Title	Supraspinal transient receptor potential subfamily V member 1 (TRPV1) in pain and psychiatric disorders
Author(s)	Madasu, M.K.; Roche, Michelle; Finn, David P.
Publication Date	2015
Publication Information	Madasu, M.K., Roche, Michelle, & Finn, David P. (2015). Supraspinal Transient Receptor Potential Subfamily V Member 1 (TRPV1) in Pain and Psychiatric Disorders. In David P. Finn & Brian E. Leonard (Eds.), Pain in Psychiatric Disorders: Modern Trends Pharmacopsychiatry (Vol. 30, pp. 80-93). Basel: Karger.
Publisher	Karger
Link to publisher's version	https://doi.org/10.1159/000435934
Item record	http://hdl.handle.net/10379/15075
DOI	http://dx.doi.org/10.1159/000435934

Supraspinal TRPV1 in Pain and Psychiatric Disorders

Manish K. Madasu[1,3], Michelle Roche[2,3], *David P. Finn[1,3].

[1]Pharmacology and Therapeutics, [2]Physiology, School of Medicine [3]Galway Neuroscience Centre and Centre for Pain Research, NCBES, National University of Ireland, Galway, Ireland

*Corresponding author

Prof. David P. Finn, Pharmacology and Therapeutics, School of Medicine, University Road, National University of Ireland, Galway, Ireland. Tel. +353 91 495280; Fax +353 91 495586 Email: david.finn@nuigalway.ie

URL: http://www.nuigalway.ie/pharmacology/professor_david_finn.html

Short Running title: TRPV1 in Pain and Psychiatry

Abstract:

The Transient Receptor Potential Subfamily V Member 1 (TRPV1) belongs to the diverse group of the transient receptor potential (TRP) family of cation channels. It was first characterized in primary afferent fibers as a receptor for capsaicin. Peripheral TRPV1 has a very well-described role in nociception. However, TRPV1 is now recognized to have a broader distribution and function, with supraspinal TRPV1 known to modulate pain processing. Recently, studies employing histological, genetic and pharmacological approaches have provided evidence that supraspinal TRPV1 also modulates brain neurobiology and behaviours related to anxiety, depression and schizophrenia. Key brain regions involved in TRPV1-mediated modulation of pain and affect include the periaqueductal grey, hippocampus and medial prefrontal cortex. Thus, TRPV1 in the brain is emerging as an important molecular substrate which is dually implicated in both pain and psychiatric disorders and represents a novel therapeutic target for these conditions and their co-morbidity.

1. Introduction to TRPV1

Although first identified as the receptor for capsaicin, Transient Receptor Potential Subfamily V Member 1 (TRPV1) can also be activated endogenously by voltage, noxious heat (>42°C), low pH and lipoxygenase products. Capsaicin is the naturally occurring pungent constituent of capsicum peppers used in many hot/spicy foods. TRPV1 expressed on primary afferent neurones that detect and encode noxious stimuli can be activated by capsaicin, resulting in neuronal excitation and release of local inflammatory mediators [1]. Endocannabinoids/endovanilloids, including anandamide and N-arachidonoyl dopamine, are endogenous ligands that can also activate TRPV1. TRPV1 nonselectively gates cations; however, channel activation results in a 10-fold higher preference for calcium [2,3,4].

TRPV1 is comprised of six transmembrane domains and intracellular N- and C-termini. The N-terminal tail contains numerous phosphorylation sites and ankyrin repeats that serve as binding sites for calmodulin and adenosine triphosphate (ATP) [5]. The C-terminal tail contains a TRP domain as well as binding sites for both calmodulin and phosphatidylinositol (4,5)-bisphosphate (PIP2), an endogenous TRPV1 inhibitor [6]. Agonist binding and receptor activation can occur intracellularly, as lipophilic capsaicin readily crosses the membrane to bind several sites on TRPV1 [7]. TRPV1 is expressed highly in the dorsal root ganglia (DRG) of C- and Aδ- fibers. In these fibres, TRPV1 activation leads to increases in intracellular calcium levels which in turn induces the release of neuropeptides (calcitonin-gene-related peptide and substance P) in the dorsal horn of the spinal cord [8].

Studies in rat and primate brain have shown that TRPV1 is widely expressed throughout the neuroaxis, including the cortex, hippocampus, basal ganglia, cerebellum and olfactory bulb, as well as in the mesencephalon and hindbrain [9,10]. Studies of the distribution of TRPV1 in human brain have been more restricted, but a post-mortem study has shown that TRPV1 receptors have been found in the third and fifth layers of the human parietal cortex [9]. However, overall TRPV1

expression in the central nervous system (CNS) is considerably lower than in the DRG [10, 11, 12, 13]. Indeed, some studies have failed to detect the presence of TRPV1 in the CNS [1,14,15,16] possibly due to complexity in genes and strain-related variations [11,17]. A sophisticated gene strategy where the TRPV1 gene was targeted by attaching two reporters, PLAP (placental alkaline phosphatase) and nlacZ (nuclear lacZ), onto the TRPV1 promoter gene and creating a specific line of mice ($TRPV1^{PLAP\text{-}nlacZ}$) was used to confirm TRPV1 expression in the CNS. This study reported that TRPV1 expression in the CNS is limited to certain brain regions and low when compared to expression in DRG [12]. This restricted expression of TRPV1 in the CNS was confirmed by *in situ* hybridization experiments in rat, monkey and human brain [12]. However, a number of recent pharmacological, genetic, radioligand binding and immunohistochemical studies suggest widespread distribution and functionality of TRPV1 across the CNS [11,12,18,19,20].

2. Role of TRPV1 in the brain

2.1. Pain

2.1.1. Acute pain

The PAG-RVM (periaqueductal grey - rostral ventromedial medulla) pathway is very important in pain processing and modulation. PAG-mediated antinociception involves the recruitment of pain-modulating RVM neurons via the descending pain pathway [21]. The existence of TRPV1 in the midbrain has been demonstrated by immunohistochemistry [9, 22, 23,], *in-situ* hybridization (ISH) [9], binding of the TRPV1-selective radioligand [3H]- resiniferatoxin (RTX) [24] and gene reporter studies [12]. The RVM contains three different types of pain-responsive neurons: “neutral cells”, which show no modification in spontaneous activity associated with nociceptive stimulation; ON cells, which show a burst of activity before withdrawal reflexes; and OFF cells, which are inhibited just before withdrawal reflexes [25,26,27]. Capsaicin, when injected into the

dorsolateral periaqueductal grey (dlPAG), increased the latency of nociceptive responding to noxious heat, indicating that stimulation of TRPV1 within the descending inhibitory pain pathway can cause antinociception [28]. Microinjection of capsaicin into the venterolateral periaqueductal grey (vlPAG) increased the threshold of thermal pain sensitivity in rats [29]. Opposite effects were found with 5-iodo-resiniferatoxin [I-RTX], a selective TRPV1 antagonist that facilitated nociceptive responses and, at an inactive dose, abolished capsaicin-mediated antinociception, implying that the effect of capsaicin is mediated by TRPV1 in the vlPAG [29]. The antinociceptive effect of intra-vlPAG capsaicin was accompanied by an increase in glutamate release in the RVM as measured by *in vivo* microdialysis, which was also blocked by a *per se* inactive dose of I-RTX. The TRPV1 antagonist itself reduced the release of glutamate, thus suggesting that vlPAG TRPV1 tonically stimulates glutamatergic output to the RVM with a concomitant inhibition of nociception [29]. Hyperalgesia or analgesia have been observed following intra-vlPAG administration of the fatty acid amide hydrolase inhibitor (FAAH) URB597 depending on whether vlPAG cannabinoid receptors or TRPV1 have been activated [30]. It was proposed that anandamide-mediated activitation of TRPV1 leads to analgesia, while hyperalgesia may be due to increases in vlPAG 2-arachidonoylglycerol (2-AG) leading to CB_1 receptor stimulation which in turn leads to inhibition of the antinociceptive PAG-RVM descending pathway [30].

The ON and OFF neurons in the RVM have been shown to respond to capsaicin administered into the PAG [29,30,31]. Intra-dlPAG microinjection of capsaicin is followed by a decrease in the tail flick-related ON cell burst activity and an increase in the tail flick latency [31]. Later on, due to desensitization of the receptor (due to prolonged exposure to capsaicin), antinociception correlating with increased OFF cell activity was reported [31]. Similarly, Starowicz et al. (2007) have shown that intra-vlPAG administration of capsaicin caused a decrease in the firing activity of RVM ON cells, and an increase in the firing of the OFF cells [29]. Moreover, microinjections of

capsaicin into the vlPAG have also been shown to increase withdrawal latency in the rat hot-plate test, with evidence that activation of TRPV1 in the vlPAG induces antinociception via mGlu receptor-mediated 2-AG retrograde signalling in the RVM [32]. Intra-vlPAG administration of the FAAH inhibitor, URB597 which is known to enhance endogenous anandamide levels, stimulated OFF cell activity in the RVM and inhibited ON cell activity [30]. This effect on RVM activity was abolished by intra-vlPAG administration of the TRPV1 antagonist capsazepine, suggesting that FAAH substrates (likely anandamide) activate TRPV1 on vlPAG neurons, with projections from the PAG to the RVM mediating the subsequent stimulation of RVM OFF cells and inhibition of ON cells. De Novellis et al. administered N-arachidonoyl-serotonin (AA-5-HT), a compound with a dual ability to inhibit FAAH and block TRPV1, into the vlPAG, and measured endocannabinoid levels, RVM ON and OFF cell activities, thermal nociception in the tail flick test and formalin-induced nociceptive behaviour [33]. They found that AA-5-HT increased anadamide levels in the vlPAG and had antinociceptive effects in both the tail flick and formalin tests. Moreover, intra-vlPAG administration of AA-5-HT depressed the activity of both OFF cell and ON cells in the RVM. These effects of AA-5-HT were similar to those seen following co-administration of of the FAAH inhibitor URB597 and the selective TRPV1 antagonist I-RTX into the vlPAG [33]. The FAAH substrate, palmitoylethanolamide (PEA), when microinjected into the vlPAG of rats, was antinociceptive in the tail-flick test, concomitantly decreasing the ongoing activity of the OFF cells in the RVM and increasing the latency of tail flick-evoked onset of ON cell activity [34]. These latter effects on RVM cell activity were blocked by the TRPV1 antagonist I-RTX, suggesting that TRPV1 modulates PEA-induced effects within the PAG-RVM circuitry [34]. PEA does not directly bind to TRPV1, but through substrate competition at FAAH it can indirectly elevate AEA levels, which in turn may bind to TRPV1 and induce antinociception.

2.1.2. Chronic pain

Intracerebroventricular (i.c.v.) administration of the TRPV1 receptor antagonist, (1-[3 -(trifluoromethyl)pyridin-2-yl]-N-[4-(trifluoromethyl sulfonyl)phenyl]-1,2, 3,6-tetrahydropyridine-4-carboxamide, A-784168, significantly reduced weight bearing in the sodium monoiodoacetate model of osteoarthritis and reduced Complete Freund's Adjuvant-induced chronic inflammatory thermal hyperalgesia, suggesting that TRPV1 in the brain plays a key role in chronic inflammatory pain [35]. Furthermore, i.c.v. administration of the plant-derived alkaloid (-)cassine prevented mechanical hyperalgesia induced by carrageenan, an effect mediated by TRPV1 receptors [36]. Site-specific delivery of the dual TRPV1 and FAAH blocker, AA-5-HT, into the prelimbic-infralimbic cortex significantly decreased mechanical allodynia in the spared nerve injury (SNI) model of neuropathic pain in mice. [37]. Similarily, intra-cortical (prelimbic-infralimbic cortex) administration of AA-5-HT was more effective in reducing SNI-induced mechanical allodynia than I-RTX [38]. In addition, evidence suggests reciprocal alterations in TRPV1 and the CB_1 receptor mediate visceral hyperalgesia in water avoidance stressed rats [39]. Thus, while fewer studies have investigated the role of supraspinal TRPV1 in animal models of chronic pain versus acute pain, these studies together suggest involvement of supraspinal TRPV1 in the development and/or maintenance of both chronic inflammatory and neuropathic pain. Table 1 provides a summary of studies to date that have investigated the effects of intracerebral administration of TRPV1 ligands on nociceptive behaviour in animal models of acute and chronic pain

2.2. Psychiatric Disorders

2.2.1. TRPV1 and Anxiety

2.2.1.1. Generalized Anxiety Disorder (GAD)

The pharmacological studies summarised in Table 2 indicate that TRPV1 in the dorsal PAG (dPAG), the hippocampus (HPC), the medial prefrontal cortex (mPFC) and the basolateral amygdala (BLA) modulates anxiety-related behaviour in the rat/mouse elevated plus maze (EPM). Systemic injection of TRPV1 antagonists (capsazepine and SB-366791) or agonist (Olvanil) has been shown to produce anxiolytic or anxiogenic effects, respectively, in the EPM [40,41]. TRPV1 KO mice exhibit an anxiolytic phenotype, suggesting that TRPV1 plays a role in anxiety-related behaviour [42]. Intra-ventromedial prefrontal cortex (vmPFC) injections of the TRPV1 antagonist capsazepine had an axiolytic effect in the EPM and Vogel conflict (VCT) tests and attenuated the expression of contextual fear conditioning in rats [43,44,45]. The role of TRPV1 was confirmed by administration of the TRPV1 antagonists 6-iodo-nordihydrocapsaicin and capsazepine [43,45]. Similar to the vmPFC, blockade of TRPV1 in the vHPC and dlPAG also elicited anxiolytic effects in the EPM [46,47].

2.2.1.2. Panic Disorder

The dlPAG is known for its role in coordinating freezing, fight and flight behaviors in threatening situations, such as the presence of a predator [50]. Evidence suggests that electrical stimulation of the dlPAG in humans induces symptoms similar to a panic attack [52]. Corroborating this finding, neuroimaging studies show increased dPAG activity in panic patients [53] or in healthy volunteers exposed to a proximal threatening stimulus such as predator exposure [54]. Panic-like responses can be modulated by several neurotransmitters including serotonin, GABA, glutamate and nitric oxide [55]. Several studies indicate the presence of TRPV1 in the PAG [Refer to section 2.1.1] which may influence the panic response. Local injection of the TRPV1 antagonists capsazepine or SB366791 into the dPAG attenuated panic-like behavior induced by electrical stimulation [47]. TRPV1 antagonism in the dlPAG had similar effects in three other animal models of panic induced by [i] local injection of the excitatory amino acid N-methyl-d-aspartate [NMDA], [ii]

local injection of the nitricoxide donor SIN-1, and [iii] exposure to the open arms of the elevated T-maze [56,57]. These results suggest that TRPV1 in the dlPAG facilitates defensive responses in threatening situations.

2.2.1.3. Obsessive compulsive disorder (OCD)

Marble-burying behaviour (MBB) is a commonly used model for assessing compulsive activity in rodents [59]. Studies indicate that the burying behaviour in rodents is an unconditioned, species-specific defensive reaction which is not associated with physical danger, and to which animals do not habituate upon repeated testing. Thus, MBB models some of the clinical symptoms of obsessive compulsive disorder (OCD) which is characterized by recurrent obsessions or compulsions that severely impair daily routine.

A recent study by Umathe et al. (2012) investigated the effects of capsaicin and capsazepine, administered i.c.v., on MBB. This study revealed that capsaicin produced compulsive effects (increased marble buying), similar to those of high-dose anandamide, whereas capsazepine dose-dependently decreased the burying behaviour [60]. These observations support the hypothesis that central TRPV1 might mediate the pro-compulsive effect of high doses of anandamide. Central administration of lower doses of anandamide, or drugs that elevate levels of anandamide (AM404/URB597), inhibited MBB, suggesting anti-compulsive effects [60]. Pretreatment with a CB_1 receptor antagonist (i.c.v.) abolished the anti-compulsive effect of anandamide whereas the TRPV1 antagonist capsazepine blocked the procompulsive effect of higher doses of anandamide [60]. Therefore these results suggest that TRPV1 activation leads to an increase in OCD-like behaviour, with blockade of TRPV1 alleviating such behaviour. Further research employing additional animal models is required to determine the precise role of central TRPV1 in regulation of compulsive behaviour. Overall, preclinical studies show that TRPV1 plays a key role in anxiety-related behaviour. Given the high degree of co-morbidity between anxiety disorders and

chronic pain, and overlap in the TRPV1-expressing neuroanatomical substrates involved in both anxiety and pain, it is likely that TRPV1 also plays an important role in anxiety-pain interactions and further research in this area is warranted. Figure 1 represents a synthesis of the pain and anxiety literature reviewed above.

[Insert Figure 1 here]

2.2.2. TRPV1 and Depression

TRPV1 antagonists, administered systemically, have been shown to produce antidepressant-like effects in both rats and mice, suggesting a role for TRPV1 in depression [40,61-64]. In the forced swim test, TRPV1 KO mice displayed lower immobility when compared to wild type mice, indicating less behavioural despair in mice lacking TRPV1 [61]. Similarily, systemic administration of the TRPV1 antagonist capsazepine decreased the immobility time in a dose-dependent manner in the forced swim test [64]. Another paradigm for assessment of antidepressant-like activity is novelty-supressed feeding. In this test, TRPV1 KO mice have decreased latency times when compared to wild type mice, indicating an antidepressant phenotype [61]. Capsazepine is known to enhance antidepressant activity when administered to fluoxetine-treated mice at a sub-threshold dose in the forced swim test [63]. Desensitization of supraspinal TRPV1 has also been shown to produce an antidepressant-like effect, as evidenced by the reduction in immobility time in the mouse forced swim test following i.c.v.injection of capsaicin at a dose that would have densitized the receptor [63]. Further evidence for involvement of central TRPV1 comes from work demonstrating that intrathecal injections of a TRPV1-desensitising dose of the agonist RTX also reduced immobility in the mouse forced swim test and inhibited the immobility induced by a lower dose of RTX [65]. Moreover, the antidepressants, amitriptyline and ketamine, administered intraperitoneally, inhibited the increase in forced swim test immobility (water at 41^{o}C) induced by a low dose of RTX administered subcutaneously [65]. These workers also demonstrated that water at 41°C elicited less immobility than cooler water (26 °C), indicating

that thermoregulatory sites do not contribute to immobility in the forced swim test. Finally, systemic administration of the TRPV1 agonist olvanil reduced immobility in the rat forced swim test due to desensitisation [40].

2.2.3. TRPV1 and schizophrenia

Schizophrenia is a neurodevelopmental disorder and while there is currently a paucity of data directly linking TRPV1 to schizophrenia, there is evidence that TRPV1 plays a role in brain development. In this regard, potential links between TRPV1 and schizophrenia include dopaminergic mechanisms and cannabinoid mechanisms.

2.2.3.1. Effect of capsaicin treatment on rat brain development

Deficits in pain sensation and altered vascular responsivity (flare response) to niacin have been reported in schizophrenic patients [66-69]. The subset of primary afferent neurons involved in both pain and flare responses is primary afferent fibres which are sensitive to capsaicin treatment i.e. TRPV1-containing afferents. Thus, patients with schizophrenia might have an abnormality in capsaicin-sensitive primary afferent neurons. Reduced neuropil (neuron density pertaining to brain grey matter) count which is seen in schizophrenic patients might also be due to reduced synaptic density in cortical regions arising from deficits in input from capsaicin-sensitive peripheral neurons [70,71]. This hypothesis was recently tested in rats treated as neonates with capsaicin to destroy primary afferent neurons, which in turn would lead to an intrinsic somatosensory deprivation [72]. Within 5-7 weeks, locomotor activity in a novel environment was increased in rats that had been treated with capsaicin as neonates. Reduced brain weight was also observed, with a substantial decrease in the weight of the hippocampus and increase in neuronal density in cortical areas [72]. The changes reported were similar to those seen in schizophrenic subjects [72]. These findings suggest that neonatal capsaicin treatment may be useful for modelling aspects of

schizophrenia. Recently, Newson et al. investigated the brain and behavioral responses in adult rats treated as neonates with capsaicin [73]. The brain changes found at 5-7 weeks persisted in adult rats of 12 weeks, but diminished in older rats of 16-18 weeks. The rats exhibited increases in prepulse inhibition of acoustic startle at the age of 8 and 12 weeks. The study also reported that cutaneous plasma extravastation responses to niacin and prostaglandin D2 were reduced in capsaicin-treated rats [72]. The neuroanatomical changes and reduced cutaneous plasma extravastation responses in capsaicin-treated rats resemble those observed on schizophrenic patients and suggest a potential role for TRPV1 in this psychiatric disorder.

2.2.3.2. TRPV1 and dopaminergic mechanisms:

Dopaminergic system hyperactivity is known to underlie the positive symptoms in schizophrenia [74]. As previously highlighted, TRPV1 has been identified in the cortex, hippocampus, basal ganglia, cerebellum, olfactory bulb, mesencephalon and hindbrain [9,10]. In rat brain slices, activation of TRPV1 by capsaicin increases the rate of firing of dopamine neurons of the midbrain ventral tegmental area (VTA) in a concentration-dependent manner [75]. Furthermore, *in vivo* experiments showed that microinjection of capsaicin into the VTA transiently increased dopamine release in the nucleus accumbens. Dopamine release by intra-VTA administration of capsaicin was inhibited by the selective TRPV1 receptor antagonist, iodoresiniferatoxin, suggesting a role for mesencephalic TRPV1 in dopaminergic transmission [75]. Regulation of dopaminergic signalling in the brain's reward circuitry implies that TRPV1 could represent an important target for schizophrenia, affective disorders and addiction.

2.2.3.3. TRPV1 and cannabinoid mechanisms

A link between cannabis use and early onset of the first episode of psychosis has been proposed, but the mechanisms that lead to psychosis are still unknown [76,77,78]. Systemic administration of the selective endocannabinoid reuptake inhibitors AM404 and VDM11 or the FAAH and TRPV1

inhibitor AA-5HT, attenuated spontaneous hyperlocomotion in dopamine transporter KO mice. These hypolocomotor effects were significantly attenuated by co-administration of the TRPV1 antagonist capsazepine [79], highlighting an important role for TRPV1 in these responses. Recently cannabidiol a non-psychotropic plant cannabinoid known to desensitize TRPV1 *in-vitro* in epileptiform activity [80] may have therapeutic potential in psychosis, but the mechanisms underlying that effect are not clear and recent studies hypothesize that TRPV1 might be involved, alongside CB_1 receptors [81].

3. Summary and conclusion

The evidence for a role of central TRPV1 in pain and neuropsychiatric disorders has been reviewed and discussed herein. Study of the role of TRPV1 in neuropsychiatric disorders is still at an early stage. There is a clear overlap of brain regions dually implicated in TRPV1-mediated modulation of both neuropsychiatric disorders and pain. As such, alterations in the function of TRPV1 may underlie the pathophysiology of psychiatric and chronic pain conditions and their comorbidity. However, no studies to date have investigated the role of TRPV1 in this comorbidity and it is an obvious area for future research. In addition, further studies (preclinical and clinical) are needed to elucidate the precise neurobiological mechanisms through which supraspinal TRPV1 modulates pain and affect. Progress in these areas may pave the way towards TRPV1-targeting therapeutics for the treatment of pain and psychiatric disorders, and their comorbidity.

Acknowledgements

This work was funded by grants from Science Foundation Ireland (10/IN.1/B2976) and a PhD Scholarship from the College of Science, National University of Ireland Galway.

Figure legend

Figure 1. A synthesis of the literature reviewed herein on the role of TRPV1 in discrete brain regions in pain and anxiety related behaviour. Green coloured text indicates the activation of TRPV1 in that brain region and red colour indicates the blockade/desensitization of the receptor in that brain region. ↑ denotes an increase in anxiety/pain related behaviour and ↓ denotes a decrease in anxiety/pain related behaviour. * denotes initial activation of the receptor followed by desensitisation. Blue shading of a brain region denotes anxiety-related studies of TRPV1 in that region and brown shading denotes pain-related studies of TRPV1 in that region. dlPAG: dorsolateral periaqueductal gray, dPAG: dorsal periaqueductal gray, mPFC: medial prefrontal cortex, vHPC: ventral hippocampus, dHPC: dorsal hippocampus, BLA: basolateral amygdala, RVM: rostral ventromedial medulla, PL-IL: prelimbic-infralimbic cortex.

References:

1. Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, Petersen-Zeitz KR, Koltzenburg M, Basbaum AI, Julius D: Impaired nociception and pain sensation in mice lacking the capsaicin receptor. Science 2000; 288:306–313.
2. Julius D: TRP channels and pain. Annu Rev Cell Dev Biol 2013; 29: 355-384.
3. Szallasi A & Sheta M: Targeting TRPV1 for pain relief: limits, losers and laurels. Expert Opin Investig Drugs 2012; 21:1351–1369.
4. Ho KW, Ward NJ, Calkins DJ: TRPV1: a stress response protein in the central nervous system. Am J Neurodegener Dis 2012; 1(1): 1-14.
5. Lishko PV, Procko E, Jin X, Phelps CB, Gaudet R: The ankyrin repeats of TRPV1 bind multiple ligands and modulate channel sensitivity. Neuron 2007; 54:905–918.

6. Garcia-Sanz N, Fernandez-Carvajal A, Morenilla-Palao C, Planells-Cases R, Fajardo-Sanchez E, Fernandez-Ballester G, Ferrer-Montiel A: Identification of a tetramerization domain in the C terminus of the vanilloid receptor. J Neurosci 2004; 24:5307–5314.
7. Jung J, Hwang SW, Kwak J, Lee SY, Kang CJ, Kim WB, Kim D, Oh U: Capsaicin binds to the intracellular domain of the capsaicin-activated ion channel. J Neurosci 1999; 19:529–538.
8. Price TJ, Louria MD, Candelario-Soto D, Dussor GO, Jeske NA, Patwardhan AM, Diogenes A, Trott AA, Hargreaves KM, Flores CM: Treatment of trigeminal ganglion neurons in vitro with NGF, GDNF or BDNF: effects on neuronal survival, neurochemical properties and TRPV1-mediated neuropeptide secretion. BMC Neurosci 2005; 6:4.
9. Mezey E, Toth ZE , Cortright DN, Arzubi MK, Krause JE, Elde R, Guo A, Blumberg PM, Szallasi A: Distribution of mRNA for vanilloid receptor subtype 1 (VR1), and the VR1-like immunoreactivity in the central nervous system of the rat and human Proc Natl Acad Sci U.S.A. 2000; 3655–3660
10. Szabo T, Biro T, Gonzalez AF, Palkovits M, Blumberg PM: Pharmacological characterization of vanilloid receptor located in the brain Brain Res. Mol Brain Res 2000; 51–57
11. Sanchez, JF, Krause JE, Cortright DN: The distribution and regulation of vanilloid receptor VR1 and VR1 5' splice variant RNA expression in rat. Neurosci 2001; 107:373–381.
12. Cavanaugh DJ, Cavanaugh DJ, Chesler AT, Jackson AC, Sigal YM, Yamanaka H, Grant R, O'Donnell D, Nicoll RA, Shah NM, Julius D, Basbaum AI: Trpv1 reporter mice reveal highly restricted brain distribution and functional expression in arteriolar smooth muscle cells. The Journal of neuroscience : the official journal of the Society for Neuroscience 2011;31(13):5067-77. doi:10.1523/JNEUROSCI.6451-10.2011

13. Han L, Ma C, Liu, Q, Weng HJ, Cui Y, Tang Z, Kim, Y, Nie H, Qu L, Patel KN, Li Z, McNeil B, He S, Guan Y, Xiao B, Lamotte RH, Dong X. A subpopulation of nociceptors specifically linked to itch. Nat. Neurosci. 2013, 16, 174–182.Benninger F, Freund, T.F., Hajos, N., 2008. Control of excitatory synaptic trans-mission by capsaicin is unaltered in TRPV1 vanilloid receptor knockout mice.Neurochem. Int. 52, 89–94.
14. Benninger F, Freund TF, Hajos N: Control of excitatory synaptic transmission by capsaicin is unaltered in TRPV1 vanilloid receptor knockout mice. Neurochem. Int. 2008; 52: 89–94.
15. Szallasi A :Autoradiographic visualization and pharmacological characterization of vanilloid (capsaicin) receptors in several species, including man. ActaPhysiol. Sc and. Suppl 1995; 629: 1–68.
16. Tominaga M, Caterina, MJ, Malmberg, AB, Rosen, TA, Gilbert H, Skinner K, Raumann BE, Basbaum AI, Julius D: The cloned capsaicinreceptor integrates multiple pain-producing stimuli. Neuron 1998; 21:531–543.
17. Sudbury JR, Ciura S, Sharif-Naeini R, Bourque CW: Osmotic and thermal control of magnocellular neurosecretory neurons-role of an N-terminal variant of TRPV1. Eur. J. Neurosci. 2010; 32:2022–2030.
18. Goswami N, Rademacher KH, Smalla V, Kalscheuer HH, Ropers ED, Gundelfinger T, Hucho. TRPV1 acts as a synaptic protein and regulates vesicle recycling J. Cell Sci 2010;123:2045–2057.
19. O'Sullivan GJ, O'Tuathaigh CM, Clifford JJ, O'Meara GF, Croke DT, Waddington JL: Potential and limitations of genetic manipulation in animals Drug Discov. Today Technol 2006;3:173–180
20. Han P, Korepanova AV, Vos MH, Moreland RB, Chiu ML, Faltyneck CR: Quantification of TRPV1 protein levels in rat tissues to understand its physiological roles J. Mol. Neurosci 2013;15: 23–32

21. Bajic D,Proudfit HK: Projections of neurons in the periaqueductal gray to pontine and medullary catecholamine cell groups involved in the modulation of nociception. J. Comp. Neurol 1999; 405: 359–379.
22. Tóth A, Boczan J, Kedei N, Lizanecz E, Bagi Z, Papp Z, Edes I, Csiba L, Blumberg PM: Expression and distribution of vanilloid receptor 1 (TRPV1) in the adult rat brain Brain Res. Mol. Brain Res 2005; 135: 162–168
23. Cristino L, de Petrocellis L, Pryce G, Baker D, Guglielmotti V, Di Marzo V: Immunohistochemical localization of cannabinoid type 1 and vanilloid transient receptor potential vanilloid type 1 receptors in the mouse brain Neuroscience 2006;139: 1405–1415
24. Roberts JC, Davis JB, Benham CD: [3H]Resiniferatoxin autoradiography in the CNS of wild-type and TRPV1null mice defines TRPV1 (VR-1) protein distribution. Brain Res 2004;195:176–183
25. Fields HL: State-dependent opioid control of pain. Nat Rev Neurosci 2004;5:565–575.
26. Fields HL, Bry J, Hentall I, Zorman G :The activity of neurons in the rostral medulla of the rat during withdrawal from noxious heat. J Neurosci 1983; 3:2545–2552.
27. Fields HL, Heinricher MM, Mason P. Neurotransmitters in nociceptive modulatory circuits. Annu Rev Neurosci 1991;14:219 –245.
28. Palazzo E, de Novellis V, Marabese I, Cuomo D, Rossi F, Berrino L, Rossi F, Maione S: Interaction between vanilloid and glutamate receptors in the central modulation of nociception. Eur. J. Pharmacol. 2002; 439: 69–75.
29. Starowicz K, Maione S, Cristino L, Palazzo E, Marabese I, Rossi F, de Novellis V, and Di Marzo V: Tonic endovanilloid facilitation of glutamate release in brainstem descending antinociceptive pathways. J Neurosci. 2007; 27:13739–13749.
30. Maione S, Bisogno T, de Novellis V, Palazzo E, Cristino L, Valenti M, Petrosino S, Guglielmotti V, Rossi F, Di Marzo V: Elevation of endocannabinoid levels in the

ventrolateral periaqueductal grey through inhibition of fatty acid amide hydrolase affects descending nociceptive pathways via both cannabinoid receptor type 1 and transient receptor potential vanilloid type-1 receptors. J. Pharmacol. Exp. Ther. 2006; 316: 969–982.

31. McGaraughty S, Chu KL, Bitner RS, Martino B, El Kouhen R, Han P, Nikkel AL, Burgard EC, Faltynek CR, Jarvis MF: Capsaicin infused into the PAG affects rat tail flick responses to noxious heat and alters neuronal firing in the RVM. J. Neurophysiol. 2003;90: 2702–2710.
32. Liao HT, Lee HJ, Ho YC, Chiou LC: Capsaicin in the periaqueductal gray induces analgesia via metabotropic glutamate receptor-mediated endocannabinoid retrograde disinhibition. Br J Pharmacol 2011; 163(2): 330-345.
33. de Novellis V, Palazzo E, Rossi F, De Petrocellis L, Petrosino S, Guida F, Luongo L, Migliozzi A, Cristino L, Marabese I, Starowicz K, Di Marzo V, Maione S: The analgesic effect of N-arachidonoyl-serotonin, a FAAH inhibitor and TRPV1 receptor antagonist, associated with changes in rostral ventromedial medulla and locus coeruleus cell activity in rats. Neuropharmacology 2008; 55(7): 1105-1113.
34. de Novellis V, Luongo L, Guida F, Cristino L, Palazzo E, Russo R, Marabese I, D'Agostino G, Calignano A, Rossi F, Di Marzo V, Maione S: Effects of intra-ventrolateral periaqueductal grey palmitoylethanolamide on thermoceptive threshold and rostral ventromedial medulla cell activity. Eur J Pharmacol 2012;676(1-3): 41-50
35. Cui M, Honore P, Zhong C, Gauvin D, Mikusa J, Hernandez G, Chandran P, Gomtsyan A, Brown B, Bayburt EK, Marsh K, Bianchi B, McDonald H, Niforatos W, Neelands TR, Moreland RB, Decker MW, Lee CH, Sullivan JP, Faltynek CR: TRPV1 receptors in the CNS play a key role in broad-spectrum analgesia of TRPV1 antagonists. J. Neurosci. 2006;26:9385–9393.

36. da Silva KA, Manjavachi MN, Paszcuk AF, Pivatto M, Viegas C Jr, Bolzani VS, Calixto JB:Plant derived alkaloid (-)-cassine induces anti-inflammatory and anti-hyperalgesics effects in both acute and chronic inflammatory and neuropathic pain models.Neuropharmacology 2012; 62(2): 967-977
37. Giordano C, Cristino L, Luongo L, Siniscalco D, Petrosino S, Piscitelli F, Marabese I, Gatta L, Rossi F, Imperatore R, Palazzo E, de Novellis V, Di Marzo V, Maione S: TRPV1-dependent and -independent alterations in the limbic cortex of neuropathic mice: impact on glial caspases and pain perception.Cereb Cortex 2012; 22(11): 2495-2518.
38. de Novellis V, Vita D, Gatta L, Luongo L, Bellini G, De Chiaro M, Marabese I, Siniscalco D, Boccella S, Piscitelli F, Di Marzo V, Palazzo E, Rossi F, Maione S: The blockade of the transient receptor potential vanilloid type 1 and fatty acid amide hydrolase decreases symptoms and central sequelae in the medial prefrontal cortex of neuropathic rats. Mol Pain 2011; 7: 7
39. Hong S, Fan J, Kemmerer ES, Evans S, Li Y, Wiley JW. Reciprocal Changes in Vanilloid (TRPV1) and Endocannabinoid (CB1) Receptors Contribute to Visceral Hyperalgesia in the Water Avoidance Stressed Rat. Gut 2009;58(2):202-210. doi:10.1136.
40. Kasckow JW, Mulchahey JJ, Geracioti TD, Jr: Effects of the vanilloid agonist olvanil and antagonist capsazepine on rat behaviors. Progress in neuro-psychopharmacology & biological psychiatry. 2004; 28(2):291-5.(Sanchez, Krause et al. 2001)
41. Micale V, Cristino L, Tamburella A, Petrosino S, Leggio GM, Drago F, Di Marzo V: Anxiolytic effects in mice of a dual blocker of fatty acid amide hydrolase and transient receptor potential vanilloid type-1 channels. Neuropsychopharmacology : American College of Neuropsychopharmacology. 2009;34(3):593-606.

42. Marsch R, Foeller E, Rammes G, Bunck M, Kossl M, Holsboer F, Zieglgans-berger W, Landgraf R, Lutz B, Wotjak CT: Reduced anxiety, conditioned fear, and hippocampal long-term potentiation in transient receptor potentialvanilloid type 1 receptor-deficient mice. J. Neurosci. 2007; 27: 832–839.
43. Terzian AL, dos Reis DG, Guimaraes FS, Correa FM, Resstel LB. Medial prefrontal cortex Transient Receptor Potential Vanilloid Type 1 (TRPV1) in the expression of contextual fear conditioning in Wistar rats. Psychopharmacology. 2014;231(1):149-57.
44. Aguiar DC, Terzian AL, Guimaraes FS, Moreira FA. Anxiolytic-like effects induced by blockade of transient receptor potential vanilloid type 1 (TRPV1) channels in the medial prefrontal cortex of rats. Psychopharmacology. 2009;205(2):217-25. Epub 2009/04/24.
45. Rubino T, Realini N, Castiglioni C, Guidali C, Vigano D, Marras E, , Petrosino S, Perletti G, Maccarrone M, Di Marzo V, Parolaro D: Role in anxiety behavior of the endocannabinoid system in the prefrontal cortex. Cereb Cortex. 2008;18(6):1292-301.
46. Santos CJ, Stern CA, Bertoglio LJ:Attenuation of anxiety-related behaviour after the antagonism of transient receptor potential vanilloid type 1 channels in the rat ventral hippocampus. Behav. Pharmacol 2008;19: 357–360.
47. Terzian AL, Aguiar DC, Guimaraes FS, Moreira FA: Modulation of anxiety-like behaviour by Transient Receptor Potential Vanilloid Type 1 (TRPV1) channels located in the dorsolateral periaqueductal gray. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2009;19(3):188-95.
48. John CS, Currie PJ: N-arachidonoyl-serotonin in the basolateral amygdala increases anxiolytic behavior in the elevated plus maze. Behavioural brain research. 2012;233(2):382-8.

49. Hakimizadeh E, Oryan S, Hajizadeh Moghaddam A, Shamsizadeh A, Roohbakhsh A: Endocannabinoid system and TRPV1 receptors in the dorsal hippocampus of the rats modulate anxiety-like behaviors. Iran. J. Basic Med. Sci 2012; 15:795–802.
50. Mascarenhas DC, Gomes KS, Nunes-de-Souza RL: Anxiogenic-like effect induced by TRPV1 receptor activation within the dorsal periaqueductal gray matter in mice. Behavioural brain research. 2013;250:308-15.
51. Blanchard DC, Blanchard RJ: Defensive behaviors, fear and anxiety. In: Blan-chard, R.J., Blanchard, D.C., Griebel, G., Nutt, D. (Eds.): Handbook of Anxiety and Fear. 1st ed. Elsevier, 2008, Amsterdam, pp. 63–99.
52. Schenberg LC, Bittencourt AS., Sudre EC, Vargas LC: Modeling panic attacks. Neurosci. Biobehav. Rev 2001; 25: 647–659.
53. Del-Ben CM, Graeff FG: Panic disorder: is the PAG involved? Neural Plas.2009, 108135.
54. Mobbs D, Petrovic P, Marchant JL, Hassabis D, Weiskopf N, Seymour B, Dolan RJ, Frith CD: When fear is near: threat imminence elicits prefrontal periaqueductal gray shifts in humans. Science 2007; 317: 1079–1083.
55. Moreira FA, Guimaraes FS: Benzodiazepine receptor and serotonin 2A receptor modulate the aversive-like effects of nitric oxide in the dorsolateral periaqueductal gray of rats. Psychopharmacology (Berl)2004;176: 362–368.
56. Almeida-Santos AF, Moreira FA, Guimaraes FS, Aguiar DC. Role of TRPV1 receptors on panic-like behaviors mediated by the dorsolateral periaqueductal gray in rats. Pharmacology, biochemistry, and behavior. 2013;105:166-72.
57. Lisboa SF, Guimaraes FS: Differential role of CB1 and TRPV1 receptors on anandamide modulation of defensive responses induced by nitricoxide in the dorsolateral periaqueductal gray. Neuropharmacology 2012;62:2455–2462.

58. Casarotto PC, Terzian AL, Aguiar DC, Zangrossi H, Guimaraes FS, Wotjak CT, Moreira FA: Opposing Roles for Cannabinoid Receptor Type-1 (CB(1)) and Transient Receptor Potential Vanilloid Type-1 Channel (TRPV1) on the modulation of panic-like responses in rats. Neuropsychopharmacology 2012;37: 478–486.
59. Broekkamp C, Rijk HW, Joly-Gelouin D, Lloyd KL: Major tranquilizers can be distinguished from minor tranquillizers on the basis of effects on marble burying behavior and swim-induced grooming in mice. Eur. J. Pharmacol. 1986:126: 223-229.
60. Umathe SN, Manna SS, Jain NS. Endocannabinoid analogues exacerbate marble-burying behavior in mice via TRPV1 receptor. Neuropharmacology. 2012;62(5-6):2024-33.
61. You IJ, Jung YH, Kim MJ, Kwon SH, Hong SI, Lee SY, Jang CG: Alterations in the emotional and memory behavioral phenotypes of transient receptor potential vanilloid type 1-deficient mice are mediated by changes in expression of 5-HT(1)A, GABA(A), and NMDA receptors. Neuropharmacology 2012;62:1034–43.
62. Kulisch C, Albrecht D: Effects of single swim stress on changes in TRPV1-mediated plasticity in the amygdala. Behav Brain Res 2013;236:344–9.
63. Manna SS, Umathe SN: A possible participation of transient receptor potential vanilloid type 1 channels in the antidepressant effect of fluoxetine. Eur JPharmacol 2012;685:81–90.
64. Hayase T: Differential effects of TRPV1 receptor ligands against nicotine-induced depression-like behaviors. BMC Pharmacol 2011;11:6.
65. Abdelhamid RE, Kovács KJ, Nunez MG, Larson AA: Depressive behavior in the forced swim test can be induced by TRPV1 receptor activity and is dependent on NMDA receptors. Pharmacological Research. 2014;79(0):21-7.
66. Kudoh A, Ishihara H, Matsuki A: Current perception thresholds and postoperative pain in schizophrenic patients, Regional Anaesth. Pain Med. 2000; 25: 475–479.

67. Blumensohn R, Ringler D, Eli I: Pain perception in patients with schizophrenia, J. Nerv. Ment. Dis. 2002; 190: 481–483.

68. Waldo MC: Co-distribution of sensory gating and impaired niacin flush response in the parents of schizophrenics, Schizophrenia Res. 1999; 40:49–53.

69. Messamore E, Hoffman WE, Janowsky A: The niacin skin flush abnormality in schizophrenia: a quantitative dose–response study, Schizophrenia Res. 2003; 62: 251–258.

70. Selemon LD, Rajkowska G, Goldman-Rakic PS: Elevated neuronal density in prefrontal area 46 in brains from schizophrenic patients: application of a 3-dimensional, stereologic counting method, J. Comp. Neurol. 1998; 392:402–412.

71. Selemon LD, Goldman-Rakic PS: The reduced neuropil hypothesis: a circuit based model of schizophrenia, Biol. Psychiatry 1999; 45: 17–25.

72. Newson P, Lynch-Frame A, Roach R, Bennett S, Carr V, Chahl LA: Intrinsic sensory deprivation induced by neonatal capsaicin treatment induces changes in rat brain and behaviour of possible relevance to schizophrenia. Br. J. Pharmacol. 2005; 146: 408–418.

73. Newson PN, van den Buuse M, Martin S, Lynch-Frame A, Chahl LA: Effects of neonatal treatment with the TRPV1 agonist, capsaicin, on adult rat brain and behaviour. Behavioural Brain Research. 2014;272(0):55-65.

74. Carlsson, A. & M. Lindqvist: Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. Acta Pharmacol. Toxicol. 1963;20: 140-144.

75. Marinelli S, Pascucci T, Bernardi G, Puglisi-Allegra S, Mercuri NB: Activation of TRPV1 in the VTA excites dopaminergic neurons and increases chemical and noxious-induced dopamine release in the nucleus accumbens. Neuropsychopharmacology 2005;30: 864–870.

76. Weiser M, Noy S: Interpreting the association between cannabis use and increased risk for schizophrenia, Dialogues Clin. Neurosci. 2005; 7: 81–85.

77. Gambi F, De Berardis D, Sepede G, Quartesan R, Calcagni E, Salerno RM, Conti CM, Ferro FM, Cannabinoid receptors and their relationships with neuropsychiatric disorders, Int. J. Immunopathol. Pharmacol. 2005; 18:15–19.

78. Schuckit MA: Comorbidity between substance use disorders and psychiatric conditions. Addiction 2006; 101 (suppl.1): 76–88.

79. Tzavara ET, Li DL, Moutsimilli L, Bisogno T, Di Marzo V, Phebus LA, Nomikos GG, Giros B: Endocannabinoids activate transient receptor potential vanilloid 1 receptors to reduce hyperdopaminergia related hyperactivity: therapeutic implications. Biol. Psychiatry 2006; 59: 508–515.

80. Iannotti FA, Hill CL, Leo A, Alhusaini A, Soubrane C, Mazzarella E, Russo E, Whalley BJ, Di Marzo V, Stephens GJ :Nonpsychotropic Plant Cannabinoids, Cannabidivarin (CBDV) and Cannabidiol (CBD), Activate and Desensitize Transient Receptor Potential Vanilloid 1 (TRPV1) Channels in Vitro: Potential for the Treatment of Neuronal Hyperexcitability. ACS Chem Neurosci 2014;5(11): 1131-1141.

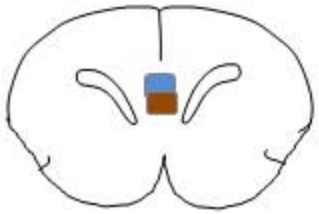
81. Campos A C, Moreira FA, Gomes FV, Del Bel EA, Guimarães FS: Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders. Philos Trans R Soc Lond B Biol Sci 2012;367(1607): 3364-3378.

Anxiety

Pain

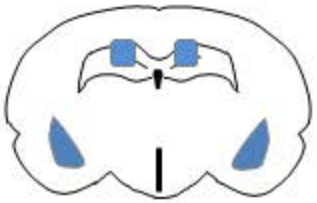
mPFC ↑

↓ PL-IL

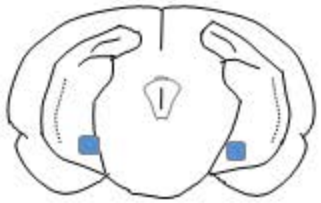


dHPC ↑

BLA ↓



vHPC ↓



DLPAG ↓

↓ *DPAG

↓ DLPAG

↓ VLPAG

↓ RVM

Drug and Dose	Route of admin /target region in CNS	Test/Effect on behaviour	Species	Reference
Capsaicin(1–3–6 nmol/rat)	i.c.(dlPAG)	Antinociceptive effect/thermosensitivity test	Rat	[28]
Capsazepine (6 nmol/rat)	i.c.(dlPAG)	Blocked the capsaicin-induced antinociception/thermosensitivity test	Rat	[28]
Capsaicin (6 nmol)	i.c.(vlPAG)	Antinociceptive effect/thermosensitivity test	Rat	[30]
Capsaicin (3 and 6 nmol/rat)	i.c.(vlPAG)	Antinociceptive effect/RVM extracellular recordings and tail flick test	Rat	[29]
I-RTX (0.5 and 1 nmol/rat)	i.c.(vlPAG)	Blocked the Antinociceptive effect of capsaicin/RVM extracellular recordings and tail flick test	Rat	[29]
Capsaicin (10 nmol)	i.c.(dPAG)	Initially produced hyperalgesia followed by analgesia/RVM extracellular recordings and tail flick test	Rat	[31]
Capsazepine (10 nmol)	i.c.(dPAG)	Blocked the hyperalgesic effect of capsaicin/RVM extracellular recordings and tail flick test	Rat	[31]
Capsaicin (6 nmol)	i.c.(vlPAG)	Antinociceptive effect/hot-plate test	Rat	[32]
SB 366791 (50 nmol)	i.c.(vlPAG)	Abolished Antinociceptive effect/hot-plate test	Rat	[32]

AA-5-HT (0.1–0.2–0.5 nmol)	i.c.(vlPAG)	Pro-nociceptive at lower doses and antinociceptive at higher doses/RVM extracellular recordings and tail flick test	Rat	[33]
I-RTX (0.5 nmol)	i.c.(vlPAG)	Blocked the AA-5-HT effects /RVM extracellular recordings and tail flick test	Rat	[33]
PEA (3 or 6 nmol)	i.c.(vlPAG)	Antinociceptive effect /RVM extracellular recordings and tail flick test	Rat	[34]
I-RTX (1 nmol)	i.c.(vlPAG)	Blocked the PEA induced effects /RVM extracellular recordings and tail flick test	Rat	[34]
A-784168(100nmol)	i.c.v	Reduced weight bearing/Sodium monoiodoacetate model of osteoarthritis	Rat	[35]
A-784168(100nmol)	i.c.v	Reduced CFA-induced chronic inflammatory thermal hyperalgesia/thermal test	Rat	[35]
Cassine (10 µg)	i.c.v	Blocked mechanical hyperalgesia/ carrageenan model	Rat	[36]
AA-5-HT (0.1-0.25-1 nmol),I-RTX (0.25-0.5-1 nmol)	Intra-cortical(PL-IL)	reducing mechanical allodynia /SNI model	Rat	[37,38]

Table 1: Effects of pharmacological modulation of supraspinal TRPV1 in animal models of pain.

i.c.: intracerebral, i.c.v: intracerebroventricular, dlPAG: dorsolateral periaqueductal gray, dPAG: dorsal periaqueductal gray, AA-5HT: N-arachidonoyl-serotonin, SB366791: N-(3-Methoxyphenyl)-4-chlorocinnamide, A-784168:1-[3 - (trifluoromethyl)pyridin-2-yl]-N-[4-(trifluoromethyl sulfonyl)phenyl]-1,2, 3,6-tetrahydropyridine-4-carboxamide,PL-IL:Prelimbic-Infralimbic cortex,SNI:Sp ared nerve injury.

Drug and Dose	Route of admin /target region in CNS	Test/Effect on behaviour	Species	Reference
Anxiety				
Olvanil 0.2-5.0 mg/kg;	i.p	EPM/Anxiogenic	Rat	[40]
Capsazepine (1–10 µg/kg)	i.p.	EPM/Anxiolytic	Rat	[40]
SB366791 (0.1–2.5 mg/kg); olvanil (0.1 mg/kg);AA-5-HT (0.1–5 mg/kg)	i.p.	EPM/Anxiolytic	Mouse	[41]
Capsazepine (1, 10 ,30 and 60 nmol)	i.c. (mPFC)	EPM and VCT/Anxiolytic	Rat	[44]
Methanamide 0.1-10 µg Capsaicin 1-10µg and 1nmol	i.c (mPFC)	EPM /Anxiogenic	Rat	[45]
AA-5-HT (0.25–0.5 nmol)	i.c. (BLA)	EPM /Anxiolytic	Rat	[48]
AMG 9810 (0.003, 0.03 and 0.3 µg)	i.c. (dHPC)	EPM /Anxiolytic	Rat	[49]
Capsaicin (0.003, 0.03 and 0.3 µg)	i.c. (dHPC)	EPM /Anxiogenic	Rat	[49]
Capsazepine (0.2–2 nmol)	i.c. (vHPC)	EPM /Anxiolytic	Rat	[46]

Capsaicin (0.01, 0.1 and 1 nmol)	i.c. (dPAG)	EPM /Anxiogenic	Mouse	[50]
Capsaicin (0.01, 0.1 and 1 nmol)	i.c. (dlPAG)	EPM and VCT /Anxiolytic	Rat	[47]
Capsazepine (1, 10 ,30 and 60 nmol)and 6-iodonordihydrocapsaicin (3 nmol)	i.c. (mPFC)	Conditioned fear/Decrease in fear-related behaviour	Rat	[43]
Capsaicin 1-10µg and 1nmol	i.c (mPFC)	Conditioned fear/Increase in fear-related behaviour	Rat	[43]
Capsazepine (1-60 nmol) 30nmol*	i.c. (dlPAG)	ETM / panicolytic-like effects	Rat	[56]
SB366791(10nmol) Capsazepine (0.1, 1 and 10 nmol)	i.c.(dlPAG)	Escape threshold determination/panicolytic-like effects	Rat	[58]
Capsazepine (30 nmol)	i.c.(dlPAG)	Escape threshold determination/panicolytic-like effects	Rat	[57]
Capsazepine (100 µg)	i.c.v	Abolished marble-burying behaviour	Mice	[60]
Depression				
Olvanil 0.2-5.0 mg/kg	i.p	Antidepressant effect/ Porsolt swimming test	Rat	[40]
Capsaicin (200 and 300 µg/mouse) and capsazepine (100 and 200 µg/mouse)	i.c.v	Antidepressant effect/ force swimming test	Mice	[63]

capsaicin (0.1, 1 and 2.5 mg/kg) and olvanil (0.1, 1 and 5 mg/kg)	i.p	Antidepressant effect/ force swimming test	Mice	[64]
RTX (0.25 µg/kg i.t.)	i.t	Increased immobility (depressive -like) /force swimming test	Rat	[65]
Amitriptyline (10 mg/kg)and Ketamine (50 mg/kg)	i.p	Decreased the immobility caused by RTX (Antidepressant effect) / force swimming test	Rat	[65]

Table 2: Effects of pharmacological modulation of TRPV1 in animal models of anxiety and depression.

i.p. : intraperitoneal, i.t : intrathecal, i.c.: intracerebral, i.c.v: intracerebroventricular, dlPAG: dorsolateral periaqueductal gray, dPAG: dorsal periaqueductal gray, ETM: elevated T-maze, EPM: elevated plus-maze,VCT: Vogel Conflict test, mPFC: medial prefrontal cortex, vHPC: ventral hippocampus, dHPC: dorsal hippocampus, BLA: basolateral amygdala, AA-5HT: N-arachidonoyl-serotonin, SB366791: N-(3-Methoxyphenyl)-4-chlorocinnamide, RTX: resiniferatoxin.