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

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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.

Keywords

Drug; Abuse; Addiction; Nicotine; Cocaine; Ethanol; Behavior; TRP; Channel; Nucleus Accumbens; Prefrontal Cortex; *C. elegans*

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

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(Koob and Volkow 2010). An increasing number of studies suggest that transient receptor potential (TRP) channels are important 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, Montell 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). 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.

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 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 Purkinje 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 expression 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 $\alpha 4\beta 2$ 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 overexpression 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 (IP₃R) with TRPC channels (Mast, et al. 2010, Yuan, et al. 2003). Homer-IP₃R interactions regulate trafficking of TRPC3 to the plasma membrane, while coupling of mGluR and IP₃R 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-arachidonylglycerol (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.

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Figure 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 Nicotine Dependence	Bang et al., 2007 Talavera et al., 2009
TRPC1	Nucleus Accumbens Prefrontal Cortex	Synaptic Plasticity	Kim et al., 2003
TRPC3	Striatum	Synaptic Plasticity Nicotine Dependence	Berg et al., 2007 Feng et al., 2006 Jia et al., 2007
TRPC4	Thalamus	Dendritic Neurotransmission	Cavalie, 2007 Uhl et al., 2008
TRPC5	Nucleus Accumbens Amygdala	Appetitive Processing CS-US Associations	Riccio et al., 2009 Schafe et al., 2005
TRPC7	Striatum	Synaptic Plasticity	Beirut et al., 2007 Berg et al., 2007 Lessov-Schlagger 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 Ethanol Dependence	Benedickt et al., 2007 Willis et al., 2011
TRPV1	Prefrontal Cortex Striatum Amygdala	Synaptic Plasticity Ethanol Dependence	Benedickt et al., 2007 Blednov & Harris, 2009 Grueter et al., 2010 Kauer & Gibson, 2009 Liu et al., 2004 McClung & Hirsch, 1998 McClung & Hirsch, 1999 Tian et al., 2010 Venkatachalam & Montell, 2007