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Supraspinal TRPV1 in Pain and Psychiatric Disorders

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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 ($>42^{\circ}\text{C}$), 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 A δ - 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-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 activation of TRPV1 leads to analgesia, while hyperalgesia may be due to increases in vlPAG 2-arachidonoylglycerol (2-AG) leading to CB₁ 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 vIPAG have also been shown to increase withdrawal latency in the rat hot-plate test, with evidence that activation of TRPV1 in the vIPAG induces antinociception via mGlu receptor-mediated 2-AG retrograde signalling in the RVM [32]. Intra-vIPAG 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-vIPAG administration of the TRPV1 antagonist capsazepine, suggesting that FAAH substrates (likely anandamide) activate TRPV1 on vIPAG 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 vIPAG, 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 anandamide levels in the vIPAG and had antinociceptive effects in both the tail flick and formalin tests. Moreover, intra-vIPAG 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 the FAAH inhibitor URB597 and the selective TRPV1 antagonist I-RTX into the vIPAG [33]. The FAAH substrate, palmitoylethanolamide (PEA), when microinjected into the vIPAG 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]. Similarly, 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 CB₁ 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 anxiolytic 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 dPAG also elicited anxiolytic effects in the EPM [46,47].

2.2.1.2. Panic Disorder

The dPAG 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 dPAG 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 dPAG 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 dIPAG 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 CB₁ 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]. Similarly, 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-suppressed 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 desensitized 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°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 extravasation responses to niacin and prostaglandin D2 were reduced in capsaicin-treated rats [72]. The neuroanatomical changes and reduced cutaneous plasma extravasation 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 CB₁ 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.

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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.

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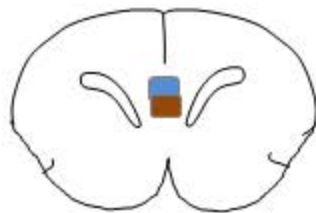
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Anxiety

mPFC ↑



dHPC ↑



BLA ↓



vHPC ↓



DLPAG ↓



Pain

↓ PL-IL

↓ *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.(dIPAG) | Antinociceptive effect/thermosensitivity test | Rat | [28] |
| Capsazepine (6 nmol/rat) | i.c.(dIPAG) | Blocked the capsaicin-induced antinociception/thermosensitivity test | Rat | [28] |
| Capsaicin (6 nmol) | i.c.(vIPAG) | Antinociceptive effect/thermosensitivity test | Rat | [30] |
| Capsaicin (3 and 6 nmol/rat) | i.c.(vIPAG) | Antinociceptive effect/RVM extracellular recordings and tail flick test | Rat | [29] |
| I-RTX (0.5 and 1 nmol/rat) | i.c.(vIPAG) | 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.(vIPAG) | Antinociceptive effect/hot-plate test | Rat | [32] |
| SB 366791 (50 nmol) | i.c.(vIPAG) | 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: Spared 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, dIPAG: 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.