intervention potential. *Pharm & Therap* 1999; 84:133-156.
19. Mycek JM, Harvey AR, Champe CP. *Lippincott's illustrated reviews: pharmacology*. Lippincott Williams & Wilkins, Philadelphia, USA, 1997.
20. Kenakin T. New bull's - eyes for drugs. *Sci Am* 2005; 293(4):32-39.
21. Gupta S, Mehrotra S, Avezaat JJC, Villalon MC, Saxena RP, MaassenVanDenBrink A. Characterisation of CGRP receptors in the human isolated middle meningeal artery. *Life Sciences* 2006; 79:265-271.
22. Szallasi A, Cruz F, Geppeti P. TRPV1: a therapeutic target for novel analgesic drugs?. *Trends in Molecular Medicine* 2006; 12(11):545-554.
23. Brunton L, Lazo J, Parker K. *Goodman and Gillmans: the pharmacological basis of therapeutics*. Mc-Graw Hill, N. York, 2005.
24. Lerma J. Kainate receptor physiology. *Curr Opin Pharm* 2006; 6:89-97.
25. Kostoudi S, Koutousi C, Mironidou-Tzouveleki M. Cannabinoids in clinical practice. *Epiteorese Klinikes Farmakologias kai Farmakokinetikes* 2005; 23: 265-272.