Journal Pre-proof

Red-hot chili receptors: a systematic review of TRPV1 antagonism in animal models of psychiatric disorders and addiction

Andrea Escelsior, Bruno Sterlini, Martino Belvederi Murri, Gianluca Serafini, Andrea Aguglia, Beatriz Pereira da Silva, Anna Corradi, Pierluigi Valente, Mario Amore

PII: S0166-4328(20)30433-2

DOI: https://doi.org/10.1016/j.bbr.2020.112734

Reference: BBR 112734

To appear in: *Behavioural Brain Research*

Received Date: 31 October 2019

Revised Date: 19 May 2020

Accepted Date: 22 May 2020

Please cite this article as: Escelsior A, Sterlini B, Murri MB, Serafini G, Aguglia A, Silva BPd, Corradi A, Valente P, Amore M, Red-hot chili receptors: a systematic review of TRPV1 antagonism in animal models of psychiatric disorders and addiction, *Behavioural Brain Research* (2020), doi: https://doi.org/10.1016/j.bbr.2020.112734

Red-hot chili receptors: a systematic review of TRPV1 antagonism in animal models of psychiatric disorders and addiction

Running title: TRPV1 antagonism in psychiatric disorders and addiction

Andrea Escelsior[1,2†], Bruno Sterlini[3,4†], Martino Belvederi Murri[5], Gianluca Serafini[1,2], Andrea Aguglia[1,2], Beatriz Pereira da Silva[1,2], Anna Corradi[2,3], Pierluigi Valente[2,3*], Mario Amore[1,2*]

[1]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Section of Psychiatry, University of Genoa, Genoa, Italy.
[2]IRCCS Ospedale Policlinico San Martino, Genoa, Italy.
[3]Department of Experimental Medicine, University of Genoa, Genoa, Italy.
[4]Center for Synaptic Neuroscience and Technology, Istituto Italiano di Tecnologia, Genoa, Italy.
[5]Institute of Psychiatry, Department of Biomedical and Specialty Surgical Sciences, University of Ferrara, Ferrara, Italy.

†,* these authors equally contributed to the manuscript

Corresponding author

Andrea Escelsior,
MD IRCCS Ospedale Policlinico San Martino, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Section of Psychiatry
University of Genoa, Largo Rosanna Benzi, 10 16132 Genoa, Italy
e-mail: andrea.escelsior@live.com Cell: +39 338 7176803

Highlights

- TRPV1 antagonists are effective in animal models of anxiety and depression
- TRPV1 antagonism reduces addictive-like behaviours in animal models
- TRPV1 modulation of endocannabinoid, opioid and reward systems might mediate these effects
- Few results include schizophrenic- and obsessive-compulsive-like behaviours and model of fibromyalgia.
- Studies on clinical populations are lacking.

Abstract

Transient Receptor Potential Vanilloid 1 (TRPV1) channels are non-selective cationic polymodal receptors gated by several different chemical and physical stimuli. TRPV1 receptors are distributed in several brain areas and interact with important neurotransmitter systems linked to mental disorders, such as endocannabinoid and opioid systems. The increasing number of results obtained in this field has recently attracted growing attention to these receptors as potential targets for the treatment of different psychiatric conditions. To review the available results on this topic, we searched on the PubMed database up to May 2020 using the following search string: "TRPV1", thus including a total of 48 studies. The results, still limited to preclinical studies, suggest that TRPV1 antagonism could represent a potential mechanism for the treatment of depression and anxiety, as well as for opioids, methamphetamine and cocaine addiction. Few available results consider schizophrenia-like behaviours, suggesting an intriguing role of TRPV1 receptors in the neurobiology of major psychoses. Single studies report the effectiveness of TRPV1 antagonists in animal models of obsessive-compulsive disorder and fibromyalgia. Future preclinical and clinical studies are required to shed further light on the feasibility of the use of TRPV1 modulators in psychopharmacology.

Keywords: TRPV1, mood disorders, panic, anxiolytic, antidepressant, drug abuse, mental health

1. Introduction

The past few years have witnessed a growing interest in Transient Receptor Potential channels (TRP), a superfamily of polymodal receptors that may be relevant in the treatment of mental disorders.

The TRP superfamily comprises approximately 30 subtypes of tetrameric six-transmembrane nonselective calcium-permeable ion channels divided into six subfamilies: ankyrin (TRPA), canonical, melastatin (TRPM), mucolipin, polycystin, and vanilloid (TRPV). They are expressed on numerous cell types and gated by several different forms of sensory stimulation [1–3]. In this context, TRP channels are activated by a broad spectrum of physical and chemical stimuli and mediate different bodily sensations, such as noxious heat, cold or pain [4,5]. Recently, among TRP channels, the subtype 1 of vanilloid subfamily (TRPV1), has been examined as potential therapeutic targets for several diseases [6] such as inflammation, pain, osteoarthritis or epilepsy [7,8]. TRPV1 respond to different stimuli such as substances containing the vanilloid chemical group in which capsaicin is the most representative member, resiniferatoxin (RTX), membrane depolarization, noxious temperatures (≥42 °C) and acidic extracellular pH [9]. TRPV1 activation also occurs by a plethora of endogenous factors/molecules indicating a potential dynamic functional relationship with different central and peripheral pathways. In particular, endocannabinoids such as anandamide (AEA) and molecules such as retinoids, N-oleoyldopamine, oxytocin, ATP, neurotrophins, and cations can activate TRPV1 receptors [3,5,9–21]. A more complex framework is due on the identification of hetero-tetrameric complexes of multiple TRP subtypes (i.e. TRPV1 with TRPA1, TRPV2, and TRPV3) which possess different sensitivity to temperature, chemicals, and proinflammatory substances [22–25].

The recent growing interest in the physiological role of TRPV1 in the field of neuroscience and psychiatry is due to the revelation of the existence of vanilloid-sensitive neurons at the central nervous system level [26]. Thus, TRPV1 receptors expression is present across different rodent brain regions, including the locus coeruleus (LC), periaqueductal gray (PAG), anterior cingulate cortex (ACC) or medial prefrontal cortex (PFC) [27–33]. Notably,

TRPV1 receptors are widely expressed also in critical brain regions that are involved in drug addiction, such as the nucleus accumbens (NAc) and dorsal striatum (DSt) [34]. TRPV1 channels are widely distributed also on nonneuronal cells such as microglia, astrocytes, oligodendrocytes and pericytes [18,28–33,35–37]. The expression of TRPV1 receptors seems dependent mainly on the developmental stage, but also reflects variable physiological and pathological conditions. For instance, an increase of TRPV1 expression and activity in the central nervous system occur under severe neuroinflammatory conditions [35].

In recent years, several results have linked inflammatory processes to the etiopathology of many psychiatric disorders [38]. In this context, TRPV1 channels seem crucial in the fine regulation of the balance between pro- and anti-inflammatory pathways, that underlie dynamic mechanisms involved in the resolution of exacerbation of the inflammatory state [35,39]. About that, synaptic communication and long-term depression processes involve TRPV1 activity [40]. TRPV1 receptors also have direct bidirectional interactions with the endovanilloid and opioid systems, both involved in the pathophysiology of disorders such as addiction and anxiety [41]. Lastly, TRPV1 indirectly modulates the activity of cannabinoid type 1 (CB1) and mu-opioid receptor (MOR) [30,41,42].

Several preclinical data suggest that TRP channels modulation could be a novel therapeutic target with a high potential translational relevance [43–50]. In particular, the TRPV1 subtype is the most relevant candidate target for the development of therapeutically useful modulators for the treatment of depression, panic, anxiety and addictive disorders [46,48,51]. Thus, we aim to provide a comprehensive review of the available experimental studies focused on the TRPV1 modulation in clinical and preclinical models of psychiatric disorders and addiction.

2. Methods

2.1 Data sources

A systematic search was carried out on Pubmed, Embase and SD (Elsevier Databases). We searched up to May 2020 using the following search term: “TRPV1”.

2.2. Eligibility criteria

We sought to include reports on the consequences of TRPV1 antagonism on psychiatric disorders and addiction, studied in humans and animals. We did not restrict the inclusion based on the date of publication or study design, but we have been considering only reports redacted in English. No studies performed on humans were identified. We extracted and tabulated data relative to TRPV1 antagonists used, other drugs co-administered, the injection sites, model employed, tasks used and main findings. All the experimental studies reviewed were performed on well-known models of psychiatric disorders. All titles, abstracts and full-text were screened for inclusion by two researchers (A.E. and B.S.)**.**

3. Results

3.1. Study selection

The search yielded a total of 8021 abstracts. After duplicates removal, we screened by Title/Abstract 6016 records. Of these, the full text of 215 articles was screened and yielded 48 studies eligible for inclusion, published between 2004 and 2020 [1,34,52–97]. Retracted studies (1 study, [98]) were excluded.

Studies employed models designed to resemble anxiety and panic disorder, depression, schizophrenia, obsessive-compulsive disorder, and fibromyalgia, as well as addictive behaviours among rodents. The studies included the following tasks: forced swim test (FST, 7 studies), elevated plus-maze (EPM, 18 studies), Vogel conflict test (VCT, 5 studies), social interaction test (SITe, 2 studies), step-down inhibitory avoidance task (IA, 1 study), contextual fear conditioning (CFC, 6 studies), Morris water maze (MWM, 1 study), repeated social defeat stress protocol (RSDSP, 1 study), escape threshold determination after dPAG electrical stimulation (ETD, 1 study), behavioural procedure of exposure to threatening stimuli (BP, 1 study), open field (OF, used to assess anxiety-like behaviour in 4 studies), light/dark box task (L/DBT, 2 studies), marble burying behaviour (MBB, 2 studies), prepulse inhibition (PPI, 1 study), conditioned place preference (CPP, 8 studies), self-administration test

(SAT, 4 studies), conditioned taste aversion (CTA, 1 study), and the handling induced convulsion (HIC, 1 study).

The following TRPV antagonists have studied: capsazepine (CPZ, 31 studies), N-arachidonoyl-serotonin (AA-5-HT, 6 studies), SB366791 (10 studies), 6-iodo-nordihydrocapsaicin (6-IODO, 4 studies), AMG9810 (4 studies), iodoresiniferatoxin (I-RTX, 1 study), and α-Spinasterol (2 studies).

3.2. Study characteristics

Table 1 and **Table 2** report the characteristic of the studies on animal models of psychiatric and addictive disorders. They include information on the TRPV1 antagonist used, addictive substances used (only for Table 2), injection site, animal model, animal strain and main findings. **Figure 1** reported detail on the specific site of injection and task used. **Supplementary material** report the characteristics of effective TRPV1 antagonists respect to the site of injection, animal model and dosages (in µg and nmol).

3.3. *TRPV1 antagonism in animal models depression and anxiety disorders*

See **Table 1**, **Figure 1** and **Supplementary material** for a description of study characteristics and results.

Studies employing animal models of psychiatric disorders used different tasks. Thus, we first report a brief description of tasks and results.

3.3.1. Forced Swim Test

Five studies examined the antidepressant-like effect of TRPV1 modulation in the context of the FST. The FST is a standard preclinical test that consists of exposure to a transparent container filled with water, where reduction of the animal immobility time is an indicator of antidepressant-like activity [99,100]. In this context, the administration of TRPV1 antagonists, either at the systemic level or in specific brain areas, i.e. medial PFC and

amygdala, decreased overall immobility time in the forced swim test in all available studies [62,63,71,78,82,91].

The systemic or intra-ventromedial PFC administration of AA-5HT, the dual blocker of TRPV1 and fatty acid amide hydrolase (FAAH), was associated with a decrease of immobility time during the FST, and with a reduction of Hypothalamic–Pituitary–Adrenal (HPA) axis activity during the FST [62,79,82]. These findings underline the potential functional relationship between TRPV1 and CB1 activity that may be important for a general physiological response to stress, and their potential modulation may exert compensatory behavioural effects [62,71,82].

Alpha-Spinasterol is a TRPV1 antagonist plant steroid that, together with an anti-immobility effect in the forced swim test, did not present any effects on locomotor activity or body temperature [78,91].

Most of these studies, however, are limited by the lack of comparison with appropriate control, such as standard tricyclic antidepressant drugs, commonly used in most preclinical trials based on the FST [100]. The few available studies that examined both the effects of TRPV modulators and antidepressants suggest that TRPV1 antagonists may lead to synergistic effects, possibly acting on neurotransmitter systems that are involved in antidepressants' mechanisms of action (e.g. serotonin). Manna and Umathe found that the antidepressant-like activity of the TRPV1 antagonist CPZ, injected in the intracerebroventricular system, was comparable to the effects of fluoxetine; moreover, the authors detected a synergistic effect due to the co-administration of ineffective doses of CPZ and fluoxetine [63]. Pretreatment with para-chlorophenylalanine, an inhibitor of serotonin tryptophan hydroxylase, attenuated the effects of capsaicin and CPZ, highlighting a probable interplay between TRPV1 receptors and the serotonin system. Moreover, pretreatment with N-Methyl-D-aspartate neutralized the effects of CPZ, suggesting that TRPV1 antidepressant-like activity may require decreased glutamatergic transmission [63]. A recent study reported the activity of α-Spinasterol and SB-366791 in to relieve the depressive-like behaviour induced on FST by reserpine, a drug with catecholamine-depleting effect [91]. Lastly, low doses of RTX

increased the immobility time in the FST, an effect in turn overcome by amitriptyline or ketamine administration, thus suggesting a TRPV1 antagonist property for these compounds [101].

3.3.2. Elevated plus-maze

The EPM is a well-recognized model of anxiety-like behaviour in rodents. Animals are allowed to freely explore two open and two closed arms, elevated by 50 cm from the floor. The passage onto the open arms of the EPM is associated with a rising in the plasma of corticosterone, increased freezing behaviour, and production of faecal boli, processes indicative of increased anxiety-like state. In particular, a longer time spent in the open arms is used as an indirect measure of anxiety-like level [102,103]. Seventeen studies assessed the anxiolytic-like effect of the administration of TRPV1 antagonists on performance in the EPM. Literature reports evidence regarding the efficacy of TRPV1 antagonists on EPM parameters. Six studies reported a significant increase of both entries and time spent in the open arms [57,60,84,93,94,97], while three studies reported only significant increases of the time spent in open arms [59,73,97] and four studies reported an only significant increase of entries in open arms [52,66,77,96]. Using the Elevated T-Maze task, Almeida-Santos and colleagues found that TRPV1 antagonism by CPZ in the dorsolateral PAG decreased escape responses [65]. On the contrary, four studies did not detect differences between the performance of animals treated with TRPV1 antagonists and controls [58,68,78,97]. Conflicting results may depend on differences in the site of drug delivery. In this context, any effects on EPM parameters were described after systemic administration of AA-5-HT or α-Spinasterol [78,97]. At the same time, Genro and colleagues performed a local injection of CPZ in the dorsal hippocampus in contrast to most of the other studies [58], and Mascarenhas and colleagues injected CPZ only in the dorsal, rather than dorsolateral, PAG [58,68,78].

Similarly to results from FST studies, TRPV1 was shown to interact with the endocannabinoid system and influence the performance in the EPM. The injection of high doses of AEA in the dorsolateral PAG induced the activation of TRPV1 receptors that, in turn,

produced a neuronal Ca^{2+} influx and the formation of nitric oxide (NO). NO, in turn, facilitated the presynaptic release of glutamate, which was associated with enhanced behavioural defensive responses [66,77]. This regulation of aversive response might be operated through a TRPV1-mediated engagement of the glutamate/NMDA/NO pathway [61]. In the PAG, activation of TRPV1 enhanced glutamatergic synaptic transmission, implicated in aversive learning, by fine-tuning of TRPV1/CB1 balance [104–106].

These results further support the role of TRPV1 inhibition in reducing anxiety-like levels, possibly through effects on the endocannabinoid and the endovanilloid systems within the dorsolateral PAG and hippocampus, key brain areas involved in defensive and anxiety-like behaviours.

Moreover, the injection of the TRPV1 antagonist CPZ and the CB1 selective agonist ACEA, that only at higher doses can bind to TRPV1 receptors, in the ACC and orbitofrontal cortex support the role of TRPV1 inhibition in reducing impulsive patterns of decision making in rats exposed to cost-benefit T-maze decision-making tasks [85].

3.3.3. Vogel conflict test

The VCT is widely used to evaluate the efficacy of anxiolytic-like compounds. In the VCT, water- or food-deprived animals are exposed to aversive stimuli (foot shocks) while they are trying to access either food or water. Thus, the rate of drinking or feeding behaviours are an index of the drugs' anxiolytic-like properties [107]. In four out of four available studies, there was an association between the administration of TRPV1 antagonists CPZ and 6-IODO in the ventromedial PFC and the dorsolateral PAG with an increase of drinking behaviour [52,57,66,94].

3.3.4. Social interaction test

The SITe is a test used to assess anxiety-like levels in rodents by evaluating the time that pairs of male rats spend engaging in social interaction. The interaction time is indexed by sniffing, following or grooming behaviours [108]. Two studies use the SITe. A seminal study

by Manna and Umathe found increased time spent in social interactions after intracerebroventricular infusion of CPZ, yielding an anxiolytic-like response of similar magnitude to diazepam [54]. Moreover, sub effective doses of CPZ potentiated the response to diazepam without inducing further locomotor impairment [54]. In the second study, Almeida and colleagues compared the CPZ effects on SITe in two population of rats, composed by spontaneously hypertensive (SHR, considered as a murine schizophrenia behavioural phenotype) and Wistar (WR) strains [89]. In contrast with capsaicin, CPZ resulted ineffective on SITe in SHR [89]. In WR, low-dose CPZ increased time spent in social interactions, whereas a higher dose mediated the opposite effect [89].

3.3.5. Step-down inhibitory avoidance task

In the IA task, animals underwent a negative stimulus (footshock) and a grid located on the floor, avoiding to step down from the platform to the grid and explore the box. This form of associative learning depends on multiple sensorial stimuli, including spatial, visual and pain perception, as well as emotional regulation. Inhibitory avoidance is associated with strong activation of subcortical structures, such as the amygdala or the hippocampus, and is modulated by the levels of HPA axis activity [109]. In the only available study employing the IA, intermediate doses of CPZ injected in the dorsal hippocampus produced a significant reduction of the avoidant behaviour [58].

3.3.6. Contextual fear conditioning paradigms

Several CFC behavioural paradigms were employed to investigate the neurobiology of fear learning, as well as the role of the hippocampus in memory [110]. In four studies TRPV1 antagonists, CPZ or 6-IODO I-RTX, were injected in the dorsolateral PAG [79], dorsal hippocampus [58], ventromedial PFC, prelimbic or infralimbic regions or systemically [75]. TRPV1 antagonists were associated with a significant decrease in short- and long-term extinction phase freezing time on contextual fear conditioning [58,67,75,79]. Moreover, CPZ was able to impair memory consolidation in the strong shock condition [58], while AA-5-HT,

affect fear-related behaviour in a manner dependent on baseline anxiety-like levels and environmental context [86]. On the other hand, recently, a single study reported the absence of effects on CFC in two population of SHR and WR after intraperitoneal injection of CPZ [88].

3.3.7. Morris water maze

In the MWM, the rat is placed in an open-field circular pool and required to find a platform to escape. This navigation task allows studying different aspects of the spatial memory (e.g. working memory) and non-spatial discrimination learning at the same time [111]. In the only available study on TRPV1 antagonists, injection of AMG9810 in the ventral hippocampus did not affect Morris water maze performance on either memory acquisition or retrieval [69].

3.3.8. Repeated social defeat stress task

Prolonged social defeat stress has excellent etiological, predictive, discriminative and face validity in experimental approaches to study depression [112]. In the only available study, the systemic administration of I-RTX did not affect RSDS performance [67].

3.3.9. Escape threshold determination after dorsal PAG electrical stimulation

The Escape behaviour induced by dorsal PAG electrical stimulation is a proposed model of panic attacks, and the intensity of panic attacks is measurable by the determination of the escape threshold (the intensity of current needed to generate the response). Indeed the electrical stimulation of dorsal PAG generates a panic response, which is characterized by running and jumping; at this regard, blockade of TRPV1 using CPZ and SB366791 enhances the threshold of the intensity of current required for inducing panic-like response after dorsal PAG electrical stimulation [56].

3.3.10. The behavioural procedure of exposure to threatening stimuli

This test provokes a predator-induced defensive behaviour (panic-like responses) in rats, using cats as threatening stimuli. Microinjections of CPZ in dorsolateral PAG in rats exposed to the presence of threatening stimuli was associated with a reduction of defensive behaviours, suggesting a role for TRPV1 in the regulation of aversive states induced by innate fear stimuli [76]. Furthermore, the activation of TRPV1 or CB1 receptors due to threatening stimuli exerts opposite effects in the modulation of defence responses, with a reduction of fear after cannabinoid exposure [76,113].

3.3.11. Open field

The OF is a very popular behavioural test for the assessment of the spontaneous locomotor activity or, in particular experimental settings, as a model of anxiety-like behaviours [114]. In Table 1 we consider OF as a behavioural test only when used to assess anxiety-like behaviour, through the observation of the time spent in the centre of the chamber, the flight reactions or the rearing frequency [61,65,86,91]. However, we specify in the main findings sections the results of the OF when it was used only to assess variations in spontaneous locomotor activity [54,65,66,68,94].

3.3.12. Light/dark box task

The L/DBT is an animal behavioural paradigm used to investigate anxiety-like behaviours. It consists of one light and one dark chamber, connected by a small opening or a tunnel [115]. In one study, TRPV1-knockout (KO) mice displayed a faster adaptation to the light compartment in the L/DBT [116]. Systemic injection of TRPV1 antagonists (AA-5HT and α-Spinasterol) provided no significant results [78,86].

3.3.13. Marble burying behaviour

The MBB is an animal model used to assess anxiety- and compulsive-like behaviour by calculating the number of marbles buried in the rodent cage [117]. Umathe et al. found the opposite effect of TRPV1 agonism and antagonism yielding pro- and anti-compulsive

behaviours, respectively. Interestingly, intracerebroventricular administration of CPZ exerted a long-term inhibitory effect on compulsive behaviours [64].

3.3.14. Prepulse inhibition

The PPI is a well-established behavioural paradigm that assesses sensorimotor gating deficits, and result disrupted in different mental disorders such as schizophrenia [118]. The N-methyl d-aspartate (NMDA) antagonists MK-801 is frequently used for its disrupting activity in PPI [118], Cannabidiol (CBD) can reverse MK-801 activity on PPI, possibly through a TRPV1-mediated effect. In fact, CPZ prevents the CBD activity in reversing the pro-disrupting effect on PPI of NMDA antagonist MK-801 [90]. However, both CPZ and CBD alone did not affect PPI [90].

3.4. The TRPV1 antagonism in animal models of addiction disorders

See **Table 2**, **Figure 1** and **Supplementary material** for a description of study characteristics and results.

Studies employing animal models of addiction are largely based on similar tasks, based on different psychoactive substances. Thus, we first report a brief description of the tasks, followed by the report of results grouped by the type of addictive substances.

3.4.1. Tasks employed in animal models of addiction

Five different tasks were used to study the effects of TRPV1 antagonism in models of addiction. The CPP is a Pavlovian animal model to assess the motivational effects of a substance. It consists of a primary exposure to a drug, used as an unconditioned stimulus, which is repeatedly paired with neutral environmental stimuli. Environmental stimuli progressively acquire the status of conditioned stimuli: when presented to the animal, they can produce an approach o withdrawal behaviour [119].

The SAT consists of an instrumental apparatus through which the animal can self-administer a dose of a drug, typically delivered via an intravenous catheter, insufflation or

inhalation. This model of addiction provides the most direct correspondence with the naturally developed addictive behaviour [120]. The mechanisms by which animals learn to avoid harmful substrates is known as CTA, it is another classical Pavlovian conditioning paradigm, where the once non-salient, consumed food (conditioned stimulus) becomes correlated with an aversive outcome such as sickness (unconditioned stimulus). The CTA can accurately determine measures of the specific taste thresholds of a tastant assessed through its consumption [121].

The HIC is a task used to evaluate the central nervous system hyper-excitability in mice during alcohol withdrawal, performed by assessing the seizure behaviour activity when picked up by the tail [122].

3.4.2. Effects of TRPV1 blockade in opioid addiction

As recently described, TRPV1 channels blockade mediate a significant activity on opioid addiction and craving behaviours.

The TRPV1 receptors interact with MOR by acting on intracellular pathways such as PKC, PKA, β-arrestin-2, and MAPK [41]. TRPV1 acts as a physiological regulator of MOR [42], a receptor highly expressed throughout the neuro-circuitry of addiction with an essential role in setting the hedonic state, in inducing the euphoric states, in mediating natural rewards and they are necessary for the rewarding effects of opiates and other drugs of abuse [123], and potential implications in the field of mood disorder treatment [124].

The explanation of the activity on the addiction of the TRPV1 channels blockade might encompass, in particular, their expression of TRPV1 receptors in NAc, a region that plays a pivotal role in addiction behaviours [125]. The blockade of TRPV1, obtained by genetic deletion, or both via systemic and intra-NAc pharmacological administration of antagonists, inhibited morphine-induced CPP in mice; CPZ, in particular, may induce prolonged and stable inhibition of morphine CPP expression [70,80]. The ability of TRPV1 to regulate excitatory glutamatergic transmission during morphine withdrawal involved the NAc but not the DSt [83]. Furthermore, this effect was entirely blocked by CPZ, with a behavioural outcome of persistent

morphine CPP attenuation [83]. Intriguingly, TRPV1 antagonism-induced attenuation of persistent morphine CPP occurs without affecting normal activity [70,80,83]. At the level of DSt, morphine administration upregulates TRPV1 expression, modifying synaptic transmission and neuroplasticity and significantly contribute to morphine reward; on the other hand, injection of different TRPV1 selective antagonists in DSt significantly suppressed morphine-CPP [72].

3.4.3. TRPV1 antagonism in cocaine addiction

Experimental findings indicate that the endovanilloid system could be valuable in the reinstatement of cocaine-seeking behaviour. Adamczyk and colleagues found that the tonic activation of TRPV1 channel is involved in cocaine-seeking behaviour, although it is not necessary for the rewarding effect of this psychostimulant [55]. The authors found that SB366791 was effective on cocaine-induced reinstatement of cocaine-seeking behaviour, although the administration did not alter cocaine reinforcements [55]. Recently, You and colleagues found a similar effect on cocaine-induced reinstatement using CPZ [1]. Interestingly, the author reported the absence of reinstatement in TRPV1-KO mice. Finally, in an elegant series of experiment, the authors found supporting data regarding the role of TRPV1 receptors in facilitating the cocaine reinstatement [1]. More recently, Galaj et al. report that CPZ did not alter cocaine self-administration and describe a dose-dependent activity in prevent a CBD-mediated attenuation of cocaine self-administration [92].

3.4.4. TRPV1 antagonism in methamphetamine addiction

The administration of methamphetamine to mice induces an up-regulation of TRPV1 in the NAc and the DSt [34,53].

Only one study examined the effects of TRPV1 antagonists on methamphetamine addiction: CPZ and SB366791 inhibited methamphetamine-induced CPP and self-administration; moreover, TRPV1-KO mice did not develop methamphetamine-induced CPP [34]. CPZ, in particular, exert a significant action in reducing dopamine levels in NAc and the

enhancement of NAc and DSt dopamine transporter binding levels in methamphetamine-induced CPP mice [34].

3.4.5. TRPV1 antagonism in ethanol addiction

Ethanol is a well-known positive modulator of TRPV1 receptors, potentiating the channel response lowering the energy of gating of various activators, such as voltage, pH, endogenous modulators and temperature, with activation at ~34^{o}C [126]. Thus, TRPV1 may be involved in ethanol activity effects inside the brain [126]. Despite this evidence, both TRPV1-KO and CPZ treated mice show an increase of ethanol preference and consumption and, at the same time, less sensitivity to sedation and motor incoordination [95,127]. On the other hand, Gregor and colleagues recently reported in rats who chronically consumed alcohol an attenuation of hyperalgesia, anxiety-like behaviour, and relapse-like drinking after administration of CPZ into the lateral habenula, [87].

4. Discussion

This systematic review summarized the available evidence on TRPV1 inhibition for the treatment of psychiatric disorders and addiction. At present, TRPV1 antagonists have been only tested in preclinical studies, employing a variety of validated behavioural tasks. Overall, studies regarding animal models of psychiatric disorders suggest that these compounds have significant antidepressant- and anxiolytic-like properties. We also found minor contrasting evidence about animal models of schizophrenia-like behaviours and single studies regarding the obsessive compulsive-like behaviour and an animal model of fibromyalgia. On the other hand, studies regarding animal models of addiction disorders suggest effectiveness in opioids, methamphetamine and cocaine addiction. However, TRPV1 channels seem to play an important role also for other addiction, such as for ethanol.

Considering depressive- and anxiety-like behaviours, TRPV1 antagonists, may exert therapeutic effects mainly by influencing the endocannabinoid system. Diverse types of receptors are co-expressed in the brain regions that may participate in the elaboration of these

disorders (i.e. PAG), including CB1 and TRPV1 channels [27,30]. These receptors bind common modulators and may act in concert to modulate behavioural responses [128–130]. Recent studies in rodents demonstrated that a relative imbalance between endovanilloid and endocannabinoid systems occurs in fear- and anxiety-related behaviours and that TRPV1 can act as ionotropic counterpart of CB1 receptors [48]. Pharmacological evidence indicating that AEA activates both TRPV1 and CB1 receptors in a dose-dependent manner, further support this model [56]. In particular, low doses of AEA induce a CB1-dependent anxiolytic-like effect, while higher dosages result in TRPV1-dependent anxiogenic-like effects [62,97,131]. These results support the notion that endocannabinoids can also act as endovanilloids by binding TRPV1 receptor at higher concentration and that the antidepressant/anxiolytic-like effects of TRPV1 antagonists depend on the enhancement of the activity of the endocannabinoid on CB1 receptors.

TRPV1 receptors are indeed an exciting field in schizophrenia research, considering, for example, their potential involvement in the alteration of the pain sensitivity and of sensorimotor gating that characterize this disorder [132]. A possible role for TRPV1 antagonists was suggested by preclinical studies of Newson and colleagues regarding the role of TRPV1 agonist capsaicin in drive developmental brain alterations that resemble those of schizophrenia [133,134]. However, available studies on schizophrenia-like behaviours report that TRPV1 antagonists exert no significant activity [88–90]. In studies on spontaneously hypertensive rats (SHR) [88,89], Almeida and colleagues reported that CPZ did not alter freezing response and time spent in social interactions. However, TRPV1 receptor activity seems to play an intricate role in SHR, considering that capsaicin ameliorates social interactions [89] but increased freezing response [88]. To further increase the complexity, despite having been suggested as an animal model of schizophrenia [135], SHR might not be an affordable model, due to the highly heterogeneous phenotype with a plethora of different behavioural features such as attention-deficit/hyperactivity disorder- and schizophrenia-like traits or cognitive deficits [136]. Considering the PPI model, Long et al. suggest a TRPV1 agonistic effect of CBD in restoring PPI disruptions [90]. This result is interesting for the

potential therapeutic implications of the modulation of the endocannabinoid/endovanilloid systems in major psychoses.

One study using MBB reports a dose-dependently activity of CPZ in relieving MBB [64], evidence that suggests the assessment of TRPV1 antagonism in obsessive-compulsive disorder treatment [46].

Recently, Fischer and colleagues report the effectiveness of TRPV1 antagonism in a reserpine-induced experimental model of fibromyalgia in mice [91]. In particular, the use of TRPV1 inhibitors rescue the monoamine depletion induced by reserpine and activity on spontaneous nociception, mechanical allodynia, and depressive-like behaviour [91].

Regarding addiction to opiates and psychostimulants, TRPV1 antagonists may exert therapeutic effects through the regulation of the activity of MOR [42] and the modulation of critical areas like NAc and DSt [34,72,125]. On the other hand, the deletion of TRPV1 receptors increases ethanol addiction [95] possibly through the abolition of a tonic long term depressant activity of TRPV1 on the NAc [74]. However, the inhibition of the glutamatergic activity in the lateral habenula by TRPV1 antagonists relieve addiction to ethanol [87].

Although impressive, the present findings are requiring a critical examination. An important assumption is a limit due to the considered models. The use of animal models of rats and mice in psychiatry is challenging because of the difficulties in distinguishing if observed signs and symptoms could be the expression of emotions, motivations, and thought processes comparable to that of humans [137]. Thus, the results obtained for each model should be considered only as relevant for assessing the effect of the treatments beyond the disease classification.

Moreover, the current findings showed the limited translational value of animals models to the clinical situation.

For example, among the animal models of depression, the use of short-term stress task such as the FST suffers from significant weakness, and do not resemble the human depression [138] accurately. To overcome these problems, the use of different models such as the chronic social defeat, chronic unpredictable stress or early life stress models might be useful, together

with the examination of critical homeostatic dimensions such as alterations in sleep [138]. The examination of sleep, in particular, should be of interest considering that an alteration in sleep architecture is a hallmark of several psychiatric disorders [139,140] and, interestingly, could be modulated by TRPV1 antagonist like AA-5-HT, that enhance the sleep duration and inhibit the activation of the neurotransmitter during wakefulness period in rats [141].

Another limit of the current literature is the paucity of studies that consider rodent models of schizophrenia, like PPI, and the lacking of animal models of bipolar disorder such as glycogen synthase kinase 3 β and Clock mutants [138].

According to these results, some potential clinical considerations should be made. First of all, the simultaneous activity of TRPV1 antagonists both on mood and anxiety-like disorders and on drug-addiction is intriguing, considering the frequency and the treatment challenge of the comorbidity between these disorders [142]. The unique antidepressant mechanism of TRPV1 antagonists represents an intriguing psychopharmacological property, considering, for example, the difficulties of the antidepressant treatment of clinical conditions such as the bipolar depression, due to the risk of iatrogenic induction of the switch toward hypo/manic or mixed states of currently available antidepressants [143,144]. Another intriguing property of TRPV1 antagonists is the efficacy on chronic pain [145], a condition frequently associated with mood disorders anxiety and to increased risk of opioid addiction [146,147].

Beyond the treatment addictive disorders and pain, the TRPV1-mediated opioid regulation mechanism should be considered for of the spectrum of psychiatric disorders linked to the dysregulation of the MOR such as depression, schizophrenia, post-traumatic stress disorder [148], borderline personality disorder [149] and non-suicidal self-injury disorder [150].

Finally, as we recently suggest, the investigation of different properties of TRPV1 antagonists like the neuroimmunomodulatory activity, the epigenetic modulation and the neuroprotective activity could be investigated for the treatment of mental disorders characterized by inflammatory processes, neuronal damage and the overactivation of stress-related genes such as major depression or psychotic disorders [39].

5. Conclusions

In summary, results achieved to date, suggesting the effectiveness of TRPV1 antagonists in specific behavioural models of psychiatric and addictive disorders. TRPV1 antagonism yields an anxiolytic/antidepressant activity that might depend on an indirect modulation of CB1 receptors, carried out mainly through a dose-dependent enhancement of the levels of AEA. Results on animal models of schizophrenia suggest that the neurobiology of psychotic disorders might encompass alterations of TRPV1 activity. Single studies on obsessive compulsive-like behaviour and animal model of fibromyalgia provide encouraging results. On the other hand, studies on animal models of addiction provide intriguing evidence regarding the addiction to opioids, methamphetamine and cocaine. These results could be explained through a TRPV1-mediated modulation of the opioid system and key structures of the reward system. Regarding ethanol addiction, available literature provided mixed findings. However, TRPV1 receptors seem to influence the preference and addiction to ethanol. Despite these exciting results, the literature on this topic remains scarce and still limited on *in vitro* and animal model experiments. Further investigation and clinical trials are required to shed light on the feasibility to use TRPV1 antagonists for the treatment of psychiatric and addictive disorders.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

This work was developed within the framework of the DINOGMI Department of Excellence of MIUR 2018-2022 (law 232; 2016).
The authors are very grateful to Dr Ilenia Bellocchio for her assistance, which significantly improved the quality of figures.

References

[1] I.J. You, S.I. Hong, S.X. Ma, T.L. Nguyen, S.H. Kwon, S.Y. Lee, C.G. Jang, Transient receptor potential vanilloid 1 mediates cocaine reinstatement via the D1 dopamine

receptor in the nucleus accumbens, J. Psychopharmacol. (2019). https://doi.org/10.1177/0269881119864943.

[2] I.S. Ramsey, M. Delling, D.E. Clapham, AN INTRODUCTION TO TRP CHANNELS doi:10.1146/annurev.physiol.68.040204.100431, Annu. Rev. Physiol. (2006). https://doi.org/10.1146/annurev.physiol.68.040204.100431.

[3] E. Cao, J.F. Cordero-Morales, B. Liu, F. Qin, D. Julius, TRPV1 Channels Are Intrinsically Heat Sensitive and Negatively Regulated by Phosphoinositide Lipids, Neuron. (2013). https://doi.org/10.1016/j.neuron.2012.12.016.

[4] I. Vandewauw, K. De Clercq, M. Mulier, K. Held, S. Pinto, N. Van Ranst, A. Segal, T. Voet, R. Vennekens, K. Zimmermann, J. Vriens, T. Voets, A TRP channel trio mediates acute noxious heat sensing, Nature. (2018). https://doi.org/10.1038/nature26137.

[5] M. Liao, E. Cao, D. Julius, Y. Cheng, Structure of the TRPV1 ion channel determined by electron cryo-microscopy, Nature. (2013). https://doi.org/10.1038/nature12822.

[6] M.M. Moran, M.A. McAlexander, T. Bíró, A. Szallasi, Transient receptor potential channels as therapeutic targets, Nat. Rev. Drug Discov. (2011). https://doi.org/10.1038/nrd3456.

[7] V. Carnevale, T. Rohacs, TRPV1: A target for rational drug design, Pharmaceuticals. (2016). https://doi.org/10.3390/ph9030052.

[8] M. Nazıroglu, TRPV1 Channel: A Potential Drug Target for Treating Epilepsy, Curr. Neuropharmacol. (2015). https://doi.org/10.2174/1570159x13666150216222543.

[9] M.J. Caterina, M.A. Schumacher, M. Tominaga, T.A. Rosen, J.D. Levine, D. Julius, The capsaicin receptor: A heat-activated ion channel in the pain pathway, Nature. (1997). https://doi.org/10.1038/39807.

[10] H. Poblete, I. Oyarzún, P. Olivero, J. Comer, M. Zuñiga, R. V. Sepulveda, D. Báez-Nieto, C.G. Leon, F. González-Nilo, R. Latorre, Molecular determinants of phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2) binding to transient receptor potential V1 (TRPV1) channels, J. Biol. Chem. (2015). https://doi.org/10.1074/jbc.M114.613620.

[11] J. Lee, V. Di Marzo, J.M. Brotchie, A role for vanilloid receptor 1 (TRPV1) and endocannabinnoid signalling in the regulation of spontaneous and L-DOPA induced locomotion in normal and reserpine-treated rats, Neuropharmacology. (2006). https://doi.org/10.1016/j.neuropharm.2006.04.016.

[12] U.A. Hellmich, R. Gaudet, High-resolution views of TRPV1 and their implications for the TRP channel superfamily, Handb. Exp. Pharmacol. (2014). https://doi.org/10.1007/978-3-319-05161-1_11.

[13] Y. Nersesyan, L. Demirkhanyan, D. Cabezas-Bratesco, V. Oakes, R. Kusuda, T.

Dawson, X. Sun, C. Cao, A.M. Cohen, B. Chelluboina, K.K. Veeravalli, K. Zimmermann, C. Domene, S. Brauchi, E. Zakharian, Oxytocin Modulates Nociception as an Agonist of Pain-Sensing TRPV1, Cell Rep. (2017). https://doi.org/10.1016/j.celrep.2017.10.063.

[14] I. Devesa, R. Planells-Cases, G. Fernandez-Ballester, J.M. Gonzalez-Ros, A. Ferrer-Montiel, A. Fernandez-Carvajal, Role of the transient receptor potential vanilloid 1 in inflammation and sepsis, J. Inflamm. Res. (2011). https://doi.org/10.2147/JIR.S12978.

[15] I. Devesa, A. Ferrer-Montiel, Neurotrophins, endocannabinoids and thermo-transient receptor potential: A threesome in pain signalling, Eur. J. Neurosci. (2014). https://doi.org/10.1111/ejn.12455.

[16] L. Cristino, T. Bisogno, V. Di Marzo, Cannabinoids and the expanded endocannabinoid system in neurological disorders, Nat. Rev. Neurol. (2020). https://doi.org/10.1038/s41582-019-0284-z.

[17] R. Planells-Cases, P. Valente, A. Ferrer-Montiel, F. Qin, A. Szallasi, Complex regulation of TRPV1 and related thermo-TRPs: Implications for therapeutic intervention, in: Adv. Exp. Med. Biol., 2011. https://doi.org/10.1007/978-94-007-0265-3_27.

[18] M.C. Marrone, A. Morabito, M. Giustizieri, V. Chiurchiù, A. Leuti, M. Mattioli, S. Marinelli, L. Riganti, M. Lombardi, E. Murana, A. Totaro, D. Piomelli, D. Ragozzino, S. Oddi, M. Maccarrone, C. Verderio, S. Marinelli, TRPV1 channels are critical brain inflammation detectors and neuropathic pain biomarkers in mice, Nat. Commun. (2017). https://doi.org/10.1038/ncomms15292.

[19] P.M. Zygmunt, A. Ermund, P. Movahed, D.A. Andersson, C. Simonsen, B.A.G. Jönsson, A. Blomgren, B. Birnir, S. Bevan, A. Eschalier, C. Mallet, A. Gomis, E.D. Högestätt, Monoacylglycerols activate TRPV1 - A link between phospholipase C and TRPV1, PLoS One. (2013). https://doi.org/10.1371/journal.pone.0081618.

[20] V. Di Marzo, L. De Petrocellis, Why do cannabinoid receptors have more than one endogenous ligand?, Philos. Trans. R. Soc. Lond. B. Biol. Sci. (2012). https://doi.org/10.1098/rstb.2011.0382.

[21] S. Yin, J. Luo, A. Qian, J. Du, Q. Yang, S. Zhou, W. Yu, G. Du, R.B. Clark, E.T. Walters, S.M. Carlton, H. Hu, Retinoids activate the irritant receptor TRPV1 and produce sensory hypersensitivity, J. Clin. Invest. (2013). https://doi.org/10.1172/JCI66413.

[22] A. Liapi, J.N. Wood, Extensive co-localization and heteromultimer formation of the vanilloid receptor-like protein TRPV2 and the capsaicin receptor TRPV1 in the adult rat cerebral cortex, Eur. J. Neurosci. (2005). https://doi.org/10.1111/j.1460-9568.2005.04270.x.

[23] G.D. Smith, M.J. Gunthorpe, R.E. Kelsell, P.D. Hayes, P. Reilly, P. Facer, J.E. Wright, J.C. Jerman, J.P. Walhin, L. Ooi, J. Egerton, K.J. Charles, D. Smart, A.D. Randall, P. Anand, J.B. Davis, TRPV3 is a temperature-sensitive vanilloid receptor-like protein, Nature. (2002). https://doi.org/10.1038/nature00894.

[24] L. Sadofsky, K. Sreekrishna, Y. Lin, R. Schinaman, K. Gorka, Y. Mantri, J. Haught, T. Huggins, R. Isfort, C. Bascom, A. Morice, Unique Responses are Observed in Transient Receptor Potential Ankyrin 1 and Vanilloid 1 (TRPA1 and TRPV1) Co-Expressing Cells, Cells. (2014). https://doi.org/10.3390/cells3020616.

[25] W. Cheng, F. Yang, S. Liu, C.K. Colton, C. Wang, Y. Cui, X. Cao, M.X. Zhu, C. Sun, K.W. Wang, J. Zheng, Heteromeric heat-sensitive transient receptor potential channels exhibit distinct temperature and chemical response, J. Biol. Chem. (2012). https://doi.org/10.1074/jbc.M111.305045.

[26] H.W. Steenland, S.W. Ko, L.J. Wu, M. Zhuo, Hot receptors in the brain, Mol. Pain. (2006). https://doi.org/10.1186/1744-8069-2-34.

[27] D.J. Cavanaugh, A.T. Chesler, A.C. Jackson, Y.M. Sigal, H. Yamanaka, R. Grant, D. O'Donnell, R.A. Nicoll, N.M. Shah, D. Julius, A.I. Basbaum, Trpv1 Reporter Mice Reveal Highly Restricted Brain Distribution and Functional Expression in Arteriolar Smooth Muscle Cells, J. Neurosci. (2011). https://doi.org/10.1523/JNEUROSCI.6451-10.2011.

[28] A. Tóth, J. Boczán, N. Kedei, E. Lizanecz, Z. Bagi, Z. Papp, I. Edes, L. Csiba, P.M. Blumberg, Expression and distribution of vanilloid receptor 1 (TRPV1) in the adult rat brain., Brain Res. Mol. Brain Res. (2005). https://doi.org/10.1016/j.molbrainres.2004.12.003.

[29] J.C. Roberts, J.B. Davis, C.D. Benham, [3H]Resiniferatoxin autoradiography in the CNS of wild-type and TRPV1 null mice defines TRPV1 (VR-1) protein distribution, Brain Res. (2004). https://doi.org/10.1016/j.brainres.2003.10.001.

[30] L. Cristino, L. de Petrocellis, G. Pryce, D. Baker, V. Guglielmotti, V. Di Marzo, Immunohistochemical localization of cannabinoid type 1 and vanilloid transient receptor potential vanilloid type 1 receptors in the mouse brain, Neuroscience. (2006). https://doi.org/10.1016/j.neuroscience.2006.02.074.

[31] S. Marinelli, C.W. Vaughan, M.J. Christie, M. Connor, Capsaicin activation of glutamatergic synaptic transmission in the rat locus coeruleus in vitro., J. Physiol. (2002). https://doi.org/10.1113/jphysiol.2002.022863.

[32] C. Zschenderlein, C. Gebhardt, O. Von Bohlen und Halbach, C. Kulisch, D. Albrecht, Capsaicin-induced changes in LTP in the lateral amygdala are mediated by TRPV1, PLoS One. (2011). https://doi.org/10.1371/journal.pone.0016116.

[33] E. Mezey, Z.E. Toth, D.N. Cortright, M.K. Arzubi, J.E. Krause, R. Elde, A. Guo, P.M.

Blumberg, A. Szallasi, Distribution of mRNA for vanilloid receptor subtype 1 (VR1), and VR1-like immunoreactivity, in the central nervous system of the rat and human, Proc. Natl. Acad. Sci. (2000). https://doi.org/10.1073/pnas.97.7.3655.

[34] T. Yu-Hua, M. Shi-Xun, K.-W. Lee, S. Wee, G.F. Koob, L. Seok-Yong, C.-G. Jang, Blockade of TRPV1 Inhibits Methamphetamine-induced Rewarding Effects, Sci. Reports (Nature Publ. Group). (2018). https://doi.org/http://dx.doi.org/10.1038/s41598-018-19207-2.

[35] W.L. Kong, Y.Y. Peng, B.W. Peng, Modulation of neuroinflammation: Role and therapeutic potential of TRPV1 in the neuro-immune axis, Brain. Behav. Immun. (2017). https://doi.org/10.1016/j.bbi.2017.03.007.

[36] J.H. Nam, E.S. Park, S.Y. Won, Y.A. Lee, K.I. Kim, J.Y. Jeong, J.Y. Baek, E.J. Cho, M. Jin, Y.C. Chung, B.D. Lee, S.H. Kim, E.G. Kim, K. Byun, B. Lee, D.H. Woo, C.J. Lee, S.R. Kim, E. Bok, Y.S. Kim, T.B. Ahn, H.W. Ko, S. Brahmachari, O. Pletinkova, J.C. Troconso, V.L. Dawson, T.M. Dawson, B.K. Jin, TRPV1 on astrocytes rescues nigral dopamine neurons in Parkinson's disease via CNTF, Brain. (2015). https://doi.org/10.1093/brain/awv297.

[37] L.E. Gonzalez-Reyes, T.P. Ladas, C.C. Chiang, D.M. Durand, TRPV1 antagonist capsazepine suppresses 4-AP-induced epileptiform activity in vitro and electrographic seizures in vivo, Exp. Neurol. (2013). https://doi.org/10.1016/j.expneurol.2013.10.010.

[38] M.E. Bauer, A.L. Teixeira, Inflammation in psychiatric disorders: What comes first?, Ann. N. Y. Acad. Sci. (2018). https://doi.org/10.1111/nyas.13712.

[39] A. Escelsior, B. Sterlini, M. Belvederi Murri, P. Valente, A. Amerio, M.R. di Brozolo, B.P. da Silva, M. Amore, Transient receptor potential vanilloid 1 antagonism in neuroinflammation, neuroprotection and epigenetic regulation: potential therapeutic implications for severe psychiatric disorders treatment, Psychiatr. Genet. (2020). https://doi.org/10.1097/YPG.0000000000000249.

[40] B.A. Grueter, G. Brasnjo, R.C. Malenka, Postsynaptic TRPV1 triggers cell type-specific long-term depression in the nucleus accumbens, Nat. Neurosci. (2010). https://doi.org/10.1038/nn.2685.

[41] F. Zádor, M. Wollemann, Receptome: Interactions between three pain-related receptors or the "triumvirate" of cannabinoid, opioid and TRPV1 receptors, Pharmacol. Res. (2015). https://doi.org/10.1016/j.phrs.2015.10.015.

[42] P.C. Scherer, N.W. Zaccor, N.M. Neumann, C. Vasavda, R. Barrow, A.J. Ewald, F. Rao, C.J. Sumner, S.H. Snyder, TRPV1 is a physiological regulator of μ-opioid receptors, Proc. Natl. Acad. Sci. (2017). https://doi.org/10.1073/pnas.1717005114.

[43] P. Valente, A. Fernández-Carvajal, M. Camprubí-Robles, A. Gomis, S. Quirce, F. Viana, G. Fernández-Ballester, J.M. González-Ros, C. Belmonte, R. Planells-Cases,

A. Ferrer-Montiel, Membrane-tethered peptides patterned after the TRP domain (TRPducins) selectively inhibit TRPV1 channel activity, FASEB J. (2011). https://doi.org/10.1096/fj.10-174433.

[44] L.A. Chahl, TRP channels and psychiatric disorders, in: Adv. Exp. Med. Biol., 2011. https://doi.org/10.1007/978-94-007-0265-3_51.

[45] D.C. Aguiar, F.A. Moreira, A.L. Terzian, M. V. Fogaça, S.F. Lisboa, C.T. Wotjak, F.S. Guimaraes, Modulation of defensive behavior by Transient Receptor Potential Vanilloid Type-1 (TRPV1) Channels, Neurosci. Biobehav. Rev. (2014). https://doi.org/10.1016/j.neubiorev.2014.03.026.

[46] M. Nazıroglu, A. Demirdas, Psychiatric Disorders and TRP Channels: Focus on Psychotropic Drugs, Curr. Neuropharmacol. (2015). https://doi.org/10.2174/1570159X13666150304001606.

[47] M.K. Madasu, M. Roche, D.P. Finn, Supraspinal transient receptor potential subfamily V Member 1 (TRPV1) in pain and psychiatric disorders, Mod. Trends Pharmacopsychiatry. (2015). https://doi.org/10.1159/000435934.

[48] S. Patel, M.N. Hill, J.F. Cheer, C.T. Wotjak, A. Holmes, The endocannabinoid system as a target for novel anxiolytic drugs, Neurosci. Biobehav. Rev. (2017). https://doi.org/10.1016/j.neubiorev.2016.12.033.

[49] S. Sawamura, H. Shirakawa, T. Nakagawa, Y. Mori, S. Kaneko, TRP channels in the brain: What are they there for?, in: Neurobiol. TRP Channels, 2017. https://doi.org/10.4324/9781315152837.

[50] L. Quagliato, R. Freire, A. Nardi, The role of acid-sensitive ion channels in panic disorder: a systematic review of animal studies and meta-analysis of human studies, Transl. Psychiatry. (2018). https://doi.org/10.1038/s41398-018-0238-z.

[51] L. Quagliato, R. Freire, A. Nardi, The role of acid-sensitive ion channels in panic disorder: a systematic review of animal studies and meta-analysis of human studies., Transl Psychiatry. 8(1):185 (2018) 1–12. https://doi.org/10.1038/s41398-018-0238-z.

[52] A.L.B. Terzian, D.C. Aguiar, F.S. Guimarães, F.A. Moreira, Modulation of anxiety-like behaviour by Transient Receptor Potential Vanilloid Type 1 (TRPV1) channels located in the dorsolateral periaqueductal gray, Eur. Neuropsychopharmacol. (2009). https://doi.org/10.1016/j.euroneuro.2008.11.004.

[53] Y.H. Tian, S.Y. Lee, H.C. Kim, C.G. Jang, Repeated methamphetamine treatment increases expression of TRPV1 mRNA in the frontal cortex but not in the striatum or hippocampus of mice, Neurosci. Lett. (2010). https://doi.org/10.1016/j.neulet.2010.01.058.

[54] S.S.S. Manna, S.N. Umathe, Transient receptor potential vanilloid 1 channels modulate the anxiolytic effect of diazepam, Brain Res. (2011).

https://doi.org/10.1016/j.brainres.2011.09.049.

[55] P. Adamczyk, J. Miszkiel, A.C. McCreary, M. Filip, M. Papp, E. Przegaliński, The effects of cannabinoid CB1, CB2 and vanilloid TRPV1 receptor antagonists on cocaine addictive behavior in rats, Brain Res. (2012). https://doi.org/10.1016/j.brainres.2012.01.030.

[56] P.C. Casarotto, A.L.B. Terzian, D.C. Aguiar, H. Zangrossi, F.S. Guimares, C.T. Wotjak, F.A. Moreira, 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). https://doi.org/10.1038/npp.2011.207.

[57] M. V. Fogaça, D.C. Aguiar, F.A. Moreira, F.S. Guimarães, The endocannabinoid and endovanilloid systems interact in the rat prelimbic medial prefrontal cortex to control anxiety-like behavior, Neuropharmacology. (2012). https://doi.org/10.1016/j.neuropharm.2012.03.007.

[58] B.P. Genro, L. de Oliveira Alvares, J.A. Quillfeldt, Role of TRPV1 in consolidation of fear memories depends on the averseness of the conditioning procedure, Neurobiol. Learn. Mem. (2012). https://doi.org/10.1016/j.nlm.2012.01.002.

[59] E. Hakimizadeh, S. Oryan, A.H. Moghaddam, A. Shamsizadeh, A. Roohbakhsh, Endocannabinoid system and TRPV1 receptors in the dorsal hippocampus of the rats modulate anxiety-like behaviors, Iran. J. Basic Med. Sci. (2012).

[60] C.S. John, P.J. Currie, N-Arachidonoyl-serotonin in the basolateral amygdala increases anxiolytic behavior in the elevated plus maze, Behav. Brain Res. (2012). https://doi.org/10.1016/j.bbr.2012.05.025.

[61] S.F. Lisboa, F.S. Guimarães, Differential role of CB1 and TRPV1 receptors on anandamide modulation of defensive responses induced by nitric oxide in the dorsolateral periaqueductal gray, Neuropharmacology. (2012). https://doi.org/10.1016/j.neuropharm.2012.02.008.

[62] C. Kirkedal, G. Wegener, F. Moreira, S.R.L. Joca, N. Liebenberg, A dual inhibitor of FAAH and TRPV1 channels shows dose-dependent effect on depression-like behaviour in rats, Acta Neuropsychiatr. (2017). https://doi.org/10.1017/neu.2016.68.

[63] S.S.S. Manna, S.N. Umathe, A possible participation of transient receptor potential vanilloid type 1 channels in the antidepressant effect of fluoxetine, Eur. J. Pharmacol. (2012). https://doi.org/10.1016/j.ejphar.2012.04.023.

[64] S.N. Umathe, S.S.S. Manna, N.S. Jain, Endocannabinoid analogues exacerbate marble-burying behavior in mice via TRPV1 receptor, Neuropharmacology. (2012). https://doi.org/10.1016/j.neuropharm.2011.12.030.

[65] A.F. Almeida-Santos, F.A. Moreira, F.S. Guimarães, D.C. Aguiar, Role of TRPV1

receptors on panic-like behaviors mediated by the dorsolateral periaqueductal gray in rats, Pharmacol. Biochem. Behav. (2013). https://doi.org/10.1016/j.pbb.2013.02.012.

[66] M. V. Fogaça, F. V. Gomes, F.A. Moreira, F.S. Guimarães, D.C. Aguiar, Effects of glutamate NMDA and TRPV1 receptor antagonists on the biphasic responses to anandamide injected into the dorsolateral periaqueductal grey of Wistar rats, Psychopharmacology (Berl). (2013). https://doi.org/10.1007/s00213-012-2927-2.

[67] D. Laricchiuta, D. Centonze, L. Petrosini, Effects of endocannabinoid and endovanilloid systems on aversive memory extinction, Behav. Brain Res. (2013). https://doi.org/10.1016/j.bbr.2013.08.010.

[68] D.C. Mascarenhas, K.S. Gomes, R.L. Nunes-de-Souza, Anxiogenic-like effect induced by TRPV1 receptor activation within the dorsal periaqueductal gray matter in mice, Behav. Brain Res. (2013). https://doi.org/10.1016/j.bbr.2013.05.023.

[69] S. Amiresmaili, A. Shamsizadeh, M. Allahtavakoli, A.A. Pourshanazari, A. Roohbakhsh, The effect of intra-ventral hippocampus administration of TRPV1 agonist and antagonist on spatial learning and memory in male rats, Pharmacol. Reports. (2014). https://doi.org/10.1016/j.pharep.2013.06.002.

[70] L.J. Heng, B. Huang, H. Guo, L.T. Ma, W.X. Yuan, J. Song, P. Wang, G.Z. Xu, G.D. Gao, Blocking TRPV1 in nucleus accumbens inhibits persistent morphine conditioned place preference expression in rats, PLoS One. (2014). https://doi.org/10.1371/journal.pone.0104546.

[71] A. Navarria, A. Tamburella, F.A. Iannotti, V. Micale, G. Camillieri, L. Gozzo, R. Verde, R. Imperatore, G.M. Leggio, F. Drago, V. Di Marzo, The dual blocker of FAAH/TRPV1 N-arachidonoylserotonin reverses the behavioral despair induced by stress in rats and modulates the HPA-axis, Pharmacol. Res. (2014). https://doi.org/10.1016/j.phrs.2014.04.014.

[72] T.L. Nguyen, S.H. Kwon, S.I. Hong, S.X. Ma, Y.H. Jung, J.Y. Hwang, H.C. Kim, S.Y. Lee, C.G. Jang, Transient receptor potential vanilloid type 1 channel may modulate opioid reward, Neuropsychopharmacology. (2014). https://doi.org/10.1038/npp.2014.90.

[73] J.W. Kasckow, J.J. Mulchahey, T.D. Geracioti, Effects of the vanilloid agonist olvanil and antagonist capsazepine on rat behaviors, Prog. Neuro-Psychopharmacology Biol. Psychiatry. (2004). https://doi.org/10.1016/j.pnpbp.2003.10.007.

[74] R. Renteria, Z.M. Jeanes, R.A. Morrisett, Ethanol attenuation of long-term depression in the nucleus accumbens can be overcome by activation of TRPV1 receptors, Alcohol. Clin. Exp. Res. (2014). https://doi.org/10.1111/acer.12542.

[75] A.L.B. Terzian, D.G. Dos Reis, F.S. Guimarães, F.M. a Corrêa, L.B.M. Resstel, Medial prefrontal cortex transient receptor potential vanilloid type 1 (TRPV1) in the expression

of contextual fear conditioning in Wistar rats, Psychopharmacology (Berl). (2014). https://doi.org/10.1007/s00213-013-3211-9.

[76] D.C. Aguiar, A.F. Almeida-Santos, F.A. Moreira, F.S. Guimarães, Involvement of TRPV1 channels in the periaqueductal grey on the modulation of innate fear responses, Acta Neuropsychiatr. (2015). https://doi.org/10.1017/neu.2014.40.

[77] P.A. Batista, M. V. Fogaça, F.S. Guimarães, The endocannabinoid, endovanilloid and nitrergic systems could interact in the rat dorsolateral periaqueductal gray matter to control anxiety-like behaviors, Behav. Brain Res. (2015). https://doi.org/10.1016/j.bbr.2015.07.019.

[78] K. Socała, P. Wlaź, Evaluation of the antidepressant- and anxiolytic-like activity of α-spinasterol, a plant derivative with TRPV1 antagonistic effects, in mice, Behav. Brain Res. (2016). https://doi.org/10.1016/j.bbr.2016.01.048.

[79] D.L. Uliana, S.C. Hott, S.F. Lisboa, L.B.M. Resstel, Dorsolateral periaqueductal gray matter CB1 and TRPV1 receptors exert opposite modulation on expression of contextual fear conditioning, Neuropharmacology. (2016). https://doi.org/10.1016/j.neuropharm.2015.12.020.

[80] S.I. Hong, T.L. Nguyen, S.X. Ma, H.C. Kim, S.Y. Lee, C.G. Jang, TRPV1 modulates morphine-induced conditioned place preference via p38 MAPK in the nucleus accumbens, Behav. Brain Res. (2017). https://doi.org/10.1016/j.bbr.2017.07.017.

[81] S.X. Ma, S.H. Kwon, J.Y. Seo, J.Y. Hwang, S.I. Hong, H.C. Kim, S.Y. Lee, C.G. Jang, Impairment of opiate-mediated behaviors by the selective TRPV1 antagonist SB366791, Addict. Biol. (2017). https://doi.org/10.1111/adb.12460.

[82] A.G. Sartim, F.A. Moreira, S.R.L. Joca, Involvement of CB1and TRPV1 receptors located in the ventral medial prefrontal cortex in the modulation of stress coping behavior, Neuroscience. (2017). https://doi.org/10.1016/j.neuroscience.2016.10.031.

[83] H. Zhang, D. Jia, Y. Wang, L. Qu, X. Wang, J. Song, L. Heng, G. Gao, Enhanced ability of TRPV1 channels in regulating glutamatergic transmission after repeated morphine exposure in the nucleus accumbens of rat, Brain Res. (2017). https://doi.org/10.1016/j.brainres.2017.02.002.

[84] T. Rubino, N. Realini, C. Castiglioni, C. Guidali, D. Viganó, E. Marras, S. Petrosino, G. Perletti, M. Maccarrone, V. Di Marzo, D. Parolaro, Role in anxiety behavior of the endocannabinoid system in the prefrontal cortex, Cereb. Cortex. (2008). https://doi.org/10.1093/cercor/bhm161.

[85] Z. Fatahi, Z. Reisi, G. Rainer, A. Haghparast, A. Khani, Cannabinoids induce apathetic and impulsive patterns of choice through CB1 receptors and TRPV1 channels, Neuropharmacology. (2018). https://doi.org/10.1016/j.neuropharm.2018.01.021.

[86] T. Freels, D. Lester, M. Cook, Arachidonoyl serotonin (AA-5-HT) modulates general

fear-like behavior and inhibits mesolimbic dopamine release., Behav Brain Res. 11;362 (2019) 140–151. https://doi.org/10.1016/j.bbr.2019.01.010.

[87] D. Gregor, W. Zuo, R. Fu, A. Bekker, J. Ye, Elevation of Transient Receptor Potential Vanilloid 1 Function in the Lateral Habenula Mediates Aversive Behaviors in Alcohol-withdrawn Rats., Anesthesiology. 22 (2019) [Epub ahead of print]. https://doi.org/10.1097/ALN.0000000000002615.

[88] V. Almeida, R. Levin, F.F. Peres, M.A. Suiama, A.M. Vendramini, C.M. Santos, N.D. Silva, A.W. Zuardi, J.E.C. Hallak, J.A. Crippa, V.C. Abílio, Role of the endocannabinoid and endovanilloid systems in an animal model of schizophrenia-related emotional processing/cognitive deficit, Neuropharmacology. (2019). https://doi.org/10.1016/j.neuropharm.2019.05.015.

[89] V. Almeida, F.F. Peres, R. Levin, M.A. Suiama, M.B. Calzavara, A.W. Zuardi, J.E. Hallak, J.A. Crippa, V.C. Abílio, Effects of cannabinoid and vanilloid drugs on positive and negative-like symptoms on an animal model of schizophrenia: The SHR strain, Schizophr. Res. (2014). https://doi.org/10.1016/j.schres.2014.01.039.

[90] L.E. Long, D.T. Malone, D.A. Taylor, Cannabidiol reverses MK-801-induced disruption of prepulse inhibition in mice, Neuropsychopharmacology. (2006). https://doi.org/10.1038/sj.npp.1300838.

[91] S.P.M. Fischer, I. Brusco, E.S. Brum, M.F.P. Fialho, C. Camponogara, R. Scussel, R.A. Machado-de-Ávila, G. Trevisan, S.M. Oliveira, Involvement of TRPV1 and the efficacy of α-spinasterol on experimental fibromyalgia symptoms in mice, Neurochem. Int. (2020). https://doi.org/10.1016/j.neuint.2020.104673.

[92] E. Galaj, G.H. Bi, H.J. Yang, Z.X. Xi, Cannabidiol attenuates the rewarding effects of cocaine in rats by CB2, 5-HT1A and TRPV1 receptor mechanisms, Neuropharmacology. (2020). https://doi.org/10.1016/j.neuropharm.2019.107740.

[93] C.J.P.A. Santos, C.A.J. Stern, L.J. Bertoglio, Attenuation of anxiety-related behaviour after the antagonism of transient receptor potential vanilloid type 1 channels in the rat ventral hippocampus, Behav. Pharmacol. (2008). https://doi.org/10.1097/FBP.0b013e3283095234.

[94] D.C. Aguiar, A.L.B. Terzian, F.S. Guimarães, F.A. Moreira, Anxiolytic-like effects induced by blockade of transient receptor potential vanilloid type 1 (TRPV1) channels in the medial prefrontal cortex of rats, Psychopharmacology (Berl). (2009). https://doi.org/10.1007/s00213-009-1532-5.

[95] Y.A. Blednov, R.A. Harris, Deletion of vanilloid receptor (TRPV1) in mice alters behavioral effects of ethanol, Neuropharmacology. (2009). https://doi.org/10.1016/j.neuropharm.2009.01.007.

[96] A.C. Campos, F.S. Guimarães, Evidence for a potential role for TRPV1 receptors in

the dorsolateral periaqueductal gray in the attenuation of the anxiolytic effects of cannabinoids, Prog. Neuro-Psychopharmacology Biol. Psychiatry. (2009). https://doi.org/10.1016/j.pnpbp.2009.08.017.

[97] V. Micale, L. Cristino, A. Tamburella, S. Petrosino, G.M. Leggio, F. Drago, V. Di Marzo, Anxiolytic effects in mice of a dual blocker of fatty acid amide hydrolase and transient receptor potential vanilloid type-1 channels., Neuropsychopharmacology. (2009). https://doi.org/10.1038/npp.2008.98.

[98] Retraction: Blocking TRPV1 in nucleus accumbens inhibits persistent morphine conditioned place preference expression in rats (PLoS ONE (2014) 9:8 (e104546) DOI: 10.1371/journal.pone.0104546), PLoS One. (2020). https://doi.org/10.1371/journal.pone.0230396.

[99] E. Yuen, S. Swanson, J.M. Witkin, Prediction of human efficacious antidepressant doses using the mouse forced swim test, Pharmacol. Biochem. Behav. (2017). https://doi.org/10.1016/j.pbb.2017.09.002.

[100] N.Z. Kara, Y. Stukalin, H. Einat, Revisiting the validity of the mouse forced swim test: Systematic review and meta-analysis of the effects of prototypic antidepressants, Neurosci. Biobehav. Rev. (2018). https://doi.org/10.1016/j.neubiorev.2017.11.003.

[101] R.E. Abdelhamid, K.J. Kovács, M.G. Nunez, A.A. Larson, Depressive behavior in the forced swim test can be induced by TRPV1 receptor activity and is dependent on NMDA receptors, Pharmacol. Res. (2014). https://doi.org/10.1016/j.phrs.2013.10.006.

[102] S. Hogg, A review of the validity and variability of the elevated plus-maze as an animal model of anxiety, in: Pharmacol. Biochem. Behav., 1996. https://doi.org/10.1016/0091-3057(95)02126-4.

[103] A.A. Costa, S. Morato, A.C. Roque, R. Tinós, A computational model for exploratory activity of rats with different anxiety levels in elevated plus-maze, J. Neurosci. Methods. (2014). https://doi.org/10.1016/j.jneumeth.2014.08.006.

[104] F.P. Back, A.P. Carobrez, Periaqueductal gray glutamatergic, cannabinoid and vanilloid receptor interplay in defensive behavior and aversive memory formation, Neuropharmacology. (2018). https://doi.org/10.1016/j.neuropharm.2018.03.032.

[105] H. Kawahara, G.M. Drew, M.J. Christie, C.W. Vaughan, Inhibition of fatty acid amide hydrolase unmasks CB 1 receptor and TRPV1 channel-mediated modulation of glutamatergic synaptic transmission in midbrain periaqueductal grey, Br. J. Pharmacol. (2011). https://doi.org/10.1111/j.1476-5381.2010.01157.x.

[106] J. Xing, J. Li, TRPV1 Receptor Mediates Glutamatergic Synaptic Input to Dorsolateral Periaqueductal Gray (dl-PAG) Neurons, J. Neurophysiol. (2007). https://doi.org/10.1152/jn.01023.2006.

[107] M.J. Millan, M. Brocco, The Vogel conflict test: Procedural aspects, γ-aminobutyric

acid, glutamate and monoamines, Eur. J. Pharmacol. (2003). https://doi.org/10.1016/S0014-2999(03)01275-5.

[108] S.E. File, P. Seth, A review of 25 years of the social interaction test, Eur. J. Pharmacol. (2003). https://doi.org/10.1016/S0014-2999(03)01273-1.

[109] R. Walz, R. Roesler, J. Quevedo, I.C. Rockenbach, O.B. Amaral, M.R.M. Vianna, G. Lenz, J.H. Medina, I. Izquierdo, Dose-dependent impairment of inhibitory avoidance retention in rats by immediate post-training infusion of a mitogen-activated protein kinase kinase inhibitor into cortical structures, Behav. Brain Res. (1999). https://doi.org/10.1016/S0166-4328(99)00077-7.

[110] J.W. Rudy, N.C. Huff, P. Matus-Amat, Understanding contextual fear conditioning: Insights from a two-process model, in: Neurosci. Biobehav. Rev., 2004. https://doi.org/10.1016/j.neubiorev.2004.09.004.

[111] R. Morris, Developments of a water-maze procedure for studying spatial learning in the rat, J. Neurosci. Methods. (1984). https://doi.org/10.1016/0165-0270(84)90007-4.

[112] S.A. Golden, H.E. Covington 3rd, O. Berton, S.J. Russo, A standardized protocol for repeated social defeat stress in mice, Nat Protoc. (2011). https://doi.org/10.1038/nprot.2011.361.

[113] S.F. Lisboa, L.H.A. Camargo, A.C. Magesto, L.B.M. Resstel, F.S. Guimarães, Cannabinoid modulation of predator fear: Involvement of the dorsolateral periaqueductal gray, Int. J. Neuropsychopharmacol. (2014). https://doi.org/10.1017/S1461145713001788.

[114] M.L. Seibenhener, M.C. Wooten, Use of the Open Field Maze to Measure Locomotor and Anxiety-like Behavior in Mice, J. Vis. Exp. (2015). https://doi.org/10.3791/52434.

[115] A. Ennaceur, Tests of unconditioned anxiety - Pitfalls and disappointments, Physiol. Behav. (2014). https://doi.org/10.1016/j.physbeh.2014.05.032.

[116] R. Marsch, E. Foeller, G. Rammes, M. Bunck, M. Kossl, F. Holsboer, W. Zieglgansberger, R. Landgraf, B. Lutz, C.T. Wotjak, Reduced Anxiety, Conditioned Fear, and Hippocampal Long-Term Potentiation in Transient Receptor Potential Vanilloid Type 1 Receptor-Deficient Mice, J. Neurosci. (2007). https://doi.org/10.1523/JNEUROSCI.3303-06.2007.

[117] G. de Brouwer, D.W. Wolmarans, Back to basics: A methodological perspective on marble-burying behavior as a screening test for psychiatric illness, Behav. Processes. (2018). https://doi.org/10.1016/j.beproc.2018.04.011.

[118] P.G. Saletti, C. Tomaz, Cannabidiol effects on prepulse inhibition in nonhuman primates, Rev. Neurosci. (2019). https://doi.org/10.1515/revneuro-2017-0101.

[119] T.M. Tzschentke, Measuring reward with the conditioned place preference (CPP) paradigm: Update of the last decade, Addict. Biol. (2007).

https://doi.org/10.1111/j.1369-1600.2007.00070.x.

[120] L. V. Panlilio, S.R. Goldberg, Self-administration of drugs in animals and humans as a model and an investigative tool, Addiction. (2007). https://doi.org/10.1111/j.1360-0443.2007.02011.x.

[121] A. Barik, M.J. Krashes, Remembering a Bad Taste, Neuron. 100 (2018) 765–767. https://doi.org/10.1016/j.neuron.2018.11.012.

[122] J.M. Farook, A. Krazem, B. Lewis, D.J. Morrell, J.M. Littleton, S. Barron, Acamprosate attenuates the handling induced convulsions during alcohol withdrawal in Swiss Webster mice, Physiol. Behav. (2008). https://doi.org/10.1016/j.physbeh.2008.05.020.

[123] E. Darcq, B.L. Kieffer, Opioid receptors: drivers to addiction?, Nat. Rev. Neurosci. (2018). https://doi.org/10.1038/s41583-018-0028-x.

[124] P.-E. Lutz, B.L. Kieffer, Opioid receptors: distinct roles in mood disorders., Trends Neurosci. (2013). https://doi.org/10.1016/j.tins.2012.11.002.

[125] T.A. LeGates, M.D. Kvarta, J.R. Tooley, T.C. Francis, M.K. Lobo, M.C. Creed, S.M. Thompson, Reward behaviour is regulated by the strength of hippocampus–nucleus accumbens synapses, Nature. (2018). https://doi.org/10.1038/s41586-018-0740-8.

[126] M. Trevisani, D. Smart, M.J. Gunthorpe, M. Tognetto, M. Barbieri, B. Campi, S. Amadesi, J. Gray, J.C. Jerman, S.J. Brough, D. Owen, G.D. Smith, A.D. Randall, S. Harrison, A. Bianchi, J.B. Davis, P. Geppetti, Ethanol elicits and potentiates nociceptor responses via the vanilloid receptor-1, Nat. Neurosci. (2002). https://doi.org/10.1038/nn0602-852.

[127] K.W. Ho, N.J. Ward, D.J. Calkins, TRPV1: a stress response protein in the central nervous system., Am. J. Neurodegener. Dis. (2012).

[128] K. Mackie, Distribution of cannabinoid receptors in the central and peripheral nervous system, Handb Exp Pharmacol. (2005). https://doi.org/10.1007/3-540-26573-2.

[129] V. Di Marzo, The endocannabinoid system: Its general strategy of action, tools for its pharmacological manipulation and potential therapeutic exploitation, Pharmacol. Res. (2009). https://doi.org/10.1016/j.phrs.2009.02.010.

[130] H.V. Curran, T.P. Freeman, C. Mokrysz, D.A. Lewis, C.J.A. Morgan, L.H. Parsons, Keep off the grass? Cannabis, cognition and addiction, Nat. Rev. Neurosci. (2016). https://doi.org/10.1038/nrn.2016.28.

[131] P.C. Casarotto, A.L.B. Terzian, D.C. Aguiar, H. Zangrossi, F.S. Guimares, C.T. Wotjak, F.A. Moreira, 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). https://doi.org/10.1038/npp.2011.207.

[132] R.N. Ruggiero, M.T. Rossignoli, J.B. De Ross, J.E.C. Hallak, J.P. Leite, L.S. Bueno-

Junior, Cannabinoids and vanilloids in schizophrenia: Neurophysiological evidence and directions for basic research, Front. Pharmacol. (2017). https://doi.org/10.3389/fphar.2017.00399.

[133] P.N. Newson, M. van den Buuse, S. Martin, A. Lynch-Frame, L.A. Chahl, Effects of neonatal treatment with the TRPV1 agonist, capsaicin, on adult rat brain and behaviour, Behav. Brain Res. (2014). https://doi.org/10.1016/j.bbr.2014.06.036.

[134] P. Newson, A. Lynch-Frame, R. Roach, S. Bennett, V. Carr, L.A. Chahl, Intrinsic sensory deprivation induced by neonatal capsaicin treatment induces changes in rat brain and behaviour of possible relevance to schizophrenia, Br. J. Pharmacol. (2005). https://doi.org/10.1038/sj.bjp.0706349.

[135] S.T. Niigaki, F.F. Peres, L. Ferreira, T. Libanio, D.A. Gouvea, R. Levin, V. Almeida, N.D. Silva, M.C. Diana, M.A. Suiama, M.B. Calzavara, V.C. Abilio, Young spontaneously hypertensive rats (SHRs) display prodromal schizophrenia-like behavioral abnormalities, Prog. Neuro-Psychopharmacology Biol. Psychiatry. (2019). https://doi.org/10.1016/j.pnpbp.2018.11.020.

[136] A.C. Panzenhagen, C.H.D. Bau, E.H. Grevet, D.L. Rovaris, An animal model of what? The case of spontaneously hypertensive rats, Prog. Neuro-Psychopharmacology Biol. Psychiatry. (2019). https://doi.org/10.1016/j.pnpbp.2019.03.012.

[137] K.R. Lezak, G. Missig, W.A. Carlezon, Behavioral methods to study anxiety in rodents, Dialogues Clin. Neurosci. (2017).

[138] E.J. Nestler, S.E. Hyman, Animal models of neuropsychiatric disorders, Nat. Neurosci. (2010). https://doi.org/10.1038/nn.2647.

[139] C. Baglioni, S. Nanovska, W. Regen, K. Spiegelhalder, B. Feige, C. Nissen, C.F. Reynolds, D. Riemann, Sleep and mental disorders: A meta-analysis of polysomnographic research, Psychol. Bull. (2016). https://doi.org/10.1037/bul0000053.

[140] P. Simor, G. van der Wijk, L. Nobili, P. Peigneux, The microstructure of REM sleep: Why phasic and tonic?, Sleep Med. Rev. (2020). https://doi.org/10.1016/j.smrv.2020.101305.

[141] E. Murillo-Rodríguez, V. Di Marzo, S. Machado, N.B. Rocha, A.B. Veras, G.A.M. Neto, H. Budde, O. Arias-Carrión, G. Arankowsky-Sandoval, Role of N-Arachidonoyl-Serotonin (AA-5-HT) in Sleep-Wake Cycle Architecture, Sleep Homeostasis, and Neurotransmitters Regulation, Front. Mol. Neurosci. (2017). https://doi.org/10.3389/fnmol.2017.00152.

[142] S. Turner, N. Mota, J. Bolton, J. Sareen, Self-medication with alcohol or drugs for mood and anxiety disorders: A narrative review of the epidemiological literature, Depress. Anxiety. (2018). https://doi.org/10.1002/da.22771.

[143] A. Viktorin, P. Lichtenstein, M.E. Thase, H. Larsson, C. Lundholm, P.K.E. Magnusson, M. Landén, The risk of switch to mania in patients with bipolar disorder during treatment with an antidepressant alone and in combination with a mood stabilizer, Am. J. Psychiatry. (2014). https://doi.org/10.1176/appi.ajp.2014.13111501.

[144] I. Pacchiarotti, D.J. Bond, R.J. Baldessarini, W.A. Nolen, H. Grunze, R.W. Licht, R.M. Post, M. Berk, G.M. Goodwin, G.S. Sachs, L. Tondo, R.L. Findling, E.A. Youngstrom, M. Tohen, J. Undurraga, A. González-Pinto, J.F. Goldberg, A. Yildiz, L.L. Altshuler, J.R. Calabrese, P.B. Mitchell, M.E. Thase, A. Koukopoulos, F. Colom, M.A. Frye, G.S. Malhi, K.N. Fountoulakis, G. Vázquez, R.H. Perlis, T.A. Ketter, F. Cassidy, H. Akiskal, J.M. Azorin, M. Valentí, D.H. Mazzei, B. Lafer, T. Kato, L. Mazzarini, A. Martínez-Aran, G. Parker, D. Souery, A. Özerdem, S.L. McElroy, P. Girardi, M. Bauer, L.N. Yatham, C.A. Zarate, A.A. Nierenberg, B. Birmaher, S. Kanba, R.S. El-Mallakh, A. Serretti, Z. Rihmer, A.H. Young, G.D. Kotzalidis, G.M. Macqueen, C.L. Bowden, S.N. Ghaemi, C. Lopez-Jaramillo, J. Rybakowski, K. Ha, G. Perugi, S. Kasper, J.D. Amsterdam, R.M. Hirschfeld, F. Kapczinski, E. Vieta, The International Society for bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders, Am. J. Psychiatry. (2013). https://doi.org/10.1176/appi.ajp.2013.13020185.

[145] M.R. Brandt, C.E. Beyer, S.M. Stahl, TRPV1 antagonists and chronic pain: Beyond thermal perception, Pharmaceuticals. (2012). https://doi.org/10.3390/ph5020114.

[146] L.A. McWilliams, B.J. Cox, M.W. Enns, Mood and anxiety disorders associated with chronic pain: An examination in a nationally representative sample, Pain. (2003). https://doi.org/10.1016/S0304-3959(03)00301-4.

[147] C. Blanco, N.D. Volkow, Management of opioid use disorder in the USA: present status and future directions, Lancet. (2019). https://doi.org/10.1016/S0140-6736(18)33078-2.

[148] T. Kantonen, T. Karjalainen, J. Isojärvi, P. Nuutila, J. Tuisku, J. Rinne, J. Hietala, V. Kaasinen, K. Kalliokoski, H. Scheinin, J. Hirvonen, A. Vehtari, L. Nummenmaa, Interindividual variability and lateralization of μ-opioid receptors in the human brain, BioRxiv. (2019). https://doi.org/10.1101/821223.

[149] A.R. Prossin, T.M. Love, R.A. Koeppe, J.K. Zubieta, K.R. Silk, Dysregulation of regional endogenous opioid function in borderline personality disorder, Am. J. Psychiatry. (2010). https://doi.org/10.1176/appi.ajp.2010.09091348.

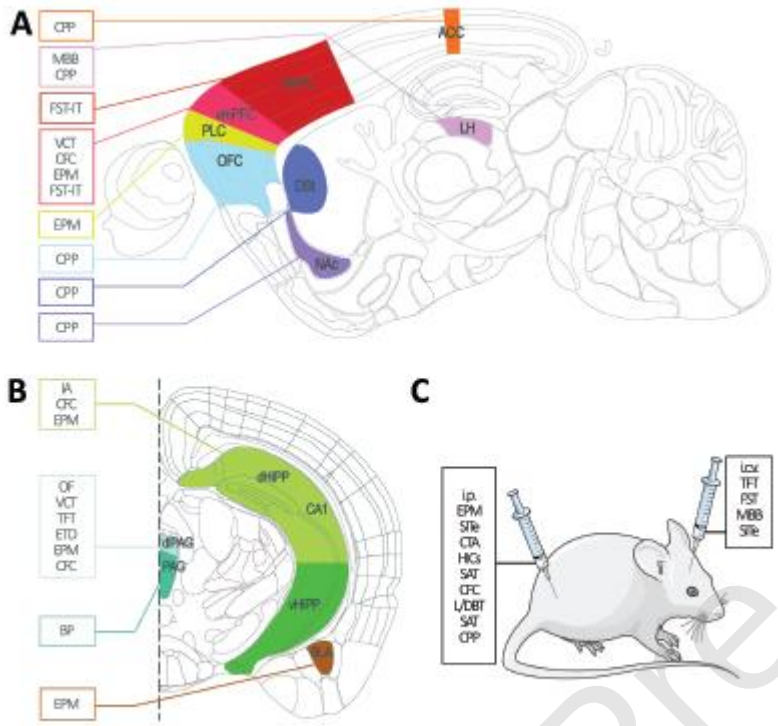
[150] B. Stanley, L. Sher, S. Wilson, R. Ekman, Y. yu Huang, J.J. Mann, Non-suicidal self-injurious behavior, endogenous opioids and monoamine neurotransmitters, J. Affect. Disord. (2010). https://doi.org/10.1016/j.jad.2009.10.028.

[151] R. Fu, J.-H. Ye, A. Bekker, D.M. Gregor, W. Zuo, Elevation of Transient Receptor Potential Vanilloid 1 Function in the Lateral Habenula Mediates Aversive Behaviors in

Alcohol-withdrawn Rats, Anesthesiology. (2019).

https://doi.org/10.1097/aln.0000000000002615.

Figure 1. Significant effects of TRPV1 antagonists on animal models of psychiatric disorders and addiction, relative to the site of injection**.**



Legend:

Site of injection: ACC, Anterior cingulate cortex**; AMG,** Amygdala**; BLA,** Basolateral amygdala**; CA1,** Cornu ammonis area 1**; dHIPP,** Dorsal hippocampus**; dPAG,** Dorsolateral periaqueductal grey**; Dst,** Dorsal striatum**; i.c.v.,** Intracerebrovascular**; i.p.,** Intraperitoneal**; LH,** Lateral habenula**; mPFC,** Medial prefrontal cortex**; NAc,** Nucleus accumbens**; OFC,** Orbitofrontal cortex**; PAG,** Periacqueductal grey**; PLC,** Prelimbic cortex**; vHIPP,** Ventral hippocampus**; vmPFC,** Ventromedial prefrontal cortex**.**

Animal models: BP, Behavioral procedure of exposure to threatening stimuli**; CFC,** Contextual fear conditioning**; CPP,** Conditioned place preference; **EPM,** Elevated plus maze**; ETD,** Escape threshold determination after dPAG electrical stimulation**; FST,** Forced swim test**; FST-IT,** Forced swim test-Immobility time**; IA,** Step-down inhibitory avoidance**; L/DBT,** Light/dark box task**; MBB,** Marble-burying behaviour**; OF,** Open field**; SAT,** Self-administration test**; SITe,** Social interaction test**; TFT,** Tail-flick test**; VCT,** Vogel conflict test.

Flow chart Legend

The selected articles are categorized according to four different parts of the search process: identification, screening, eligibility and inclusion. The format of this figure is based on PRISMA 2009 guideline (ref : Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21;6(7):e1000097. doi: 10.1371/journal.pmed.1000097.)

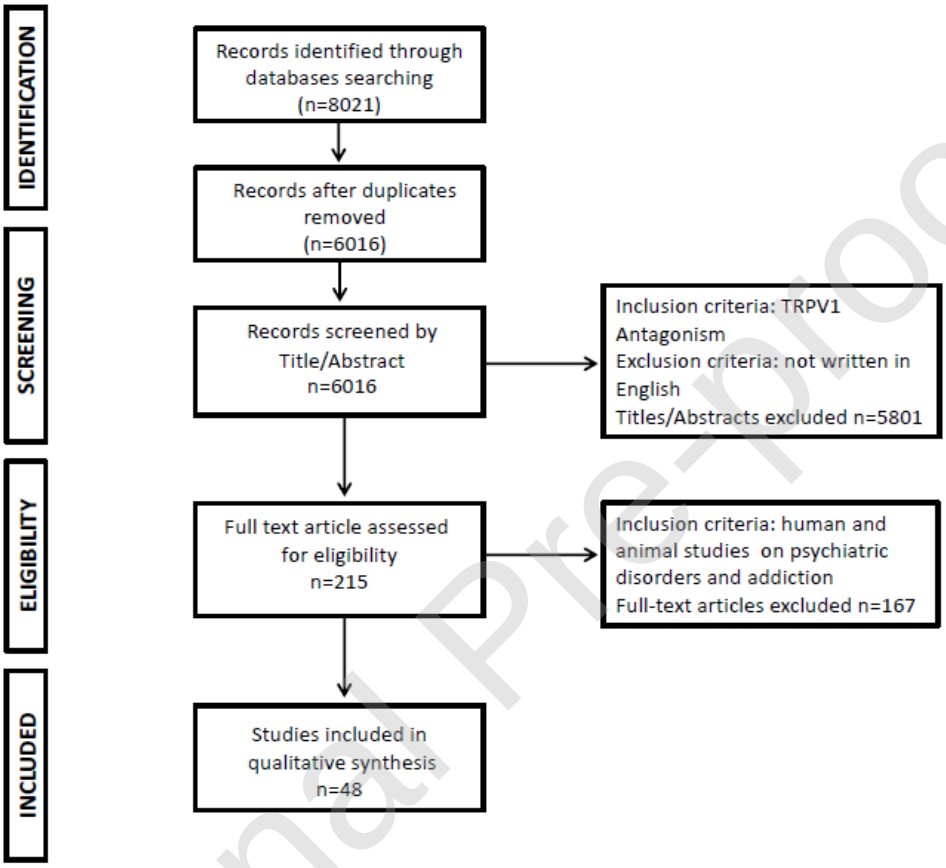


Table 1. Overview of studies on TRPV1 antagonism in animal models of psychiatric disorders

TRPV1 antagonists	Injection site	Model	Main findings	Strain	Reference
CPZ (1-5-10 µg/kg)	i.p.	EPM	CPZ increases the percentage of time spent in open arms.	SDR	[73]
CPZ (10 µg)	PFC	EPM	CPZ (10 µg) increased the percentage of entries in open arms and the percentage of time spent in open arms. CPZ (5 µg) prevented the AEA (10 µg) induced decrease in the percentage of entries in open arms and the percentage of time spent in open arms.	SDMR	[84]
CPZ (2.0 nmol)	vHipp	EPM	CPZ increases the percentage of entries in open arms and the percentage of time spent in open arms.	WR	[93]
CPZ (1-10-60 nmol)	vmPFC	EPM VCT WCE TFT	CPZ (1 nmol) increased the percentage of entries in open arms and the percentage of time spent in open arms on EPM. CPZ (10 nmol) significantly increased the percentage of entries in open arms on EPM. CPZ (1-10-60 nmol) increased the number of punished licks on VCT.	WR	[94]
CPZ (10 pmol)	dlPAG	EPM	Low dose CPZ alone did not alter the percentage of entries in open arms. On the contrary, WIN 55, 212–2 (a CB1 receptor agonist; 10 pmol) increased the percentage of entries in open arms and the percentage of time spent in open arms. However, the coadministration of CPZ and WIN 55, 212–2 did not alter the percentage of entries in open arms and the percentage of time spent in open arms. CBD (30 mmol) alone increased the percentage of entries in open arms but did not when co-administered with CPZ. OAE. Conversely, the use of CBD alone (60 nmol) did not alter the percentage of entries in open arms but increased the percentage of entries in open arms in coadministration with CPZ. These results suggest that the activation of TRPV1 receptors by high doses of cannabinoid compounds is responsible for the bell-shaped dose-response curves to cannabinoids.	WR	[96]
AA-5-HT (0.1-0.5-1-2.5-5 mg/kg) SB366791 (0.1-0.5-1-2.5 mg/kg)	i.p.	EPM	AA-5-HT increased the percentage of time spent in open arms and the percentage of entries in open arms in C57BL/6J mice, an effect comparable to diazepam (1 mg/kg), and abolished by olvanil (a TRPV1 agonist; 0.1mg/kg) and reversed by the CB1 receptor antagonist AM251 (1 mg/ kg). Similarly, SB366791 (1mg/kg) increased the percentage of time spent in open arms and the percentage of entries in open arms. Acute administration of low/intermediate (0.1- 1-2.5 mg/kg) but not high (5 mg/kg) doses of AA-5-HT produce an elevation of AEA, similarly to diazepam (1 mg/kg). At high doses of AA-5-HT(5 mg/kg) and SB366791 (2.5 mg/kg,) there was no anxiolytic-like effect or even an anxiogenic-like effect. In SM strain, no effect on EPM performance was found after acute or subchronic administration of AA-5-HT (0.1-0.5-1-2.5 mg/kg), while an anxiogenic-like effect resulted at the highest dose (5 mg/kg). On the other hand, chronic daily treatment (7 days) with AA-5-HT produced a dose-dependent decrease of a slightly anxiolytic-like effect for 1-2.5 mg/kg per day, abolished by olvanil. A significant opposite effect of an	C57BL/6J mice SM	[97]

			increase in the percentage of time spent in open arms and the percentage of entries in open arms was produced at the highest dose (5 mg/kg per day), an effect not abolished after the coadministration with SB366791, thus suggesting that this effect is not due to activation of TRPV1. Chronic, but not acute, administration of an intermediate dose of AA-5-HT (2.5 mg/kg per day) caused only the elevation of AEA, while diazepam (1mg/kg) produced the elevation of AEA or 2-AG.		
CPZ (10-30-60 nmol)	dlPAG	EPM VCT WCE TFT	CPZ (60 nmol) increased the percentage of OAE and the percentage of OAT during EPM and the number of punished licks on VCT. The administration of CPZ (60 nmol) outside dlPAG did not alter the performance on EPM.	WR	[52]
CPZ (0.1-1-10- 100 µg)	i.c.v.	SITe	CPZ (10 and 100 µg) increased social interaction time on SITe. Conversely, CAP (1 and 100 µg) reduced interaction time, an effect that was abolished by pretreatment with CPZ. Pretreatment with CAP (0.1 µg) significantly decreased interaction time due to administration of diazepam [2 mg/kg (i.p.)]. A combination of sub-effective or effective dosages of CPZ (1 and 100 µg) and diazepam [0.25 and 2 mg/kg (i.p.)] increased social interaction, without sedative or locomotor deficits. Absence of locomotor activity alterations assessed by OF.	SM	[54]
CPZ (0.1-1-10 nmol) SB366791 (1 nmol)	dPAG	ETD	CPZ (1-10 nmol) and SB366791 increased the electric current threshold required to inducing a panic-like response. Subeffective doses of CPZ (0.1 nmol), when co-administered with no- effective doses of ACEA (a CB1 agonist, 0.5 pmol) increase the electric current threshold required to inducing a panic-like response. The coadministration of CPZ (10 nmol) or of SB366791 with the CB1 receptor antagonist AM251 (75 pmol) suppress their effectiveness.	WR	[56]
6-IODO (1-3 nmol)	PLC	EPM VCT WCE TFT	6-IODO (1 nmol) did not exert any significant effect on EPM and VCT, while 6-IODO (3 nmol) increased the percentage of entries in open arms and the percentage of time spent in open arms on EPM and increased the number of punished licks on VCT. On EPM, coadministration between sub effective doses of 6-IODO (1 nmol) and the CB1/TRPV1 selective agonist ACEA (50 pmol) result in an increased percentage of entries in open arms and of the percentage of time spent in open arms on EPM. Pretreatment with the CB1 receptor antagonist AM251 (100.0 pmol) blocked the effect of 6-IODO (3 nmol) on EPM.	WR	[57]
CPZ (2-10-20 µM)	dHipp	IA (0.5-0.7 mA) CFC (0.3-0.7 mA) EPM	Intermediate doses of CPZ (10 µM) decrease the freezing behaviour on CFC at an electric current threshold of 0.7 mA. There were no significant differences between training and test session latencies on IA at an electric current threshold of 0.7 mA.	WR	[58]
AMG 9810 (0.003-0.03-0.3 µg)	CA1	EPM	AMG 9810 (0.03-0.3 µg) increased the percentage of time spent in open arms.	WR	[59]
AA-5-HT (0.125-0.25-0.5 nmol)	BLA	EPM	AA-5-HT (0.25-0.5 nmol) increased the percentage of time spent in open arms and the percentage of entries in open arms. On the contrary, CZP (1-10 nmol) and the inhibitor of the fatty acid amide hydrolase enzyme URB597 (0.01-0.01 µg)	SDR	[60]

CPZ (1-10 nmol)			administration did not alter the task performance. However, coadministration between CPZ (1-10 nmol) and of URB597 (0.01-0.01 μg) show differential effect, with an increase of the percentage of time spent in open arms and the percentage of entries in open arms at lower doses, and an opposite effect at higher doses.		
CPZ (10-30 nmol)	dlPAG	OF	The administration of the nitric oxide donor SIN-1 (150 nmol) alone or in combination with AEA (200 pmol) increased respectively, the distance travelled and the maximum speed. The coadministration of CPZ (30 nmol) abolished the flight reaction effects, thus implicating the role of TRPV1 or CB1 receptors, activated by AEA in the pro-aversive effects mediated by nitric oxide.	WR	[61]
CPZ (1-10-100-200 μg)	i.c.v.	TST FST	Both CPZ (100 and 200 μg) and a high dose of CAP (300 μg) significantly reduced the FST-IT and the TST-IT, an effect shared with fluoxetine (2.5-10 μg). The combination of a sub effective dose of CPZ (10 μg) with fluoxetine (1.75 μg) produced a synergistic effect in FST-IT and TST-IT. On the contrary, ineffective doses of CAP (10-100 μg) contrast the fluoxetine (10 μg) activity, while a higher dose (200 μg) produced a synergistic effect. The coadministration of an ineffective dose of CPZ (10 μg) with CAP (300 μg) produced no significant differences in FST-IT and TST-IT, suggesting that the antidepressant-like effect is TRPV1-mediated. Moreover, the coadministration with NMDA (0.1 μg) or with the tryptophan hydroxylase inhibitor PCPA (300 mg/kg/day) attenuated the antidepressant-like effect suggesting an activity mediated in part respectively by the glutamatergic tone inhibition and by a serotonergic activity. Absence of locomotor activity alterations assessed by OF.	SM	[63]
CPZ (0.1-1-10-100 μg)	i.c.v.	MBB	A high dose of CPZ (100 μg) decreases the MBB. Pretreatment with intermediate-dose CPZ (10 μg) decreased the MBB induced by CAP, high-dose AEA, AM40,4, and URB597.	SM	[64]
CPZ (1-10-30-60 nmol)	dlPAG	EPM OF	CPZ (1-30-60 nmol) decreased the number of crossing and the jumps on flight reaction on OF induced by NMDA. CPZ (60 nmol) increased the escape latency on EPM, an effect reversed by the coadministration of the CB1 receptor antagonist AM 251 (100 pmol), thus suggesting activity of AEA through CB1 receptors in TRPV1 antiaversive effectiveness.	WR	[65]
CPZ (10 nmol)	dlPAG	EPM VCT WCE TFT	CPZ or AEA (50 or 200 pmol) alone did not exert any significant effect on EPM; however, they increased the percentage of entries in open arms on EPM ($p<0.05$) in coadministration. The combination of AEA (50 or 200 pmol) and CPZ increased the number of punished licks on VCT and the latency of tail withdrawal on TFT.	WR	[66]
I-RTX (0.025 mg/kg)	i.p.	CFC RSDSP	I-RTX reduced the long and short term extinction phase freezing time on CFC.	C57BL/6JO laHsd mice	[67]
CPZ (10-30-60 nmol)	dPAG	EPM	CAP (1 nmol) decreased the percentage of entries in open arms and the percentage of time spent in open arms, an effect abolished by pretreatment with CPZ (30 mmol).	SAM	[68]
AMG9810 (0.003-0.03-0.3 mg)	vHipp	MWM	AMG9810 administration did not alter the performance on MWM.	WR	[69]

AA-5-HT (2.5-5mg/kg)	i.p.	FST	AA-5-HT (2.5 mg/kg) increased hippocampal BDNF mRNA expression level in stressed versus non-stressed rats. Stressed rats treated with AA-5-HT (2.5 mg/kg) showed an increase in hippocampal BDNF protein level at a higher dose of AA-5-HT (5 mg/kg) inducing the opposite effect on hippocampal mRNA expression level, with an increase in stressed rats and a decrease in non-stressed rats.	WR	[71]
CPZ (1-10- 60 nmol) 6-IODO (3 nmol)	vmPFC PL or IL regions	CFC	CPZ (10- 60 nmol) and 6-IODO is active on a panic-like response decreasing freezing behaviour, Δ heart rate and Δ mean arterial pressure. Pretreatment with 6-IODO reversed the effect of the panic-like response induced by CAP (1 nmol).	WR	[75]
CPZ (60 nmol)	dlPAG dmPAG vlPAG	BP	The comparison between rats exposed to cat vs rats not exposed or exposed to dummy cat provided no significant differences in the number of TRPV1 cells. However, there was an increase in the number of TRPV1-positive neurons expressing c-Fos and in the percentage of double-stained cells in rostral and medial dlPAG and dmPAG, thus suggesting an increased TRPV1 activity. Moreover, there was an increased number of TRPV1 cells in caudal dlPAG and dmPAG after the comparison between rats exposed to cat and rats exposed to dummy cat versus not exposed rats. Compared to rats not exposed ta o cat, exposed rats showed an increase of double-stained cells also in rostral and medial PAG and an increased number of TRPV1 cells in caudal vlPAG. An increased number of c-Fos cells was found in caudal dlPAG and dmPAG after the comparison between rats exposed to cat versus rat not exposed an exposed to a dummy cat.	WR	[76]
6-IODO (1-3 nmol)	dlPAG	EPM VCT WCE TFT	6-IODO (3 nmol) increased the percentage of entries in open arms on EPM. An ineffective dose of 6-IODO (1 nmol) increases the percentage of entries in open arms while co-administered with c-PTIO (a NO scavenger; 0.3nmol), suggesting a relationship between nitrergic and endovanilloid systems.	WR	[77]
AA-5HT (0.125-0.250-0.500 nmol)	mPFC	FST	AA-5HT (0.250 nmol) decreased FST-IT, an effect not entirely abolished by the CB1 receptor antagonist rimonabant (1.6 μg). Absence of locomotor activity alterations assessed by OF.	SDR	[62]
α-Spinasterol [0.5-1-2 mg/kg (i.p.)] CPZ [50 μg (i.c.v.)]	i.p. i.c.v.	FST EPM L/DBT	α-Spinasterol (1 and 2 mg/kg) decrease FST-IT. Coadministration of sub effective dose of α-Spinasterol (0.5 mg/kg) with CPZ (50 μg) decreased FST-IT. Absence of locomotor activity alterations assessed by OF.	SM	[78]
6-IODO (3nmol)	dlPAG	CFC	Pretreatment with 6-IODO reversed the effect of increased freezing behaviour, Δ heart rate and Δ mean arterial pressure and of decreased Δ cutaneous temperature mediated by the CB1 receptor antagonist AM251 (0.3nmol).	WR	[79]
AA-5HT (0.125-0.25-0.5 nmol) SB366791 (0.5-1-10 nmol)	vmPFC	FST	AA-5HT (0.25- 0.5 nmol) and SB366791 (10 nmol) decrease FST-IT. Coadministration of sub effective dose of SB366791 (0.5 nmol) with ineffective doses of the fatty acid amide hydrolase inhibitor URB 597 (0.001 nmol) decreased FST-IT. Coadministration of an effective dose of AA-5HT (0.25 nmol) and the CB1 receptor antagonist AM251 (10 pmol) abolished the effect of AA-5HT on FST-IT. AM 251 (10 pmol) did not abolish	WR	[82]

			the activity of the decrease of FST-IT due to an effective dose of SB366791 (10 nmol). Absence of locomotor activity alterations assessed by OF.		
CPZ (1-10-100 nmol)	ACC OFC	EPM	CPZ (100 nmol) reduced the percentage of high reward choice during effort-based and delay-based decision making. The same effect resulted from the administration of the CB1 agonist ACEA (100 pmol). Moreover, coadministration of sub effective doses of CPZ (10 nmol) with ACEA (100 pmol) showed an effect in reducing the percentage of high reward choice during effort-based decision making. However, the comparison between a group treated with this combination versus a group treated only with ACEA (100 pmol) resulted in an increase of the percentage of high reward choice during effort-based and delay-based decision making, thus suggesting a complex role of TRPV1 in decision making.	WR	[85]
AA-5-HT (1 mg/kg)	i.p.	L/DBT CFC OF	Compared with control and CB1 agonist ACEA (1 mg/kg) groups, AA-5-HT treated BCJ mice showed rearing frequency and an increase in total distance travelled on L/DBT. Compared with control and ACEA (1 mg/kg) groups, AA-5-HT treated B6 mice showed a decrease in the percentage of baseline movement and total distance travelled on L/DBT. No differences in % of time spent in the centre of the chamber, rearing frequency and absence of locomotor activity alterations assessed by OF. AA-5-HT and ACEA (1 mg/kg) reduced dopamine release in the BLA of BCJ mice and decreased the dopamine efflux in the NAc of B6 mice. No differences in % of time spent in the centre of the chamber, rearing frequency and absence of locomotor activity alterations assessed by OF.	male low anxiety-like mice (C57BL/6 J; [B6]) male high anxiety-like mice (BALB/cJ; [BCJ])	[86]
CPZ (20 mg/kg)	i.p.	PPI	CPZ and CBD (5 mg/kg) did not affect PPI by themselves. However, CPZ prevent the CBD-mediated restoration of the deficit in sensorimotor gating induced by the administration of the NMDA receptor antagonist MK-801 (1 mg/kg),	SM	[90]
CPZ (1-5-10 mg/kg)	i.p.	SITe	In SHR, CPZ did not alter the time spent on SITe, while CAP (2.5 mg/kg) increased the time spent on SITe. In WR, CPZ (5 mg/kg) increased the time spent in SITe. The opposite effect was mediated by CPZ (10 mg/kg). ACEA (0.1-0.3-1 mg/kg) did not alter the time spent in SITe both in SHR and in WR.	SHR WR	[89]
CPZ (1-5-10 mg/kg)	i.p.	CFC	CPZ (1-5-10 mg/kg) did not alter CFC freezing response in SHR and WR. CAP increased CFC freezing response in SHR (0.5 mg/kg). In WR CAP (0.1 mg/kg) increased CFC freezing response while CAP (0.5-2.5 mg/kg) decreased CFC freezing response. TRPV1 immunoreactivity in SHR is lower in CA1 and PLC, and increased in BLA.	SHR WR	[88]
α-Spinasterol (0.1-0.3-1 mg/kg, p.o.) SB-366791 (1 mg/kg, p.o.)		FST OF	Reserpine (1 mg/kg/day for 3 days) induced mechanical allodynia and depressive-like behaviours in an experimental model of fibromyalgia. α-spinasterol (0.1-0.3-1 mg/kg, p.o.), and SB-366791 were effective against the reserpine-induced mechanical allodynia. α-Spinasterol (0.3 mg/kg, p.o.) and SB-366791 significantly reduced the FST-IT induced by reserpine.	SM	[91]

Abbreviations: 2-AG, 2-arachidonoylglycerol**; 6-IODO,** 6-iodo-nordihydrocapsaicin**; AA-5-HT,** N-arachidonoyl-serotonin**; ACC,** Anterior cingulate cortex**; ACEA,** Arachidonyl-2-chloroethylamide**; AEA,** Anandamide**; AM251,** 1-(2,4-Dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide**; AMG,** Amygdala**; BLA,** Basolateral amygdala**; BP,** Behavioral procedure of exposure to threatening stimuli**; CA1,** Cornu Ammonis area 1**; CAP,** Capsaicin**; CFC,** Contextual fear conditioning**; c-PTIO,** 2-4-carboxyphenyl-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide**; CPZ,** Capsazepine**; d,** Dorsal**; dl,** Dorsolateral**; dm,** Dorsomedial**; EPM,** Elevated plus maze**; ETD,** Escape threshold determination after dPAG electrical stimulation**; FST,** Forced swim test**; Hipp,** Hippocampus**, IA,** Step-down inhibitory avoidance**; i.c.v.,** Intracerebrovascular**, IL,** Infralimbic**; i.p.,** Intraperitoneal**; I-RTX,** Iodoresiniferatoxin**; IT,** Immobility time**; L/DBT,** Light/dark box task**; m,** Medial**; MBB,** Marble-burying behavior**; MWM,** Morris water maze**; NMDA,** N-methyl-D-aspartate**; NAc,** Nucleus Accumbens**; OF,** Open field**; OFC,** Orbitofrontal cortex**; PAG,** Periacqueductal grey**; PCPA,** Para-chlorophenylalanine**; PFC,** Prefrontal cortex**; PL,** Paralimbic**; PLC,** Prelimbic cortex**; p.o.,** Per os; **PPI,** Prepulse inhibition; **RSDSP,** Repeated social defeat stress protocol**; s.c.,** Subcutaneous injection**; SDR,** Sprague Dawley rats**; SHR,** Spontaneously hypertensive rat; **SIN-1,** 3-morpholinosylnomine hydrochloride**; SITe,** Social interaction test**; SM,** Swiss mice; **SP,** Stress protocol**; TFT,** Tail-flick test**; VCT,** Vogel conflict test**; v,** Ventral**; vl,** Ventrolateral**; vm,** Ventromedial**; WR,** Wistar rats**; WCE,** Water consummatory evaluation**.**

Table 2. Overview of studies on TRPV1 antagonism in animal models of addiction

Drug	TRPV1 antagonist	Injection site	Model	Main findings	References
Ethanol	CPZ (10 mg/kg)	i.p.	CTA HIC	TRPV1-KO mice show increased ethanol preference and consumption the in confront of WT mice. There were no differences in preference to other solutions (saccharine or quinine). TRPV1-KO mice reported reduced sensitivity to ethanol-induced sedation (3.2-3.4 g/kg) and faster recovery from ethanol-induced motor incoordination (2 g/kg). No differences were found between TRPV1-KO and WT mice for CTA or acute ethanol withdrawal severity measured with HICs. In WT mice CPZ (10 mg/kg) decreased the sedative effects of low dose-ethanol (3.4 g/kg) and on the recovery time for the ethanol-induced motor impairments (2 g/kg).	[95]
MAP (2 mg/kg/day x 3 treatment)	-	i.p.	CPP	Repeated MAP treatment increased TRPV1 mRNA expression at 1, 2, 6, 24, 48 h, and 1 week in frontal cortex but not in the striatum or hippocampus.	[53]
Cocaine	SB366791 (0.1–1 mg/kg)	i.v.	SAT	SB366791 did not alter cocaine reinforcements but significantly reduced the cocaine-induced reinstatement of cocaine-seeking behaviour.	[55]
Morphine 1-3-10 mg/kg, s.c.	CPZ (0.1-1-10 nM)	NAc DSt	CPP	CPZ (1-10 nM) injected the in bilateral NAc core showed a dose-dependent effect in decreasing persistent morphine CPP after both one week and three weeks withdrawal. Low-dose CPZ (0.di hat no effect on CPP. Unilateral NAc or DSt administration failed to influence persistent morphine CPP. Morphine administration increased TRPV1 immunoreactivity only at high dosage (10 mg/kg) and was associated with higher TRPV1-positive asymmetric synapses in withdrawal animals.	[70]
Ethanol 40mM		-	-	LTD in NAc induced by ethanol was rescued by endocannabinoid signalling acting on TRPV1 receptors, thus demonstrating a novel form of TRPV1-dependent LTD in the NAc shell that may be critical for ethanol dependence.	[74]
Morphine 5 mg/kg, s.c.	CPZ [1.25-2.5 mg/kg; (i.p.)] SB366791 [37.5-75-150 µg/kg (i.p.)]; [0.2 ng (in DSt)	i.p. DSt	CPP	Morphine increased the TRPV1 mRNA expression of protein levels and the [^{3}H]resiniferatoxin receptor binding in the DSt. Pretreatment with CPZ (2.5 mg/kg) and with SB366791 (150 µg/kg) decreased CPP. Local injection of SB366791 into DSt decreased CPP. On the other hand, CAP (200 µg/kg) increased CPP, an effect blocked by pretreatment with SB366791 (150 µg/kg). [^{3}H]DAMGO autoradiography showed increased binding in DSt after repeated morphine treatments, an effect diminished after CPZ (2.5 mg/kg) treatment. SB366791 (150 µg/kg) blocked the adenylyl cyclase type 1 cells increasing in DSt of morphine-CPP mice. The p38/ NF-κB pathway, involved in morphine reward in rats, is suppressed by SB366791 administration in DSt.	[72]
Morphine 5mg/kg	SB366791 [0.15-0.3-0.6mg/kg (i.p.)];	i.p. NAc	CPP	In CD-1 mice, SB366791 (0.15-0.3 mg/kg; i.p. and 0.5 ng/site, unilateral) decreased CPP mice. SB366791 (0.15 mg/kg) induced a reduction of the number of cells and expression morphine reward-associated proteins phospho-p38 MAPK, adenylyl cyclase type 1 and p-NF-κB in the NAc of morphine CPP CD-1 mice. TRPV1-KO mice did not develop morphine-induced CPP.	[80]

(every 2 days for 10 days)	[0.2-0.5-2 ng/site (unilateral in NAc)]				
Morphine self-administration	SB366791 (150-300 µg/kg) AMG9810 (300 µg /kg)	-	SAT	SB366791 (150-300 µg/kg) and AMG9810 decreased morphine self-administration. AMG9810 prevented morphine-induced c-fos expression into the NAc. SB366791 decreased both the morphine-priming reinstatement and the anxiolytic-like effect during morphine abstinence period.	[81]
Morphine (10 mg/kg/day, for 7 days)	CPZ (10nM)	-	CPP	CPZ decreased the excitatory glutamatergic transmission only in NAc during reinstatement, contrary to CAP (1-10 µM) and the CB1 receptor antagonist AM251 (10 µM).	[83]
MAP (1 mg/kg)	CPZ (2.5-5 mg/kg) SB366791 (0.3-0.6-5-10 mg/kg)	i.p.	CPP SAT	Pretreatment with CPZ (5 mg/kg) SB366791 (0.6 mg/kg) inhibit the effect on MAP-induced CPP reinstatement. SB366791 (5-10 mg/kg) significantly decreased MAP self-administration. Pretreatment with CPZ (5 mg/kg) and SB366791 (5 mg/kg) significantly decreased the MAP-seeking behaviour on SASA significant increased binding of [^{3}H]resiniferatoxin was founded in MAP-treated mice. Dopamine transporter binding levels in NAc and DSt was significantly lower in MAP-treated mice, a down-regulation reversed by CPZ (5 mg/kg). Pretreatment with CPZ (5 mg/kg) reduced the extracellular dopamine release induced by MAP in NAc. After CPP development, TRPV1 mRNA was significantly higher in NAc, but not in the DSt region, after both CPP development and reinstatement. The level of TRPV1 protein was higher both in NAc and DSt after CPP development but up-regulated only in the NAc after the reinstatement. TRPV1-KO mice did not develop MAP-induced CPP.	[34]
Ethanol	CPZ (0.1 to 100 µM) AMG9810 (0.1 to 100 µM)	Lat. Hab.	CPP EPM MBB FST	CPZ decreased ethanol consumption and CPP upon resuming drinking and elicited a CPP in EtOH-WD. EtOH-WD showed an increased excitatory glutamatergic transmission in Lat. Hab., an activity reversed by CPZ and AMG9810 administration. CPZ or CAP significantly increased %OAT on EPM and decreased the MBB In EtOH-WD; on FST CPZ did not alter the latency or total immobility time.	[151]
Cocaine	CPZ (3 and 5 mg/kg)	i.p.	SAT	CPZ (5 mg/kg) did not alter cocaine self-administration. Pretreatment with CPZ (3 and 5 mg/kg) dose-dependently prevent the CBD (20 mg/kg)-mediated attenuation of cocaine self-administration.	[92]
Cocaine	CPZ (5 mg/kg) SB366791 (5-10µM)	i.p. NAc	CPP	Pretreatment with CPZ abolished the cocaine-primed reinstatement of CPP; the opposite effect was obtained with the administration of CAP (0.3 mg/kg). CAP combined with CPZ prevented enhanced reinstatement of cocaine CPP. TRPV1 mRNA and protein expression in the NAc are increased after the reinstatement of cocaine CPP.	[1]

	Cocaine-induced reinstatement was absent in TRPV1-KO mice. NAc microinjections of SB366791 (5-10μM) decreased D1-like dopamine receptor and cocaine-induced Ca^{2+} influx and reduced the increase of total CaMKII and phospho-CaMKII induced by cocaine. Moreover, SB366791 attenuated the cocaine reinstatement mediated by the administration of SKF-81297 (a D1-like receptors agonist).

Abbreviations: AM251, 1-(2,4-Dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide**; CAP,** Capsaicin**; CPP,** Conditioned place preference**; CPZ,** Capsazepine**; condition,** Conditioned taste aversion**; DA,** Dopamine**; DAT,** Dopamine transporter**; DSt,** Dorsal striatum**; eCB,** Endocanaobinoids**; EP,** Ethanol preference**; EPM,** Elevated plus maze**; EtOH-N,** Ethanol naïve rats**; EtOH-WD,** Ethanol-withdrawn rats**; FST,** Forced swim test**; HIC,** Handling-induced convulsions**; ICR (CD1),** Institute for cancer research mice**; i.p.,** Intraperitoneal**; i.v.,** Intravenous**; KO,** Knockout**; Lat. Hab.,** Lateral habenula**; LTD,** Long-term depression**; MAP,** Methamphetamine**; MBB,** Marble-burying behaviour**; MOR,** Mu-opioid receptors**; SDR,** Sprague dawley rats**; NAc,** Nucleus Accumbens**; RRS,** Rotarod test**; SAT,** Self-administration test**.**