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Mas Receptor as a Target for Neuropathic Pain Management: Insights into Angiotensin-(1-7) Signaling and Therapeutic Opportunities

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ABSTRACT

Mas is a G protein-coupled receptor (GPCR) that binds to Angiotensin (1-7) and it is evaluated as an important element of non classical Renin Angiotensin System. While the RAS axis has been considered as pro-inflammatory and pro-nociceptive by leveraging the Angiotensin II and AT1 receptor, the Angiotensin (1-7) /Mas axis offers anti-inflammatory, vessels dilating, and neuroprotective functions. It is produced by two mechanisms first, Angiotensin (1-7) is obtained from Angiotensin II via the mechanism of angiotensin converting enzyme 2 (ACE2) and also by the binding of the formed Ang-(1-7) to its receptor, Mas receptor, it activates several signaling pathways such as PI3K/Akt, ERK1/2 and nitric oxide (NO). These pathways together prevent neuronal death, decrease oxidative stress and inhibit the nuclear factor-kappa B (NF-κB), and reduces the expression of various cytokines like TNF-α, IL-1β and IL-6. With regard to neuropathic pain, the Mas receptor contributes to regulation of glial-neuronal crosstalk and negative regulation of microglial and astrocytic activity and neuroimmune balance. Experimental studies have shown that the use of Mas receptor by Angiotensin (1-7) or synthetic activators attenuates mechanical alodynia and thermal hypoesthesia, proving that the Marques and colleagues' hypothesis has possible therapeutic applications. Also, the Mas receptor has functional cross-talk with other pain-modulatory systems, including the endogenous opioid and endocannabinoid systems, contributing to the enhancer of this sort of analgesia. Thus, the novel Angiotensin (1-7)/Mas receptor pathway can be considered as the novel promising candidate for the use of new non-opioid analgesic for the treatment of neuropathic pain. Further research in Mas receptor agonists, peptide analogs, and targeted drug delivery system shows that there is potential to practical application of these discoveries.

Keywords- Neuropathic pain, Mas receptor, Angiotensin (1-7), Renin angiotensin system, Neuro-inflammation, pain management, Analgesia.

I. INTRODUCTION

Neuropathic pain, which occur in the second phase of the SOM, as a result of disruption of the somatosensory nerve system. When attempting to define this disease, which is a reaction for multiple pathogenic factors, use is made of the anatomical localisation or aetiology technique[1]. Other causes of neuropathy and neuropathic pain include viruses like post-herpetic neuralgia, HIV, leprosy, among others. Other leading yet frequent causes are metabolic diseases for instance PDN, peripheral neuropathy as interrelated to virus[2]. Other causes include autoimmune diseases of the central nervous system, multiple sclerosis and Guillain–Barre syndrome, peripheral neuropathies due to chemotherapy, trauma to the nervous system through spinal cord injury, amputation and post-traumatic neuropathy, inflammation, hereditary neuropathies and channelopathies. The following are some of the causes of neuropathic pain[3-5].

Allodynia occurs when a subject gets a pain sensation on contact with a stimulus that is generally non-threatening; hyperalgesia on the other hand occurs where a person gets increased pain sensations when exposed to a stimulus that is generally painful; paraesthesia occurs when a person feels things like tingling sensations, itching, reduced or loss of sensation, or a needle prick feeling[6]. In people who suffer from

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neuropathic pain, the sense of pain often manifests itself on its own, without any external cause. This pathological disease has a significant impact on the quality of life of patients because of the negative consequences it has on the mental health of patients[7].

It is difficult to obtain accurate information regarding the frequency and prevalence of neuropathic pain in the general population since there is no definition of neuropathic pain that is universally accepted[8]. After conducting a comprehensive analysis of the epidemiology of chronic pain, the following findings were discovered: the incidence of post-herpetic neuralgia ranges from 3.9-42.0/100,000 person-years, the incidence of trigeminal neuralgia ranges from 12.6-28.9/100,000 person-years, the incidence of post-disease neuralgia ranges from 15.3-72.3/100,000 person-years, and the incidence of glossopharyngeal neuralgia ranges from 0.2-0.4/100,000 person-years[9]. Pain caused by neuropathy was also more prevalent among people who worked in physical labour and those who lived in rural areas. Furthermore, it was more prevalent among women (60.5% of the population) and people who were between the ages of 50 and 64.

II. RENIN ANGIOTENSIN SYSTEM (RAS)

Renin-angiotensin-aldosterone system (RAAS) is another machinery generic to regulation of blood pressure and fluid and electrolyte homeostasis[10]. It has been established that it exerts remarkable effect on the cardiovascular system; however, the data revealing influence of the former on various physiological and pathological processes are also available. Some of the components of RAS that exist in the brain are involved in managing numerous mental functions Fig.1[11]. These processes include perception, emotion, behaviour, anxiety, learning, and memory management. Because angiotensin neuropeptides are known to interfere with cognitive functions, angiotensin inhibitors are able to improve both memory and learning while simultaneously lowering blood pressure[12]. Angiotensin neuropeptides, on the other hand, have been found to boost memory and make learning easier, according to research that was carried out by our group as well as by other researchers[13]. In addition, several pharmacological studies have demonstrated that RAAS is capable of modulating both stress and the anxiety that is associated with it in a variety of different stress situations. One of the primary reasons for these effects is that the expression of AT1 and AT2 receptors varies in a distinct way in the regions of the brain that are susceptible to stress. This is true both inside and outside of the blood-brain barrier.

There are a number of areas in the brain that contain the AT1 and AT2 receptor subtypes[14]. These locations include the thalamus, the anterior cingulated cortex (ACC), the nucleus accumbens, the amygdala, the periaqueductal grey matter (PAG), and the spinal cord. These regions are of great significance since they are responsible for regulating nociception. There is evidence that shows that through PAG the midbrain region stimulates enkephalin-releasing neurones that goes to the raphe nuclei to the brain stem in order to modulate descending pain[15]. The amygdala is a structure that is situated in the region of the medial temporal lobes and it is a region that is involved in the affective component of pain, including neuropathic pain. Different parts of the Amygdala exist, they are the lateral nucleus (LA), basolateral nucleus (BLA), and central nucleus (CeA) and these trillion is entail for the sensory signal and pain[16]. Anterior cingulate cortex, or ACC, is the term often used when discussing this part of the brain which has been proven to be involved in secondary processing of the affective component of both, normal and pathological pain. One of the cortex that make up an adaptive network in the PFC is the orbitofrontal which has the capacity to perceive both acute and chronic pain[17]. Human clinical research along with the other research anim al has also shown that the thalamus has a role to playa in the generation of chronic pain. In addition, it can be cited that this process is one of the most crucial links of the connection with subcortical zones and cerebral cortex[18]. Following are some of the features involving neuropathic pain: a central sensitisation to pain. This is so as far as a number of biochemical changes that take place in spinal cord and several areas of the brain. The spinal cord can be understood as the main cranial nerve through which sensory information from periphery is frequently relayed to the brain.

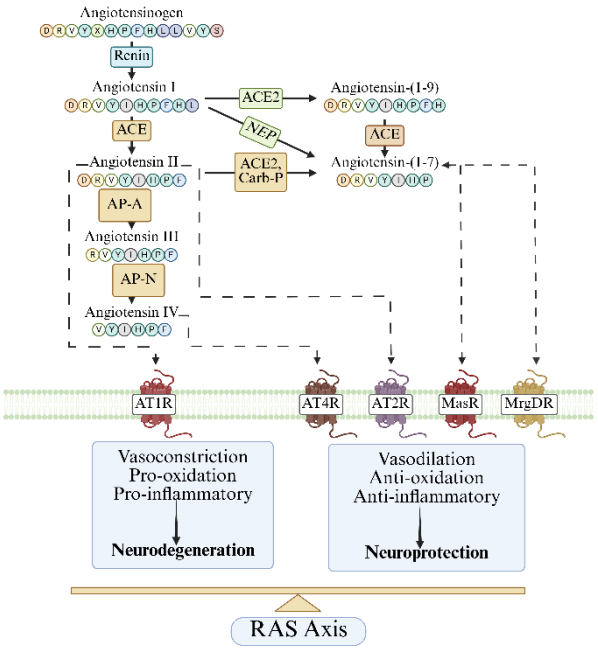

Fig.1: Renin Angiotensin system

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III. MAS RECEPTOR AND ANGIOTENSIN (1-7): MOLECULAR INSIGHTS

Structure and signaling of the Mas receptor (GPCR) family

G protein-coupled receptors (GPCRs) are involved in a wide variety of physiological processes and responses, including sensory perception (which includes the senses of sight, taste, and smell), immunological response, hormone control, and neurotransmission, to name just a few of them[19]. Recently, the pharmaceutical industry has been paying a lot of attention to them as a result of the several critical tasks that they perform within the body. At the moment, around 35 percent of all drugs that are currently on the market are centred on GPCRs because of the significance of these molecules as therapeutic targets. Recent developments in structural biology have significantly contributed to an improvement in our comprehension of the processes involved in the activation of G-protein coupled receptors (GPCRs) and their linkages with G-protein and arrestin signalling pathways[20]. In addition to providing structure-based insights into the mechanisms of ligand identification and receptor activation, it investigates the mechanics of canonical and noncanonical signalling pathways that are located downstream of GPCRs. In addition to this, it highlights recent advancements in the research and development of medications that target GPCRs[21]. Antibody medicines, polypharmacology, biassed and allosteric signalling, and GPCR selective drugs are the primary areas of concentration in this field. We are primarily concerned with the investigation of GPCR structures, signalling pathways, and the creation of new drugs. Our objective is to provide researchers with the most up-to-date and comprehensive information that is available in this field. This foundation's goal is to create revolutionary therapeutic strategies that target GPCRs, building on recent discoveries about the biassed signalling pathways, activation, and ligand selectivity of G protein-coupled receptors (GPCRs)[22].

Researchers have explored the signalling pathways that involve G-protein couple receptors and the effectors that regulate cellular signal transduction and physiological processes. This is due to the volume of data that has been collected. In order to better understand the complex network of GPCR pathways and the impact that these pathways have on the physiology and biology of living things, the findings have proven to be of great assistance. Based on research conducted on humans, nematodes, insects, and other organisms, it has been determined that the GPCR regulatory pathways play a crucial role in the cell signalling transduction process, which is responsible for controlling essential cellular processes (Fig. 2). There are many diverse processes that fall under this category, including as cell division, differentiation, migration, angiogenesis, cancer, metastasis, and the dissolution of extracellular matrix[23]. As part of their efforts to develop innovative therapies for the treatment and prevention of human disease, researchers have identified GPCR downstream effectors in a variety of signalling pathways as potential targets. For instance, clinical trials are now being conducted to assess the efficacy of a number of inhibitors that are aimed at downstream effectors in the phosphoinositide 3-kinase pathway[24]. Within this category of inhibitors include those that specifically target receptor tyrosine kinases, as well as AKT and mTOR. Another system that is being investigated is the Hippo pathway, which is a pathway that is shared between fruit fly flies and mammals. This pathway is known to regulate gene transcription and is also known to have a role in cell proliferation, cell death, and cell differentiation[25].

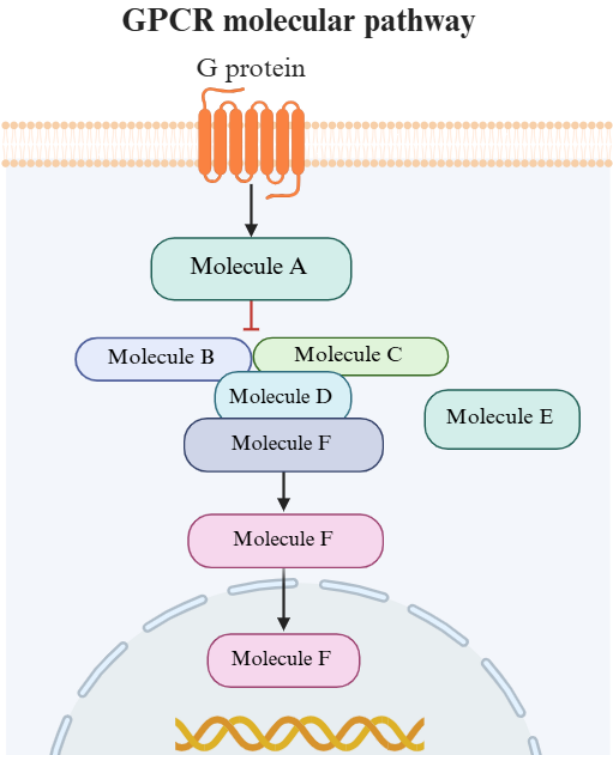

Fig.2: GPCR molecular pathway

Angiotensin (1-7) synthesis via ACE2

Renin is involved in the catalysis of angiotensinogen hence producing Angiotensin I (Ang I) which is an inactive peptide[26]. According to the circulating endocrine system, the conversion of Ang I to Ang II is performed by Renin-Angiotensine-Converting Enzyme which is labeled commonly as ACE and is a part of renin-angiotensin system (RAS). Ang II being linked to the detection of the angiotensin type 1 receptor (AT1R), it is able to trigger the peripheral and central mechanisms that control blood pressure[27]. Therefore, this study postulated possible link between extended activation of the ACE-Ang II-AT1R pathway and several pathological responses such as fibrosis,

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inflammation, metabolic disorder, heart failure, cancer, aging, and diabetes impairment. Despite the fact that ACE inhibitors and AR antagonists are useful antihypertensive agents, and regardless of the presumed invocation of only the classic RAS, recent literature has ascribed some of the antihypertensive effects of these drugs to still other components of the RAS[28]. This is so even though both these kinds of drugs are beneficial in treating for cardiovascular disease. Thus, our pioneering investigation was aimed at identifying and measuring endogenous Ang-(1-7) levels in the brain, blood, and peripheral organs. Ang-(1-7) may counteract with the effects of the Ang II-AT1R pathway as deduced from later investigations in animals and humans whereby ACE inhibition increases the levels of circulating Ang-(1-7)[29]. When the AT1R is occupied, the Ang II moves to the AT2R pathway owing to some resemblance to the Ang-(1-7) system and induces the formation of Ang-(1-7) with the help of ACE2 to break down Ang II. We described enzymatic formation and degradation of the Ang-(1-7) axis in blood, central and peripheral tissues, CSF and urine since the RAS functional actions are now related to much more complex peptidome formation as compared to earlier conventional concept of RAS containing only seven peptides formed by two propelinease enzymes[30]. This paper aims at presenting the functions of renin and angiotensin converting enzyme in the creation of angiotensin I as well as angiotensin II that is part of angiotensin 1–7[31]. Furthermore, the effects of ACE and dipeptidyl peptidase I (DPP3) on the metabolic process of angiotensin-1–7 will be also explained. Over the last years, several novel RAS components remain unidentified. The Mas receptor and angiotensin converting enzyme-2 (ACE2) are two major proteins in the ACE2/ANG-(1-7)/Mas system that has become the newly identified branch of RAS. This reconsideration of the initial cascade is what led to the creation of this new limb of the RAS[32]. For this reason, the new system is now acknowledged as the balance between one arm that increases the formation of new blood vessels and the thickening of the walls of the blood vessels through the activation of the ACE/ANG-II/AT1 receptor and a second arm that helps expand blood vessels and the slowing of the constriction of blood vessels through the activation of the ACE2/ANG-(1-7)/Mas receptor. However, it is now increasingly clear that the traditional cascade of angiotensin converting enzyme (ACE) and angiotensin II, in addition to their main products ANG-(1-12) and (pro)renin receptor is becoming much more complex and simply involving angiotensin-IV, and other peptides is a mere start. The objective of this page is to briefly describe the role of the ACE2/ANG-(1-7)/Mas receptor in neurological and cardiovascular diseases including hypertension, chronic heart failure, stroke[33].

Mas receptor signaling pathway

MasR is a class A GPCR that was first characterized in 1986. The results proved that MasR had the capacity to convert and create foci in NIH 3T3 cells and support the tumorigenicity in nude mice. At this time it is claimed it became the first receptor placed among the Mas-related GPCR family or Mrgpr[34]. This family of orphan receptors comprises of around forty receptors that share similarities in terms of structure and function with MasR and has tetrad effects among the sensory neurons that have specialized in the feeling of pains. However, to date, the MasR remains the orphan GPCR according to the IUPHAR/BPS Guide to Pharmacology although the information regarding the physiological role of the receptor has been amassed. This classification is hereby in accord with the various approaches used in the proposition of an orphan receptor for a particular ligand[35]. Of the components of the renin-angiotensin system, the ACE2-Ang-(1-7) pathway is potential for modulation and one of the receptors is the MasR, regarded as an orphan G protein-coupled receptor. Besides the function of the control of the activity of the CNS, this receptor is possibly involved in the preservation of the function of the cardiovascular and renal systems and other essential physiological processes[36]. However, despite the fact that this information is quite valuable for therapeutic effect, the signalling systems linked to MasR are still not well characterized. Due to this, we deemed it necessary to do this experiment with an aim of identifying signalling pathways activated by MasR. Thus, to accomplish this goal of our work, we decided to determine the levels of cAMP and intracellular calcium ([Ca2+]i in the naïve and in MasR transfected cells. This was done both in the basal condition and after incubation with probable MasR ligands. In addition, to assess Ang-(1-7) activity in activating ERK1/2 in cells transfected with MasR, we[37]. The results of the study then led it to be concluded that there is a large constitutive activity of MasR with regards to cAMP. Instead, this impact was achieved by the receptor linked to the Gαi-adenylyl cyclase signaling, although not the PDZ-binding motif of the MasR. Time course of Ang-(1-7) or the related synthetic ligand AVE 0991 with MasR transfected cells lead to decreased regulation of cAMP via MasR. However, it became clear that Ang-(1–7) does not alter a set of stimuli related to MasR Ca2+. It was also found that MasR contributed to reducing the phosphorylation of ERK1/2 which was caused by Ang-(1-7) phosphorylation of AT1R[38].

EPOR and PI3K signalling pathway is in charge for receiving signals that allow erythroid progenitor cells to survive, duplicate and transform into cancer cells. The PI3K protein is made up of two distinct parts namely the P85 regulatory subunit and the P110 catalytic subunit. EPOR has tyrosine residues namely Y 607 and Y508 which are located at the P 85 subunit. This leads to the activation of the PI3K pathway thereby detrimental to the growth of the tumor. Subsequent to EPO binding to its receptor, the p85-α subunit has an important role to play in EPOR internalisation. This subunit is also

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involved in ubiquitination of Epsin1 and Cbl proteins among the functions that it performs. The names of the secondary messenger molecules that are active for PI3K phosphorylate are phosphoinositide 3,4 bisphosphate (PI(3,4)/P2) and phosphoinositide 3,4,5-trisphosphate (PI(3,4,5)/P3. PDK1 which is also known as phosphoinositide-dependent kinase 1 phosphorylates the serine threonine kinase AKT when activated. This can be considered as a crucial factor that modulates the activity of the PI3K/AKT signaling pathway (scheme 3). One of the other components of the signal transduction that is mandatory for EPO to elicit differentiation into erythroid cells is the translocation of AKT into the nucleus. Among the two proteins in the PI3K/AKT signaling pathway that is affected by hyperglycemia, FOXO3 and GATA-1 are critical for the generation of normal erythroid cells. Also included is hypoxia-inducible factor 1α (HIF1α) and mammalian target of rapammycin (mTOR) as other targets of this enzyme group. In addition, carboxyl-terminal modulator protein C and phosphatase, tensin homologue (PTEN) are other negative receptors that can prevent the activation of PI3K/AKT signaling pathway. To this end, with regards to the EPO-mediated PI3K/AKT signalling map, this work explored the first observable erythroid progenitor of human bone marrow detected as CD34+ cells with a view of identifying transcription factors that respond to EPO. Main target genes include GNG2 and RDS20 which are responsible for G-protein signalling; PABPN1 and CPSF5 necssary for efficient and progressive polymerization of poly(A) tails on the 3’ ends of eukaryotic genes; many other genes of the latter group were considered as the most significant among the genes which were identified by gene expression profiling. PTPRC as a negative regulator of JAK kinases were also identified and other proteins that are relevant to semaphorin signaling involved ANAPC4, SEMA3-F and KIAA0746 that is involved in NOTCH signaling. Besides, the cyclin D3, E & A were also up-regulated also some of the markers of erythroid progenitor immature, including c-KIT and E-cadherin were also elevated [39]. These together came to determine the progression of the cell cycle and differentiation by the phosphorylation of the component protein RB by EPO and PI3K. Some of these genes that were considered involved in transcriptional repression includes; CNOT3, THG-1, and KLF8 and the results showed that these genes had low expression levels. Beside CISH and PIM1, which are known to be activated for STAT5, Sivertsen et al. found out that the majority of EPO sensitive genes operate in the PI3K dependent ways. This is the case except for two proteins, CISH and PIM1.

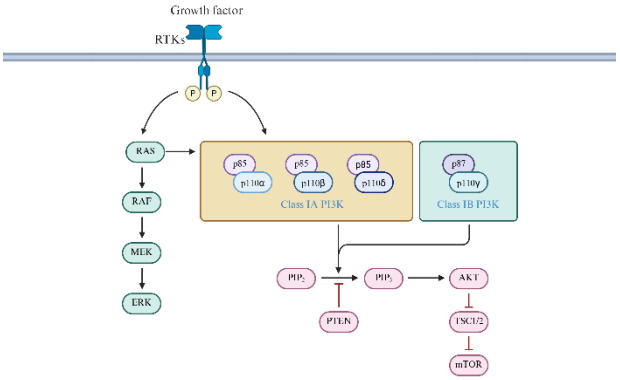

Fig.3: PI3K signaling pathway

Pathophysiology of Neuropathic pain

Neuropathy could therefore be a complex and persistent pain condition that is brought about by damage to the peripheral nerves[40]. It is also different from nociceptive pain that originates from injury or actual tissue inflammation since neuropathic pain has changes in nerve functioning and transmission. Neuropathic pain is the chronic painful condition due to the disease or injury in the nervous system and involves both peripheral as well as central factors participating in the generation of pain, its exaggeration, and sustenance[41].

Peripheral mechanism

Peripheral nerves damage, there are many neuroinflammatory and neurochemical changes arise at the site of the injury. There is also axonal degeneration, demyelization, and other forms of regeneration that take place in injured neuronal cells[42]. The first characteristic is the generation of ectopic impulses from the injured and healthy nerve fibres in what transmits abnormal signals of pain. They also found that there is an increased expression of voltage-gated sodium channel (Nav1.7, Nav1.8, Nav1.9) and calcium channel, which enhances the threshold of nervous sensory neuron[43]. Moreover, various ion channels, particularly TRP derivatives such as TRPV1 and TRPA1, are also vindicated, which are related to thermal and mechanical hypersensitivity. Neuroinflammation is also aanctioned on the peripheral site. Macrophages, mast cells, and Schwann cells enter into the injured nerve and then with the help of cytokines such as TNF-α, IL-1β, IL- 6, chemokines, prostaglandins and ROS. These mediators also sensitize nociceptors and strengthen the excitability of the peripheral nerve[44].

Central mechanisms

CNS is also affected by peripheral nerve injury, and its major manifests in the spinal dorsal horn. As always mentioned, central sensitization refers to altered function of the spinal neurons that enhances the responses of the nervous system to sensory stimuli that are normally non-noxious or subthreshold[45]. This is done through the activation of the N-methyl-D-aspartate (NMDA) receptors which determines the influx of

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calcium intracellularly and the subsequent phosphorylation of protein kinases like PKC and MAPKs. These signaling events consequently lead to improved synaptic transmission, as well as enlargement of receptive fields of dorsal horn neurons. Besides, central sensitization is characterized by the absence of inhibitory controls. The Glut: There is decreased amount of inhibitory neurotransmitters like gamma-aminobutyric acid (GABA) and glycine and their receptors are also have lesser in number. This increase in spinal cord excitation over inhibition leads to some effects like allodynia and hyperalgesia of the nervous system[46].

Microglia and astrocytes form the largest population of the glial cells that are actively involved in the process of central sensitization. The pro-inflammatory mediators cytokines, nitric oxide and the brain-derived neurotrophic factor (BDNF) are also released by glial cells in response to nerve injury, which, in turn, influences the signaling of synaptic plasticity so as to maintain pain.

Involvement of Mas receptor in pain modulation

The Mas receptor is a G protein-coupled receptor that binds Ang-(1-7), a peptide component of the renin-angiotensin system and is involved in regulation pain pathways especially chronic and neuropathic pain[47]. Based on the knowledge of the non-classical RAS, the Mas receptor opposes the pro-inflammatory and nociceptive processes elicited by the classical RAS via Angiotensin II and AT1 receptor activity.

It has been established that through the activation of the Mas receptor by Ang-(1-7), there are subsequent generations of different intracellular signaling pathways such as PI3K/Akt, MAPK/ERK1/2 and NOS. They all play a role in reduction in inflammation, free radical scavenging and neuroprotection[48]. Through the blocking of nuclear factor-kappa B (NF-κB), which is a transcription factor in the synthesis of pro-inflammatory cytokines, the Mas receptor activation decreases the level of TNF-α, IL-1β, as well as IL-6 cytokines that contribute to peripheral and central sensitization of pain signals. In the peripheral nervous system, Ang-(1-7)/Mas signaling assists in limiting exaggerate excitement of nociceptor and inflammation at the injury site of the peripheral nerves[49]. In the central nervous system especially in the spinal dorsal horn, Mas receptor activation regulates the activities of glial cells. They have been evidenced that it has an ability to minimize the activity of the microglial and astrocytic cells, as a result, the shifting of neuroinflammatory factors which intensify pain signaling is also reduced[50]. Moreover, the Mas receptor is helpful in the course of rebuilding the inhibitory neurotransmission that is usually impaired at the neuropathic pain. Such as, this action is important in the management of central sensitization, which is a central drive that underlies chronic pain. Intraperitoneal or intrathecal application of Ang-(1-7) or Mas receptor agonist has been shown to reverse the mechanical allodynia and thermal hyperalgesia in various rodent models of neuropathic pain[51-53]. These analgesic effects occurred along with the absence of tolerance or motor complications; therefore, the Mas receptor would be therapeutically favorable compared to traditional analgesics including opioids[54]. Besides, it appears that there might be an interaction between Mas receptor and other native inflammatory pain control systems, such as opioid and endocannabinoid systems, which provides for new analgesic synergistic effects. Such interactions can nonetheless potentially improve the efficacy of pain relief and even decrease drug intensity and side effects of the current pharmacological approaches[55].

IV. CONCLUSION

Neuropathic pain is still a challenging symptom to manage and treat and despite the existing drugs and protocols, patients continue to endure relatively low-quality improvement. Drugee therapies such as opioids and their derivatives, anticonvulsants, as well as antidepressants are often ineffective and come with side effects and withdrawability. Such drawbacks underline the need for new approach to the treatment of neuropathic pain based on mechanisms to alleviate the defect rather than just symptoms. Thus, the Mas receptor, stimulated by Ang-(1-7), is considered as a promising target for the treatment within the frame of the n-RAS. While RAS axis participates in neuro-inflammation, constriction of blood vessels and damage of tissues by Ang II and AT1 receptor, the Ang-(1-7)/Mas axis has multiple beneficial effects. These include anti-inflammatory, anti-oxidative, vasodilatory, and neuroprotective effects which are very pertinent to the development of neuropathic pain. Investigations on the molecular basis of the Mas receptor signal transduction have shown that Mas receptor activation leads to activation of PI3K/Akt, MAPK signaling, up-regulation of NO and down-regulation of LPS-stimulated NF-κB activity thereby suppressing pro-inflammatory gene expression. In addition, its effect on glial neuronal communication, inhibition of central sensitization and interaction with endogenous opioid and endocannabinoid systems establishes its diverse responsible unit in acclimating pain. Published studies of the Mas receptor and Ang-(1-7) show time and again decreased mechanical and thermal hyperalgesia in the models of nerve injury and inflammation. Taken together, these data indicate that the Ang-(1-7) / Mas receptor is not only involved in the endogenous pain relief of neuropathy but can also be the basis for creation of new, non-opioid analgesics of a new generation. All in all, the research highlights the existence of a new therapeutic approach focused on the Mas receptor to manage neuropathic pain. Further expansion of the thought of Mas receptor agonists, peptide delivery systems, and combinational results in them

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demonstrating great promise for carrying the molecular advantages of these pieces into secure, efficient, and target inbound clinical therapies.

FUTURE PROSPECTS

The drawbacks of the present pharmacologically administered remedies to neuropathic pain, it is essential to look for new signals to intervene. Angiotensin-(1-7) can modulate pain through activating Mas receptor and showing defined anti-inflammatory, neuroprotective and antinociceptive properties thus becoming a potential candidate for the third generation analgesics. Among them, the key strategies are the development of stable and bioavailable Mas receptor agonists. However, due to its very short half-life and also because angiotensin-(1-7) can easily be cleaved and inactivated by angiotensin-converting enzyme (ACE), its direct pharmacological application is rather limited. To address this challenge, great efforts have been channeled towards the development of non-peptide Mas agonists, cyclic Ang-(1-7) mimetics, and fusion peptides which are more stable, specific to the receptor as well as penetrate the tissues better. Furthermore, other formulations such as, liposomal, polymeric nano-particles and hydrogel-based delivery systems are under scrutiny to achieve specificity towards the CNS with befitting side effects. Another noteworthy line of work can be coupled with the gene and cell therapy to increase the density of ACE2 or Mas receptors in the Area Postrema and other related regions of injury. They may therefore result in a persistent shift of the balance of the Ang-(1-7)/Mas and thus turn the compound into a disease-altering rather than a disease-palliating treatment. Moreover, Mas receptor agonist combined with the other co-analgesic antalgic drugs (painkillers such as opioids, gabapentinoids) may lead to minimized doses and, thereby, waiting for tolerance or necessity for drugs' dependence. The combination of genomics, proteomics, and metabolomics will also be helpful in defining biomarkers that can help in selection of patients likely to benefit from Mas-based therapies. Lastly, clinical trial approaches regarding safety, pharmacokinetic profile, and analgesic efficacy of MasRMs will also be a crucial method in affirming pre-clinical studies. To sum up, the paper indicates promising prospects in evolving of Mas receptor-targeted therapies for treatment of neuropathic pain. The given axis is rather promising for non-opioid pain treatment with the enhancement of drug design and delivery systems, as well as upcoming trends of targeted and individualized medicine.

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