Life Sciences 92 (2013) 410–414

Contents lists available at SciVerse ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Minireview

# When a TRP goes bad: Transient receptor potential channels in addiction

Seth A. Wescott [a,1], Manish Rauthan [c,1], X.Z. Shawn Xu [a,b,*]

[a] Life Sciences Institute and Neuroscience Graduate Program, University of Michigan, Ann Arbor, MI 48109, USA
[b] Department of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, MI 48109, USA
[c] Department of Cellular & Molecular Biology, University of Gothenburg, Gothenburg, 41390, Sweden

ARTICLE INFO

*Article history:*
Received 10 March 2012
Accepted 7 July 2012

*Keywords:*
Drug
Abuse
Addiction
Nicotine
Cocaine
Ethanol
Behavior
TRP
Channel
Nucleus accumbens
Prefrontal cortex
*C. elegans*

ABSTRACT

Drug addiction is a psychiatric disease state, wherein a drug is impulsively and compulsively self-administered despite negative consequences. This repeated administration results in permanent changes to nervous system physiology and architecture. The molecular pathways affected by addictive drugs are complex and inter-dependent on each other. Recently, various new proteins and protein families have been discovered to play a role in drug abuse. Emerging players in this phenomenon include TRP (Transient Receptor Potential) family channels, which are primarily known to function in sensory systems. Several TRP family channels identified in both vertebrates and invertebrates are involved in psychostimulant-induced plasticity, suggesting their involvement in drug dependence. This review summarizes various observations, both from studies in humans and other organisms, which support a role for these channels in the development of drug-related behaviors.



**Contents**



## Introduction

In humans, drugs of abuse target different neurotransmitter systems, but they all converge on midbrain dopamine (DA) neurons in the ventral tegmental area or in the projections of these neurons to forebrain structures, such as the amygdala, striatum, especially the nucleus accumbens, and prefrontal cortex (Lammel et al., 2008). Some drugs have a straightforward action on DA signaling, such as cocaine and amphetamine, which act as indirect monoamine agonists by blocking the clearance of DA from the parenchyma, thereby prolonging the activity of the transmitter at its cognate receptors (Porter-Stransky et al., 2011; Stuber et al., 2005). The action of other drugs, such as nicotine and ethanol, seems to be more complex. These drugs mainly interact with G protein-coupled receptors, monoamine transporters, or alter the function of ion channels to modulate DA levels in appetitive motivation (Luscher and Ungless, 2006), learning (Jones et al., 2010), and executive control circuits in the brain (Koob and Volkow, 2010). An increasing number of studies suggest that transient receptor potential (TRP) channels are important

* Corresponding author at: Life Sciences Institute and Neuroscience Graduate Program, University of Michigan, Ann Arbor, MI 48109, USA, Tel.: +1 734 615 9311.
*E-mail address:* shawnxu@umich.edu (X.Z.S. Xu).
[1] These authors contributed equally to this review.

0024-3205/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.lfs.2012.07.008

targets of second messengers in these mammalian neural circuits that become compromised in addiction.

TRP channels are perhaps best known for their role as one of the prominent protein superfamilies modulating sensory signaling pathways (Montell, 2001, 2005; Nilius and Owsianik, 2011). The members of the TRP channel superfamily have six transmembrane domains that form homo- or heterotetrameric cation channels, with strong homology to its founding member, the *Drosophila* protein, TRP. The TRP superfamily includes seven subfamilies: canonical (TRPC), vanilloid (TRPV), ankyrin (TRPA), melastatin (TRPM), polycystin (TRPP), MucoLupin (TRPML) and NompC-like (TRPN) (Fig. 1). These functionally divergent, non-selective cation channels are conserved from nematodes to vertebrates and are considered to be coincidence detectors and convergent signal integrators (Kang et al., 2010; Xiao and Xu, 2009). The diverse activation mechanisms and biophysical properties of different TRP family members allow these proteins to modulate complex behaviors, especially behaviors related to drug-seeking and drug-taking (Cavalie, 2007; Gulbransen et al., 2008; Oliveira-Maia et al., 2009). Here, we outline the emerging role for TRP channels in drug dependence (Table 1).

## Canonical TRP (TRPC) channels in drug dependence

Of the TRP channel superfamily, TRPC channels are most closely homologous to the *Drosophila* TRP, the founding member of the TRP channel superfamily (Montell and Rubin, 1989). These channels are mainly activated in a phospholipase C (PLC)-dependent manner (Venkatachalam and Montell, 2007). In humans, there are six TRPC channels that form homo- and heterotetramers (Venkatachalam and Montell, 2007). These are multi-functional channels implicated in the regulation of diverse physiological functions, such as kidney filtration, acrosomal reaction, vascular tone and pheromone recognition (Nilius and Owsianik, 2011). Specific to drug dependence, genome-wide association (GWA) studies between smoker and non-smoker cohorts implicate TRPC channels in nicotine addiction. These studies particularly identify the TRPC7 channel among other novel genes that were previously not associated with addiction (Bierut et al., 2007; Lessov-Schlaggar et al., 2008). TRPC7 is enriched in brain tissue, especially in striatal regions where it impinges on neurons imperative for behavioral responses to drugs of abuse (Numaga et al., 2007). Interestingly, another GWA study implicates TRPC4 in drug dependence, based on comparisons between European-American and African-American polysubstance abusers or non-abusing controls (Uhl et al., 2008). TRPC4 is important for the vasorelaxation of arteries and neurotransmitter release from thalamic dendrites (Cavalie, 2007).

While direct evidence demonstrating a role for mammalian TRPC channels in drug addiction is still lacking, rodent fear-learning studies reveal a clear role for TRPC5 in forming associations between an unconditioned stimulus (US) and a conditioned stimulus (CS) in the amygdala (Riccio et al., 2009). The amygdala is critical for learning associations between the CS and US (Schafe et al., 2005), and human drug users show event-related potentials (ERP) viewing drug-related paraphernalia similar to the ERPs they show when viewing positive emotional stimuli (Dunning et al., 2011). In a functional MRI study, the amygdala showed

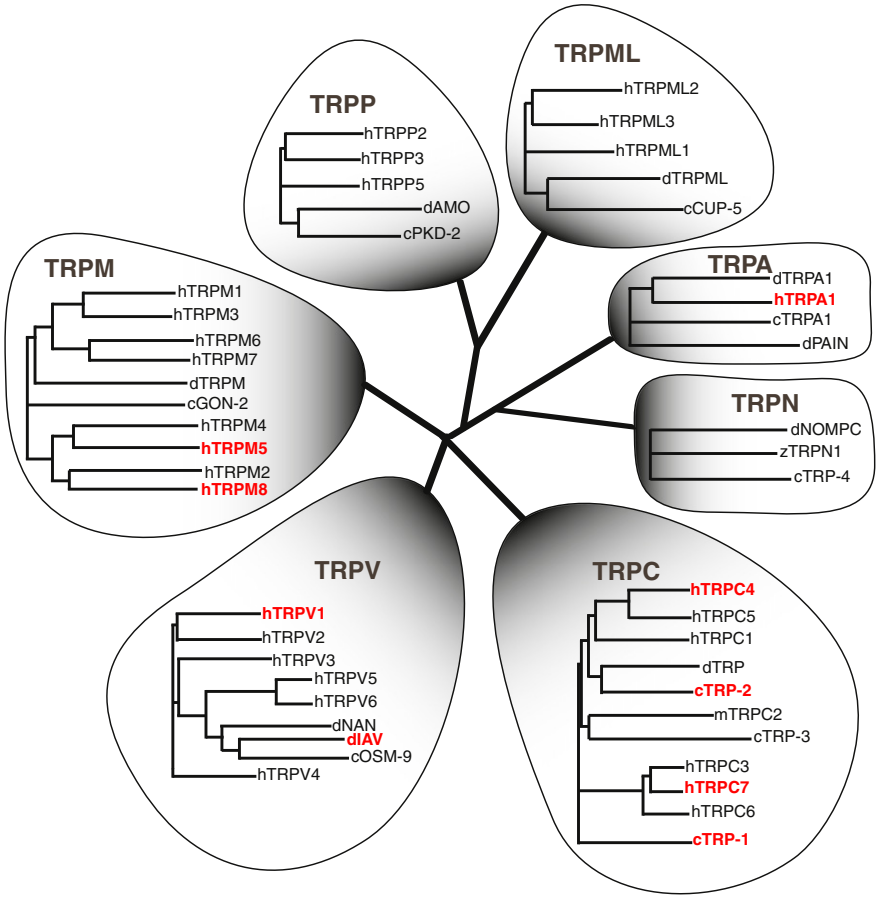


**Fig. 1.** Phylogenetic tree of all the human TRP channel families along with representative members from other species. Protein marked in red are involved in drug addiction. Different species are represented by prefixes: c. *C. elegans*, d. *Drosophila melanogaster*, z. *Danio rerio*, m. *Mus musculus*, h. *Homo sapiens*.

**Table 1**
Putative roles for mammalian TRP channels in drug abuse.

| Mammalian channel | Brain region/ pathway | Putative role(s) | References |
|---|---|---|---|
| TRPA1 | Nociceptive pathways | Withdrawal pain | Bang et al. (2007) |
| | | Nicotine dependence | Talavera et al. (2009) |
| TRPC1 | Nucleus accumbens Prefrontal cortex | Synaptic plasticity | Kim et al. (2003) |
| TRPC3 | Striatum | Synaptic plasticity | Berg et al. (2007) |
| | | Nicotine dependence | Feng et al. (2006) |
| | | | Jia et al. (2007) |
| TRPC4 | Thalamus | Dendritic neurotransmission | Cavalie (2007) |
| | | | Uhl et al. (2008) |
| TRPC5 | Nucleus accumbens | Appetitive processing | Riccio et al. (2009) |
| | Amygdala | CS-US associations | Schafe et al. (2005) |
| TRPC7 | Striatum | Synaptic plasticity | Bierut et al. (2007) |
| | | | Berg et al. (2007) |
| | | | Lessov-Schlaggar et al. (2008) |
| | | | Numaga et al. (2007) |
| TRPM5 | Gustatory pathways | Peripheral CS processing | Gulbransen et al. (2008) |
| | | | Oliveira-Maia et al. (2009) |
| TRPM8 | Nociceptive pathways | Peripheral CS processing | Benedikt et al. (2007) |
| | | Ethanol dependence | Willis et al. (2011) |
| TRPV1 | Prefrontal cortex | Synaptic plasticity | Benedikt et al. (2007) |
| | Striatum | Ethanol dependence | Blednov and Harris (2009) |
| | Amygdala | | Grueter et al. (2010) |
| | | | Kauer and Gibson (2009) |
| | | | Liu et al. (2004) |
| | | | McClung and Hirsch (1998) |
| | | | McClung and Hirsch (1999) |
| | | | Tian et al. (2010) |
| | | | Venkatachalam and Montell (2007) |

decreased focal signal in response to an unpredicted cocaine administration (Breiter et al., 1997).

Cocaine modulates intrinsic plasticity of accumbens neurons (Kourrich et al., 2007) and affects metabotropic glutamate receptor (mGluR)-dependent synaptic plasticity in the nucleus accumbens (Huang et al., 2011) and prefrontal cortex (Huang et al., 2007). TRPC1 is an mGluR target in cerebellar Purkinjie cells (Kim et al., 2003), while both TRPC3 and TRPC7 are known targets of mGluR activity in striatal cholinergic interneurons (Berg et al., 2007). Moreover, TRPC5 mRNA is located within the shell subregion of the nucleus accumbens (Fowler et al., 2007), which is preferentially activated by cocaine (Aragona et al., 2008) and is particularly responsive to the unconditioned aspects of stimuli (Wheeler et al., 2011). It will be interesting to test whether TRPC channels have a role in the motivational, learning and executive control circuits drugs of abuse undermine when recreational drug users succumb to addiction.

The most direct evidence supporting a role for TRPC channels in drug-related behaviors comes from the nematode *Caenorhabditis elegans*. *C. elegans* requires the TRPC homologues TRP-1 and TRP-2 for nicotine-dependent behaviors (Feng et al., 2006). The *C. elegans* genome encodes members of all the seven TRP channel subfamilies (Xiao and Xu, 2011). Most of these members are involved in various chemosensory or mechanosensory pathways, either as primary sensors or as signal transducers or amplifiers (Xiao and Xu, 2011). There are three TRPC subfamily members in *C. elegans*: TRP-1, TRP-2 and TRP-3. While TRP-3 is enriched in sperm, the neuronally-expressed TRP-1 and TRP-2 modulate nicotine-dependent behavior in *C. elegans* (Feng et al., 2006; Xu and Sternberg, 2003).

*C. elegans* exhibits a variety of behavioral responses to nicotine, including acute response, adaptation, withdrawal and sensitization. Specifically, acute nicotine treatment stimulates locomotion (Feng et al., 2006), an innate behavior that forms the foundation of most, if not all behaviors (Piggott et al., 2011). Repeated intermittent administration of nicotine sensitizes *C. elegans* to nicotine, and long-term nicotine treatment elicits tolerance to the drug (Feng et al., 2006). Nicotine-adapted worms exhibit hyperlocomotion when placed in a nicotine-free environment, a withdrawal response to nicotine (Feng et al., 2006). These nicotine dependent behaviors require the *C. elegans* nicotinic acetylcholine receptor (nAChR) genes *acr-15* and *acr-16* (Feng et al., 2006). Both genes function in neurons to modulate nicotine responses in worms. Notably, *trp-1* and *trp-2* mutant animals are severely defective in nicotine dependent behaviors (Feng et al., 2006). Interestingly, TRP-1 and TRP-2 appear to act downstream of the nAChRs ACR-15 and ACR-16 in a PLC-dependent manner (Feng et al., 2006). This work further demonstrates that neuronal expressions of ACR-15 and ACR-16 as well as TRP-1 and TRP-2 are required for nicotine-induced behaviors in *C. elegans* (Feng et al., 2006). Moreover, neuronal $Ca^{2+}$ influx is greatly diminished in response to nicotine exposure in *trp-1* or *trp-2* null mutant worms, suggesting that these TRPC channels functionally regulate neuronal nicotine responses (Benowitz, 2010; Feng et al., 2006). Interestingly, the mouse α4β2 nAChR, which is known to be essential for nicotine-associated behaviors, can rescue nicotine behavioral defects in *acr-15* null mutant animals; similarly, the human TRPC3 channel functionally substitutes for worm TRP-2 in nicotine responses (Feng et al., 2006), suggesting that the role of TRPC channels and nAChRs in nicotine responses may be evolutionarily conserved.

In addition to this functional interaction with nAChR, TRPC channels interact with both CREB and Homer proteins, which are important for gene transcription related to drug dependence and drug-related changes in neural plasticity (Pandey et al., 2005; Ron and Jurd, 2005; Talavera et al., 2008). Both TRPC3 and TRPC6 overexpressions potentiate phosphorylation of CREB which stimulates both early and late CREB-dependent gene transcription (Jia et al., 2007). The role of this CREB-dependent transcription in drug-induced neural plasticity is well documented (Kumar et al., 2011; Philpot et al., 2012). Homer proteins are a group of EVH1 domain-containing scaffolding proteins involved in coupling metabotropic glutamate receptors (mGluR1) and inositol-1,4,5-triphosphate receptors ($IP_3R$) with TRPC channels (Mast et al., 2010; Yuan et al., 2003). Homer-$IP_3R$ interactions regulate trafficking of TRPC3 to the plasma membrane, while coupling of mGluR and $IP_3R$ with TRPC channels results in mGluR-mediated neuronal conductance, which may have a role in drug-related behavioral plasticity (Kim et al., 2006). Together, these data make a case for more in-depth studies of mammalian TRPC channels in relation to drugs of abuse.

## Vanilloid TRP (TRPV) channels in drug dependence

TRPV channels share homology with the founding member of the subfamily, TRPV1, which was identified through its response to the vanilloid capsaicin. These channels respond to a range of stimuli, such as heat, mechanical stimulation, and pro-inflammatory agents as well as other chemical stimuli (Kauer and Gibson, 2009; Venkatachalam and Montell, 2007). Mammalian neurons expressing TRPV1 show a decrease in the amplitude of capsaicin-induced action potentials after acute nicotine treatment. Moreover, repeated and intermittent nicotine treatment sensitizes capsaicin-induced currents in these cells (Liu et al., 2004). Moreover, TRPV1 is also known to interact with many nAChRs and is associated with anxiogenic behavioral responses, indicating that this channel might be responsible for the

anxiety and 'nervousness' associated with nicotine withdrawal responses (Casarotto et al., 2012). Besides, the TRPV1 activity is potentiated by ethanol, and *Trpv1* null mutants show higher preference to ethanol and higher consumption in two-bottle choice assays as compared to wild-type mice (Blednov and Harris, 2009). These findings suggest the role for TRPV1 channels in specific behaviors associated to ethanol dependence.

In invertebrates, the *Drosophila* TRPV homologue *inactive* (*iav*) mediates behavioral sensitization to cocaine (McClung and Hirsh, 1998). In this model, stereotypical behavioral responses to cocaine include intense grooming at low doses, with moderate doses affecting rapid rotations and sideways or backward movements. High doses, in turn, result in tremors and paralysis. With repeated cocaine administration, these behaviors become more vigorous in response to decreased cocaine concentrations. This behavioral sensitization, however, is not present in *iav* null mutants despite a wild-type response to acute cocaine exposure (McClung and Hirsh, 1998). This sensitization deficit appears to result from decreased levels of the monoamines tyramine and octopamine, implicating TRPV proteins in the regulation of monoamine neurotransmitter systems (McClung and Hirsh, 1999). It should be noted, however, that this behavioral sensitization phenotype has not been rescued transgenically in *iav* mutants, which allows the possibility that the phenotype may be due to some unidentified background mutation in this line. Regardless, these invertebrate studies and the findings in rodents suggest TRPV proteins as targets for understanding the action that drugs of abuse have on the brain.

In mammals, the endocannabinoid anandamide (AEA) activates not only the CB1 and CB2 GPCRs but also TRPV1. A recent study demonstrates that TRPV1 is critical for long-term depression (LTD) of medium spiny neurons (MSN) in the rodent nucleus accumbens and cocaine administration disrupts this phenomenon (Grueter et al., 2010). TRPV1 channels are also critical for coupling ACh signals with the endocannabinoid 2-archidonylglycerol (2AG) in the striatum. This coupling is vital for both LTD and long-term potentiation (LTP) at corticostriatal synapses (Musella et al., 2010). Furthermore, the TRPV1 agonist capsaicin induces LTP in the amygdala (Zschenderlein et al., 2011). In addition, repeated methamphetamine exposure increases TRPV1 mRNA within the prefrontal cortex (Tian et al., 2010), a brain region responsible for inhibiting unwanted actions whose dysfunction can lead to hyperactivity and compulsive behaviors such as drug-taking (Koob, 2009). Collectively, these studies suggest that TRPV1 channels may play a role in usurping natural motivational, learning and executive control circuits to effect addiction.

## Other TRP channel subfamilies in drug dependence

Besides TRPC and TRPV subfamilies, other TRPs (mainly TRPA and TRPM) are involved either in primary sensing of addictive drugs or in their long-term effects. In vertebrates, nicotine activates both TRPM5-dependent and independent gustatory pathways. The TRPM5-dependent mechanism affects a general taste pathway and is required for nicotine-specific behavioral and gustatory cortex circuit responses. It has also been shown to be involved in peripheral sensing of nicotine in the nasal cavity (Gulbransen et al., 2008; Oliveira-Maia et al., 2009).

TRPA1, meanwhile, is involved in nicotine-induced irritation and facilitates the mouse airway constriction reflex to nasal administration of nicotine (Talavera et al., 2009). This channel is also known to be responsible for the airway neurological inflammation caused by α,β-unsaturated aldehydes, one of the main caustic agents in cigarette smoke (Andre et al., 2008). These facts make TRPA1 a potential nicotine target for developing smoking cessation therapeutics with milder side effects. While TRPA1 acts as an irritant-sensing channel in cigarette smoke, the menthol receptor TRPM8 acts as a counterirritant channel in menthol-flavored cigarettes (Willis et al., 2011). Activation of TRPM8 by menthol suppresses the irritant sensation caused by TRPA1 during smoking, thus masking the caustic irritants and promoting smoking behavior. These differential actions of TRP channels in the periphery might be important in the preliminary stages of nicotine dependence. In addition, ethanol inhibits TRPM8, while potentiating the activity of TRPV1 (Benedikt et al., 2007). Further evidence of the complicated role TRP channels play in drug use is seen with 'hangover pain', a pathological symptom after ethanol consumption, which is mediated by TRPA1 (Bang et al., 2007).

## Conclusion

The effects of addictive drugs on primary targets, such as their cognate receptors, and secondary targets, such as kinases and lipases that those receptors modulate, are well known. However, the role of those gene families with less obvious involvement in drug addiction, such as TRP family channels, remains unclear. Interestingly, there is growing evidence implicating TRP channels in drug dependence. TRPC channels, in particular TRPC4/7 were identified in two GWA studies. Similarly, two *C. elegans* TRPC homologues (TRP-1 and TRP-2) are essential for nicotine dependent behaviors, and their mammalian counterparts can functionally substitute for them, suggesting a functional conservation among species.

On the other hand, TRPV channels are implicated in the control of extracellular monoamine levels, as well as in anxiety-related behaviors, suggesting that these channels might be responsible for the neural changes that lead to the adverse effects of withdrawal and behavioral sensitization following repeated drug use. This TRP channel subfamily is not only implicated in behavioral responses to several drugs of abuse, but also performs conserved roles in motivational, learning and executive control circuits usurped by drugs of abuse to elicit addiction.

Beyond the TRPC and TRPV families, it is important to note that many more members of the TRP superfamily are implicated in responses to drugs of abuse. TRP superfamily proteins are involved both at the primary sensing level (TRPA1 and TRPM8) and in maintaining long-term neural changes (TRPM5). These properties, with the ever-growing evidence related to their association with drugs of abuse, support a role for TRP channels in the development of drug dependence.

Nevertheless, we are only beginning to appreciate the role of TRP channels in drug dependence, and many unanswered questions remain. For example, despite the mounting data in invertebrates, genetic and behavioral studies showing a role for TRP channels in mammalian addiction-related behaviors are limited. While mice lacking functional TRPC, TRPV, TRPA1, and TRPM5 channels exist, the performance of these null mutants in standard paradigms to test drug-taking or drug-seeking behaviors has not been examined. Moreover, there persists a lack of understanding as to how these channels function to influence terminal release of monoamines related to addiction as well as to how they alter the firing rates of cells within brain regions known to have an impact in addiction-related behaviors. Future studies, particularly, genetic, behavioral and pharmacological studies in rodents promise exciting insights into the possible interactions among these TRP channels and the classical neurotransmitter systems canonically associated with drugs of abuse in mammals.

### Conflict of interest statement

None.

## Acknowledgments

The authors thank NIDCD, NIDA and NIGMS for funding.

## References

Andre E, Campi B, Materazzi S, Trevisani M, Amadesi S, Massi D, et al. Cigarette smoke-induced neurogenic inflammation is mediated by alpha, beta-unsaturated aldehydes and the TRPA1 receptor in rodents. J Clin Invest 2008;118(7):2574–82.

Aragona BJ, Cleaveland NA, Stuber GD, Day JJ, Carelli RM, Wightman RM. Preferential enhancement of dopamine transmission within the nucleus accumbens shell by cocaine is attributable to a direct increase in phasic dopamine release events. J Neurosci 2008;28(35):8821–31.
Bang S, Kim KY, Yoo S, Kim YG, Hwang SW. Transient receptor potential A1 mediates acetaldehyde-evoked pain sensation. Eur J Neurosci 2007;26(9):2516–23.
Benedikt J, Teisinger J, Vyklicky L, Vlachova V. Ethanol inhibits cold-menthol receptor TRPM8 by modulating its interaction with membrane phosphatidylinositol 4,5-bisphosphate. J Neurochem 2007;100(1):211–24.
Benowitz NL. Nicotine addiction. N Engl J Med 2010;362(24):2295–303.
Berg AP, Sen N, Bayliss DA. TrpC3/C7 and Slo2.1 are molecular targets for metabotropic glutamate receptor signaling in rat striatal cholinergic interneurons. J Neurosci 2007;27(33):8845–56.
Bierut LJ, Madden PA, Breslau N, Johnson EO, Hatsukami D, Pomerleau OF, et al. Novel genes identified in a high-density genome wide association study for nicotine dependence. Hum Mol Genet 2007;16(1):24–35.
Blednov YA, Harris RA. Deletion of vanilloid receptor (TRPV1) in mice alters behavioral effects of ethanol. Neuropharmacology 2009;56(4):814–20.
Breiter HC, Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, et al. Acute effects of cocaine on human brain activity and emotion. Neuron 1997;19(3):591–611.
Casarotto PC, Terzian AL, Aguiar DC, Zangrossi H, Guimaraes FS, Wotjak CT, et al. Opposing roles for cannabinoid receptor type-1 (CB) and transient receptor potential vanilloid type-1 channel (TRPV1) on the modulation of panic-like responses in rats. Neuropsychopharmacology 2012;37(2):478–86.
Cavalie A. Ionic channels formed by TRPC4. Handb Exp Pharmacol 2007(179):93-108.
Dunning JP, Parvaz MA, Hajcak G, Maloney T, Alia-Klein N, Woicik PA, et al. Motivated attention to cocaine and emotional cues in abstinent and current cocaine users—an ERP study. Eur J Neurosci 2011;33(9):1716–23.
Feng Z, Li W, Ward A, Piggott BJ, Larkspur ER, Sternberg PW, et al. A *C. elegans* model of nicotine-dependent behavior: regulation by TRP-family channels. Cell 2006;127(3):621–33.
Fowler MA, Sidiropoulou K, Ozkan ED, Phillips CW, Cooper DC. Corticolimbic expression of TRPC4 and TRPC5 channels in the rodent brain. PLoS One 2007;2(6):e573.
Grueter BA, Brasnjo G, Malenka RC. Postsynaptic TRPV1 triggers cell type-specific long-term depression in the nucleus accumbens. Nat Neurosci 2010;13(12):1519–25.
Gulbransen BD, Clapp TR, Finger TE, Kinnamon SC. Nasal solitary chemoreceptor cell responses to bitter and trigeminal stimulants in vitro. J Neurophysiol 2008;99(6):2929–37.
Huang CC, Yang PC, Lin HJ, Hsu KS. Repeated cocaine administration impairs group II metabotropic glutamate receptor-mediated long-term depression in rat medial prefrontal cortex. J Neurosci 2007;27(11):2958–68.
Huang CC, Yeh CM, Wu MY, Chang AY, Chan JY, Chan SH, et al. Cocaine withdrawal impairs metabotropic glutamate receptor-dependent long-term depression in the nucleus accumbens. J Neurosci 2011;31(11):4194–203.
Jia Y, Zhou J, Tai Y, Wang Y. TRPC channels promote cerebellar granule neuron survival. Nat Neurosci 2007;10(5):559–67.
Jones JL, Day JJ, Aragona BJ, Wheeler RA, Wightman RM, Carelli RM. Basolateral amygdala modulates terminal dopamine release in the nucleus accumbens and conditioned responding. Biol Psychiatry 2010;67(8):737–44.
Kang L, Gao J, Schafer WR, Xie Z, Xu XZ. *C. elegans* TRP family protein TRP-4 is a pore-forming subunit of a native mechanotransduction channel. Neuron 2010;67(3):381–91.
Kauer JA, Gibson HE. Hot flash: TRPV channels in the brain. Trends Neurosci 2009;32(4):215–24.
Kim SJ, Kim YS, Yuan JP, Petralia RS, Worley PF, Linden DJ. Activation of the TRPC1 cation channel by metabotropic glutamate receptor mGluR1. Nature 2003;426(6964):285–91.
Kim JY, Zeng W, Kiselyov K, Yuan JP, Dehoff MH, Mikoshiba K, et al. Homer 1 mediates store- and inositol 1,4,5-trisphosphate receptor-dependent translocation and retrieval of TRPC3 to the plasma membrane. J Biol Chem 2006;281(43):32540–9.
Koob GF. Neurobiological substrates for the dark side of compulsivity in addiction. Neuropharmacology 2009;56(Suppl. 1):18–31.
Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology 2010;35(1):217–38.
Kourrich S, Rothwell PE, Klug JR, Thomas MJ. Cocaine experience controls bidirectional synaptic plasticity in the nucleus accumbens. J Neurosci 2007;27(30):7921–8.
Kumar D, Deb I, Chakraborty J, Mukhopadhyay S, Das S. A polymorphism of the CREB binding protein (CREBBP) gene is a risk factor for addiction. Brain Res 2011;1406:59–64.
Lammel S, Hetzel A, Hackel O, Jones I, Liss B, Roeper J. Unique properties of mesoprefrontal neurons within a dual mesocorticolimbic dopamine system. Neuron 2008;57(5):760–73.
Lessov-Schlaggar CN, Pergadia ML, Khroyan TV, Swan GE. Genetics of nicotine dependence and pharmacotherapy. Biochem Pharmacol 2008;75(1):178–95.
Liu L, Zhu W, Zhang ZS, Yang T, Grant A, Oxford G, et al. Nicotine inhibits voltage-dependent sodium channels and sensitizes vanilloid receptors. J Neurophysiol 2004;91(4):1482–91.
Luscher C, Ungless MA. The mechanistic classification of addictive drugs. PLoS Med 2006;3(11):e437.
Mast TG, Brann JH, Fadool DA. The TRPC2 channel forms protein–protein interactions with Homer and RTP in the rat vomeronasal organ. BMC Neurosci 2010;11:61.
McClung C, Hirsh J. Stereotypic behavioral responses to free-base cocaine and the development of behavioral sensitization in Drosophila. Curr Biol 1998;8(2):109–12.
McClung C, Hirsh J. The trace amine tyramine is essential for sensitization to cocaine in Drosophila. Curr Biol 1999;9(16):853–60.
Montell C. Physiology, phylogeny, and functions of the TRP superfamily of cation channels. Sci STKE 2001;2001(90):re1.
Montell C. The TRP superfamily of cation channels. Sci STKE 2005;2005(272):re3.
Montell C, Rubin GM. Molecular characterization of the Drosophila trp locus: a putative integral membrane protein required for phototransduction. Neuron 1989;2(4):1313–23.
Musella A, De Chiara V, Rossi S, Cavasinni F, Castelli M, Cantarella C, et al. Transient receptor potential vanilloid 1 channels control acetylcholine/2-arachidonoylglicerol coupling in the striatum. Neuroscience 2010;167(3):864–71.
Nilius B, Owsianik G. The transient receptor potential family of ion channels. Genome Biol 2011;12(3):218.
Numaga T, Wakamori M, Mori Y. Trpc7. Handb Exp Pharmacol 2007(179):143–51.
Oliveira-Maia AJ, Stapleton-Kotloski JR, Lyall V, Phan TH, Mummalaneni S, Melone P, et al. Nicotine activates TRPM5-dependent and independent taste pathways. Proc Natl Acad Sci U S A 2009;106(5):1596–601.
Pandey SC, Chartoff EH, Carlezon Jr WA, Zou J, Zhang H, Kreibich AS, et al. CREB gene transcription factors: role in molecular mechanisms of alcohol and drug addiction. Alcohol Clin Exp Res 2005;29(2):176–84.
Philpot RM, Engberg ME, Wecker L. Effects of nicotine exposure on locomotor activity and pCREB levels in the ventral striatum of adolescent rats. Behav Brain Res 2012;230:62–8.
Piggott BJ, Liu J, Feng Z, Wescott SA, Xu XZ. The neural circuits and synaptic mechanisms underlying motor initiation in *C. elegans*. Cell 2011;147(4):922–33.
Porter-Stransky KA, Wescott SA, Hershman M, Badrinarayan A, Vander Weele CM, Lovic V, et al. Cocaine must enter the brain to evoke unconditioned dopamine release within the nucleus accumbens shell. Neurosci Lett 2011;504(1):13–7.
Riccio A, Li Y, Moon J, Kim KS, Smith KS, Rudolph U, et al. Essential role for TRPC5 in amygdala function and fear-related behavior. Cell 2009;137(4):761–72.
Ron D, Jurd R. The “ups and downs” of signaling cascades in addiction. Sci STKE 2005;2005(309):re14.
Schafe GE, Doyere V, LeDoux JE. Tracking the fear engram: the lateral amygdala is an essential locus of fear memory storage. J Neurosci 2005;25(43):10010–4.
Stuber GD, Roitman MF, Phillips PEM, Carelli RM, Wightman RM. Rapid dopamine signaling in the nucleus accumbens during contingent and noncontingent cocaine administration. Neuropsychopharmacology 2005;30(5):853–63.
Talavera K, Nilius B, Voets T. Neuronal TRP channels: thermometers, pathfinders and life-savers. Trends Neurosci 2008;31(6):287–95.
Talavera K, Gees M, Karashima Y, Meseguer VM, Vanoirbeek JA, Damann N, et al. Nicotine activates the chemosensory cation channel TRPA1. Nat Neurosci 2009;12(10):1293–9.
Tian YH, Lee SY, Kim HC, Jang CG. Repeated methamphetamine treatment increases expression of TRPV1 mRNA in the frontal cortex but not in the striatum or hippocampus of mice. Neurosci Lett 2010;472(1):61–4.
Uhl GR, Drgon T, Johnson C, Fatusin OO, Liu QR, Contoreggi C, et al. “Higher order” addiction molecular genetics: convergent data from genome-wide association in humans and mice. Biochem Pharmacol 2008;75(1):98-111.
Venkatachalam K, Montell C. TRP channels. Annu Rev Biochem 2007;76:387–417.
Wheeler RA, Aragona BJ, Fuhrmann KA, Jones JL, Day JJ, Cacciapaglia F, et al. Cocaine cues drive opposing context-dependent shifts in reward processing and emotional state. Biol Psychiatry 2011;69(11):1067–74.
Willis DN, Liu B, Ha MA, Jordt SE, Morris JB. Menthol attenuates respiratory irritation responses to multiple cigarette smoke irritants. FASEB J 2011;25(12):4434–44.
Xiao R, Xu XZ. Function and regulation of TRP family channels in *C. elegans*. Pflugers Arch 2009;458(5):851–60.
Xiao R, Xu XZ. *C. elegans* TRP channels. Adv Exp Med Biol 2011;704:323–39.
Xu XZ, Sternberg PW. A *C. elegans* sperm TRP protein required for sperm-egg interactions during fertilization. Cell 2003;114(3):285–97.
Yuan JP, Kiselyov K, Shin DM, Chen J, Shcheynikov N, Kang SH, et al. Homer binds TRPC family channels and is required for gating of TRPC1 by IP3 receptors. Cell 2003;114(6):777–89.
Zschenderlein C, Gebhardt C, von Bohlen Und Halbach O, Kulisch C, Albrecht D. Capsaicin-induced changes in LTP in the lateral amygdala are mediated by TRPV1. PLoS One 2011;6(1):e16116.