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Neuropsychiatric implications of transient receptor potential vanilloid (TRPV) channels in the reward system

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ABSTRACT

Neuropsychiatric disorders (NPDs) exert a devastating impact on an individual's personal and social well-being, encompassing various conditions and brain anomalies that influence affect, cognition, and behavior. Because the pathophysiology of NPDs is multifactorial, the precise mechanisms underlying the development of such disorders remain unclear, representing a unique challenge in current neuropsychopharmacotherapy. Transient receptor potential vanilloid (TRPV) type channels are a family of ligand-gated ion channels that mainly include sensory receptors that respond to thermal, mechanical and chemical stimuli. TRPV channels are abundantly present in dopaminergic neurons, thus playing a pivotal role in the modulation of the reward system and in pathophysiology of diseases such as stress, anxiety, depression, schizophrenia, neurodegenerative disorders and substance abuse/addiction. Recent evidence has highlighted TRPV channels as potential targets for understanding modulation of the reward system and various forms of addiction (opioids, cocaine, amphetamines, alcohol, nicotine, cannabis). In this review, we discuss the distribution, physiological roles, ligands and therapeutic importance of TRPV channels with regard to NPDs and addiction biology.

1. Introduction

Neuropsychiatric disorders (NPDs) have a devastating impact on an individual's personal and social well-being. NPDs which are characterized by a combination of abnormal thoughts, perceptions, emotions, behaviors, and social interactions encompass various conditions and brain anomalies that influence affect, cognition, and behavior (Pitkanen et al., 2010). NPDs include both neurological and psychiatric disorders such as schizophrenia, depression, bipolar affective disorder (BPAD), dementia, obsessive-compulsive disorder (OCD), autism spectrum disorder (ASD), attention deficit/hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), and drug/substance abuse disorders (i.e., addiction). Due to the significant impact of NPDs on social, occupational, and personal functioning among patients, there has been a global increase in the socioeconomic burden of such disorders: The World Health Organization (WHO) reports that the prevalence rates of depression, BPAD, schizophrenia, and other psychoses/dementia are 300 million, 60 million, 21 million, and 47.5 million, respectively (WHO, 2018).

Addiction is a chronic relapsing disorder mainly characterized by compulsive drug seeking and uncontrolled intake despite the debilitating consequences (Copersino, 2017; Koob, 2006), and is often accompanied by symptoms such as anxiety, irritability, and dysphoria. Addiction can lead to permanent dependence, the development of

Abbreviations: NPDs, neuropsychiatric disorders; BPAD, bipolar affective disorder; OCD, obsessive-compulsive disorder; ASD, autism spectrum disorder; ADHD, attention deficit-hyperactivity disorder; PTSD, posttraumatic stress disorder; WHO, World Health Organization; TRP, transient receptor potential; ER, endoplasmic reticulum; IP3, inositol-1,4,5 triphosphate; PLC, phospholipase C; TRPC, classical/canonical TRP channels; TRPV, vanilloid or capsaicin-sensitive TRP channels; TRPM, melastatin TRP channels; TRPP, polycystin TRP channels; TRPML, mucolipins TRP channels; TRPA, ankyrin TRP channels; CNS, central nervous system; NAc, nucleus accumbens; VTA, ventral tegmental area; PVN, paraventricular nucleus; ARC, arcuate nucleus; SON, supraoptic nucleus; ANS, accessory neurosecretory nuclei; SOR, retrochiasmatic area of the SON; GlyR, glycine receptor; LTD, long-term depression; LTP, long-term potentiation; CPZ, capsazepine; AA-5HT, arachidonoyl serotonin; vmPFC, ventral medial prefrontal cortex; CB1, cannabinoid receptor 1; PKC, protein kinase C; CaMKII, calcium/calmodulin-dependent protein kinase II; DA, dopamine; mGluR, metabotropic glutamate receptor; 2-AG, 2-arachidonoyl-glycerol; AC, adenylate cyclase

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psychiatric disorders, disability, socio-occupational and economic losses, and even death. Common substances associated with addiction include opioids, alcohol, nicotine, cannabinoids, and other psychotropic agents (Koob, 2006; Koob and Le Moal, 1997). Although the prevalence of addiction has increased to approximately 230 million, its pathophysiology remains enigmatic, necessitating the exploration of novel pharmacotherapeutic targets. Indeed, one in every 20 adults has used an illicit substance at least once in his or her life, and worldwide drug-related morbidity has reached 39.6 million (WDR, 2017). The dramatic surge in the worldwide prevalence of NPDs and different forms of addiction is of the utmost concern in the development of novel neuropsychopharmacotherapeutic approaches and treatments.

Transient receptor potential (TRP) proteins represent a large family of polymodal Ca^{2+}-permeable nonselective cation channels that were originally identified for their role in sensory transduction pathways. Extensive evidence from the last two decades suggests that TRP proteins can serve as therapeutic targets in many diseases (Venkatachalam and Montell, 2007). TRP channels comprise six transmembrane-spanning types, as follows: classical or canonical (TRPC), vanilloid or capsaicin-sensitive (TRPV), melastatin (TRPM), polycystin (TRPP), mucolipins (TRPML), and ankyrin (TRPA). Mammalian TRP channels are activated by different modes of stimulation (e.g., mechanical, thermal, chemical, osmolarity, light, oxidative stress, lipids, acid, and pheromones) (Marwaha et al., 2016). TRPV channels comprise the six transmembrane domains, possess a short, hydrophobic pore between fifth and sixth domain. Cations likeCa^{2+} and Na^{+} trigger TRPV-linked intracellular signaling (Rosenbaum and Simon, 2006), while TRPV5 and TRPV6 are highly selective to Ca^{2+} (Kumar et al., 2017b). TRPV channels are activated by stimuli (thermal, mechanical and chemical) via direct binding of Ca^{2+} and adapter proteins such as calmodulin. The downstream signaling pathway involves, phosphorylation of protein kinase A (PKA), PKC, activation of phospholipase C (PLC), inositol-1,4,5-triphosphate (IP3) generation and binding (IP3R), and liberation of more Ca^{2+} from the endoplasmic reticulum (EPR), which is followed by an increase in intracellular Ca^{2+} concentration (Clapham et al., 2001). Because TRPV channels are extensively distributed throughout the brain (Cristino et al., 2006; Kauer and Gibson, 2009a; Kumar et al., 2017a), they have emerged as novel therapeutic targets for NPDs (Chahl, 2011; Terzian et al., 2009) and various forms of addiction (Blednov et al., 2007; Marsch et al., 2007; Tian et al., 2010). In a nutshell, it could be said that modulation of TRPV channels plays a pivotal role in pathophysiology of NPDs, reward-seeking behavior and addiction. TRPV modulators can be used in the management of NPDs and addiction. In this review, we discuss the localization and functions of TRPV channels in key brain regions involved in the pathophysiology of NPDs and addiction.

2. TRPV channels in the brain

The discovery of capsaicin afferents marked a turning point in our understanding of the physiological role of TRPV1 channel in the brain. Although TRPV channels are distributed extensively in central nervous system (CNS) and their role in many physiological events and CNS disorders remain to be elucidated. TRPV1 expression is observed in the CA1 and CA2 regions of the hippocampus, dentate gyrus, thalamic and hypothalamic nuclei, cerebral cortex, corticolimbic structures (including the amygdala, caudate putamen, and substantia nigra pars compacta), cerebellum, locus coeruleus, basal ganglia, mesolimbic pathways, nucleus accumbens (NAc), and ventral tegmental area (VTA) (Kauer and Gibson, 2009b; Marinelli et al., 2005; Marzo et al., 2008). TRPV1 and TRPV2 are mainly expressed in the cortex, while TRPV3 is expressed in the cortex, thalamus, cerebellum, and thalamus (Caterina, 2007; Clapham, 2003). TRPV4 expression has been observed in the lamina terminalis, medial preoptic area, optic chiasm, anterior hypothalamic area, basal ganglia, cerebellum and hippocampus (Kauer and Gibson, 2009b). Expression of *TRPV5* mRNA has been observed in human brain tissue (Hoenderop et al., 2001), while both TRPV5 and TRPV6 have been observed in the mouse brain (Nijenhuis et al., 2003). Recently, distribution of TRPV5 and TRPV6 channels in rat and mouse brain were implicated for neuroendocrine regulation. mRNA expression of TRPV5 and TRPV6 were observed in brain regions like cortex, hippocampus, hypothalamus, olfactory bulb, mid brain, brain stem and cerebellum. The abundance of TRPV5 and TRPV6 immunoreactive neurons were observed in brain regions like paraventricular (PVN), accessory neurosecretory and supraoptic nucleus, arcuate (ARC), retrochasmatic and medial tuberal nuclei, midbrain, brainstem, cerebellum and hippocampus whereas glial cells also showed immunoreactivity for TRPV5 (Kumar et al., 2017a, 2017b). Inactivation of TRPV2 has been reported in glioblastoma which induces aberrant cell proliferation, apoptosis and cell death (Liberati et al., 2014). Hypothalamic neurons in rat brain showed co-expression TRPV5 with vasopressin, oxytocin, estrogen receptors and cocaine- and amphetamine-regulated transcript (CART). TRPV6 was co-expressed with estrogen receptor alpha (ERα) and found to be a key regulator of estrous cycle in mouse brain (Kumar et al., 2017a, 2017b). Clinical studies have indicated that TRPV channel expression is upregulated in patients with gliomas, as these channels are also present within glial cells (Amantini et al., 2007; Kim et al., 2006). Activation of TRPV1 by anandamide stimulated long-term depression (LTD) and regulated the excitatory neurotransmission in dentate gyrus of rat and mouse and potentiated the synaptic plasticity (Chávez et al., 2010). TRPV1 controls the LTD in the developing superior colliculus (shows synaptic refinement particularly) in mice where, glutamatergic and GABAergic neurons were found to be TRPV1 positive (Maione et al., 2009). Detail of localization, functions, endogenous and exogenous ligands of TRPV channels in the brain are further summarized in Table 1.

3. TRPV channels and NPDs

TRPV channels have been associated with NPDs including depression, stress, anxiety (Chahl, 2011, 2007). *TRPV1*$^{(-/-)}$ mice exhibit reduced vulnerability to stress associated with anxiety and fear (Marsch et al., 2007). TRPV1 agonists such as capsaicin and olvanil are reported to exert antidepressant-like effects in animal models (Kasckow et al., 2004). In contrast, *TRPV1*$^{(-/-)}$ exerts anxiolytic and antidepressant-like effects associated with altered expression of 5-HT_{1A}, $GABA_A$, and NMDA receptors in mice (Hayase, 2011; Kasckow et al., 2004; You et al., 2012). TRPV4 agonists increase the function and expression of glycine receptor (GlyR), protein kinase C (PKC), and calcium/calmodulin-dependent protein kinase II (CaMKII). Thus, these findings indicate that TRPV4 modulates inhibitory neurotransmission in the hippocampus (Qi et al., 2018).

TRPV1 channels have been shown to regulate synaptic functioning in different brain areas via diverse mechanisms. Increased long-term depression (LTD) at glutamatergic synapses of GABAergic interneurons in the hippocampus is dependent on TRPV1 channels (Brown et al., 2013). These excitatory synapses are depressed by the TRPV1 agonist capsaicin, and by endogenous eicosanoids. Previous studies have also demonstrated that TRPV1 antagonists (Capsazepine and 5′-iodoresiniferatoxin) inhibit the induction of interneuron LTD, and that LTD does not occur in brain slices from *TRPV1*$^{(-/-)}$ mice (Gibson et al., 2008). Additional studies have revealed that TRPV1 agonists (capsaicin and resiniferatoxin) exert anti-stress effects by altering hippocampal synaptic plasticity (i.e., increased LTP but decreased LTD) and spatial memory in rats (Li et al., 2008). In nucleus accumbens (NAc), endocannabinoids (eCBs) activates CB2 receptors and induces LTD and also activates postsynaptic TRPV1 (Grueter et al., 2010). Furthermore, *TRPV1*$^{(-/-)}$ and *TRPV3*$^{(-/-)}$ mice exhibit altered hippocampal synaptic plasticity, directly implicating these channels in hippocampal output. Blockade of GABAergic inhibition restores LTP in brain slices from *TRPV1* and *TRPV3*$^{(-/-)}$ mice (Brown et al., 2013). Wild-type mice treated with a TRPV1 activator (incensole acetate) exhibit anxiolytic

Table 1
TRPV channels overview- Locations, activators, agonist, antagonists, ligands, physiological functions and association with disease.

Property		TRPV1	TRPV2	TRPV3	TRPV4	TRPV5	TRPV6
CNS Localization		Cerebral cortex, hippocampus, cerebellum, thalamus, hypothalamus, locus coeruleus, periaqueductal gray, amygdala, striatum, mesencephalon, and olfactory bulb	Cerebral cortex, hypothalamus, motor neurons, nucleus, ambiguous, trigeminal, and motor nucleus	Cerebral cortex, hippocampus, cerebellum, thalamus, striatum	Hippocampus, cerebellum, the hypothalamus, basal ganglia, lamina terminalis, optic chiasm	cortex, hippocampus, hypothalamus, olfactory bulb, mid brain, brain stem and cerebellum, bones, kidney, epithelium	
Activators	Thermal	Heat $>43\,^{\circ}C$	Heat $>53\,^{\circ}C$	Heat >24–$30\,^{\circ}C$	Heat >24–$34\,^{\circ}C$	–	–
	Mechanical	Bladder distension sensation	Mechanical stretch or swelling	Pain	Cell swelling, shear stress,	–	–
	Chemical	pH <5.9, H^{+}	–	–	–	–	–
Agonists	Endogenous	AEA, NADA, ODA, 12- and 15- HPETE, 5- and 15-HETE, LTB4, 9- and 13-hydroxy-ODE, 9 and 13-oxoODE, OEA, PEA, LPA	LPC, LPI	FPP	Citric acid, 5,6- and 8,9- EET, DMAPP	–	–
	Exogenous	Capsaicin, *Ornithoctonus huwena* toxin, piperine, resiniferatoxin, 2-APB	Cannabidiol, THC, 2-APB, probenecid	Camphor, eugenol, thymol, carvacrol, 6-*t*-butyl-m-cresol, 2-APB, dihydrocarveol, (+)-borneol, incensole acetate	4α-Phorbol 12, 13-decanoate, apigenin bisandrographolide, GSK1016790A, RN-174716790A, RN-1747	–	–
Antagonists	Endogenous	Resolvin D2		Isopentenyl pyrophosphate, Resolvin D1	Resolvin D1	–	–
	Exogenous	Capsazepine, I-RTX, BCTC, Thapsigargin, Yohimbine, AG489, AG505, Ruthenium red	Tranilast, Ruthenium red	Ruthenium red, GRC15300	Ruthenium red, HC-067047, RN-1734, GSK2193874	–	–
Functions		Sensing hot (spicy) peppers, pain sensation, hyperalgesia (inflammatory, thermal), hypothalamic vasopressin release, vasopressin release, locomotion, emesis, mitochondrial damage, and apoptosis	Sensing thermal pain, mechanosensing	Sensing warmth, osmolarity sensing	Sensing warmth, CNS osmosensing, nociception, hyperalgesia (thermal, osmotic, mechanical)	Neuro-endocrine regulations, Hormonal control of calcium homeostasis,	
Disease Implication		Depression and anxiety, substance abuse and alcohol addiction	–	Food reward anticipation	–	–	–

In the table: N-arachidonoylethanolamine (AEA, Anandamide), N-arachidonoyldopamine (NADA), N-oleoyldopamine (ODA), 12- and 15-hydroperoxyeicosatetraenoic acid (HPETE), 5- and 15-hydroxyeicosatetraenoic acid (HETE), Leukotriene B4 (LTB4), octadecadienoic acid (ODE), Oleoylethanolamide (OEA), Palmitoylethanolamide (PEA), Lysophosphatidic acid (LPA) Lysophosphatidylcholine (LPC), Lysophosphatidylinositol (LPI), Farnesyl pyrophosphate (FPP), 2-Aminoethoxydiphenyl borate (2-APB), Δ9-tetrahydrocannabinol cannabinol (THC), Iodo-resiniferatoxin (I-RTX), N-(4-Tertiarybutylphenyl)-4-(3-cholorphyridin-2-yl)tetrahydropyrazine −1(2H)-carboxamide (BCTC), Epoxyeicosatrienoic acid (EET), Dimethylallyl pyrophosphate (DMAPP), Transient receptor potential vanilloid type channels (TRPV) (Kaneko and Szallasi, 2014; Kauer and Gibson, 2009b).

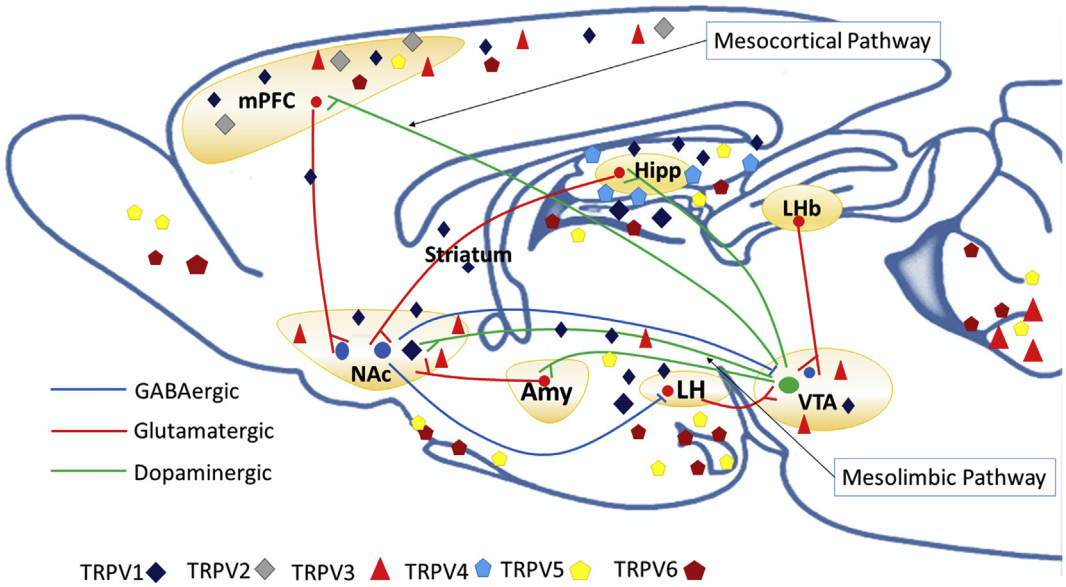

Fig. 1. Localization of TRP channels in brain regions and circuits involved in NPD and addiction pathophysiology. TRPV3 channels present on mesolimbic dopaminergic neurons are associated with active food reward anticipation. TRPV1, V2 and V3 present in cortex, hippocampus, nucleus accumbens and ventral tegmental area. TRPC present in striatal neurons have been associated with drugs and nicotine dependence (Russo and Nestler, 2013). mPFC- medial prefrontal cortex, Hipp- hippocampus, NAc- nucleus accumbens, Amy- amygdala, LH- lateral hypothalamus, VTA- ventral tegmental area, LHb- lateral habenula.

and antidepressant-like behaviors, which are absent in *TRPV3*$^{(-/-)}$ mice (Moussaieff et al., 2008).

TRPV1 channel expression in dopaminergic neurons of the hippocampus, thalamus, hypothalamus, basal ganglia and cerebral cortex has been associated with emotional responses and pain detection. Expression of TRPV1 channels with cannabinoid (CB1) receptors immunopositivity have been observed on the cell bodies of pyramidal neurons in CA1 and CA3 regions of hippcampus, substantia nigra, globus pallidus, thalamic and hypothalamic neurons(Cristino et al., 2006). Activation of TRPV1 channels also leads to an increase in glutamate release at the synaptic cleft, in addition to decreases in the release of GABA and dopamine (DA) (Edwards et al., 2012; González-Aparicio and Moratalla, 2014; You et al., 2012). Activation of TRPV1 channels has been shown to exert effects on locomotion, emotion, and cognitive behaviors (Pegorini et al., 2006). Capsazepine, a TRPV1 antagonist, reverses capsaicin-induced hyperlocomotion and exerts anxiolytic effects in mice treated with anandamide (Terzian et al., 2009). Knockout, antagonization and desensitization of TRPV1 channels have been reported to decrease immobility time in the forced swim test, suggesting a role of central TRPV1 receptors in depression (Abdelhamid et al., 2014). Arachidonoyl serotonin (AA-5HT), a TRPV1 receptor antagonist, demonstrates antidepressant-like activity when injected directly into the ventral medial prefrontal cortex (vmPFC), although this effect can be attenuated using a cannabinoid receptor 1 (CB1) antagonist (Sartim et al., 2017). TRP channels have also been implicated in the pathophysiology of schizophrenia (Chahl, 2007). Numerous studies regarding the roles of TRP channels in neurodevelopment (Greka et al., 2003; Hui et al., 2006), their interaction with dopaminergic neurons (Mezey et al., 2000; Tóth et al., 2005), the cannabinoid system (Harkany et al., 2007; Zygmunt et al., 1999), synaptic alterations (Krapivinsky et al., 2006; Li et al., 2008; Munsch et al., 2003), thermoregulation (Guatteo et al., 2005; Lee et al., 1985), and sensory processing (Holzer, 1991; Hwang et al., 2004) further support the notion of a shared pathophysiology with schizophrenia. Thus, targeting TRP channels may represent a viable therapeutic alternative for schizophrenia.

4. Role of TRPV channels in substance abuse and addiction

Drug addiction or substance use disorder is a chronically relapsing condition involving in impulsive drug seeking, uncontrolled/unlimited intake leading to negative behavioral changes (irritability, hypohedonia, dysphoria, anhedonia and anxiety) when drug use is controlled. In addition, majorly affected areas and neurotransmitter systems includes dopamine dysregulations in mesocorticolimbic pathways, glutamate in corticostriatal areas and corticotrophin-releasing factor (CRF) in amygdala (Nestler, 2005). DA is the major neurotransmitter involved in drug/reward-seeking behaviors, reward reinforcement, and addiction. Mesolimbic dopaminergic reward circuits, along with DA neurons in the amygdala and cortico-striatal region, are mainly involved in reward-seeking (Koob, 2006; Koob and Le Moal, 1997). Some drugs such as amphetamine and cocaine act directly on DA signaling (Porter-Stransky et al., 2011; Stuber et al., 2005), while others (e.g., alcohol, nicotine) exhibit complex mechanisms of action (Lüscher and Ungless, 2006).Accumulating evidences are suggesting the pivotal role of TRPV channels in neuro-circuitry of addiction and highlighting the need to explore the role of TRPV channels in reward system modulation (Wescott et al., 2013). Reward-dependent learning is associated with synaptic modification of medium spiny neurons (MSNs) in nucleus accumbens (NAc). Metabotropic glutamate receptors (mGluRs) indirectly activate MSNs by indirect pathways and lead to production of endocannabinoids (eCBs). eCBs activate CB1 receptor which triggers eCB-mediated LTD and also activate postsynaptic TRPV1. Activation of TRPV1 channels induces endocytosis of AMPA receptors and triggers another form of LTD. These kind of interactions could be implicated for reward system modulation and addiction (Grueter et al., 2010).

Acute nicotine treatment decreased the amplitude of capsaicin-induced action potential in the mammalian neurons expressing TRPV1 (Liu et al., 2004). Interaction of TRPV1 with nAChRs has also been associated with nicotine withdrawal-induced anxiety and nervousness (Casarotto et al., 2012). *TRPV1*$^{(-/-)}$ mice exhibit reduced vulnerability to addictive symptoms, along with an increased preference for alcohol (Blednov and Harris, 2009). TRPV1 channels are also associated with methamphetamine and cocaine addiction (Blednov and Harris, 2009; Marsch et al., 2007; McClung and Hirsh, 1999, 1998; Tian et al., 2018, 2010). As shown in Fig. 1, TRP channels are present in different brain

regions and are associated with several NPDs and substance abuse disorders.

4.1. Cocaine and amphetamine addiction

Cocaine is psychoactive substance that produces addiction mainly through activation of limbic system. Initially cocaine raises the dopamine surge, which produces euphoria followed by drug seeking behavior. Although it's more than 30 years when cocaine addiction has been highlighted but still the pathophysiology is illusive and no pharmacological treatment is available (Nestler, 2005). Cocaine alters intrinsic neuroplasticity in the NAc, which is mediated through the metabotropic glutamate receptor 5 (mGluR5) (Huang et al., 2011, 2007; Kourrich et al., 2007), whereas cocaine withdrawal impaired the mGluR5-LTD in NAc (Huang et al., 2015) TRPV1 modulation is found to be associated with cocaine addiction. TRPV1 homolog inactive (*iav*) mediated behavioral sensitization to cocaine in fruit fly (*Drosophila melanogaster*). These stereotypical behavioral effects were dose dependent, where low dose showed intense grooming, moderate dose showed rapid rotations, while high dose showed tremors and paralysis. Repeated cocaine treatment worsens these behavioral changes (McClung and Hirsh, 1998). With repeated administration, cocaine sensitization took place and drastic behavioral changes were observed at even lower concentrations of cocaine, whereas these changes were absent in *iav* null mutants. Decreased levels of monoamines (tyramine and octopamine) regulated by TRPV proteins was found to be the mechanism underlying these defects (McClung and Hirsh, 1999, 1998).

Repeated methamphetamine treatment leads to an increase in levels of *TRPV1* mRNA in the frontal cortex, hippocampus, and striatum in the mouse brain (Tian et al., 2010). TRPV1 antagonist SB366791 reversed drug-seeking behavior in rats followed by cocaine-induced reinstatement, while cocaine self-administration remained unaffected (Adamczyk et al., 2012). Recently, TRPV1 antagonists (capsazepine and SB366791) have been found to be reducing methamphetamine-induced conditioned place preference and self-administration in mice, whereas $TRPV1^{(-/-)}$ mice did not show these rewarding behaviors after methamphetamine administration. Upregulation in protein and mRNA expression of TRPV1 in NAc and dorsal striatum, while capsazepine treatment decreased DA levels in NAc of methamphetamine treated mice. Further, methamphetamine treated mice also showed reduced dopamine transporter (DAT) binding in NAC and dorsal striatum which was reversed by capsazepine treatment (Tian et al., 2018). These findings suggest that TRPV1 activation is associated with cocaine and methamphetamine dependence, highlighting the need for further studies regarding the use of TRPV modulators in the treatment of substance abuse disorders.

4.2. Opioid addiction

Rates of opioid dependence and abuse have dramatically increased in recent years, accompanied by NPDs in many cases. Opioids include morphine, heroin and prescription analgesics, which are highly capable of producing dependence. Opioid addiction is characterized as chronic, compulsive, and often relapsing (Veilleux et al., 2010). TRPV1 present in the NAc has been associated with opioid relapse (Micale et al., 2009). TRPV1 is located within presynaptic terminals and cell bodies in the NAc and is known to potentiate glutamate transmission (Musella et al., 2009). Injection of the TRPV1 antagonist CPZ into the NAc attenuates morphine-induced persistent morphine conditioned place preference (Guo et al., 2014). Blocking TRPV1 with CPZ attenuates morphine tolerance as well as withdrawal phenotypes in mice (Nguyen et al., 2010).

Emerging evidence indicates that TRPV1 inhibition may be effective in the treatment of opioid addiction. Inhibition of TRPV1 in the dorsal striatum reduces morphine reward preference by altering NAc activity (Hong et al., 2017) and significantly reduces naloxone-induced withdrawal symptoms (Nguyen et al., 2010). $TRPV1^{-/-}$ mice didn't show response to morphine reward, while selective TRPV1 antagonist (SB366791) reduced morphine-induced conditioned place preference via TRPV1/p38 MAPK (mitogen-activated protein kinase) (Hong et al., 2017; Nguyen et al., 2014) and cAMP-dependent PKA/MAPK signaling pathway (Bao et al., 2015). SB366791 and AMG9810 (another selective TRPV1 antagonist) have significantly reduced the morphine self-administration as well as the morphine-induced c-fos expression in NAc of male rats (Ma et al., 2017). Very recently, reduction in morphine self-administration by SB366791 treatment was found to be through activation of the Ca^{2+}/calmodulin-dependent protein kinase II - cAMP response element binding protein (CaMKII-CREB) pathway in rat NAc (Ma et al., 2018).These findings suggest that TRPV1 has a putative role in opioid addiction and its antagonists can be used as a novel treatment strategy for opioid addiction.

4.3. Cannabinoid addiction

Cannabinoids are active constituents if cannabis or marijuana plant *(Cannabis sativa)*. Despite cannabinoids have gained the attention of scientific community for their medical use and several countries have legalized their production/cultivation, cannabinoid abuse disorders are extensively prevalent worldwide but no promising cure is available. Delta-9-tetrahydrocannabinol (THC) is the main psychoactive compound of cannabis plant and is a partial agonist of CB1 receptors. Cannabis preparations also contains cannabidiol (CBD) which acts on multiple receptors (CB1, CB2, 5-HT_{1A}, PPAR-γ, opioids, and TRPV1) and modulates endocannabinoids (eCBs) metabolism and intracellular Ca^{2+} concentration (Panlilio et al., 2015). eCBs such as anandamide and 2-arachidonoyl-glycerol (2-AG), act on post to presynaptic nerve endings, serving as retrograde neurotransmitters. Anandamide is an endogenous ligand for TRPV1 and modulates some cannabinoid functions. CB1 receptor activation inhibits adenylate cyclase (AC) as well as GABAergic and glutamatergic neurotransmitter release (Vaughan et al., 2000), whereas activation of TRPV1 channels leads to membrane depolarization, followed by action potential generation and increases in firing rate. CB1 receptors and TRPV1 channels are co-expressed in most of the brain areas involved in anxiety and fear (medial prefrontal cortex (mPFC), hypothalamus, hippocampus, and midbrain) (Cavanaugh et al., 2011; Mezey et al., 2000; Uliana et al., 2016). Previous studies have also reported associations between the *TRPV1* gene and cannabis addiction (Agrawal and Lynskey, 2009; Nguyen et al., 2014). Tonic activation of CB1 receptors modulates extinction and reinstatement of cocaine seeking-behavior without altering cocaine self-administration. Conversely, CB1 receptors (neither CB2 nor TRPV1) play a role in cue-induced reinstatement of cocaine-seeking behavior (Adamczyk et al., 2012). Additional research has indicated that TRPV1 channels in the basal ganglia interact with CB1 receptors to induce hypokinesia (Cristino et al., 2006). TRPV1 channels have also been found to mediate the antihyperalgesic effect of the cannabidiol in rats with intraplanter carrageenan-induced acute inflammation (Costa et al., 2004). Such findings highlight the needs for further exploration of the role of TRPV channels in cannabinoid addiction.

4.4. Nicotine addiction

Cigarette smoking kills more than 6 million people worldwide, and annual deaths caused by smoking are expected to exceed 8 million by 2030 (Li, 2018). Nicotine, one of the most widely consumed addictive substances, is known for its ability to alter mood (i.e., anxiety, depression) (Picciotto, 1998). Indeed, the most common withdrawal symptom reported in tobacco/nicotine users is depression (Hayase, 2011). Nicotine acetylcholine receptors (nAChR) have been found on capsaicin sensitive neurons in cerebral cortex and dorsal root ganglionic (DRG) neurons of spinal cord (Roberts et al., 1995). Nicotine-induced depressive behaviors and reward reinforcement have been linked to

endocannabinoids. Chronic nicotine administration in rats decreased the levels of 2-arachidonoyl-glycerol (2-AG) and arachidonoylethanolamide (AEA) (which are endogenous ligands of cannabinoid receptors) in hippocampus, striatum and cerebral cortex. Chronic nicotine exposure also decreased the mRNA expression of cannabinoid receptors (CB1) (González et al., 2002). Nicotine self-administration reduced the baseline levels of dialysate oleoylethanolamide (OEA) in ventral tegmental area (VTA), while increased release of AEA during nicotine intake in rats (Buczynski et al., 2013). Nicotine-induced depressive symptoms are also associated with cannabinoid signaling (Hayase, 2008). Interactions as well as co-localizations of CB receptors with TRPV1 channels is well documented in human and rodent central nervous system (Cristino et al., 2006; de Lago et al., 2004; Huang et al., 2002). Repeated nicotine treatment in mouse induced depression like behavioral changes which were reversed by TRPV1 agonists (capsaicin and olvanil) which was antagonized by TRPV1 antagonist (capsazepine). In addition, endogenous TRPV1-CB1 agonist (AEA and N-arachidonyldopamine, NADA) failed to reverse the depressive behaviors. However, synthetic TRPV1-CB1 agonist (arvanil) significantly attenuated the depressive behaviors (Hayase, 2011). Nicotine-induced elevated dopamine levels in nucleus accumbens and its rewarding effects were attenuated by AEA transport inhibitor AM404 and VDM11 (Gamaleddin et al., 2011; Scherma et al., 2012). Taking together, interplay between modulation of TRPV1 channels, endocannabinoid and CB1 receptors need to be explored systematically, which could give more significant insights into possible role of TRPV channels in nicotine addiction and could provide novel therapeutic approaches.

4.5. Alcohol addiction

Alcohol dependence is the most common form of substance abuse and addiction. Several factors including genetic predisposition, previous history, provocative environmental experiences and social context can lead to compulsive alcoholism, which may in turn, evolve into addictive behavior. Despite substantial advancements in our understanding of the pharmacology and mechanisms underlying alcohol addiction, there is no precise treatment available for those with alcohol dependence. Due to its complexity, it is difficult to design an animal model of alcohol addiction. However, alcohol preference, consumption, seeking, and relapse have been modeled in experimental animals (Vengeliene et al., 2008).

Alcohol activates TRPV1 channels and may exert certain central and peripheral effects, although the mechanisms by which these effects occur remain unclear. Previous study has indicated that TRPV1 channels are present in HEK293 cells, which respond to alcohol at concentrations ranging from 0.3 to 3% (Trevisani et al., 2002). Alcohol potentiates the effect of capsaicin and protons (TRPV1 activators) and lowers the heat activation threshold of TRPV1 (from 42 °C to 34 °C), which is near the physiological temperature of the tongue. This may be associated with alcohol-induced sensory responses in inflamed tissues (Hirota et al., 2003). Endocannabinoid system also plays important role in alcohol addiction. Alcohol and cannabinoids follow the same pattern of reward system activation. CB1 receptors regulates the relapse and reinforcing effects of alcohol. CB1 knockout mice showed reduced alcohol self-administration and alcohol-induced dopamine release in NAc (Hungud et al., 2003), while CB1 antagonist (SR141716A) also reduced alcohol seeking in rats (Cippitelli et al., 2005). Further, AM404, an anandamide transport inhibitor and TRPV1 agonist reduced the alcohol seeking and self-administration rats (Cippitelli et al., 2007). Blednov and Harris reported that *TRPV1*$^{(-/-)}$ mice consumed more ethanol than wild-type mice, further reporting that low doses of alcohol are associated with decreased loss-of-righting responses. In *TRPV1*-null mice, CPZ treatment is associated with decreased sensitivity to alcohol-induced sedation and faster recovery of lost motor coordination. These effects can be reversed using a selective TRPV1 agonist (capsaicin) in wild-type mice, suggesting the involvement of TRPV1 in alcohol-induced behavioral alterations (Blednov and Harris, 2009). Thus, inhibition of TRPV channels may represent a therapeutic alternative for alcohol addiction.

5. TRPV channels and food reward modulation

Dopaminergic neurons in the mesolimbic pathways (VTA to NAc and mPFC) control the mesolimbic-reward pathway, which also regulates food reward. Previous studies have suggested that TRPV channels in these dopaminergic neurons indirectly control food intake by modulating DA neurotransmission. TRPV3 agonists (carvacrol and thymol) present in certain spices drive reward anticipation. Research has indicated that TRPV3 is expressed in the substantia nigra pars compacta, which is rich in dopaminergic neurons and lies adjacent to the VTA (Guatteo et al., 2005), although these regions differ in localization and function.. Because TRPV channels modulate activity within mesolimbic DA neurons, they have emerged as novel targets for modulation of the reward circuitry. Capsaicin (a TRPV1 agonist) has been found to modulate dopaminergic neurotransmission in the mesolimbic pathway, likely via presynaptic glutamate release (Marinelli et al., 2005). Some exogenous modulators of TRPV3 (thymol and carvacrol), are TRPV3 agonists (Vogt-Eisele et al., 2007; Xu et al., 2006). These components can be found in spices such as oregano, possibly playing a role in cravings for pleasurable food. Studies have indicated that carvacrol modulates activity in the reward system by altering dopaminergic neurotransmission (Melo et al., 2011; Zotti et al., 2013) and stimulating DA projections from the NAc to the VTA (as shown in Fig. 2). A recent study reported the effects of TRPV3 inhibition on palatable food reward anticipation and expression of TRPV3 in dopaminergic neurons of the NAc and VTA. The use of TRPV3 agonists (thymol and carvacrol) increased active lever pressing during operant conditioning. However, these effects were reversed by the administration of selective D1 and D2 antagonists (SCH23390, sulpiride respectively) (Singh et al., 2016). Furthermore, TRPV1 channels are co-expressed in proopiomelanocortin (POMC) neurons arcuate nucleus (ARC) of hypothalamus (feeding area) and regulates body temperature and feeding behavior in mice. Ontogenetic stimulation of POMC neurons expressing TRPV1 channels decreased feed intake (Jeong et al., 2018). These findings suggest that targeting TRPV channels in the reward system represents a viable, novel approach to the treatment of disorders such as obesity, metabolic syndrome, drug-induced hyperphagia and weight gain.

6. Conclusion

TRP channels are widely distributed throughout the brain, playing roles in diverse physiological functions. TRPV channels have been well explored in the CNS, and have been implicated in many NPDs, including stress, anxiety, depression, bipolar disorder, schizophrenia and different forms of addiction. TRPV1 and TRPV3 channels modulate dopaminergic neurotransmission in many areas of the brain mainly in the mesolimbic dopaminergic pathways (VTA to nucleus accumbens) and are associated with active reward anticipation. Inhibition of TRPV/TRPV3channels may represent a novel pharmacotherapeutic approach to the teratment of neuropsychiatric disorders, substance abuse and addiction.

Conflicts of interest

Authors have none to declare.

Author's contribution

Raghunath Singh: Conceptualized and wrote the manuscript.

Yashika Bansal: Formatted the manuscript and provided graphical inputs.

Ishwar Parhar, Tomoko Soga and Anurag Kuhad: Supervised the

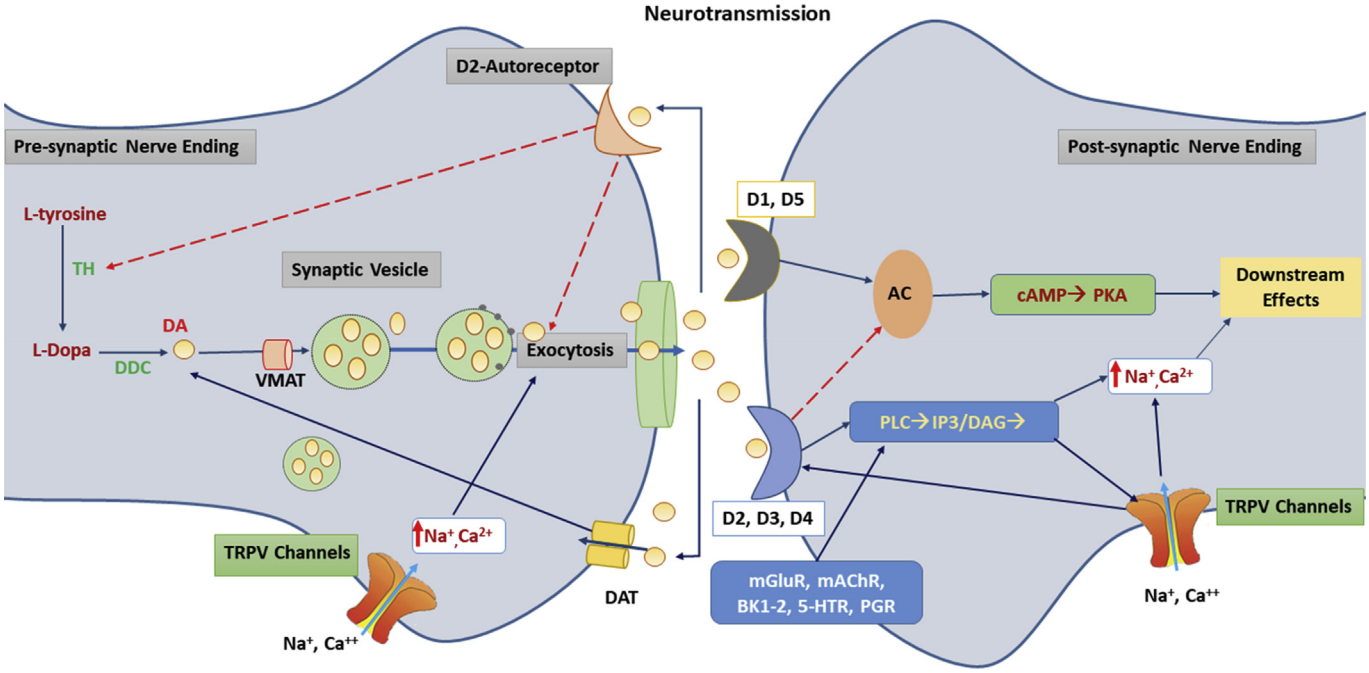

Fig. 2. Possible involvement of TRPV channels on Dopaminergic neurotransmission. TRPV channels mainly TRPV3 present pre-synaptically, while TRPV1 has been reported to present on post-synaptic nerve terminals. TRPV1 mad V3 also present on DAergic neurons increases the influx of Ca^{++} which promotes exocytosis and subsequent release of DA while postsynaptic TRPV channels activated by IP3/DAG, increases intracellular Ca^{++} and also sensitizes DA receptors. DA (Dopamine) DAT (dopamine transporter), TH (Tyrosine hydroxylase, VMAT (vascular monoamine transporter), AC (adenylyl cyclase), PLC (Phospholipase C), cAMP (cyclic adenosine monophosphate), PKA (Protein kinase A), TRPV (transient receptor protein vanilloid) mGluR (metabotropic glutamatergic receptor), mAChR (muscarinic acetylcholine receptors), BK1-2 (bradykinin 1-3), 5-HTR (5-HT receptors), PGR (prostaglandin receptor).

entire work.

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