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PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - REVIEW ARTICLE

Therapeutic potential of transient receptor potential (TRP) channels in psychiatric disorders

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Abstract
Psychiatric disorders such as Bipolar disorder, Anxiety, Major depressive disorder, Schizophrenia, Attention-deficit/hyperactivity disorder, as well as neurological disorders such as Migraine, are linked by the evidence of altered calcium homeostasis. The disturbance of intra-cellular calcium homeostasis disrupts the activity of numerous ion channels including transient receptor potential (TRP) channels. TRP channel families comprise non-selective calcium-permeable channels that have been implicated in variety of physiological processes in the brain, as well as in the pathogenesis of psychiatric disorders. Through a comprehensive review of current research and experimentation, this investigation elucidates the role of TRP channels in psychiatric disorders. Furthermore, this review discusses about the exploration of epigenetics and TRP channels in psychiatric disorders.

Keywords Psychiatric disorders · Transient receptor potential (TRP) channels · Calcium signalling · Schizophrenia · ADHD

Introduction

Psychiatric disorders are a major burden on global health, impacting millions of people globally and providing considerable hurdles to effective treatment options. Despite advances in medicine and psychotherapy, many patients still experience terrible symptoms and inadequate relief (Wainberg et al. 2017). These diseases include bipolar disorder (BD), Anxiety, Major depressive disorder (MDD), Migraine, Attention-deficit/hyperactivity disorder (ADHD) and schizophrenia (SCZ). All of these conditions are quite frequent, yet they affect people in a way that is exceedingly detrimental (Rihal et al. 2022). Psychiatric disorders are complex and diverse disorders that not only reduce one's quality of life but also have a significant impact on behaviour and cognitive capacities (Logsdon et al. 2002). Transient receptor potential (TRP) channels have emerged as attractive targets for the development of new pharmacological interventions in psychiatric disorders. TRP channels are versatile signalling molecules that contribute to various aspects of brain function and behaviour. Importantly, dysregulation of transient receptor potential channels has been linked to the pathophysiology of psychiatric disorders (Nazıroglu and Demirda, 2015). These channels are non-selective cation permeable channels that exhibit low selectivity for calcium (Ca2+) ions and are related with disruptions in the homeostasis of calcium (Ca2+) (Vennekens et al. 2012). Being a key regulator of Ca^{2+} influx TRP channels plays a major role in psychiatric disorders. Through a comprehensive review of current research and experimentation, this review highlights the role of TRP channels in psychiatric diseases including BD, Anxiety, MDD, SCZ, Migraine and ADHD.

Search strategy

Through the use of a number of different search engines like Scopus, PubMed, Bentham and Elsevier data-bases, a literature review was carried out using keywords 'Psychiatric

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diseases', 'Calcium signalling', 'Transient receptor potential channels', and 'TRP activation pathways. Using the keywords that were given above, this review was carried out in order to collect the most recent publications and gain an understanding of the breadth of the extensive research that has been conducted on the function of TRP channels in the pathogenesis of psychiatric diseases (Fig. 1)

Calcium signalling in psychiatric disorders

Ca^{2+} signalling is critical in the central nervous system (CNS) for the variety of physiological activities, including synaptic plasticity, neuronal excitability, release of neurotransmitters, and Ca^{2+} -induced gene regulation (Sawamura et al. 2017). Ca^{2+} channels are regarded to be a primary target for the pathogenesis of psychiatric diseases due to their involvement in the brain signalling. Indeed, genes encoding these channels have been linked to psychiatric diseases (Griesi-Oliveira et al. 2017). One of the classes of Ca2+-permeable channels, known as transient receptor potential channels gets activated. Given the importance of abnormal Ca2 + signalling in psychiatry disorders, TRP channels serves as a cue for understanding the molecular pathogenesis of these disorders.

TRP channels: overview

TRP family proteins are either homo-tetramers or hetero-tetramers. Each subunit contains intra-cellular amino (N) and carboxy (C) terminal and six trans-membrane helical segments (S1-S6), with the 5th and 6th segments and the re-entrant loop between them forming the ion-conducting pore (Fig. 2). Specifically, they perform the role of non-selective permeable cation channels (Cao 2020). The activation of transient receptor potential channels causes the membrane potential to become depolarized, which can result in the activation/in-activation of voltage-gated ion channels. Additionally, TRP channels regulate Ca2 + signaling, which is responsible for a variety of cellular processes (Wu et al. 2010; Nilius and Flockerzi 2014). Mammalian TRP

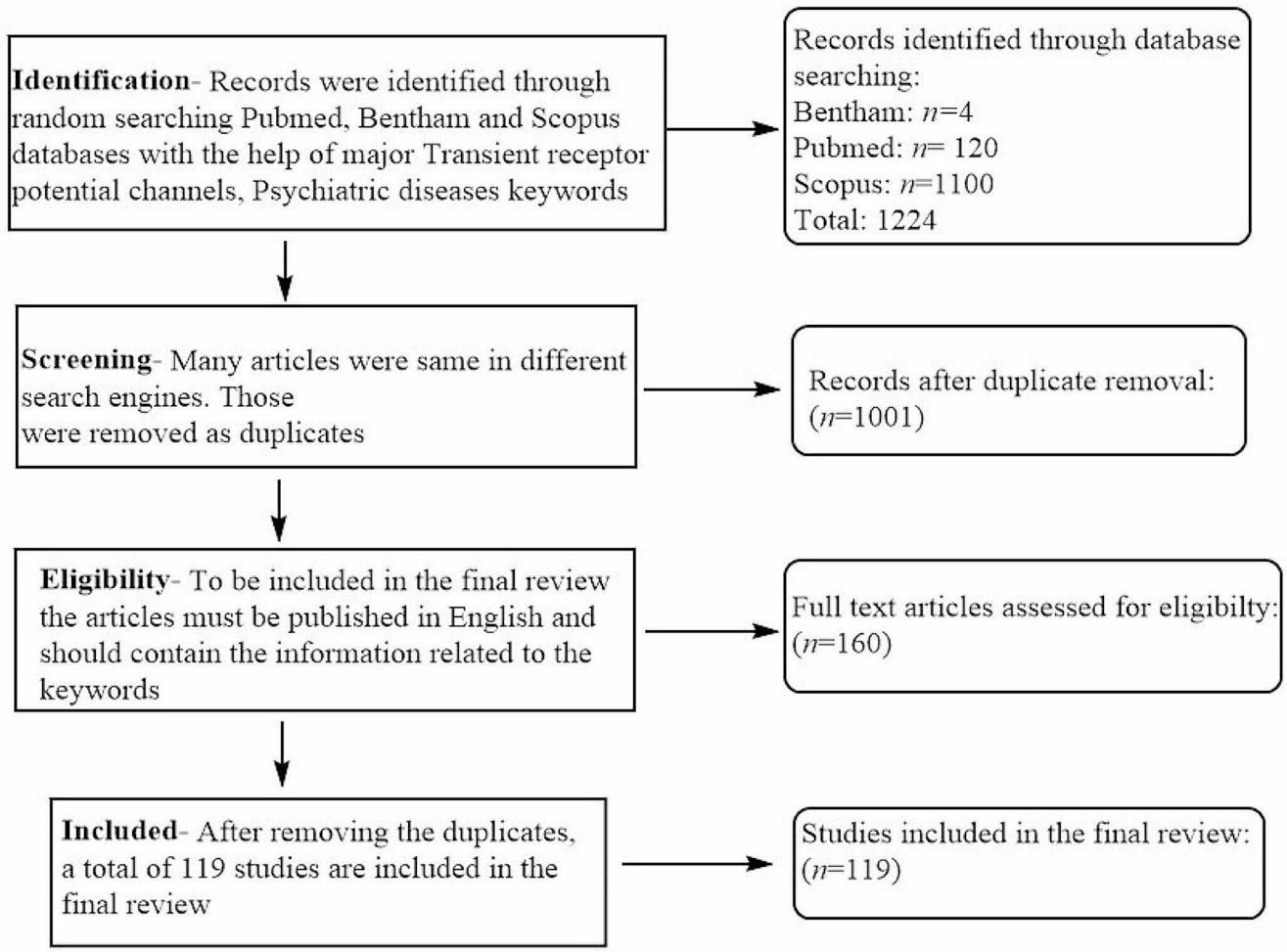

Fig. 1 Flowchart of the methodology

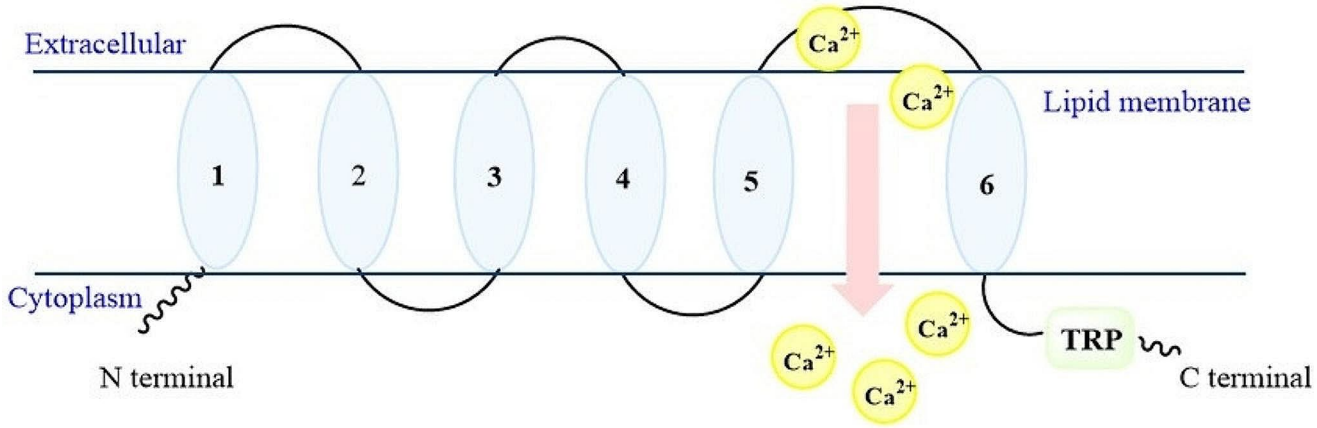

Fig. 2 Structure of transient receptor potential channel

channels comprise twenty-eight members and are divided into 6 subfamilies: Vanilloid (TRP-V), Canonical (TRP-C), Melastatin (TRP-M), Polycystin (TRP-P), Mucolipin (TRP-ML) and Ankyrin (TRP-A) based on their homology of amino-acid sequences (Table 1) (Fig. 3) (Wu et al. 2010; Nelson et al. 2011). As of today, the ankyrin subfamily has only one member, TRP-A1, which is rich in ankyrin repeats at its N-terminus. They control a wide range of neuronal and glial processes, including brain development and homeostasis.

Implication of TRP channels in psychiatric disorders

Considering the widespread expression and different roles of TRP channels in the CNS, it is possible that TRP channel functions dysregulation is implicated in many pathophysiological events of psychiatric disorders, which are connected with changes in Ca2 + homeostasis (Vennekens et al. 2012; Behl et al. 2021). TRP channels, which regulate Ca2 + influx, have an important role in psychiatric disorders. One of the primary causes for such dysfunction is coupled with identified defects in the gene encoding the channels. Furthermore, variations in channel abundance, sensitization/de-sensitization of channels, results in increased or decreased responses to various pathogenic stimuli, have more subtle role in the development of various diseases. Therefore, in this part of the review we will discuss about the role of TRP channels in various psychiatric disorders such as BD Anxiety, MDD, SCZ, Migraine and ADHD.

BD: TRP channels

It is a chronic, relapsing mental condition characterized by un-usual mood swings, swinging from periods of maniac episodes, when the person experiences an over-excited state (very happy, energised & irritable), to depressed state (sadness, poor interest & pleasure) which are associated with altered Ca2 + homeostasis (Kerner 2015). It is categorized into 2 types (bipolar-1 & bipolar-2 disorder). A person with BD-1 is usually characterized by the alternation between manic and depressive episodes, whereas BD-2 patients have hypomanic episodes and depressive episodes. Despite extensive investigation, various pathways have been associated to BD, however altered Ca2 + homeostasis is one of the major factors that plays a role in the BD. Moreover, a series of studies utilising lithium therapy, a medicine commonly used to treat BD, showed that lithium impacts Ca2 + signalling in neurons as well as in lymphocytes, platelets and glial cells. However, recent data suggests that TRP channels (TRP-V1, -C3, -C7 and -M2) plays an important role in the pathophysiology of BD (Nazıroglu and Demirdas 2015) including abnormal Ca^{2+} homeostasis in BD. In BD, the enzyme activity of calcium in-dependent phospholipases-A2 is increased, which mobilises the poly-unsaturated fatty acid (arachidonic acid) pathway and causes calcium dysregulation, apoptosis and oxidative stress in cells (Xu et al. 2013; Zeari et al., 2015). Besides, mice lacking TRP-M2 also showed increased BD-related behaviour and significantly higher glycogen synthase kinase-3β (GSK-3β) levels, an important protein that is up-regulated in bipolar disorder. However, the activation of TRP-M2 leads to increased de-phosphorylation of GSK-3β through calcineurin-dependent pathway, hence this demonstrates the significance of maintaining Ca^{2+} homeostasis for the prevention of BD. Decreased levels of TRP-C3 proteins are reported in cortex region of rats treated with lithium (Zaeri et al.

Table 1 This table consists of important properties of TRP channels

Sr. No.	TRP	Brain regions	General features	Permeation	Activation mechanism	References
1	TRP-V1	Cortex, hippocampus & cerebellum	Controls synaptic plasticity, locomotion & temperature	Ca2 + permeable Non-selective (NS)	Protein kinase-A (PKA), PKC	(Tóth et al. 2005; Nilius 2007)
2	TRP-V2	Hippocampus & hypothalamus	Control of axon growth	Ca2 + permeable (NS)	PKC, PI3-K	(Nilius 2007; Nedungadi et al. 2012)
3	TRP-V3	Cerebellum	Emotional response regulation	Ca2 + permeable (NS)	Voltage dependent	(Nilius 2007; Singh et al. 2020)
4	TRP-V4	Thalamus, hippo-campus cortex & cerebellum	Thermo-sensitivity	Ca2 + permeable (NS)	PKC	(Nilius 2007; Wang et al. 2019)
5	TRP-V5	Cerebellum, midbrain, hippocampus, cortex & hypothalamus	Neurite out-growth	Highly Ca2 + selective	Serum & glucocor-ticoid dependent kinase-1 (SGK-1)	(Nilius 2007; Kumar et al. 2017)
6	TRP-V6	Cerebellum, amygdala & hippocampus	Neurite out-growth	Highly Ca2 + selective	Hyper-polarisation	(Nilius 2007; Kumar et al. 2017)
7	TRP-C1	Substantia nigra, cer-ebellum, hippocampus & amygdala	Neurite out-growth	Ca2 + permeable (NS)	Phosphoinositide-3 kinase (PI3-K), upregulation by hypoxia-inducible factor (HIF-1)	(Nilius 2007; Martinez-Galan et al. 2018)
8	TRP-C2	Cerebral cortex	Neurite out-growth	Ca2 + permeable (NS)	Diacylglycerol (DAG)	(Kunert-Keil et al. 2006; Nilius 2007)
9	TRP-C3	Cerebellum & striatum	Neuronal survival	Ca2 + permeable (NS)	DAG, Brain-derived nuclear factor (BDNF)	(Riccio et al. 2002; Nilius 2007)
10	TRP-C4	Cortex &amygdala	Neuronal signalling	Ca2 + permeable (NS)	PLC	(Fowler et al. 2007; Nilius 2007)
11	TRP-C5	Cortex, striatum, hip-pocampus, hypothala-mus & cerebellum	Neuronal survival	Ca2 + permeable (NS)	PLC	(De et al., 2006; Nilius 2007)
12	TRP-C6	Cortex, hippocampus & substantia nigra	Neuronal survival	Ca2 + permeable (NS)	PLC	(Nilius 2007; Nagy et al. 2013)
13	TRP-C7	Striatum & hypothalamus	Neuronal survival	Ca2 + permeable (NS)	PLC, DAG	(Kumar et al. 2017; Nilius 2007)
14	TRP-ML1	Cortex	Control zinc homeostasis	H + permeable	Increased Ca2+	(Nilius 2007; Grish-chuk et al. 2015)
15	TRP-ML2	Minimal distribution	Control zinc homeostasis	N.D	N.D	(Nilius 2007; Cua-jungco et al. 2016)
16	TRP-ML3	Minimal distribution	Maintenance of neuro-nal polarity	N.D	Low pH	(Nilius 2007; Cua-jungco et al. 2016)
17	TRP-P1	Not much known	Maintenance of neuro-nal polarity	Ca2 + permeable (NS)	Low pH	(Nilius 2007)
18	TRP-P2	Blood brain barrier	Regulation of Ca^{2+} in astrocytes	Ca2 + permeable (NS)	Mechanical stress	(Nilius 2007; Du et al. 2016)
19	TRP-P3	Thalamus, mid-brain, cerebellum & hippocampus	Regulation of Ca^{2+} in astrocytes	Ca2 + permeable (NS)	Low pH	(Li et al. 2007; Nilius 2007)
20	TRP-M1	Basal ganglia & forebrain	Cell death induced by oxidative stress	N.D	Translocation	(Kunert-Keil et al. 2006; Nilius 2007)
21	TRP-M2	Cortex, striatum & hippocampus	Cell death induced by oxidative stress	Ca2 + permeable (NS)	Reactive oxygen species (ROS)	(Nilius 2007; Sita et al. 2018)
22	TRP-M3	Brain stem, cortex & hippocampus	Cell death induced by oxidative stress	Ca2 + permeable (NS)	Cell swelling	(Nilius 2007; Hoff-mann et al. 2010)
23	TRP-M4	Hypothalamus, hip-pocampus & cortex	Activation of burst firing	Selective for mono-valent cations, Ca^{2+} impermeable	PKC	(Nilius 2007; Riquelme et al. 2018)

Table 1 (continued)

Sr. No.	TRP	Brain regions	General features	Permeation	Activation mechanism	References
24	TRP-M5	Cerebellum & hypothalamus	Processing of semio-chemical signals	Selective for mono-valent cations, Ca^{2+} impermeable	Voltage dependent	(Nilius 2007; Kim et al. 2013)
25	TRP-M6	Not much known	Microglial function	highly Mg^{2+} permeable, Ca^{2+} permeable	Decreased Mg2+	(Kunert-Keil et al. 2006; Nilius 2007)
26	TRP-M7	Cerebrum, cerebellum & hippocampus	Microglial function	highly Mg^{2+} permeable, Ca^{2+} permeable	Membrane translocation	(Nilius 2007; Sun et al. 2015)
27	TRP-M8	Thalamus, cortex & hypothalamus	Contribution to cold sensing	Ca2 + permeable (NS)	Depolarisation	(Nilius 2007; Ordás et al. 2021)

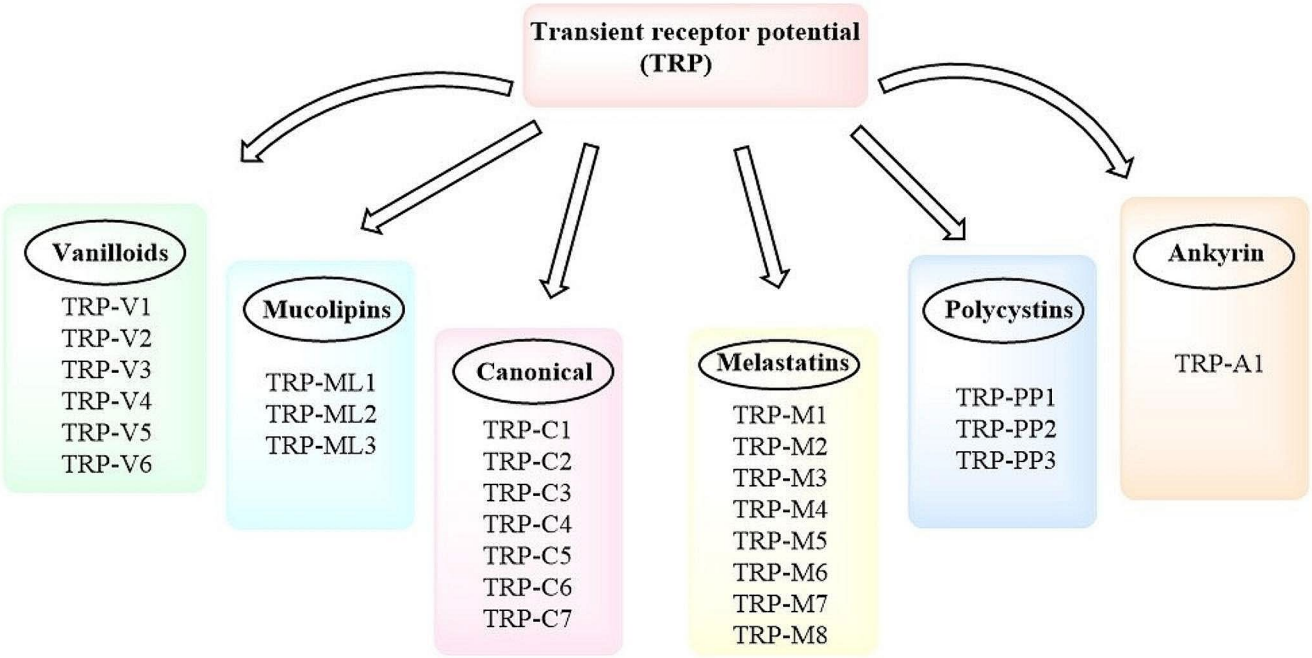

Fig. 3 This figure shows various TRP channels

2015). Andreopoulos and colleagues also reported that long term lithium treatment significantly decreases TRP-C3 protein levels in people with BD (Andreopoulos et al. 2004). Oxidative stress lowers TRP-C3 protein levels as well as the Ca^{2+} influx via these channels in patients having BD. A comparable decrease was seen in rat cortical neurons subjected to stress conditions (Roedding 2013; Behl et al. 2021). Escelsior and colleagues found that BD is associated with higher TRP-V1 gene expression, particularly in the depressed phase (Escelsior et al. 2023). Although studies done on TRP channels in BD are limited but TRP-C3, -C7, and -M2 are promising therapeutic targets in BD. These lines of evidences suggest a link between TRP channels and the pathophysiology of BD.

Anxiety: TRP channels

Anxiety is the most widespread mental disease in the world, with the highest lifetime prevalence, which results in significant expenses for both economy and society. Nowadays, medications for anxiety are associated with number of adverse effects and lack of effectiveness (Songtachalert et al. 2018). It is defined by intense expectation of forthcoming hazards and is accompanied by extreme fear, which refers to an emotional response to impending danger. Persistent anxiety and fear result in behavioural abnormalities and impairments. These anxiety-related disorders are characterized by the shunning actions, fearfulness episodes and decreased sense of well-being (Sharma et al. 2023). This leads to dysfunctional families, decreased economic growth, and an increased chance of suicide. Generalized anxiety disorder, social anxiety disorder and specific phobia are examples of anxiety disorders. According to various studies, anxiety-like

behaviours in rodents were attenuated by genetic deletion of TRP channels (C4, C5, V1, M2 & A1). TRP-V1 channels plays a crucial role in anxiety. TRP-V1 knockout (KO) mice were shown to exhibit decreased fear and anxiety behaviour (Marsch et al. 2007; Wright et al. 2020) which was confirmed by the elevated plus-maze (EPM) and light & dark test. In rats, Capsazepine (CPZ) (TRP-V1 antagonist), showed the anxiolytic effects, indicating that TRP-V1 channels have role in anxiety disorder (Santos et al. 2008). Another study found that capsaicin (TRP-V1 agonist) has an anxiogenic effect but capsazepine inhibits TRP-V1 and produces an anxiolytic response (Manna et al., 2011). The activities of CPZ and capsaicin, appear to be dose-dependent. Specifically, low doses of CPZ seem mostly ineffective, and higher doses of capsaicin have an anxiolytic effect, which is hypothesized to be due to TRPV1 receptor down-regulation. This is reported in studies on various animal models of anxiety disorders with systemic or intracerebroventricular (i.c.v.) administration (Treat et al. 2022). N-arachidonoyl-serotonin (AA-5-HT) has been demonstrated to inhibit TRP-V1 channels, demonstrating anxio-lytic action (Micale et al. 2009). AA-5-HT is also an inhibitor of the fatty acid amide hydrolase (FAAH) enzyme, as the effect on the endocannabinoid system is presumably relevant in inducing anxiolysis (Freels 2018). N-acylethanolamine has been shown to activate TRP-V1 channels. Although N-acylethanolamine in the CNS is unlikely to reach sufficiently high concentrations to activate TRP-V1, it might do so in conjugation with another brain-derived endo-vanilloids. Cannabinoids (CB) are thought to be anxiolytic via interacting with pre-synaptic CB-1 receptors, but they can have the opposite (anxiogenic) effect by activating post-synaptic TRP-V1 receptors. In fact, CB-1 and TRP-V1 were reported to be co-localized in the hippocampus area (Marzo et al. 2008; Casarotto et al. 2012). In addition, synaptic responses that are mediated by activation of cholecystokinin (CCK-2) receptors are implicated in anxiety, are diminished in lateral nucleus of the amygdala derived from TRP-C5-null mice. Interestingly, both TRP-C3 KO mice and moon-walker mice exhibit similar impaired walking behaviours (Hartmann et al. 2008; Becker et al. 2009; Riccio et al. 2009). TRP-C6 which is a close homologue of TRP-C3, promotes BDNF-mediated cell survival and growth-cone turning in brain granular cells (Jia et al. 2007). In the Morris water maze (MWM) test, TRP-C6 transgenic mice showed better spatial learning and memory, which suggests that it plays a critical role in the establishment of learning and memory through the control of synaptic plasticity (Zhou et al. 2008). TRP-V1 knockout mice were also reported to show reduced fear and anxiety behaviour (Marsch et al. 2007). TRP-C5 is present in the amygdala, frontal cortex, temporal cortex & hippocampus (Chung et al. 2006; Fowler et al. 2007). TRP-C5 KO rodent show less innate fear behaviour than wild-type in open-field, EPM test and nose bumping assays. These findings are consistent with brain slice recordings, which revealed that TRPC-5 KO animals had normal membrane excitability and synaptic function but had reduced synaptic responses to CCK receptors activation. These findings suggest the relation between TRP-C5 and cholecystokinin-4 signalling, the activation of which causes anxiety. Steroids are known to affect anxiety. In this regard, it is worth noting that neuro-active steroids block TRP-C5 channels (Riccio et al. 2009; Majeed et al. 2011). Together, this data implies that TRP-C5 antagonists might be effective anxiolytic. Further investigation on the role on TRP channels in memory is also required. Therefore, from the above instances it can be speculated that TRP channels plays an important role in the pathophysiology of anxiety.

MDD: TRP channels

MDD is a common psychological disorder that affects around 7% of individuals worldwide. Environmental, genetic, and psychological factors cause MDD (Fan et al. 2020). It influences the person's ideas, behaviour, and emotions (Rush 2007). Its pathology and etiology remain unknown, although it is thought to be linked to decreased function of monoamine neurotransmitters like serotonin and nor-epinephrine. In fact, the most effective techniques to treat MDD is to target mono-amine system by either the serotonin and nor-epinephrine re-uptake inhibitors or by selective serotonin re-uptake inhibitors, which increases mono-amine transmission (Dale et al. 2015). The monoaminergic theory of depression is prevalent although currently being challenged, particularly concerning the classical serotonergic model (Moncrieff et al. 2023). However, only around 50% of people diagnosed with major depressive disorder evolve into clinical remission with these treatments. The anterior cingulate of the brain has been implicated with depression in several studies. As this area of brain is the critical hub for the mood disorders and have been implicated in the treatment response. Hyperforin, primary bioactive component of the *Hypericum perforatum* shows the anti-depressant activity. It is a potent TRP-C6 activator and promotes the expressions of the channel (Griffith et al. 2010; Leuner et al. 2010). TRP-C6 are permeable to $Na2+$ in the pre-synaptic membrane, and their activation contributes to reducing the $Na2+$ gradient that promotes the neuro-transmitters absorption through the transporters, leading to increased levels of the neurotransmitters in the synaptic cleft (Leuner et al. 2007, 2013). It has also been found that it lower BDNF levels in the hippocampus region are typically connected with depression (Sen et al. 2008). It

is hypothesized that depression is connected with the loss of hippocampal synapses and dendritic spines, which contributes to failure of synaptic plasticity (Pittenger and Duman 2008). This is due to the fact that BDNF is a neurotrophic protein that plays a crucial role in the regulation of dendritic architecture and synapse (Pittenger and Duman 2008). It is believed that the synaptogenic features of BDNF are partially mediated by Ca2 + transients that are induced by TRPC channels (Amaral and Pozzo-Miller 2007). In the regulation of BDNF expression, TRP-V1 is involved. Navarria and colleagues showed that that AA-5-HT (2.5 mg/kg) increased hippocampal BDNF mRNA expression levels in stressed versus non-stressed rats. Stressed rats treated with AA-5-HT (2.5 mg/kg) showed an increase in hippocampal BDNF protein levels, while a higher dose of AA-5-HT (5 mg/kg) induced the opposite effect on hippocampal mRNA expression levels, with an increase in stressed rats and a decrease in non-stressed rats (Navarria et al. 2014). The Ca2 + influx through the TRP-C6 channel, which contributes to the modification of dendritic spine density and shape, is also ascribed to the potential efficacy of hyperforin in the treatment of depression. This suggests that hyperforin may be an effective therapy for depression (Leuner et al. 2013). Liu and colleagues demonstrated that TRP-C6 expression was shown to be considerably decreased in the hippocampus region in the chronic unpredictability stress (CUS) model of depression (Liu et al. 2015). Recent reports showed that the TRPV family also plays an important part in the development of depression (Hayase 2011). Increased long-term depression (LTD) at glutamatergic synapses of GABAergic neurons in the hippocampus region is dependent on TRP-V1 channels (Brown et al. 2013). These excitatory synapses are depressed by the capsaicin (TRP-V1 agonist). Previous studies have also demonstrated that TRP-V1 antagonists (5′-iodo-resiniferatoxin & Capsazepine) inhibit the induction of inter-neuron long term depression, and that LTD does not occur in TRP-V1 knockout mice (Gibson et al. 2008). AA-5-HT, a TRPV-1 receptor antagonist, showed antidepressant activity when injected directly into the ventral medial pre-frontal cortex (vmPFC) in rodents. Sartim and colleagues demonstrated that administration of AA-5-HT in the vmPFC decreases immobility time (IT) in the forced swim test (FST), also the co-administration of an effective dose of AA-5-HT (0.25 nmol) and the CB-1 receptor antagonist AM251 (10 pmol) abolished the effect of AA-5-HT on FST-IT (Sartim et al. 2017). Similarly, in another study AA-5-HT administered in the mPFC, the same improvement in FST-IT was observed, but it was partially, though not completely, abolished by the administration of the CB-1 receptor antagonist rimonabant (1.6 µg). These findings suggest that the anxiolytic effect may depend on the interaction between TRP-V1 and CB-1 receptors. Moreover, it seems that the primary mechanism might involve an increase in anandamide levels both directly (through FAAH inhibition) and indirectly (via TRP-V1 antagonism), which leads to an increased availability of anandamide for CB-1 receptors (Kirkedal et al. 2017). In another study, TRP-M2 channels are also linked to MDD. TRP-M2 KO reduced the CUS-induced reactive oxygen species and calpain activation and prevented hyper-activation of CDK-5 (cyclin-dependent kinase-5) pathway. In the CUS mice model, the removal of TRP-M2 by genetic modification resulted in behaviour that was similar to that of an anti-depressant. This indicates that TRP-M2 may be a potential therapeutic target for the treatment of depressive illnesses (Ko et al. 2019). Therefore, from the above instance one can conclude that TRP channels plays an important part in the pathogenesis of MDD.

SCZ: TRP channels

SCZ is a persistent, severe mental illness marked by hallucinations, delusions and cognitive impairments. The symptoms first appear in late adolescence or early adulthood (Chahl 2007). Two facts point to the idea that the somatosensory system is implicated in the pathophysiology of SCZ. The first is that patients with this disorder have abnormalities in pain feeling (Kudoh et al. 2000; Stubbs et al. 2015). The second is that patients have reduced flare responses to nicotinic acid and methyl-nicotinate due to altered vascular responsiveness (Messamor et al., 2003). Capsaicin-sensitive small-diameter primary afferent neurons are implicated in pain and flare responses. These findings revealed that in persons having SCZ may have abnormal capsaicin-sensitive primary afferent neurons. The latter symptoms suggest a problem with TRP-V1 expressing afferent nerve fibers. Capsaicin therapy in newborn rats generates brain alterations that match those reported in SCZ patients, indicating a probable function for TRP-V1 during development in the pathophysiology of this disease (Newson et al. 2005). The findings of Newson and colleagues imply that neonatal capsaicin-treated rats might be a useful animal model of SCZ. However, the study assumed that capsaicin's main site of action was the TRP-V1 channel on the primary afferent neuron (Newson et al. 2005). Although neonatal capsaicin administration would surely have targeted the main afferent neuron in this investigation, it is possible that capsaicin caused the observed brain alterations through CNS effects. Capsaicin's neurotoxic impact on TRP-V1 channels, comparable to that reported in the peripheral sensory system, was believed improbable since neonatal capsaicin administration has not been proven to influence TRP-V1 receptor mRNA expression in rat brain (Mezey et al. 2000; Sharma and Singh 2023). However, target molecules other than

TRP-V1 channels may have been affected. Capsaicin affects membrane proteins other than TRP-V1 channels, such as voltage-dependent Na2 + channels. By changing lipid bilayer flexibility, capsaicin and its antagonist, capsazepine, modulate these proteins (Lundbaek et al. 2005). Therefore, from the above data it can be speculated that TRP channels plays an important part in the pathophysiology of SCZ.

Migraine: TRP channels

Migraine is a multi-factorial neurovascular illness in which hereditary factors play an important role in both predisposing and influencing the underlying processes. Migraine was the second leading cause of disability around the world, but they were the main cause of impairment among women aged 15–50. Recently, the link of environmental, genetics, and migraines as well as associated co-morbidities of depression and anxiety has gained extensive attention (Steiner et al., 2023). Depression and migraine are co-morbid due to aberrant brain development, a shared genetic background, sex hormones, 5-hydroxy-tryptamine, and other processes (Yang et al. 2022; Lv et al. 2023). The calcitonin gene-related peptide (CGRP) is known to have an important role in the pathogenesis of migraine episodes (Wattiez et al. 2020; Rees et al. 2022). Meanwhile, CGRP can operate on the bed nucleus of the stria terminals (BNST) in rats, eliciting responses similar to those associated with anxiety, activate structural neurons associated with anxiety, and modulating stress-related behaviour. Given the shared etiology of depression, anxiety, and migraine, it may be speculated that migraine and the co-morbidities of anxiety and depression may share unique genetic traits (Sink et al. 2011). Activation of TRP channels leads to an increase release of CGRP from sensory nerve endings. They have been extensively employed to investigate the function of CGRP in a variety of processes (Shibata and Tang 2021). Furthermore, TRP channels have an important role in migraine pain (Russell et al. 2014; Spekker et al. 2022). Several research have examined the impact of TRP channel gene poly-morphisms in migraine pain across ethnic groups, but the findings have been inconsistent (Carreno et al. 2012; Chansman et al., 2014; Yakubova et al. 2021; Siokas et al. 2022). According to animal research, TRP-A1 and TRP-V1 antagonists might be a therapeutic target for depression and anxiety (Escelsior et al. 2020; Ngoc et al. 2023). TRP-A1 mRNA regulates depression-like behaviour and stress-adaptive responses in rodents. Furthermore, it is well known that TRP-V1 controls glutamate in the brain, and a lack of TRP-V1 induces anti-depressant and anxiolytic effects via modifying the expression of N-methyl-D-aspartate (NMDA) receptors and serotonin (Kormos et al. 2022; Fawley et al. 2014). The NMDA receptors have an important role in mechanical allodynia, whereas TRP-A1 channels interact with NMDA receptors to increase acute and chronic pain signals and govern mu-opioid receptor anti-nociception (Cortés-Montero et al. 2020). TRP-V1 may affect anxiety and depression through interactions with CB-1 receptors and modulation of the NMDA signalling (Lisboa and Guimarães 2012; Sartim et al. 2017). In conclusion, TRP channels modulate glutamate in the CNS and can cause migraines via cortical spreading depression (CSD); also, activation of TRP channels promotes the production of CGRP, which can cause migraine episodes. Wang and colleagues discovered that TRP-V1 was linked to migraine comorbidities like anxiety and sadness. TRP-M8 was linked to migraine comorbidity anxiety. TRP-V4 and TRP-M8 were related with migraine comorbidity, depression risk (Wang et al. 2023). Therefore, from the above findings one can conclude that TRP channels are associated with migraine comorbidity anxiety and depression risk.

ADHD: TRP channels

ADHD is one of the most prevalent neurodevelopmental disorders, affecting around 6–10% of children globally. It is a disorder characterized by the presence of symptoms such as inattention, hyperactivity, and impulsivity, as well as alterations in motor performance and various cognitive domains. Genetic predisposition is thought to be a primary factor of risk for ADHD in children, as expression of some genes is connected to age-specific phases (Bonvincini et al., 2018). Genes involved in dopaminergic signalling and neurodevelopmental processes are associated with children ADHD. Oxidative stress-related proteins have been linked to both children and adult ADHD. In fact, new research has revealed that oxidative stress processes as well as dopamine metabolism are involved in ADHD, regardless of age. There is abundant evidence at the pharmacological, genetic, and cognitive levels indicating disruption of the dopaminergic system plays an important role in the pathogenesis of ADHD (Del Campo et al. 2011). Several studies show that pre-natal diesel exhaust inhalation in mice causes dysregulation of dopamine or its metabolites in several brain areas (Suzuki et al. 2010). Early life exposure to particulate matter appears to disrupt the dopamine system or its metabolites in the mouse brain (Allen et al. 2014). The phospholipase C (PLC) pathway is a critical mediator of dopamine, since it regulates Ca2 + release from internal reserves such as the endoplasmic reticulum and TRPC channel activity. TRPC channels regulate Ca2 + excess and toxicity (Zhou and Jia 2017). As a result of the findings presented above, we may suggest that transient receptor potential channels could play a role in the pathophysiology of ADHD. However, further

research is necessary to confirm and clarify these potential mechanisms.

Interplay between epigenetics and TRP channels

Epigenetic regulatory system provides the molecular system through which an organism can adapt its genetic expression to specific environmental demands (Jaenisch and Bird 2003; Sharma et al. 2024). Gene expression is regulated by direct de-oxyribose nucleic acid (DNA) changes or by the action of proteins linked with certain genes, such as histone de-acetylases (HDAC) (Jaenisch and Bird 2003). HDAC are essential for synaptic plasticity, neurogenesis, mood control and cognitive processes (Wang et al. 2018). HDAC can alter chromatin state by removing/adding acetyl groups from histone tails, resulting in transcriptional repression (Mahgoub and Monteggia 2013). This effect is counter-balanced by the activity of histone acetyl-transferases (HATs), resulting in an antagonistic enzymatic dynamic that modifies various essential pathological and physiological processes (Haberland et al. 2009). HDAC are categorized into 4 classes such as 1, 2a, 2b, 3, and 4 (Ganai et al. 2016). HDAC inhibitors can target whole HDAC classes or its particular isoforms, and have shown anxiolytic and anti-depressant activities (Ganai et al. 2016). The potential effectiveness of HDAC-2 inhibitors on cognitive symptoms is very significant for psychiatric diseases (MDD, SCZ & BD) (Otte et al. 2016; Zai et al. 2017; Hsu et al. 2018). By an in-direct interaction with HDAC-2, TRP-V1 is responsible for shaping the epigenetic regulation that occurs in response to biological stress. Wang and colleagues showed that the administration of capsaicin (TRP-V1 agonist), to wild-type mice resulted in an over-expression of HDAC-2 in the hippocampus region, as well as deficits in the synaptic plasticity of neural progenitor cells in the hippocampus area. In contrast, these effects were not observed in TRP-V1 KO mice (Wang et al. 2018). Several pre-clinical studies suggested that the TRP-V1 antagonists could be useful to treat MDD and anxiety (Chahl 2011; Aguiar et al. 2014; Madasu et al. 2015; Patel et al. 2017). The efficacy of TRP-V1 inhibitors appears to be primarily mediated by an interaction between TRP-V1 and CB1 receptors for the treatment of anxiety and MDD (Patel et al. 2017). Specifically, it appears that TRP-V1 antagonists have the ability to modify the activity of the neuro-immune axis, prevent Ca2+-mediated neurotoxicity, and alter genetic expression through an indirect activity as HDAC-2 inhibitor (Kong et al. 2017; Wang et al. 2018). Therefore, investigating these pathways might lead to the development of innovative therapeutic approaches that could be utilised in the treatment of a variety of psychiatric diseases. In conclusion, TRP-V1 antagonists could be a viable therapeutic target for the treatment of BD, SCZ and other psychiatric diseases. As TRP-V1 inhibitors were shown to exert anti-oxidative properties and neuroprotective effects, other TRP channels can also be explored in various other psychiatric diseases.

Conclusion

The brain processes underlying psychiatric disorders are poorly understood and pose a significant challenge to neuroscience. Current medication therapies for these diseases have significant limits, necessitating an ongoing search for novel targets for therapeutic development. TRP channels are implicated in CNS activities, which suggests they might be attractive novel pharmacological targets, however there is little knowledge of their functions in the CNS to draw clear conclusions regarding their potential roles in psychiatric disorders. The discovery of selective agonists or antagonists targeting selective TRP channels offers promise for the creation of more effective and well-tolerated medications with fewer side effects than present pharmacotherapies. There is currently insufficient direct evidence connecting TRP channels to some diseases, such as schizophrenia and migraine. Future research on the central activities of TRP channels has the potential to improve knowledge of the aetiology of psychiatric diseases and lead to the development of novel therapeutic methods for their treatment.

Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
BD	Bipolar disorder
CB	Cannabinoids
CNS	Central nervous system
MDD	Major depressive disorder
MWM	Morris water maze
SCZ	Schizophrenia
TRP	Transient receptor potential

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