A REVIEW ON :TRP CHANNELS AND BRAIN SCIENCE INTERVENTIONS : ADVANCES IN THE TREATMENT OF CNS DISORDERS

Dr.M.Lakshmi Prasanna,Tejaswi.Bandaru,S.S.R.Navya Lakshmi.Chakka,Lavanya Devi .Bonda,Hari Chandan.Bandi,Kushma Sri Bhavya.Bandaru, Dr.N.V.V.Jagan Mohan Reddy, Dr.D.Narendra

ABSTRACT:

Transient Receptor Potential (TRP) channels are non-selective cation channels that regulate calcium signaling, neuronal excitability, synaptic transmission, and cellular homeostasis in the central nervous system (CNS). Increasing evidence indicates that dysfunction of TRP channels contributes to the pathogenesis of several neurological and psychiatric disorders through mechanisms involving neuroinflammation, oxidative stress, and altered calcium homeostasis. Various TRP channel subtypes, including TRPV, TRPA, TRPM, and TRPC channels, have been implicated in Alzheimer's disease, Parkinson's disease, epilepsy, depression, anxiety, migraine, and neuropathic pain. Pharmacological modulation of these channels using selective agonists, antagonists, and natural compounds has shown promising neuroprotective, anti-inflammatory, and analgesic effects in preclinical and clinical studies. Although challenges such as limited selectivity and blood–brain barrier penetration remain, TRP channels represent attractive therapeutic targets for CNS disorders. This review highlights the physiological roles of TRP channels, their involvement in CNS disease mechanisms, and recent advances in TRP channel-targeted therapeutic strategies.

KEYWORDS: TRP channels, central nervous system, neurodegenerative disorders, neuroinflammation, calcium signaling, therapeutic targets.

1. INTRODUCTION TO TRP CHANNELS

Transient Receptor Potential (TRP) channels constitute a large and diverse superfamily of non-selective cation channels that play essential roles in sensing and transducing a wide range of physical and chemical stimuli. Initially discovered in *Drosophila melanogaster*, TRP channels have since been identified in mammals and are recognized as critical regulators of cellular signaling, sensory perception, and homeostasis. These channels are widely distributed throughout the body, including the central nervous system (CNS), peripheral nervous system, cardiovascular system, and immune cells. Their ability to regulate intracellular calcium (Ca^{2+}) and sodium (Na^{+}) levels enables them to influence numerous physiological processes, such as neuronal excitability, synaptic transmission, inflammation, pain sensation, thermoregulation, and cell survival [1].

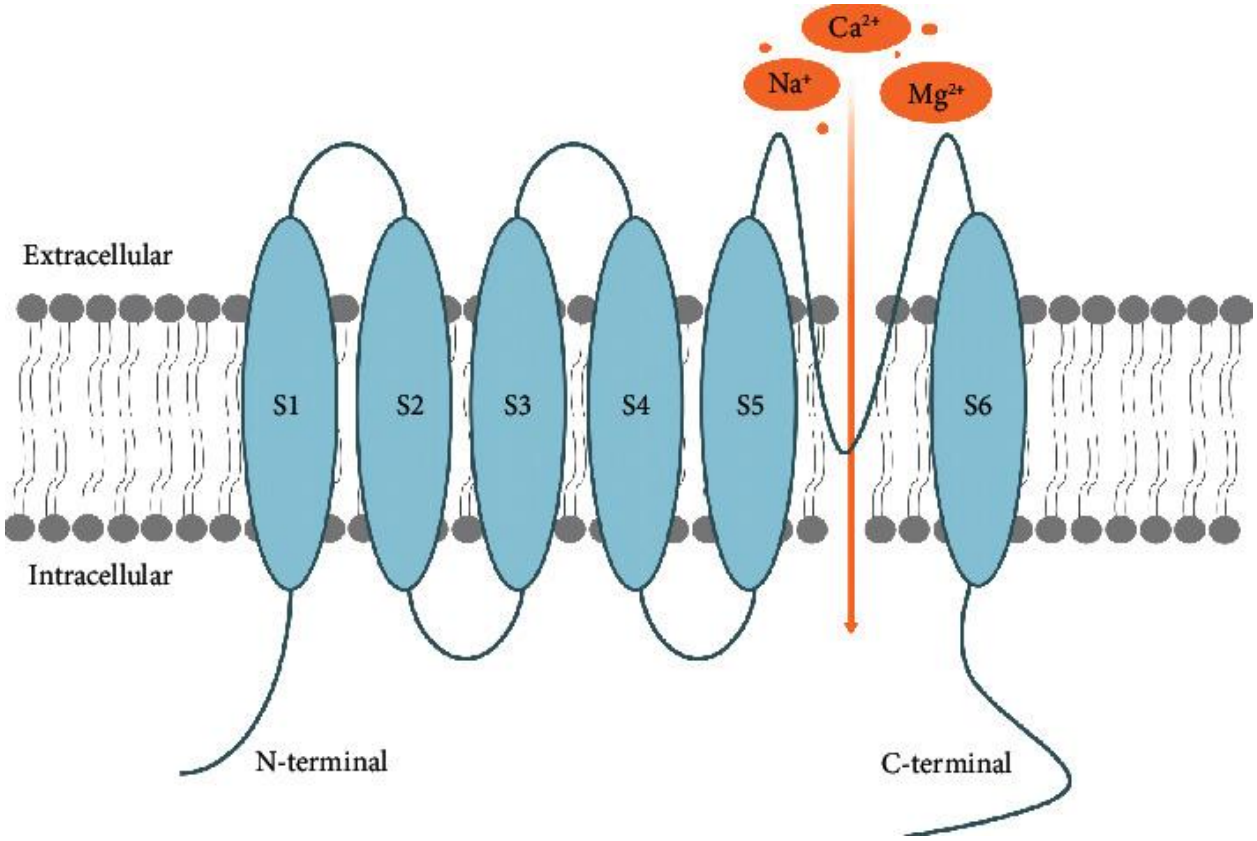
Structurally, TRP channels are tetrameric membrane proteins composed of four subunits, each containing six transmembrane domains (S1–S6) with a pore-forming region located between S5 and S6. Both the amino-terminal and carboxyl-terminal regions are situated intracellularly and contain regulatory domains involved in channel gating and protein interactions. TRP channels can be activated by a variety of stimuli, including temperature changes, mechanical stress, osmotic pressure, pH alterations, endogenous lipids, and exogenous

compounds. This polymodal activation property allows TRP channels to function as versatile cellular sensors that integrate environmental and intracellular signals [2].

Based on sequence homology and structural characteristics, mammalian TRP channels are classified into six major subfamilies: TRPV (Vanilloid), TRPA (Ankyrin), TRPM (Melastatin), TRPC (Canonical), TRPML (Mucolipin), and TRPP (Polycystin). The TRPV family includes channels involved in thermosensation and nociception, particularly TRPV1, which is activated by heat and capsaicin. TRPA1 functions as a sensor for noxious chemicals and oxidative stress. Members of the TRPM family regulate cellular magnesium and calcium homeostasis and participate in neuronal survival and oxidative stress responses. TRPC channels are receptor-operated channels that contribute to calcium entry following activation of G-protein-coupled receptors and receptor tyrosine kinases. TRPML channels are primarily localized in intracellular organelles, particularly lysosomes, where they regulate vesicular trafficking and ion homeostasis. TRPP channels are associated with mechanosensation and cellular signaling and have been implicated in polycystic kidney disease [3].

A fundamental characteristic of TRP channels is their permeability to cations, particularly Ca^{2+} and Na^{+}. Upon activation, these channels facilitate the influx of extracellular ions into the cell, leading to membrane depolarization and activation of downstream signaling pathways. Calcium entry through TRP channels serves as a critical second messenger mechanism that regulates gene expression, neurotransmitter release, synaptic plasticity, apoptosis, and inflammatory responses. In neurons, TRP-mediated calcium signaling influences neuronal communication and network activity, while dysregulation of these processes has been linked to various CNS disorders, including Alzheimer's disease, Parkinson's disease, epilepsy, depression, and neuropathic pain [4].

Growing evidence suggests that TRP channels are important contributors to the pathophysiology of numerous neurological and psychiatric disorders. Their involvement in calcium homeostasis, neuroinflammation, oxidative stress, and neuronal survival has attracted significant attention for therapeutic intervention. Consequently, pharmacological modulation of TRP channels through selective agonists and antagonists has emerged as a promising strategy for the treatment of CNS disorders. Understanding the structure, classification, and physiological functions of TRP channels is therefore essential for exploring their therapeutic potential in neuropharmacology and drug development[5].



2. DISTRIBUTION OF TRP CHANNELS IN THE CENTRAL NERVOUS SYSTEM (CNS)

Transient Receptor Potential (TRP) channels are widely distributed throughout the central nervous system (CNS) and are expressed in both neuronal and non-neuronal cells. Their broad distribution enables them to regulate numerous physiological processes, including calcium signaling, neurotransmitter release, synaptic plasticity, neuroinflammation, and neuronal excitability. Different TRP channel subtypes exhibit distinct expression patterns within specific brain regions and cell types, suggesting specialized functional roles in CNS physiology and pathology [6].

2.1 EXPRESSION IN NEURAL CELLS

TRP channels are abundantly expressed in neurons, where they participate in membrane depolarization, intracellular calcium regulation, and synaptic communication. Several TRP subfamilies, including TRPV, TRPM, and TRPC channels, influence neuronal development, neurotransmitter release, and long-term synaptic plasticity. These channels act as cellular sensors that respond to chemical, thermal, mechanical, and oxidative stimuli, thereby modulating neuronal activity and survival [7].

In addition to neurons, TRP channels are expressed in glial cells such as astrocytes, microglia, and oligodendrocytes. Astrocytic TRP channels regulate calcium waves, gliotransmitter release, and neuron–glia communication. Microglial TRP channels contribute to immune responses within the CNS by regulating inflammatory mediator production and migration of activated microglia. Oligodendrocytes express specific TRP channels involved in myelination, cellular differentiation, and maintenance of white matter integrity. Dysregulation of TRP channel activity in these cells has been associated with neuroinflammation and neurodegenerative diseases [8].

2.2 LOCALIZATION IN MAJOR BRAIN REGIONS

2.2.1HIPPOCAMPUS

The hippocampus, a critical region for learning and memory, expresses several TRP channel subtypes, including TRPV1, TRPC6, and TRPM2. These channels regulate synaptic plasticity, long-term potentiation (LTP), and memory formation through modulation of intracellular calcium signaling. Altered TRP channel activity in the hippocampus has been linked to cognitive impairment and neurodegenerative disorders such as Alzheimer's disease [9].

2.2.2CEREBRAL CORTEX

HYPOTHALAMUS TRP channels are widely distributed in cortical neurons and glial cells. They participate in sensory information processing, neuronal communication, and cortical network excitability. TRPC and TRPM family members are particularly important for maintaining calcium homeostasis and regulating neuronal responses to external stimuli [10].

Within the hypothalamus, TRP channels contribute to the regulation of body temperature, energy balance, feeding behavior, and neuroendocrine functions. TRPV1 and related channels act as temperature-sensitive receptors and participate in homeostatic responses to environmental and physiological changes [11].

2.2.3CEREBELLUM

The cerebellum contains multiple TRP channel subtypes that influence motor coordination, balance, and motor learning. TRPC channels are highly expressed in Purkinje cells and are involved in synaptic signaling pathways that regulate cerebellar function. Disturbances in TRP-mediated signaling may contribute to motor dysfunction and neurodegenerative conditions [12].

2.2.4SPINAL CORD

TRP channels are extensively expressed in the spinal cord, particularly in sensory pathways involved in pain transmission. TRPV1, TRPA1, and TRPM8 are important mediators of nociceptive signaling and central sensitization. Their activation influences neurotransmitter release and neuronal excitability associated with chronic pain and neuropathic conditions [13].

2.3 ROLE IN SYNAPTIC TRANSMISSION AND NEURONAL EXCITABILITY

A major function of TRP channels in the CNS is the regulation of intracellular calcium levels, which are essential for synaptic transmission and neuronal excitability. Activation of TRP channels facilitates calcium influx, triggering signaling cascades that control neurotransmitter release, gene expression, and synaptic remodeling. Through these mechanisms, TRP channels influence learning, memory, sensory perception, and adaptive neuronal responses [14].

Furthermore, TRP channels modulate membrane potential and neuronal firing patterns. Excessive activation of certain TRP channels may lead to calcium overload, oxidative stress, and excitotoxicity, contributing to

neuronal injury and disease progression. Conversely, controlled modulation of TRP channel activity may provide neuroprotective benefits and represents a promising therapeutic strategy for various CNS disorders [15].

3. PHYSIOLOGICAL ROLES OF TRP CHANNELS IN THE NERVOUS SYSTEM

Transient Receptor Potential (TRP) channels play crucial roles in maintaining normal nervous system function by regulating ion homeostasis, neuronal excitability, and intracellular signaling pathways. As non-selective cation channels, they facilitate the influx of calcium (Ca^{2+}) and sodium (Na^{+}) ions in response to various physical and chemical stimuli. Through these actions, TRP channels contribute to numerous physiological processes, including neurotransmission, sensory perception, learning, memory, neurodevelopment, and neuronal survival [16].

3.1 REGULATION OF INTRACELLULAR CALCIUM SIGNALING

One of the most important functions of TRP channels is the regulation of intracellular calcium levels. Calcium acts as a universal second messenger that controls a wide range of cellular activities, including gene transcription, enzyme activation, neurotransmitter release, and cell survival. Activation of TRP channels allows extracellular calcium to enter neurons and glial cells, initiating signaling cascades essential for normal neuronal function. TRPV, TRPM, and TRPC channel families are particularly involved in maintaining calcium homeostasis within the CNS. Dysregulation of TRP-mediated calcium signaling can lead to excitotoxicity, oxidative stress, and neuronal degeneration, which are associated with several neurological disorders [17].

3.2 NEUROTRANSMITTER RELEASE AND SYNAPTIC PLASTICITY

TRP channels contribute significantly to synaptic transmission by regulating neurotransmitter release at both presynaptic and postsynaptic sites. Calcium influx through TRP channels promotes the fusion of synaptic vesicles with the neuronal membrane, facilitating the release of neurotransmitters such as glutamate, dopamine, serotonin, and gamma-aminobutyric acid (GABA). In addition, TRP channels influence synaptic plasticity, the ability of synapses to strengthen or weaken over time in response to neuronal activity. Processes such as long-term potentiation (LTP) and long-term depression (LTD), which are essential for information storage and neural adaptation, are partly regulated by TRP-mediated calcium signaling. Therefore, these channels play a key role in maintaining efficient neuronal communication and network function [18].

3.3 THERMOSENSATION AND PAIN PERCEPTION

Several TRP channel subtypes function as molecular sensors for temperature and pain stimuli. TRPV1 is activated by high temperatures, acidic conditions, and capsaicin, the pungent component of chili peppers. TRPM8 responds to cool temperatures and menthol, whereas TRPA1 is activated by noxious chemicals and environmental irritants. These channels are expressed in sensory neurons and are involved in detecting thermal and painful stimuli, converting them into electrical signals that are transmitted to the brain. Through their role in nociception and thermosensation, TRP channels contribute to protective physiological responses and maintenance of body homeostasis. Abnormal activation of these channels is frequently associated with chronic pain and inflammatory conditions [19].

3.4 LEARNING AND MEMORY PROCESSES

TRP channels are involved in higher brain functions, particularly learning and memory. They are highly expressed in the hippocampus and cerebral cortex, regions responsible for cognitive processing and memory formation. By regulating intracellular calcium dynamics and synaptic plasticity, TRP channels influence neuronal connectivity and information storage. TRPV1, TRPC6, and TRPM2 have been implicated in hippocampal long-term potentiation and memory consolidation. Experimental studies suggest that alterations in TRP channel expression or activity can impair cognitive function and may contribute to neurodegenerative diseases characterized by memory deficits, such as Alzheimer's disease [20].

3.5 NEURODEVELOPMENT AND NEURONAL SURVIVAL

TRP channels play important roles during nervous system development by regulating neuronal proliferation, migration, differentiation, and maturation. Calcium signals generated through TRP channel activation influence the expression of genes involved in neuronal growth and circuit formation. In the mature nervous system, TRP channels contribute to neuronal survival by maintaining calcium homeostasis and cellular energy balance. Some TRP channels also protect neurons against oxidative stress and cellular injury. However, excessive or prolonged activation may result in calcium overload and activation of cell death pathways. Consequently, proper regulation of TRP channel activity is essential for both neuronal development and long-term neuronal health [21].

Overall, TRP channels serve as key regulators of nervous system physiology by integrating sensory, electrical, and biochemical signals. Their involvement in calcium signaling, synaptic transmission, sensory perception, cognition, and neuronal survival highlights their importance in maintaining normal CNS function and their potential as therapeutic targets in neurological disorders.

4. TRP CHANNELS AND NEUROINFLAMMATION

Neuroinflammation is a protective response of the central nervous system (CNS) to infection, injury, or toxic stimuli. However, chronic or excessive neuroinflammation can contribute to neuronal dysfunction and the progression of numerous neurological disorders. Transient Receptor Potential (TRP) channels have emerged as important regulators of neuroinflammatory processes because of their ability to control calcium influx, oxidative stress responses, and inflammatory signaling pathways. Several TRP channel subtypes, including TRPV1, TRPA1, TRPM2, and TRPC channels, are expressed in neurons and glial cells, where they modulate inflammatory responses and neuronal survival [22].

4.1 ACTIVATION OF MICROGLIA AND ASTROCYTES

Microglia and astrocytes are the principal immune-responsive cells of the CNS. Under pathological conditions, TRP channel activation influences the functional state of these cells. TRPM2 channels, which are activated by oxidative stress and reactive oxygen species (ROS), play a major role in microglial activation. Increased TRPM2 activity promotes calcium influx, leading to the release of inflammatory mediators and enhancement of neuroinflammatory responses. Similarly, TRPV1 and TRPA1 channels expressed in astrocytes regulate intracellular calcium signaling and gliotransmitter release, influencing neuron–glia communication and inflammatory processes [23].

4.2 PRODUCTION OF INFLAMMATORY CYTOKINES

Activation of TRP channels can stimulate the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). Elevated intracellular calcium levels resulting from TRP channel activation trigger signaling pathways involving nuclear factor-kappa B (NF-κb) and mitogen-activated protein kinases (MAPKs), which regulate inflammatory gene expression. Sustained activation of these pathways contributes to chronic neuroinflammation and neuronal dysfunction observed in several CNS disorders [24].

4.3 OXIDATIVE STRESS AND NEURONAL INJURY

Oxidative stress is characterized by excessive production of reactive oxygen species that damage cellular proteins, lipids, and DNA. TRPM2 is particularly sensitive to oxidative stress and acts as a cellular sensor of ROS. Excessive activation of TRPM2 channels promotes calcium overload, mitochondrial dysfunction, and neuronal injury. Other TRP channels, including TRPA1 and TRPV1, also participate in oxidative stress-mediated signaling pathways. Persistent oxidative damage can initiate apoptotic and necroticcell death mechanisms, contributing to neurodegeneration [25].

4.4 RELATIONSHIP BETWEEN NEUROINFLAMMATION AND CNS DISORDERS

Chronic neuroinflammation is a hallmark of many CNS disorders, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, epilepsy, and stroke. Dysregulated TRP channel activity contributes to the initiation and maintenance of inflammatory responses through modulation of calcium signaling, cytokine production, and oxidative stress. Consequently, TRP channels have attracted considerable attention as potential therapeutic targets for controlling neuroinflammation and preventing disease progression. Pharmacological modulation of these channels may reduce inflammatory damage and improve neurological outcomes [26].

5. ROLE OF TRP CHANNELS IN NEURODEGENERATIVE DISEASES

Neurodegenerative diseases are characterized by progressive loss of neuronal structure and function, leading to cognitive and motor impairments. Accumulating evidence suggests that TRP channels contribute to the pathogenesis of several neurodegenerative disorders through mechanisms involving calcium dysregulation, oxidative stress, neuroinflammation, and neuronal apoptosis. Modulation of specific TRP channel subtypes has therefore emerged as a promising therapeutic strategy [27].

5.1 ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common neurodegenerative disorder and is characterized by progressive memory loss, cognitive decline, and accumulation of amyloid-β plaques and neurofibrillary tangles. Several TRP channels have been implicated in AD pathology.

5.1.1INVOLVEMENT OF TRPV1, TRPM2, AND TRPC6

TRPV1 activation has been associated with reduced neuroinflammation and improved cognitive function in experimental models. TRPM2 channels contribute to oxidative stress-induced neuronal injury and are

upregulated in response to amyloid-β accumulation. TRPC6 plays a neuroprotective role by promoting neuronal survival and maintaining synaptic function [28].

5.1.2AMYLOID-B-INDUCED CALCIUM DYSREGULATION

Amyloid-β peptides disrupt calcium homeostasis by altering the activity of various ion channels, including TRP channels. Excessive calcium influx leads to mitochondrial dysfunction, oxidative stress, and activation of cell death pathways. TRPM2-mediated calcium overload has been identified as a major contributor to neuronal degeneration in AD [29].

5.1.3POTENTIAL NEUROPROTECTIVE EFFECTS OF TRP MODULATION

Experimental studies indicate that modulation of TRPV1 and enhancement of TRPC6 activity may reduce amyloid pathology, improve synaptic plasticity, and protect neurons from degeneration. These findings support the development of TRP-targeted therapies for Alzheimer's disease [30].

5.2 PARKINSON'S DISEASE

Parkinson's disease (PD) is characterized by degeneration of dopaminergic neurons in the substantia nigra, leading to tremors, rigidity, and impaired motor function.

5.2.1TRPV1-MEDIATED DOPAMINERGIC NEURON REGULATION

TRPV1 channels are expressed in brain regions involved in motor control and dopamine signaling. Activation of TRPV1 may influence dopamine release and neuronal excitability, potentially affecting disease progression and symptom severity [31].

5.2.2TRPM2 INVOLVEMENT IN OXIDATIVE STRESS

Oxidative stress is a major pathogenic factor in PD. TRPM2 activation by reactive oxygen species contributes to calcium overload and neuronal damage. Increased TRPM2 activity has been linked to degeneration of dopaminergic neurons in experimental models [32].

5.2.3THERAPEUTIC IMPLICATIONS FOR MOTOR DYSFUNCTION

Targeting TRPV1 and TRPM2 channels may provide neuroprotection and improve motor function by reducing oxidative stress, neuroinflammation, and neuronal loss. Several preclinical studies have demonstrated beneficial effects of TRP channel modulation in PD models [33].

5.3 HUNTINGTON'S DISEASE

Huntington's disease (HD) is an inherited neurodegenerative disorder caused by expansion of CAG repeats in the huntingtin gene, resulting in progressive motor, cognitive, and psychiatric symptoms.

5.3.1ALTERED CALCIUM HOMEOSTASIS

Disruption of intracellular calcium regulation is a key feature of HD. Abnormal calcium signaling contributes to mitochondrial dysfunction, excitotoxicity, and neuronal death, particularly in the striatum [34].

5.3.2ROLE OF TRPC AND TRPM CHANNELS IN NEURONAL DEGENERATION

TRPC and TRPM channels participate in calcium entry pathways that influence neuronal survival. Dysregulation of these channels may exacerbate calcium overload and accelerate neurodegenerative processes. Modulation of TRP channel activity has shown potential in reducing neuronal injury and improving cellular resilience in experimental studies [35].

5.4 AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by the loss of upper and lower motor neurons, leading to muscle weakness and paralysis.

5.4.1EXCITOTOXICITY AND CALCIUM OVERLOAD

Excessive glutamate-mediated excitotoxicity and calcium overload are major contributors to motor neuron degeneration in ALS. Abnormal activation of TRP channels may enhance calcium influx and worsen neuronal injury [36].

5.4.2POTENTIAL TARGETS AMONG TRPM AND TRPV CHANNELS

TRPM2 and TRPV1 have been investigated as potential therapeutic targets due to their involvement in oxidative stress, inflammation, and calcium signaling. Inhibition of these channels may reduce neuronal damage and slow disease progression. Although clinical evidence remains limited, TRP channel modulation represents a promising area for future ALS research [37].

6. TRP CHANNELS IN PSYCHIATRIC DISORDERS

Transient Receptor Potential (TRP) channels are increasingly recognized as important regulators of brain functions associated with mood, emotion, cognition, and behavior. Alterations in TRP channel activity can disrupt intracellular calcium signaling, neurotransmitter release, and neuronal plasticity, thereby contributing to the development of psychiatric disorders. Growing evidence suggests that specific TRP channel subtypes are involved in depression, anxiety disorders, and schizophrenia, making them potential therapeutic targets for psychiatric interventions [38].

6.1 DEPRESSION

Depression is a complex psychiatric disorder characterized by persistent sadness, loss of interest, impaired cognition, and altered emotional regulation. Recent studies indicate that TRPV1 channels play a significant role in mood regulation and emotional behavior. TRPV1 is expressed in brain regions associated with emotional processing, including the hippocampus, amygdala, and prefrontal cortex. Dysregulation of TRPV1 activity has been linked to depressive-like behaviors in experimental models [39].

6.1.1TRPV1 INVOLVEMENT IN MOOD REGULATION

Activation of TRPV1 influences neuronal excitability and neurotransmitter release, thereby affecting mood-related neural circuits. Experimental evidence suggests that modulation of TRPV1 activity can alter depressive behaviors, indicating its potential role in the pathophysiology of depression [40].

6.1.2INTERACTION WITH SEROTONERGIC AND ENDOCANNABINOID SYSTEMS

TRPV1 channels interact closely with serotonergic and endocannabinoid signaling pathways, both of which are important in mood regulation. Endocannabinoids such as anandamide can activate TRPV1 channels and influence emotional responses. This interaction may contribute to the antidepressant effects observed with modulation of the endocannabinoid system [41].

6.2 ANXIETY DISORDERS

Anxiety disorders are characterized by excessive fear, worry, and stress responses. TRP channels contribute to the regulation of neuronal circuits involved in stress adaptation and emotional processing.

6.2.1MODULATION OF STRESS RESPONSES

TRPV1 channels are involved in the regulation of hypothalamic-pituitary-adrenal (HPA) axis activity and stress-related behaviors. Altered TRPV1 signaling may enhance anxiety-like responses through changes in neurotransmitter release and neuronal excitability [42].

6.2.2TRPV1 AND TRPC CHANNEL CONTRIBUTIONS

Both TRPV1 and TRPC channels have been implicated in anxiety-related behaviors. TRPC-mediated calcium signaling influences neuronal plasticity and emotional regulation, while TRPV1 activity affects stress responsiveness. Pharmacological modulation of these channels has shown anxiolytic effects in several preclinical studies [43].

6.3 SCHIZOPHRENIA

Schizophrenia is a severe psychiatric disorder characterized by hallucinations, delusions, cognitive impairment, and social dysfunction. Although its exact pathophysiology remains unclear, disturbances in calcium signaling pathways have been implicated in disease development.

6.3.1ALTERED CALCIUM SIGNALING PATHWAYS

Calcium signaling abnormalities can disrupt synaptic communication and neuronal network activity, contributing to cognitive and behavioral deficits observed in schizophrenia. Since TRP channels regulate intracellular calcium homeostasis, their dysfunction may influence disease progression [44].

6.3.2EMERGING EVIDENCE FOR TRPC CHANNEL DYSFUNCTION

Recent studies have identified altered expression and function of TRPC channels in schizophrenia. TRPC-mediated signaling is involved in neuronal development, synaptic plasticity, and cognitive function. These

findings suggest that TRPC channels may represent novel therapeutic targets for schizophrenia management [45].

7. TRP CHANNELS AND EPILEPSY

Epilepsy is a neurological disorder characterized by recurrent seizures resulting from abnormal neuronal activity. TRP channels play important roles in regulating neuronal excitability and calcium homeostasis, both of which are critical factors in seizure generation and propagation [46].

7.1 REGULATION OF NEURONAL HYPEREXCITABILITY

Neuronal hyperexcitability is a hallmark of epilepsy. TRP channels influence membrane depolarization and intracellular calcium levels, thereby affecting neuronal firing patterns. Dysregulated TRP channel activity may increase neuronal excitability and facilitate seizure development [47].

7.2 TRPV1 AND TRPM7 INVOLVEMENT IN SEIZURE GENERATION

TRPV1 channels are highly expressed in the hippocampus, a brain region frequently involved in epilepsy. Activation of TRPV1 can increase excitatory neurotransmission and promote seizure activity. TRPM7 channels also contribute to calcium influx and neuronal injury during seizures, making them important mediators of epileptic pathology [48].

7.3 EFFECTS OF CHANNEL ANTAGONISTS ON SEIZURE CONTROL

Several experimental studies have demonstrated that inhibition of TRPV1 and TRPM7 channels reduces seizure frequency, severity, and neuronal damage. These findings suggest that TRP channel antagonists may provide a novel therapeutic approach for epilepsy treatment [49].

8. TRP CHANNELS IN PAIN AND MIGRAINE

TRP channels are widely recognized for their roles in sensory perception, particularly pain signaling and migraine pathophysiology. Their expression in sensory neurons allows them to detect thermal, chemical, and mechanical stimuli and transmit nociceptive signals to the CNS [50].

8.1 NEUROPATHIC PAIN MECHANISMS

Neuropathic pain arises from damage or dysfunction of the nervous system and is often associated with chronic inflammation and abnormal sensory signaling. TRP channels contribute to peripheral and central sensitization processes that underlie chronic pain states [51].

8.2 TRPV1 AND TRPA1 ACTIVATION

TRPV1 and TRPA1 are key mediators of nociception. TRPV1 is activated by heat, capsaicin, and inflammatory mediators, while TRPA1 responds to environmental irritants and oxidative stress. Activation of these channels enhances pain signaling and contributes to hyperalgesia and allodynia [52].

8.3 ROLE IN MIGRAINE PATHOPHYSIOLOGY

Migraine is a neurovascular disorder involving activation of the trigeminovascular system and release of neuropeptides such as calcitonin gene-related peptide (CGRP). TRPV1 and TRPA1 activation can stimulate CGRP release, promote neurogenic inflammation, and contribute to migraine attacks [53].

8.4 DEVELOPMENT OF TRP CHANNEL ANTAGONISTS AS ANALGESICS

Because of their central role in pain transmission, TRP channels have become attractive targets for analgesic drug development. Selective antagonists targeting TRPV1 and TRPA1 have demonstrated pain-relieving effects in preclinical studies and are being investigated as potential treatments for chronic pain and migraine disorders [54].

9. THERAPEUTIC MODULATION OF TRP CHANNELS

Therapeutic modulation of TRP channels has gained significant attention as a strategy for treating CNS disorders, chronic pain, and neuroinflammatory diseases. Both agonists and antagonists have demonstrated beneficial pharmacological effects in experimental and clinical studies [55].

9.1 TRP CHANNEL AGONISTS

9.1.1CAPSAICIN (TRPV1 AGONIST)

Capsaicin is a naturally occurring compound derived from chili peppers and a well-known TRPV1 agonist. Prolonged activation of TRPV1 by capsaicin leads to desensitization of sensory neurons, reducing pain perception and providing analgesic effects [56].

9.1.2CANNABIDIOL (CBD)

Cannabidiol, a non-psychoactive constituent of *Cannabis sativa*, can modulate multiple TRP channel subtypes, including TRPV1, TRPV2, and TRPA1. CBD exhibits anti-inflammatory, neuroprotective, anxiolytic, and anticonvulsant properties through these interactions [57].

9.1.3ENDOGENOUS LIGANDS

Several endogenous molecules, including anandamide and other lipid mediators, regulate TRP channel activity. These naturally occurring ligands influence pain perception, mood regulation, neuroprotection, and inflammatory responses [58].

9.2 TRP CHANNEL ANTAGONISTS

9.2.1TRPV1 Antagonists

TRPV1 antagonists have been investigated for the treatment of chronic pain, migraine, epilepsy, and neuroinflammatory conditions. By reducing excessive calcium influx and neuronal activation, these agents may provide therapeutic benefits [59].

9.2.2TRPA1 BLOCKERS

TRPA1 antagonists inhibit nociceptive signaling and inflammatory responses. These compounds are being explored as treatments for neuropathic pain, migraine, and inflammatory disorders [60].

9.2.3TRPM2 INHIBITORS

TRPM2 inhibitors reduce oxidative stress-induced calcium overload and neuroinflammation. They have shown promise in experimental models of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease [61].

9.3 NATURAL PRODUCTS TARGETING TRP CHANNELS

Natural compounds have emerged as valuable modulators of TRP channels and may offer safer therapeutic alternatives.

9.3.1CURCUMIN

Curcumin, derived from *Curcuma longa*, exhibits anti-inflammatory and antioxidant properties and can modulate TRPV1 and TRPA1 activity, contributing to neuroprotection [62].

9.3.2RESVERATROL

Resveratrol is a polyphenolic compound with antioxidant and neuroprotective effects. It influences TRP-mediated calcium signaling and may reduce oxidative stress-related neuronal damage [63].

9.3.3MENTHOL

Menthol activates TRPM8 channels, producing cooling sensations and analgesic effects. It is widely used in topical formulations for pain relief [64].

9.3.4EUGENOL

Eugenol, a major component of clove oil, modulates TRPV1 and TRPA1 channels and possesses analgesic, anti-inflammatory, and neuroprotective properties[65].

10. DRUG DELIVERY STRATEGIES FOR TRP MODULATORS

Effective therapeutic modulation of Transient Receptor Potential (TRP) channels in central nervous system (CNS) disorders requires efficient delivery of drugs to the brain. However, achieving adequate drug concentrations within the CNS remains challenging because of the presence of the blood–brain barrier (BBB), which restricts the entry of many pharmacological agents. Recent advances in drug delivery technologies have focused on improving BBB penetration, enhancing drug stability, and enabling targeted delivery to neural tissues [66].

10.1 BLOOD–BRAIN BARRIER CHALLENGES

The BBB is a highly selective barrier formed by endothelial cells, tight junctions, pericytes, and astrocytic end-feet. While it protects the brain from harmful substances, it also limits the delivery of many TRP modulators, particularly large molecules and hydrophilic compounds. Factors such as poor permeability, efflux transporter activity, and rapid systemic clearance can significantly reduce the therapeutic efficacy of TRP-targeted drugs. Therefore, overcoming BBB-associated limitations is a major objective in the development of CNS therapeutics [67].

10.2 NANOPARTICLE-BASED DELIVERY SYSTEMS

Nanoparticle-based drug delivery systems have emerged as promising platforms for transporting TRP modulators across the BBB. Polymeric nanoparticles, solid lipid nanoparticles, dendrimers, and metallic nanoparticles can encapsulate therapeutic agents and protect them from degradation. These carriers enhance drug solubility, prolong circulation time, and facilitate BBB penetration through mechanisms such as receptor-mediated transcytosis and adsorptive endocytosis. Nanoparticles can also be engineered to release drugs in a controlled manner, thereby improving therapeutic outcomes and reducing systemic toxicity [68].

10.3 LIPID-BASED FORMULATIONS

Lipid-based delivery systems, including liposomes, nanoemulsions, and solid lipid carriers, are particularly useful for delivering lipophilic TRP modulators to the CNS. These formulations enhance drug absorption, improve stability, and increase BBB permeability. Liposomes can encapsulate both hydrophilic and lipophilic compounds and may be surface-modified with targeting ligands to improve brain uptake. Such lipid-based systems have shown potential for delivering neuroprotective agents and TRP channel modulators in experimental models of neurological disorders [69].

10.4 TARGETED CNS DELIVERY APPROACHES

Targeted delivery strategies aim to maximize drug accumulation in specific brain regions while minimizing peripheral exposure. Approaches include ligand-conjugated nanoparticles, antibody-mediated transport, intranasal delivery, and stimuli-responsive systems. Intranasal administration is particularly attractive because it allows direct transport of drugs from the nasal cavity to the brain via olfactory and trigeminal pathways, bypassing the BBB. Targeted delivery not only enhances therapeutic efficacy but also reduces adverse effects associated with systemic administration of TRP modulators [70].

Overall, advances in nanotechnology and targeted delivery systems are expected to play a crucial role in the successful clinical translation of TRP channel-based therapies for CNS disorders.

11. CONCLUSION

Transient Receptor Potential (TRP) channels have emerged as crucial regulators of central nervous system (CNS) function due to their involvement in calcium homeostasis, neuronal excitability, synaptic transmission, sensory perception, and neuroinflammatory processes. These channels are widely expressed in neurons and glial cells, where they participate in maintaining normal physiological functions and responding to environmental

and pathological stimuli. Growing evidence indicates that alterations in TRP channel expression and activity contribute significantly to the pathogenesis of numerous neurological and psychiatric disorders.

Various TRP channel subtypes, including TRPV1, TRPA1, TRPM2, TRPM7, and TRPC channels, have been implicated in the development and progression of Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, epilepsy, depression, anxiety disorders, schizophrenia, migraine, and neuropathic pain. Their involvement in oxidative stress, neuroinflammation, excitotoxicity, and disrupted calcium signaling highlights their importance as key molecular mediators of CNS pathology. Experimental studies have demonstrated that modulation of TRP channel activity can reduce neuronal damage, suppress inflammatory responses, improve synaptic function, and alleviate disease symptoms.

The development of TRP channel-targeted therapies has gained considerable attention in recent years. Both agonists and antagonists, as well as naturally occurring compounds such as capsaicin, cannabidiol, curcumin, resveratrol, menthol, and eugenol, have shown promising neuroprotective, anti-inflammatory, anticonvulsant, and analgesic effects. Furthermore, advances in nanotechnology, lipid-based formulations, and targeted drug delivery systems have improved the prospects for effective CNS delivery of TRP modulators.

Despite these encouraging findings, several challenges remain. Limited subtype selectivity, potential off-target effects, safety concerns, and difficulties in crossing the blood–brain barrier continue to hinder clinical translation. Therefore, further research is needed to better understand TRP channel biology, identify highly selective modulators, and develop efficient delivery strategies. With continued progress in neuroscience, pharmacology, and drug delivery technologies, TRP channels are expected to become valuable therapeutic targets for next-generation treatments aimed at improving outcomes in a wide range of CNS disorders.

REFERENCES

1. Venkatachalam K, Montell C. TRP channels. *Annu Rev Biochem*. 2007;76:387–417.
2. Nilius B, Owsianik G. The transient receptor potential family of ion channels. *Genome Biol*. 2011;12(3):218.
3. Clapham DE. TRP channels as cellular sensors. *Nature*. 2003;426(6966):517–524.
4. Moran MM. TRP channels as potential drug targets. *Annu Rev Pharmacol Toxicol*. 2018;58:309–330.
5. Nilius B, Szallasi A. Transient receptor potential channels as drug targets: from the science of basic research to the art of medicine. *Pharmacol Rev*. 2014;66(3):676–814.
6. Nilius B, Owsianik G. The transient receptor potential family of ion channels. *Genome Biology*. 2011;12(3):218
7. Venkatachalam K, Montell C. TRP channels. *Annual Review of Biochemistry*. 2007;76:387–417.
8. Shibasaki K. TRP channels in glial cells. *Frontiers in Cellular Neuroscience*. 2016;10:114.
9. Grueter BA, Brasnjo G, Malenka RC. Postsynaptic TRPV1 triggers cell type-specific long-term depression in the nucleus accumbens. *Nature Neuroscience*. 2010;13(12):1519–1525.
10. Tai Y, Feng S, Du W, Wang Y. Functional roles of TRP channels in the mammalian central nervous system. *Pflugers Archiv*. 2008;456(5):855–867.
11. Dhaka A, Viswanath V, Patapoutian A. TRP ion channels and temperature sensation. *Annual Review of Neuroscience*. 2006;29:135–161.
12. Hartmann J, Dragicevic E, Adelsberger H, et al. TRPC3 channels are required for synaptic transmission and motor coordination. *Neuron*. 2008;59(3):392–398.
13. Moran MM, McAlexander MA, Bíró T, Szallasi A. Transient receptor potential channels as therapeutic targets. *Nature Reviews Drug Discovery*. 2011;10(8):601–620.

14. Clapham DE. TRP channels as cellular sensors. *Nature*. 2003;426(6966):517–524.
15. Nilius B, Szallasi A. Transient receptor potential channels as drug targets. *Pharmacological Reviews*. 2014;66(3):676–814.
16. Venkatachalam K, Montell C. TRP channels. *Annu Rev Biochem*. 2007;76:387–417.
17. Clapham DE. TRP channels as cellular sensors. *Nature*. 2003;426(6966):517–524.
18. Tai Y, Feng S, Du W, Wang Y. Functional roles of TRP channels in the mammalian central nervous system. *Pflugers Arch*. 2008;456(5):855–867.
19. Dhaka A, Viswanath V, Patapoutian A. TRP ion channels and temperature sensation. *Annu Rev Neurosci*. 2006;29:135–161.
20. Grueter BA, Brasnjo G, Malenka RC. Postsynaptic TRPV1 triggers synaptic plasticity. *Nat Neurosci*. 2010;13(12):1519–1525.
21. Nilius B, Szallasi A. Transient receptor potential channels as drug targets. *Pharmacol Rev*. 2014;66(3):676–814.
22. Shibasaki K. TRP channels in glial cells. *Front Cell Neurosci*. 2016;10:114.
23. Ryskamp DA, Redmon S, Jo AO, et al. TRP channels and neurodegenerative diseases. *Pflugers Arch*. 2014;466:1115–1132.
24. Moran MM. TRP channels as potential drug targets. *Annu Rev Pharmacol Toxicol*. 2018;58:309–330.
25. Belrose JC, Jackson MF. TRPM2: a candidate therapeutic target for neurological diseases. *Acta Pharmacol Sin*. 2018;39:722–732.
26. Nilius B, Szallasi A. Transient receptor potential channels as drug targets. *Pharmacol Rev*. 2014;66:676–814.
27. Ryskamp DA, et al. TRP channels in neurodegenerative disorders. *Pflugers Arch*. 2014;466:1115–1132.
28. Sun F, Xiong L, et al. TRP channels and Alzheimer's disease. *Neurosci Bull*. 2017;33:213–221.
29. Ostapchenko VG, et al. TRPM2 and amyloid-beta toxicity. *J Neurosci*. 2015;35:15157–15169.
30. Wang J, et al. Neuroprotective role of TRPC6 in Alzheimer's disease. *Neurobiol Dis*. 2010;38:514–522.
31. Bido S, et al. TRPV1 and Parkinson's disease. *Neurobiol Dis*. 2011;43:356–367.
32. Sun Y, Sukumaran P, et al. TRPM2 in oxidative stress-induced neurodegeneration. *Cell Calcium*. 2016;60:27–34.
33. Hong Z, et al. Therapeutic potential of TRP channel modulation in Parkinson's disease. *Front Neurosci*. 2020;14:709.
34. Bezprozvanny I, Hayden MR. Deranged calcium signaling in Huntington's disease. *Biochem Biophys Res Commun*. 2004;322:1310–1317.
35. Wu J, Shih HP, et al. TRP channels and Huntington's disease. *Neuroscience*. 2011;174:181–190.
36. Grosskreutz J, Van Den Bosch L, Keller BU. Calcium dysregulation in ALS. *Cell Calcium*. 2010;47:165–174.
37. Belrose JC, Jackson MF. TRP channels as therapeutic targets in neurodegenerative diseases. *Acta Pharmacol Sin*. 2018;39:722–732.
38. Mori Y, et al. TRP channels and psychiatric disorders. *Neurosci Res*. 2015;92:1–7.
39. Madasu MK, et al. TRPV1 and depression. *Neurosci Lett*. 2015;589:23–29.
40. Kasckow JW, et al. Mood regulation and TRPV1 channels. *Brain Res*. 2014;1575:1–9.
41. Cristino L, et al. Endocannabinoid-TRPV1 interactions in emotional regulation. *Pharmacol Res*. 2020;152:104545.
42. Terzian AL, et al. TRPV1 and anxiety behavior. *Neuropharmacology*. 2009;56:244–252.
43. Riccio A, et al. TRPC channels in emotional behavior. *Nat Neurosci*. 2009;12:142–150.
44. Berridge MJ. Calcium signalling and schizophrenia. *Cell Tissue Res*. 2014;357:477–492.

45. Lin YF, et al. TRPC channels and schizophrenia. *Front Psychiatry*. 2019;10:438.
46. Sun FJ, et al. TRP channels in epilepsy. *Neurosci Bull*. 2018;34:245–256.
47. Naziroğlu M. TRP channels and epilepsy. *Neurochem Res*. 2015;40:2255–2265.
48. Mo M, et al. TRPV1 and TRPM7 in seizure activity. *Brain Res*. 2013;1521:1–10.
49. Bhaskaran MD, Smith BN. TRP antagonists and seizure control. *Epilepsy Res*. 2010;92:188–196.
50. Moran MM, et al. TRP channels in pain. *Nat Rev Drug Discov*. 2011;10:601–620.
51. Julius D. TRP channels and pain mechanisms. *Annu Rev Cell Dev Biol*. 2013;29:355–384.
52. Basbaum AI, Bautista DM, et al. Cellular mechanisms of pain. *Cell*. 2009;139:267–284.
53. Benemei S, et al. TRP channels and migraine. *J Headache Pain*. 2015;16:57.
54. Nilius B, Szallasi A. TRP channels as therapeutic targets. *Pharmacol Rev*. 2014;66:676–814.
55. Moran MM. TRP channels as drug targets. *Annu Rev Pharmacol Toxicol*. 2018;58:309–330.
56. Anand P, Bley K. Capsaicin and pain therapy. *Br J Anaesth*. 2011;107:490–502.
57. Iannotti FA, et al. Cannabidiol and TRP channels. *Br J Pharmacol*. 2014;171:2159–2173.
58. Di Marzo V, De Petrocellis L. Endogenous ligands of TRP channels. *Handb Exp Pharmacol*. 2014;223:1009–1041.
59. Gunthorpe MJ, Szallasi A. TRPV1 antagonists. *Nat Rev Drug Discov*. 2008;7:643–664.
60. Chen J, Hackos DH. TRPA1 antagonists in pain management. *Curr Opin Pharmacol*. 2015;20:111–117.
61. Belrose JC, Jackson MF. TRPM2 inhibitors and neuroprotection. *Acta Pharmacol Sin*. 2018;39:722–732.
62. Aggarwal BB, Harikumar KB. Curcumin and inflammatory pathways. *Int J Biochem Cell Biol*. 2009;41:40–59.
63. Baur JA, Sinclair DA. Resveratrol and health benefits. *Nat Rev Drug Discov*. 2006;5:493–506.
64. McKemy DD. TRPM8 and menthol. *Neurosci Lett*. 2005;387:1–6.
65. Park CK, et al. Eugenol as a TRP channel modulator. *J Dent Res*. 2011;90:870–875.
66. Pardridge WM. Drug transport across the blood–brain barrier. J Cereb Blood Flow Metab. 2012;32(11):1959–1972.
67. Abbott NJ, et al. Structure and function of the blood–brain barrier. Neurobiol Dis. 2010;37(1):13–25.
68. Saraiva C, et al. Nanoparticle-mediated brain drug delivery. J Control Release. 2016;235:34–47.
69. Patel T, et al. Lipid-based nanocarriers for CNS drug delivery. Int J Nanomedicine. 2013;8:399–412.
70. Illum L. Intranasal delivery to the central nervous system. J Pharm Pharmacol. 2000;52(1):3–17.