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Psychiatric Disorders and TRP Channels: Focus on Psychotropic Drugs

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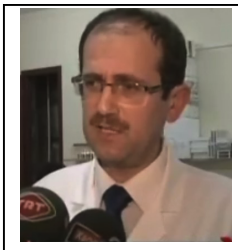

M. Nazıroğlu

Abstract: Psychiatric and neurological disorders are mostly associated with the changes in neural calcium ion signaling pathways required for activity-triggered cellular events. One calcium channel family is the TRP cation channel family, which contains seven subfamilies. Results of recent papers have discovered that calcium ion influx through TRP channels is important. We discuss the latest advances in calcium ion influx through TRP channels in the etiology of psychiatric disorders.

Activation of TRPC4, TRPC5, and TRPV1 cation channels in the etiology of psychiatric disorders such as anxiety, fear-associated responses, and depression modulate calcium ion influx. Evidence substantiates that anandamide and its analog (methanandamide) induce an anxiolytic-like effect *via* CB1 receptors and TRPV1 channels. Intracellular calcium influx induced by oxidative stress has an significant role in the etiology of bipolar disorders (BDs), and studies recently reported the important role of TRP channels such as TRPC3, TRPM2, and TRPV1 in converting oxidant or nitrogen radical signaling to cytosolic calcium ion homeostasis in BDs. The TRPV1 channel also plays a function in morphine tolerance and hyperalgesia. Among psychotropic drugs, amitriptyline and capsazepine seem to have protective effects on psychiatric disorders *via* the TRP channels. Some drugs such as cocaine and methamphetamine also seem to have an important role in alcohol addiction and substance abuse *via* activation of the TRPV1 channel.

Thus, we explore the relationships between the etiology of psychiatric disorders and TRP channel-regulated mechanisms. Investigation of the TRP channels in psychiatric disorders holds the promise of the development of new drug treatments.

Keywords: Anandamide, anxiety, bipolar disorders, calcium ion, depression, TRP channels.

INTRODUCTION

Calcium ion (Ca^{2+}) influxes through the cell membrane *via* various ion channels such as voltage-gated calcium channels (VGCC), receptor-gated calcium ion channels, store-operated calcium channels and transient receptor potential (TRP) channels. In addition, calcium ion pumping out through a plasma membrane calcium pump is decreased in neuronal diseases. Calcium ion is released from the endoplasmic reticulum (ER) stores through the inositol trisphosphate (InsP3) and ryanodine receptors [1].

The ER and mitochondria are organelles intimately connected to calcium ion homeostasis, and the ER contributes in neuronal calcium ion signaling, either as a modulator of calcium ion release or as a death [2,3]. Mitochondria are seen as a low-affinity, high capacity calcium ion overload, preventing an excessive cytosolic calcium ion overload. However, it is clear that their contribution in calcium ion homeostasis is much broader [4,5].

Transient receptor potential (TRP) channels are cation channel family. Cation channels term instead of calcium channels use for the TRP channels because massive Ca^{2+} and limited Na^{+} influx through the TRP channels. The TRP channels are responsible different pathophysiology and physiological functions such as oxidative stress, temperature regulation, inflammation and pain. These channels are highly expressed among species such as fungi and flies but not in plants, bacteria, and protozoa. First report of TRP channels is coming from *Drosophila* retina cells in 1969 and then their channel function was responsible for the impaired vision of these flies [6]. The TRP channels are the principal mediators of many diseases such as peripheral pain, inflammatory disease, bipolar disorders (BD) and Alzheimer's disease in neuronal cells and brain [7, 8]. In these neurons, TRP channels play poorly understood although they have important roles in regulating the etiology of psychiatric disorders as well as normal cell function. Abnormalities were observed in physiological function of cellular function of neurons by defect or deletion of the TRP channels. The defect or deletion of the TRP channels have important role in the etiology of psychiatric disorders.

In the literature, there are limited reports on TRP channels in psychiatric disorders such as anxiety, fear-associated responses, and depression. The TRP channels involved in psychiatric disorders are TRPC3, TRPM2 and TRPV1 [9]. For example, it was reported that anxiety and impaired fear decreased in TRPV1 knockout mice [10]. Oxidative stress and cytosolic Ca^{2+} ion entry have important role in the etiology of bipolar disorders [11,12]. In addition to TRPM2, TRPM7 and TRPC3 channels, TRPV1 channels

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have also a significant role in responses to oxidative stress and cytosolic Ca^{2+} entry [11, 12].

The endocannabinoid system includes endogenous ligands such as arachidonylethanolamide (anandamide) or 2-arachidonylglycerol. The cannabinoid receptors types are type 1 (CB1) and type 2 (CB2) and many brain functions are regulated by the CB1 and CB2 receptors. The anti-compulsive effects of cannabidiol as a non-psychotomimetic component of *Cannabis sativa* was recently reported in experimental animal models [13]. In addition to activation of CB1 receptors, anandamide also activates the transient receptor potential vanilloid type 1 (TRPV1) channel [13]. TRPV1 is a nonselective cation channel that when activated increases influxes of sodium and calcium ions and it's well known that influxes of the ions facilitate depolarization, and cause neurotransmitter releases [2, 3, 14]. It's well known that the TRPV1 mediates glutamate in the brain [15]. In contrary, CB1 activation blocks VGCCs, induces hyperpolarization *via* increase of potassium ion efflux, and decreases neurotransmitter release [16, 17]. Activation of CB1 receptors and TRPV1 at low and high doses of anandamide, respectively and behavioral actions are affected by the anandamide [18]. The TRPV1 is activated by at high dose of anandamide. In addition to the dose, the TRPV1 is activated different functions such as receptor reserve, phosphorylation, voltage, temperature and protons changes [13]. Please use 'TRPV1 and CB1 receptors modulate different pathophysiological processes, including pain, seizures, movement [19, 20], and anxiety [21, 22]. For example, depressive symptoms, increase of anxiety and decrease of sensitivity to reward were reported in CB1 knockout mice [19, 23, 24]. In contrary, TRPV1 knockout induction in mice reduced anxiety and impaired fear [10].

In the current review, we summarize previous results and novel recent advances in the understanding of calcium ion entry *via* TRP channels in different neurons and psychiatric disorders. We discuss the possible use of psychotropic drugs in TRP channels in psychiatric disorders. Regulation of the activation of TRP channels leads to the development of new treatments for numerous psychiatric disorders, such as bipolar disorders, depression, and anxiety.

2. OVERVIEW OF TRP CHANNELS

In 1989, the TRP protein was first identified as being encoded by the *trp* gene of *Drosophila* [6]. The TRP family is a diverse group of channels that regulates calcium and sodium ions influxes and contributes to a vast variety of physiological conditions. According to homology 30 mammalian TRP channels are divided into seven subfamilies namely canonical (TRPC) with 7 members, vanilloid (TRPV) with 6 members, melastatin (TRPM) with 7 members, ankyrin (TRPA), polycystin (TRPP), and mucolipin (TRPML) with 3 members each, and no-mechano-potential (NOMCP, TRPN) [7, 8, 25-27]. All of the subfamilies have a common structure of six transmembrane domains. Hydrophobic pore located between the fifth and sixth domains in the seven members and the Ca^{2+} and Na^{+} influx into the cytosol from the hydrophobic pore. Unlike many other types of ion channel, the activity is not gated by changes in voltage, and there is no fast neurotransmitter-dependent gating. Instead, the channels respond slowly to various chemical and physical factors. Positively charge isn't present in fourth transmembrane segment. Multiple ankyrin binding repeats are present in the N domain of TRPV and TRPC chanels [25, 28] although the ankyrin binding repeats aren't present in TRPM channels. The C-terminal domain of the sixth transmembrane segment in the TRPC and TRPM channels but not TRPV1 channels includes the TRP domain [13]. TRP channels are sensitive to various stimuli, including receptor stimulation, temperature, plant-derived compounds, environmental irritants, osmotic pressure, mechanical stress, pH, and voltage from the extracellular and intracellular milieu, and are involved in diverse physiological and pathological processes [1, 29].

Oxidative stress is determined as an imbalance between high reactive oxygen species (ROS) and low antioxidant levels. Generation of ROS is a physiological process since ROS are generated during aerobic metabolism, mitochondrial oxidations and phagocytic activates. For scavenging ROS, different antioxidant defense systems are exist in the brain and neurons. The TRPM2 channel was first discovered as a candidate of an oxidative stress–dependent TRP channel in 2002. Since then, the number of oxidative stress–dependent activated TRP channels has increased. Today, it is well-known that the TRPA1, TRPC5, TRPM2, TRPM7, TRPV1, TRPV3, and TRPV4 cation channels are activated by ROS and reactive nitrogen species (RNS) [29-32]. Members of one class of TRP channels have emerged as ROS and RNS sensors. Hydrogen peroxide, an ROS, induces the production of ADP-ribose, which binds and activates TRPM2. In addition to TRPM2, TRPC5, TRPV1, and TRPA1 are also activated by hydrogen peroxide *via* modification of cysteine (Cys) free sulfhydryl groups [25]. Nitric oxide is synthetized from L-arginine by nitric oxide sytnhatase enzyme. Some TRP channels such as TRPC5, TRPA1 and TRPV1 are activated by nitric oxide. Some TRP channels are directly activated *via* Cys S-nitrosylation by nitric oxide and they are also indirectly activated *via* cyclic GMP/protein kinase G-dependent phosphorylation pathways by nitric oxide. TRPM7 channels are activated by oxygen-glucose deprivation-induced anoxia. TRPC6 channel is activated by intensive hypoxia whereas TRPA1 channel is activated in vagal and sensory neurons by mild hypoxia and hyperoxia. TRPA1 activation is also sensitive hydrogen sulfide and carbon dioxide [29-32].

A tetrameric complex is present in TRPC channel structure. The TRPC is formed by the seven subunits of two subfamilies, TRPC1/4/5 and TRPC3/6/7 [8, 33]. TRPC channels are activated by G_q/11- coupled receptors [3, 34]. All TRPC channels except TRPC2 are expressed in the brain [8, 33].

TRPV1 channel is mostly expressed in small fiber which are pain-transmitting C fibers [31, 35]. As it was mentioned above, vanilloid receptors have important roles in many physiological and pathophysiological functions including pain, anxiety, thermoregulation, and inflammation [31, 36, 37]. TRPV1 channels are activated by numerous agonists. For instance, TRPV1 is activated by painful physical stimuli such as high temperature (>43 ^{o}C), protons, or chemicals

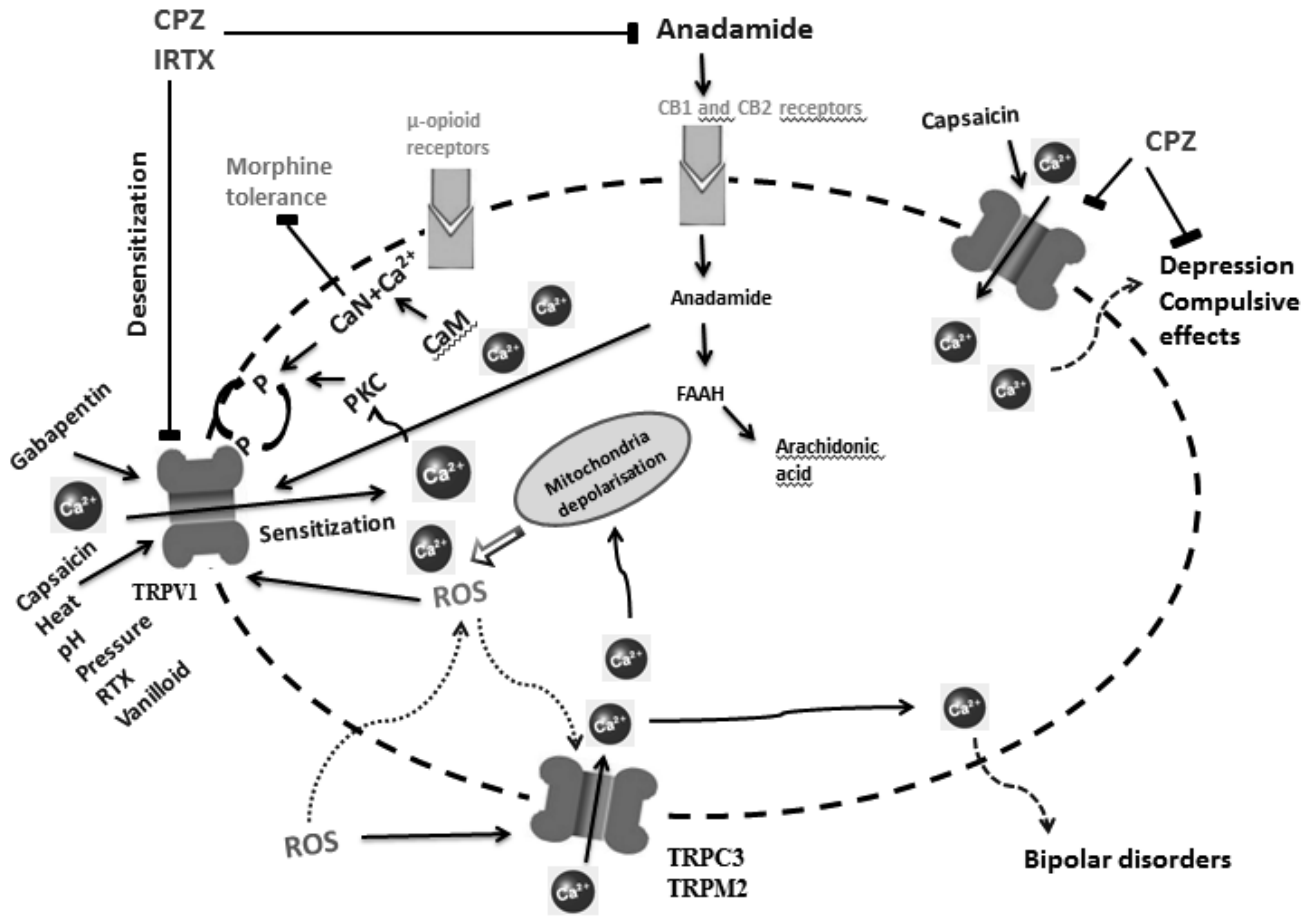

Fig. (1). TRPV1 is a polymodal cation channel. TRPV1 is activated by various noxious stimuli such as capsaicin, heat, pH, resiniferatoxin (RTX), and pressure although it was blocked capsazepine (CPZ) and 5'-Iodoresiniferatoxin (IRTX). PKC through phospholipase C and adenylyl cyclase phosphorylates TRPV1 and sensitizes the channel. Increases in intracellular Ca^{2+} from TRPV1 can activate CaM *via* calmodulin to further modulate TRPV1 activity. Supraspinal or spinal inhibition of CaM has been shown to prevent or reverse morphine tolerance and dependence [40]. TRPM2, TRPC3, and TRPV1 respond to mitochondrial-dependent oxidative stress, and indicates the role of oxidative stress-induced calcium ion signaling in depression and anxiety. AA (arachidonic acid), AEA (anandamide), CB1 (cannabinoid receptor type I), CB2 (cannabinoid receptor type II), FAAH (fatty acid amide hydrolase), PKC (protein kinase C).

Table 1. Roles of TRP channels in psychiatric disorders in neurons and animals.

TRP Channels	Material	Effect(s)	References
TRPC4	Null mice	Modular role of anxiety	Riccio *et al*. [34]
TRPC4	Null mice	No effects on motor coordination	Riccio *et al*. [34]
TRPC5	Null mice	Diminished innate fear and responsible from conditioned stimulus	Riccio *et al*. [65]
TRPV1	Rat	Anxiolytic-like effect	Kasckow *et al*. [65]
TRPV1	Rat hippocampus	Anxiolytic-like effect	Santos *et al*. [24]
TRPV1	Knockout mice	Decreased anxiety and impaired fear conditioning	Marsch *et al*. [10]
TRPV1	Rat hippocampus	Facilitates LTP but suppresses LTD	Li *et al*. [47]
TRPV1	Control and knockout mice	Faster recovery from ethanol-induced effects through TRPV1 activation	Blednow and Harris [85]
TRPV1	Rat	Mediates behavioral effects of drug-induced addiction	Adamczyk *et al*. [86]

Transient receptor potential (TRP); TRP canonical (TRPC); TRP vanilloid (TRPV).

Table 2. Role of psychotropic drugs in the TRPV1 channel in psychiatric disorders.

Material	Drugs	Effects	Reference
Rat	Amitriptyline	Facilitates passage of amitriptyline into nociceptors	Colvin *et al*. [88]
Mice	Fluoxetine	Modulator role in depression	Manna and Umathe [91]
Rat	Resiniferatoxin	Enhances depressive behaviors	Abdelhamid *et al*. [49]
Rat	Amitriptyline and Ketamine	Decreases depressive behaviors *via* desensitization of the TRPV1 channel	Abdelhamid *et al*. [49]
Mice	Olvanil	Antidepressant-like effect	Hayase, [45]
Rat	Capsaicin	Antidepressant-like effect	Kasckow *et al*. [44]

Transient receptor potential (TRP); TRP canonical (TRPC); TRP vanilloid (TRPV).

such as capsaicin, the pungent ingredient of hot chili peppers or endogenous ligands like anandamide, N-arachidonoyl dopamine, or oxidized linoleic acid metabolites that are known as endovanilloids, oxidative stress such as hydrogen peroxide and nitric oxide, neutrophil activity, and electromagnetic radiation such as mobile phone and Wi-Fi frequencies [13, 27, 31, 37, 38].

Calcium/calmodulin-dependent protein kinase II (CaMKII) has significant function on activation of different specific kinase transcription factor cascades and diseses, including morphine tolerance. The CaMKII in the superficial laminae of the spinal dorsal horn and the dorsal root ganglion (DRG) sensory neurons with small and medium diameters is co-localized with the α-opioid receptor [39]. The CaMKII is activated by calmodulin and increased cytosolic calcium ion. Morphine tolerance and dependence are prevented by supraspinal or spinal inhibition of CaMKII [40]. Opioid-induced thermal hyperalgesia and morphine tolerance are induced by simultaneously administration of opioids. Although implicated in thermal hyperalgesia under pathological conditions, TRPV1 channel is activated by morphine tolerance-induced thermal hyperalgesia [41]. Chronic stimulation of μ-opioid receptors induces increase of PKC activity and then the PKC increases N-methyl-D-aspartate (NMDA) receptors on TRPV1-expressing primary afferent terminals in the sensory neurons [42]. It was also reported that morphine reduced postsynaptic NMDA receptor currents although the currents were modulated in primary efferent of sensory neurons by TRPV1 channel agonist resiniferatoxin pretreatment [42].

3. PSYCHIATRIC DISORDERS AND TRPV1 CHANNELS

3.1. Depression and TRPV1 Channels

Depression is common psychiatric disease on the world. In the disease, a person's ability to function at work and also in in other areas of life is enormous affected by depressive disorder. Major depression is detected when a persistent and unreactive low mood or loss of interest and pleasure [43].

Few studies have demonstrated the antidepressant-like role of TRPV1 agonists such as capsaicin and olvanil in animal models of depression [44,45]. Conversely, a recent study showed that the absence of TRPV1 induced antidepressant, anxiolytic, and abnormal social and reduced memory behaviors through changes in the expression of serotonin, gamma aminobutyric acid (GABA) and NMDA receptors [46].

Li *et al*. [47] investigated the anti-stress roles of the TRPV1 channels on synaptic plasticity and spatial memory in Wistar albino rats with electrophysiology (patch-clamp) and Morris water maze analysis. The researchers observed an increase in long-term potentiation (LTP) but decrease in a long-term depression (LTD) in the rat hippocampus, and the results indicated that the TRPV1 channels were involved in acute stress-induced synaptic plasticity and spatial memory retrieval in the rat hippocampus.

The TRPV1 channel acted as a novel mediator of LTD at excitatory synapses on hippocampus. Brown *et al*. [48] investigated the roles of TRPV1, TRPV3, and TRPV4 channels in synaptic plasticity in the hippocampus of TRPV knockout mice. The researchers observed an important role of TRPV1 and TRPV3 channels in synaptic plasticity of hippocampus.

It's well known that TRPV1 channels are also activated by resiniferatoxin (RTX) and high temperature (43 °C). In study of Aldelhemid *et al*. [49] the role of heat-sensitive TRPV1 receptors in mice is investigated by high temperature (41 °C), a low dose of RTX, and two distinct types of antidepressants (amitriptyline and ketamine). The low dose RTX-induced immobility through desensitization of TRPV1 channel is modulated by amitriptyline and ketamine.

3.2. Anxiety and TRPV1 Channels

The term anxiety disorder encompasses a variety of complaints. Anxiety presents as a mix of psychiatric, physical, and behavioral symptoms. Some of these symptoms are determinant for different disorders with anxiety although others are also present some psychiatric disorders [50]. The many anxiety disorders are mostly treated by selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors [51].

Immunocytochemical evidence indicated TRPV1 is expressed in brain regions such as the dopaminergic neurons of the hippocampus, thalamus, basal ganglia, hypothalamus, periaqueductal gray matter, pontine nuclei, cerebral

peduncle, and cerebellar cortex, and neurons in the locus coeruleus and various layers of the cortex [52-54,59-60], suggesting TRPV1 has a role in emotional responses in addition to the function as the polymodal signal detector of pain. The influxes of cations such as sodium and calcium ions were increased by stimulation of these receptors, and they induced depolarized and fire action potentials in the neurons [1]. Glutamate release is increased in the synaptic terminals by activation of TRPV1 channel [55] although release of GABA, dopamine, and other catecholamines are decreased by the TRPV1 channel activation [46,53,56]. As it was mentioned above, TRPV1 has been shown to modulate activity-dependent synaptic efficacy: the LTP and LTD of hippocampal neurons are facilitated by TRPV1 channel activation [10,47]. Moreover, various behavioral assays indicate that TRPV1 plays a role in locomotion, emotion, and cognitive behaviors. For instance, Pegorini *et al*. [57] showed that capsaicin and ischemia-induced hyperlocomotion were reversed with capsazepine (CPZ) pretreatment. In addition, anxiolytic-like effects were observed after systemic or site-specific injections of CPZ in brain areas [18,58]. Similar effects such as hippocampus-dependent fear and impairment in LTP in hippocampal CA1 slices [10] and spatial memory [47] were observed in TRPV1 knockout mice. As it was mentioned above, the anandamide is a member of the endocannabinoid system and its receptors are CB1 and CB2. Specific CB1 receptor antagonist AM251 induced a reducing effect on the anxiolytic effect of low-dose anandamide. However, the anxiogenic effect of anandamide was totally blocked by pretreatment with a low dose of CPZ (5 μg) whereas anxiolytic effects was observed in mice by a high dose of CPZ pretreatment [18].

In the literature, the reports on TRP channels in anxiety are limited. The role of TRPV1 channels in anxiety-induced behavior, conditioned fear, and synaptic plasticity values in wild-type and TRPV1 knockout mice were investigated by Marsch *et al*. [10], and they observed important role of TRPV1 in regulating values in knockout mice although there was no difference in the general activity in wild-type mice. Presence of CB1 and TRPV1 receptors were indicated by immunocytochemical studies [52, 59, 60]. TRPV1 and CB1 are co-localized within several brain structures such as the hippocampus, basal ganglia, thalamus, cerebellar cortex, and hypothalamus and can be found in important vicinity at the molecular level [52] although TRPV1 was co-localized in postsynaptic dendritic spines and cell somata [60]. Activation of CB1 induces a decrease in cytosolic calcium ion in presynaptic terminal of neuron and thus decreased transmitter release [61]. In contrary, promotes calcium ion entry in postsynaptic sites is increased by anandamide-dependent activation of TRPV1 channel [62]. The results of anandamide and capsaicin in presynaptic terminal of neuron indicated that TRPV1 and CB1 induced opposite effects on important brain functions such as cognition, emotionality, and synaptic plasticity [20].

Santos *et al*. [24] found that the presence of TRPV1 channels in the ventral hippocampus in rats and TRPV1 channel antagonist CPZ administration decreased inhibitory avoidance in the rat elevated plus-maze test and they concluded TRPV1 channels had an active role in regulating anxiety. Similarly, decreased expression of TRPV1 channels and inhibitory avoidance behavior were observed in rats that received CPZ on the elevated plus-maze test [44].

3.3. Involvement of TRPC4 and TRPC5 Channels in Anxiety

Recently, expression of TRPC5 channels has been observed in brain areas such as the thalamus, the amygdala and the cortical areas that are responsible from control fear-related behavioral responses. Hence the channels are responsible in auditory fear conditioning for transmitting conditioned stimulus information to the amygdala [63,64]. A similar result was reported by Riccio *et al*. [65], who also reported that TRPC5 had an important responsibility in fear induction and attenuates to conditioned fear under certain conditions.

The effect of the lack of a TRPC4 subunit on the fear and anxiety controls in brain areas of mutant mice investigated by Riccio *et al*. [65]. They observed expression of TRPC4 in auditory cortex but TRPC5 was not able to express in the auditory thalamus. In addition, they observed that the auditory thalamus motor coordination didn't affect in the TRPC4 knock out mice. The researchers concluded that the deletion of TRPC4 was responsible an anxiolytic-like behavioral phenotype and normal expression of the TRPC4 subunit in brain circuits might be required for behavioral responses in anxiety-inducing stimuli.

3.4. Bipolar Disorders and TRPM2 and TRPC3 Channels

Bipolar disorder is a chronic psychiatric illness whose etiology remains unknown. Bipolar disorder has courses of mania and depression and affects nearly 1% of the population [66].

Oxidative stress occurs during physiological functions such as phagocytic activity and mitochondrial function [66-68]. Oxidative stress increases cytosolic free calcium ion through activation of TRPM2 channels in DRG and hippocampal neurons [7, 8, 69]. TRPM2 is activated ADP-ribose which was produced in mitochondria and nucleolus *via* three ways from NAD^+ by oxidative stress [70-73]. The N tail of TRPM2 channel is containing the ADP-ribose pyrophosphatase enzyme. If the enzyme will be activated by oxidative stress and ADP-ribose the channel will be gated [71-73]. ADP-ribose generation in the nucleus of neurons is attributed to a pathway that involves poly(ADPR) polymerase-1 (PARP-1), and may be initiated by DNA damage through different oxidant factors such as ROS, ischemia/reperfusion, brain injury, and radiation [28, 70].

Many N-terminal truncated isoforms of TRPM2 have been identified and they are responsible from the channel activation [29, 32]. In general, the N terminus is obligator for activation of the channels. The deletion of a stretch of 20 amino acid residues (Δ537-556) was observed in the TRPM2-ΔN splice variant of human neutrophils [74]. This ΔN stretch contains an IQ-like sequence motif that represents a CaM binding domain [75]. The ΔN stretch contains also two PxxP motifs that are characteristic of sites that enable interaction with other proteins [76]. Within the last decade, striking genetic findings have strongly implicated

TRPM2 in the pathogenesis of bipolar disorders [77-79]. Presence of a correlation between the exchange of a single amino acid residue (D543E) of ΔN and the presence of bipolar disorder was reported [77, 78]. Very recently, two striking genetic findings were discussed in a Ph.D. thesis by Angele Selina Rotting [11, 12], who strongly implied that TRPM2 has a role in the pathogenesis of bipolar disorders. She observed that human B lymphoblast cell lines from patients with bipolar disorder I induced high susceptibility to cell death and TRPM2-related Ca^{2+} influx to acute oxidative stress than in healthy subjects. Thus, TRPM2 is a highly relevant pathophysiological candidate for bipolar disorders, as its dysfunction may affect calcium ion signaling and cellular resilience. Contrary to results of Roedding *et al*. [11, 12], we observed that the TRPM2 channel didn't participated to any structure within the ΔN stretch in the N terminus [80].

Another TRP channel of interest in the pathophysiology of bipolar disorders I is the canonical TRP subtype 3 (TRPC3) channel. Neuronal TRPC3 channel activity is involved in different neuronal growth and changes such as BDNF-induced growth-cone turning [81] and dendritic arborization [82]. TRPC channels are thought to act as signal transducers for regulating intracellular calcium ion homeostasis [33]. Roedding *et al*. [83] investigated TRPC3 protein expression in the postmortem prefrontal cortex and cerebellum of healthy subjects which have age between 8 days and 83 years. The researchers found that the expression of the TRPC3 protein in the prefrontal cortex of the newborn and babies was higher (25%) as compared to the adolescent and adult (11 to 83 years) age group. They remarked that TRPC3 expression developmentally changed in the prefrontal cortex and the expression changes of TRPC3 suggested an important function for TRPC3 during postnatal and adult life.

TRPC3 is expressed in human B lymphoblast cell lines, and researchers have hypothesized that TRPC3 functionality may change in bipolar disorders [11, 12]. In addition, chronic lithium treatment of the cell lines in patients with bipolar disorder significantly decreased TRPC3 protein levels but not TRPC1 protein and mRNA levels, as determined with immunoblotting [84]. These results suggest that lithium may correct abnormal calcium ion homeostasis through down-regulation of TRPC3 channels in the cell lines in bipolar disorders [84]. Recently, Roedding *et al*. [11, 12] investigated whether the TRPC3 channel is differentially affected by oxidative stress in cell lines of bipolar disorder patient origin and TRPC3 protein expressions in the studies are decreased as a rotenone dose-dependent in human B lymphoblast cell lines. The results induced function of oxidative stress and overload calcium ion entry, all of which have been implicated in the pathophysiology of bipolar disorder.

3.5. Role of TRPV1 on Substance Abuse and Alcohol Addiction

The role of TRPV1 was investigated in drug addiction by several studies [10, 85-87]. The increased TRPV1 expression level was reported in the frontal cortex of methamphetamine-addicted rats [85-87]. The addictive behaviors of nicotine-addicted, cocaine-addicted, and ethanol-addicted animals were affected by TRPV1 expression or activation [45, 85-87] and the results supported a role for the TRPV1 channel in drug addiction.

Recent reports indicated that the extinction and cocaine related behavior occurrence was affected by cannabinoid CB1 receptors although the cannabinoid CB1 receptors haven't affect in the maintenance of cocaine self-administration. Hence, effects of cocaine addiction on the importance of other endocannabinoid-related receptors were investigated in cocaine addiction-induced mice by Blednow and Harris [85] and they reported that CPZ treatment of TRPV1-null mice accelerated recovery from ethanol-induced effects. However, capsaicin-induced TRPV1 activation induced opposite effects as low preference and slow recovery from ethanol.

The behavioral effects of drug-induced addiction might be modulated through TRPV1. Recently, role of TRPV1 antagonist SB366791 in a model of cocaine-induced addiction was investigated by study of Adamczyk *et al*. [86]. They observed that cocaine-induced reinstatement of cocaine-searching movements was recovered by SB366791 treatment although the treatment did not change cocaine self-administration. The results suggested that TRPV1 activity is not necessary for the reward response of cocaine wasn't affected by TRPV1 activity but the cocaine relapse was modulated by TRPV1 channel activity.

mRNA levels of TRPV1 channel in the frontal cortex, striatum, and hippocampus of the mouse brain following repeated methamphetamine treatment were recently investigated at different treatment times [87]. The mRNA levels of TRPV1 channel were increased in the frontal cortex by the methamphetamine treatment [87]. The results indicated that that the TRPV1 channels activation in the brain area involved in methamphetamine dependence.

3.6. Role of Psychotropic Drugs in TRPV1 Channels

Amitriptyline, a tricyclic antidepressant, is used to treat symptoms of depression. In addition, amitriptyline has been used in treatment for neuropathic pain, attention deficit hyperactive disorders, and enuresis nocturna for a long time. Amitriptyline works by inhibiting serotonin and noradrenaline from being reabsorbed in the neurons of brain. High doses of capsaicin induce analgesic effects. Colvin *et al.* [88] found that the combination of capsaicin and amitriptyline as a transdermal patch elicits cutaneous analgesia leads to increased analgesic efficacy.

One of psychiatric disorder is obsessive-compulsive disorder. The main symptom of obsessive-compulsive disorder is repeated obsessions to cause marked distress to the person although the etiology of obsessive-compulsive disorder is unclear. Reports on TRPV1 channels in obsessive-compulsive disorder are scarce. The studies revealed that capsaicin produced compulsive effects although CPZ dose-dependently decreased marble-burying behavior in mice [89]. These observations were supported by Umathe *et al*.'s results [90], and they observed in marble-burying behavior test that pretreatment with the per se inactive dose (10 μg/mouse) but not the lower dose of anandamide (10-20 μg/mouse) of CPZ prevented the increased the behavior test of anandamide at a high dose (40 μg/mouse). Role of

TRPV1 receptors in the anandamide-mediated compulsive induction effect was confirmed by anandamide results [90].

Reports on psychotropic drugs in depression are scarce. Recently, Manna and Umathe [91] used the forced swim test and the tail suspension test to investigate the possible influence of capsaicin and CPZ on depression either alone or in combination with glutamatergic (NMDA) drugs and serotonergic drugs such as para-chlorophenylalanine, a tryptophan hydroxylase inhibitor, and fluoxetine, a selective serotonin reuptake inhibitor. They observed that both agents decreased the immobility time comparable to the standard antidepressant, fluoxetine, in both tests. However, capsaicin at a dose >300 µg/mouse decreased locomotor activity.

More recently, Abdelhamid *et al*. [49] investigated the role of increased TRPV1 activity in immobility and depression in mice exposed to the forced swim test. The researchers kept mice in different temperatures, and RTX induced increased immobility in the mice through desensitization of the TRPV1 channel. They concluded that exogenous depressive behavior in the forced swim test was increased by TRPV1 ligands increase.

4. CONCLUSIONS AND FUTURE SUBJECTS

TRPM2, TRPC3, and TRPV1 respond to mitochondrial-dependent oxidative stress, and indicate oxidative stress signaling cytosolic C calcium ion cellular responses. The indicator for the interaction between TRP channels such as TRPM2, TRPC3, and TRPV1 and neurological disorders such as bipolar disorders and anxiety suggested that genetic deletions in TRP channels may change susceptibility to these disorders. There are striking genetic findings for the TRPM2 and TRPC3 channels in bipolar disorders. Thus, it seems that TRPM2 and TRPC3 have an important role in the etiology of bipolar disorders. Because presence of novel and certain evidences for the degeneration effect of oxidative stress in neuron and brain dysfunction, manipulating TRPM2, TRPC3, and TRPV functions in neuronal cells may be highly useful in the future for drug discoveries for treatment of the brain and neuron dysfunctions. Antioxidants that contain thiol such as glutathione and N-acetyl cysteine may useful in the diseases.

According to the results in recent publications, similar results are present in anxiety and depression, and there were important correlations between TRPV1 genetic defects, anxiety, and depression. In addition, the discovery of TRPV1 as a key channel of the neurological Ca^{2+} influx systems in response to capsaicin and anandamide indicates new ways on the pathophysiology of neurons in the brain.

The incidence of obsessive-compulsive disorder has been increasing and the etiology of the disease is still unclear. Studies have revealed that capsaicin through the TRPV1 channel produced compulsive effects although CPZ dose-dependently decreased marble-burying behavior in experimental animals. In the future, TRPV1 channel blockers may be useful in treating obsessive-compulsive disorder.

The role of TRPV1 in central nervous system pathways is unclear and its important role to important brain functions, including addiction, mood, and cognition, has also been indicated by results of recent papers although conflicting results are present. Further investigations on the physiological importance of TRPV1 in the important brain functions are needed before its potential as a target for new brain function-related medicine can be fully improve to use it [92].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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LIST OF ABBREVIATIONS

BD	=	bipolar disorders
CaMKII	=	calcium ion/calmodulin-dependent protein kinase II
CB1	=	cannabinoid receptors type 1
CB2	=	cannabinoid receptors type 2
CPZ	=	capsazepine
DRG	=	dorsal root ganglion
ER	=	endoplasmic reticulum
LTD	=	long-term depression
LTP	=	long-term potentiation
NMDA	=	N-methyl-D-aspartate
RNS	=	reactive nitrogen species
ROS	=	reactive oxygen species
RTX	=	resiniferatoxin
TRP	=	transient receptor potential
TRPC	=	transient receptor cononcial
TRPM	=	transient receptor melastatin
TRPV	=	transient receptor vanilloid
VGCC	=	voltage gated calcium channels

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