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EMERGING THERAPEUTIC STRATEGIES OF NEUROPATHIC PAIN

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Abstract

Abnormal action potential can be generated from enhanced expressions by ion channels, receptors and/or neurons and such synaptic transmission can result in neuropathic pain. Now days, many pharmaceutical industries are investing to develop analgesic drugs, but approved analgesics acting at novel molecular targets are rare. Historically, less than 50% of patients provided relief from pain effectively by treatments with anti-convulsants or anti-depressants. But there are limitations in their therapeutic utility due to significant unwanted adverse effects. Neurophysiological changes occurring in neurons should be targeted in the treatment of neuropathic pain. Since past few years, neuronal excitability is altered by many drugs, so modification in excitability of neurons is the emerging target to develop new analgesic drugs. The present review provides the reader advanced scenario of research in the same field and unraveled research options for this convincing field of therapeutic demand.

Keywords: *Ion channels, receptors, targets, neuropathic pain.*

Introduction

Physiological insult by direct neuronal trauma, inflammatory conditions, metabolic disturbances, viral infections, cancer, use of chemotherapeutic drugs and primary neurological diseases can cause alteration in neuronal functions and damage which initiate neuropathic pain. Long lasting changes in neurophysiology occur after nerve injury due to which, pain are triggered by any non-specific stimulus, even of small intensity. Motivation to researchers to review the emerging approaches for treating neuropathic pain is non-specificity of currently available analgesics for molecular target on the basis of neurophysiology. Neuropathic pain should be treated by targeting neurophysiological changes occurring in neurons (1). Limited success of pharmacotherapy for neuropathic pain with commonly used pain reducing drugs, such as NSAIDS and opiates contributed to delve into unaccustomed treatment protocols (2). Abnormal action potential can be generated from enhanced expressions by ion channels, receptors and/or neurons and such synaptic transmission can result in neuropathic pain (3), which is currently targeted as novel drug discovery opportunity.

1. Glutamate receptors:

The dominant excitatory neurotransmitter in mammalian CNS is glutamate. It acts through activation of either ionotropic glutamate receptors (iGluRs) which are fast acting or metabotropic glutamate receptors (mGluRs). Eight different types of metabotropic glutamate receptors are grouped as: Group I (mGluR1 and mGluRs 5), group II (mGluR2 and mGluR3) and group III (mGluR4, mGluR6, mGluR7, mGluR8). Group II and III mGluRs are Gαi protein linked and group I mGluRs are operated through Gq coupled receptors. Group I mGluRs works through stimulation of enzyme phospholipase C, releases IP_3 (Inositol 1, 4, 5-triphosphate) and DAG (Diaceylglycerol). IP_3 releases calcium from storage and together with DAG activated protein kinase C to follow the downstream pathway. Also, glutamate gated calcium ion channels are opened through NMDA receptors causing physiological and pathological excitatory response like observed in neuropathic pain (4). The synaptic action of glutamate is influenced by mGluRs, present at nerve endings, postsynaptic locations and glial cells. So development of class of iGluRs and mGluRs, is associated with perceptions of neuronal glutamatergic transmission. Now a days, important aspect is to develop selective mGluR molecules and to know about contribution of mGluRs. in triggering pain pathway persisting for long time. Inhibition of group I mGluRs and/or stimulation of group II and III mGluR-is on target of researchers to treat neuropathic pain (5). Glutamate is released after neuronal lesions by tissue trauma or neuroinflammation. At the same time, substance P, like some neuropeptides are released there which causes neuronal membrane depolarization which is long-lasting. This contributes to chronic pain. Excitatory synaptic transmission in the spinal cord is

mediated by postsynaptically localized mGluR1, mGluR5. Additionally, GluRs which are presynaptically present on nerve endings of primary sensory nerves contributes in divided transmission of nociceptive pathway, more including kainite (6). Thus, there are opportunities to target distinguished types of glutamate receptors in pharmacotherapy of neuropathic pain.

2. NMDA receptors:

NMDA (N–methyl-D-aspartate), kainite and AMPA (amino-3- hydroxy-5-methyl-4-isoxazolepropionic acid) receptors are the major three subgroups of glutamate gated ion channels. It is suggested that NMDA receptors mediate transduction sensitivity in sensory receptors at the point of injury and excitability of spinal cord neuron, which gives hyperalgesia and allodynia. Previous studies proved involvement of NMDA receptors in initiation of pain as NMDA antagonist attenuated chemical induced, surgery induced and peripheral inflammation associated pain (7). The NMDA receptor, highly permeable to calcium ions, is proved to trigger prolonged synaptic changes e.g. synaptic malleability resulting chronic pain. NMDA receptors are assembled by three basic subunits, NR1, NR2, and NR3. Genetic junctions of NR1 gene, generates eight different subunits of NR1, four different subunits of NR2 (A, B, C, and D) and two subunits of NR3 (A and B). Among these, NR2B, NR2C and NR2D subunits are present on peripheral nociceptive fibers. Researchers are focusing currently advanced development in NR2B-subunit containing NMDA receptors for neuropathic pain. The functional expressions of NMDA receptors in maintaining synaptic malleability is to be reviewed before targeting these receptors in the treatment, thus NMDA receptors containing NR2B subunit, are significantly effective targets in treating neuropathic pain (8). Furthermore, histamine , polyamines or protons like some endogenous substances causes alteration in functions of the NMDA receptor, which selectively alters NR2B subtype also. Ifenprodil-like compounds potentiates inhibition mediated by protons and oppose potentiation of NR2B receptors mediated by polyamines (6). But evidences suggested that various cognitive functions are controlled through NMDA NR2B receptors so disturbances learning and memory functions are challenges against NMDA NR2B receptor targets for pain treatment (8). The therapeutic utility of these agents in chronic pain depends on the equilibrium of gain and loss of brain functions. There are many encouraging results obtained by different studies, but their undesirable adverse effects have limited usefulness of this class of compounds (7). Ifenprodil like selective antagonists of NR2B , are effective in neuropathic pain preclinically and clinically also, and show improved effectiveness with minimum adverse effects than nonselective NMDA receptor blockers. Hence more research is required at cellular and molecular mechanistic level of these receptors to advance the pharmacotherapy of neuropathic pain (8).

3. Chemokine receptors CCL2/CCR2:

Chemokine induced neuroinflammation is evidenced in pathophysiology of neurodegeneration and neuropathic pain. Neurodegeneration, inflammation and pain are mediated by defending immune cells, supporting glial cells and neurons which release inflammatory mediators, interacting through neurotransmitters through their respective receptors. The chemokine MCP-1/CCL2 upregulates monocyte integrin, modulates leucocyte integrins and production of various cytokines during neuroinflammation, thus neuroinflammation is mediated which motivate to target CCL2/CCR2 to control neuropathy induced by neuroinflammation and associated pain response. Extracellular signals such as growth factors, mitogens and cellular stress release mitogen activated protein kinase (MAPK), belong to serine/threonine kinase class and this MAPK controls survival, proliferation, differentiation of mammalian cells. Neuroinflammation, neuronal survival and synaptic activity are regulated by cellular signaling mechanism such as phosphorylation and subsequent activation of MAPK-p38 and its substrate MAPK- activated protein MAPKAP Kinase (MK) MK-2. Thus, pain signaling pathway is primiarly mediated by MAPKs such as extracellular signal regulated kinases (ERK), c-jun N-terminal kinase (JNK) and p38 which further sensitizes peripheral and central neurons involved in chronic pain. Antagonistic approach of CCL2/CCR2 and MAPK signaling networks can be unexplored therapeutic targets to control neuroinflammation and neuropathic pain (9). Chemokine MCP-1 acting through CCL2 receptor, can initiate neuropathic pain and this has been proved by study in mice genetically modified to lack gene of CCL2 receptors. These mice have not shown mechanical hyperalgesia after sciatic nerve ligation. Oppositely transgenic animals with MCP-1 showed hyper expression and increased hyperalgesia. Thus chemokines are series of molecules that co-ordinates neuronal injury with pain and regulate neuroinflammation (10).

4. Peroxisome proliferator-activated receptors (PPARs):

Onset and prolongation of neuropathic pain is due to inflammation caused by neuropathy. Several chemokines and cytokines (MCP-1, MIP-1α, fractalkine, SDF-1) are contributing for neuropathic pain in both humans and animals. As, inflammation and pain are regulated by chemokines, can be aimed for good therapeutic efficacy against neuropathic pain. PPARs, belonging to class of nuclear receptors contributes significantly in metabolism (11). PPARs critically regulates metabolism of lipids and activated by fatty acids and derived substances. Also, it works to control protein and carbohydrate metabolism (12).Three different isoforms are present in this family as: PPARα, PPARβ/δ, and PPARγ distributed in different tissues and having distinguished biological functions. Recent research has revealed inflammatory gene expression; chemokine expression and pain

behavior are reduced by PPARs agonist. In one clinical study, PPARα agonist, palmitoyl ethanol amide (PEA), shown promising chronic pain relieving effect, which is new therapy for neuropathic pain to be used clinically. PPAR agonists are effective agents with significant anti-inflammatory and antinociceptive effects. Thus, for neuropathic pain PPAR agonists may be utilized as novel therapeutic strategy (11). Agonist of PPARγ, have shown anti-inflammatory effect by IL-6 and IL-8. Gene knockout mice with PPARγ deficiency have shown hyperactivation of arachidonic acid pathway and LB4 to present enhanced inflammation. Also agonist of PPARα decreased hyperalgesia after sciatic nerve injury suggesting analgesic effect of PPARα agonist. Recently, functional contribution of PPARs is emerging for research (12).

5. **Endocannabinoid and endovanilloid receptors:**

Nociception is protective phenomenon but if it is persistent and damages nervous system could result into chronic pain. Different types of neuropathic pain can not be treated by any single well-tolerated drug. Opioid analgesics, due to their multiple adverse effects are less promising in neuropathic pain. They develop tolerance and addiction. Cannabinoid system is much sensitized in neuropathic pain so that it can be appropriate target to unfold possibility of novel drugs resisting pain (13). There are two major subclasses of cannabinoid receptors as CB-1 and CB-2. CB-1 receptors are present on heart, lungs, spleen and CB-2 receptors on haemopoetic cells. Apart from these currently, cannabinoids bind with serotonin $5HT_{1A}$ regulating sleep pattern, mood and vanilloid TRPV1 receptors regulating nociceptive signals (14). As per previous research, the agonist of cannabinoid receptor (CB1/CB2) significantly reduced hyperalgesia and Allodynia resulted by sciatic nerve injury and antagonist of CB1 have increased it. This study suggests that, endogenous endocannabinoids inhibited neuropathic pain. Also, one study proved inhibition of carrageenan and formaline induced hyperalgesia by low doses of the endocannabinoid anandamide and its congener palmitylethanolamide administered locally. Recently, it is proved that most competent candidates to treat certain types of pain are those inhibits reuptake of endocannabinoid and another those prevents enzymatic hydrolysis catalyzed by FAAH. Presently, many evidences proved the anti-hyperalgesic characteristics of cannabinoids in nociceptive pathways. Capsaicin and its congeners activate nonselective cation channel i.e. VR1/TRPV1 receptor, which is more permeable to calcium. Thus, TRPV1 receptors are key components in both nociception and chronic pain. Pain signaling by any destructive stimulant in the peripheral terminals of primary sensory neurons is considered to be mediated through TRPV1. Thus role of this ion channel mediated through TRPV1 to initiate pain and hyperalgesia have made it a major therapeutic target for analgesic drugs. The CB1 and TRPV1 are importantly found to have role in neuropathic pain so signaling system of endocannabinoids and

vanilloid may be integrated studied to explore novel therapeutic approaches for analgesic drugs (13). Alteration in endocannabinoid system, may also act prophylactically to reduce neuropathic pain (14).

6. Angiotensin II type 2 receptors:

Many peptides e.g. endothelins, calcitonin gene-related peptide, cholecystokinin, substance P and now angiotensin II that firstly were demonstrated to have a nonnociceptive physiological role but later proved to be present in sensory neurons and to be pro-hyperalgesic mediators. Thus, new mechanistic approach is inhibition of pro-hyperalgesic mediator signalling. Peripheral neuropathic pain can be initiated by Angiotensin II signaling via the AT2R. AT2R antagonist is untapped category of analgesic agents to relive pain in peripheral neuropathy and chronic inflammation. The analgesic effects of small-molecule AT2R antagonists in these pathological pain conditions appear to be underpinned by i) attenuation of augmented angiotensin II/AT2R signaling-induced hyperexcitability of DRG neurons as well as angiotensin II-induced potentiation of TRPV1 activity; ii) attenuation of increased NGF/TrkA signaling; and iii) attenuation of p38 MAPK and p44/p42 MAPK activation in DRG neurons. These effects in turn may reduce MAPK-dependent phosphorylation of many receptors and ion channels involved in hyperexcitability of DRG sensory neurons and chronic pain. This includes enhanced neuronal membrane expression mediated through TRPV1 and its NGF, also overexpression of voltage-gated sodium and calcium channels (15). Analgesic effect of antagonist of AT2 receptors have been proved clinically by EMA401 molecule. Activation of Ang II during inflammation or injury, stimulates noceceptors in nerve fibers, showing inflammatory hypersensitivity. EMA401, being antagonists to AT2 receptor act on peripheral nerve endings by paracrine/autocrine mechanisms, to decrease neuropathic pain (16).

7. Lysophosphatidic acid receptors (LPARs):

Lysophosphatidic acid (LPA), a bioactive lipid acting through its receptors (LPARs), is considered to be key contributors in onset and prolongation of neuropathic pain. After lesions to nerves, primary afferent neurons release glutamate and substance P which increases synthesis of lysophosphatidylcholine (LPC), which further produces LPA. Autotaxin (ATX) converts LPC to LPA which alters neuronal functioning. Preclinical studies of damaged nerve shown demyelination which is the important characteristic feature thought to be contributed by LPA through different mechanistic way e.g. 1) LPA are highly produced after macrophage/microglial activation that initiates a self-sustaining feed-forward loop of *de novo* LPA synthesis 2) Neuropathic pain are triggered due to neuroinflammation and axonal demylination which is considered due to macrophage/microglial activation. Thus if production of LPA and/or its activated receptors are targeted, may be

promising strategy to treat demyelination and the associated neuropathic pain (17). Neuropathic pain were found to be decreased in gene knockout lacking lpa1. After nerve injury, released LPA acting through LPA1 receptors causing demyelination due to decreased myelin proteins. It also causes morphological alterations in neuron and Schwann cells. MAG i.e. myelin-associated glycoprotein is also rapidly decrease by LPA (18).

8. Neurotrophic growth factors:

In maturing nervous system, neuronal growth and its functional durability is supported by neurotrophic growth factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), glial cell line–derived neurotrophic factor (GDNF), insulin-like growth factor-I (IGF-I), and ciliary neurotrophic factor (CNTF). These factors are efficacious in preclinical studies of disease or injury. The neurotrophic factors NGF, BDNF, NT-3, and NT-4/5 belong to the neurotrophin superfamily. Macrophages, fibroblasts and Schwann cells release NGF at the site of peripheral nerve injury. Thus, neurological injuries can be potentially treated by neurotrophic growth factors. Unlike specific neurotransmitter modulators or blockers of specific ion channel, a neurotrophic growth factor can start many molecular pathways inside a cell, which can alter pathological condition to modify the disease. Presently, novel promising approach to treat neuropathic pain is alterations in neurotrophic growth factors e.g. antagonism of NGF and supplementation of artemin. Artemin, neurturin, persephin are the most recently developed GDNF ligands which supports neuronal growth, survival, and maintenance. These may be promising therapeutic candidates acting on a neurotrophic growth factor (19). It is considered that NGF upregulates mu opioid receptors, voltage sensitive sodium ion channels, many peptides that lead to pain. Oppositely beneficiary effects of NGF are also demonstrated that it helps to maintain homeostasis in spinal cord to relieve pain (20).

9. Neuronal nicotinic acetylcholine receptor:

Nicotinic neuronal receptors (nAChR) belongs to ligand- gated ion channels and are

structurally similar to 5-HT3 and $GABA_A$ receptors. There are two main subunits for nAChR as a and b, further cloning of nine of a (a2 to a10) and three of b (b2 to b4) is done. Preclinically, agonists of nAChR shown antinociceptive, antihyperalgesic, and antiallodynic effects but yet from this class no any drug is approved in treatment of pain . The common adverse effects of this class like nausea, emesis, and dizziness are main hurdles which restrict their utility in treating neuropathic pain. From this class ABT-594 was the first compound developed clinically but not achieved required separation. In preclinical studies, promising effects are observed by targeting specific subunit of nAChR but it is also not validated clinically. Tolerance, abuse liability, and addiction required to be bypassed for successful development of these drugs in treatmentment of neuropathic pain (21). Epibatidine, agonist of

nAChR, proved as analgesic, motivated researchers to focus nAChR as target.This analgesic effect is thought to be due to either increased monoamine inhibition or increased GABA and glycine activity (22).

10. Glial cells and glia receptors:

Emerging evidences indicated involvement of microglia in onset and prolongation of neuropathic pain. Microglia is activated in chronic pain after peripheral nerve injury. Activated microglia can release various proinflammatory cytokines that induces and transmits pain by neuron (23). Spinal microglia evidenced to establish neuropathic pain by chain of events. In spinal microglia, neuronal injury upregulates P2X4 receptors. Its expressions are also increased by chemokines. Inhibition of P2X4 receptors have shown to inhibit neuropathic pain (24) As, glial cells are importanat in maintaining CNS homeostasis, and in disease pathogenesis, glial-modulating agents are now attended to treat different neurodegenerative diseases and chronic pain (25). Glias are active genetically and immunologically, so their regulation is significant in neuronal pathways (26). Presently, specific glial modulators available are: (i) a non-selective metabolic inhibitor i.e. fluorocitrate (ii) a tetracycline derivative i.e. minocycline with selective in-vitro microglial inhibition (iii) a non-selective PDE inhibitor i.e ibudilast (iv) an astrocytic glutamine synthetase inhibitor i.e. methionine sulfoximine (MSO) (v) a methylxanthine i.e. propentofylline,. Some of the CNS glial-modulating properties of these agents may be downstream from their primary mechanism of action and this fact should be primiarly considered (25). Roll of microglia in the spinal cord to develop and maintain neuropathic pain is proved by research through involvement of toll-like receptor 4 (TLR4). If internally derived molecule binds to TLR4, may control activity of microglia pain facilitation. This suggests inhibition of such binding could be convincing to treat neuropathic pain. Hyperalgesia and allodynia may observed due to release of soluble nociceptive factors by activated microglia within the spinal cord such as prostaglandins, nitric oxide, proinflammatory cytokines, excitatory amino acids. Although microglial signal transduction after nerve injury is not clear, it is reported that, after nerve injury microglia activation is expressed by TLR2 and TLR4, among the various microglial receptors expressed by microglia, which also drives pain hypersensitivity. The mice which are genetically modified, lacking TLR4 or TLR2 showed significant reduction in microglia activation and pain hypersensitivity after nerve injury. Downregulation of glia activation is resulted by antagonists of TLR4, which relieves neuropathic pain exploring new opportunity for effective therapeutic approach to treat chronic pain (23).

11. Sigma receptors:

Intracellular ion permeability and neuron survival is controlled by involvement of some proteins e. g. sigma 1 receptor (σ1R) and the sigma 2

receptor (σ2R). In general, these sigma receptors (σRs) are transmembrane proteins present in the CNS and in some peripheral tissues (27). σ1R is important dominating part in CNS. The antiallodynic and antihyperalgesic effects exerted by the σ1R antagonist MR3069 meaning antagonist of these receptors are potential targets in neuropathic pain therapeutics. It is shown at the molecular level, the σ1R interacts and coupled to NMDAR and this interaction accounts for its modulatory effects: σ1R antagonists decreased glutamate NMDAR currents (28). σ1R activation has been associated with NMDA-NR2 phosphorylation in the hippocampus. Phosphorylation of NMDA receptor subunits mainly results in increased postsynaptic glutamate signalling (increased calcium permeability) and thus hyperexcitability /sensitization of spinal cord neurons. Also, σ1R may modulate central neuropathic pain and point to regulation of sensitization-related phenomena as a possible mechanism. (27). Recently, σ1R and σ2R are novel neuropathic pain target.

Conclusion:

Presently available drug therapy for neuropathic pain has many limitations, so there is need to explore novel approach for drug discovery. This novel drug discovery should consider neuronal expression, neuronal action potential, ion channels and receptors. The present review focus the emerging therapeutic strategies and helps researcher to explore unraveled opportunities in treatment of neuropathic pain.

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