Minireview

The Neurokinin-1 Receptor in Addictive Processes

Jesse R. Schank
Department of Physiology and Pharmacology, College of Veterinary Medicine, University of Georgia, Athens, Georgia

Received March 23, 2014; accepted July 17, 2014

ABSTRACT
Stress can trigger drug-seeking behavior, increase self-administration rates, and enhance drug reward. A number of stress-related neuropeptides have been shown to mediate these behavioral processes. The most studied peptide in this category is corticotropin-releasing hormone (CRH), which has been shown to mediate stress-induced reinstatement of drug seeking, escalated self-administration, and drug withdrawal, but it does not seem to be involved in baseline drug self-administration or cue-induced reinstatement. This pattern of effects holds for many classes of drugs, including alcohol, opiates, and psychostimulants. The neurokinin-1 receptor (NK1R) is the preferred receptor for the endogenous stress-related neuropeptide substance P (SP).

The SP/NK1R system is a major mediator of stress and anxiety, and over the last several years, it has been demonstrated that the SP/NK1R system can have effects similar to those of CRH on drug taking and drug seeking. Specifically, NK1R inhibition attenuates escalated self-administration of alcohol as well as stress-induced reinstatement of alcohol and cocaine seeking; however, in contrast to other stress systems, the NK1R also appears to have a role in primary reward and reinforcement for opiates. This review outlines the role of NK1R in drug-seeking behaviors and highlights recent results from clinical studies that suggest that the NK1R may be a promising drug target going forward.

Introduction

Substance P (SP) is an 11-amino-acid neuropeptide of the tachykinin family, which also includes neurokinin A and neurokinin B. There are three receptor subtypes for the tachykinins, and SP preferentially binds to the neurokinin-1 receptor (NK1R) (Pennefather et al., 2004). Whereas SP has historically gained attention for its physiologic actions in the periphery, there is extensive literature indicating a role for the SP/NK1R system in complex behaviors, such as stress and anxiety (reviewed in Ebner and Singewald, 2006). Recent work has also indicated a role of the NK1R in responses to drugs of abuse (including alcohol), and those findings are outlined in detail in this review. Importantly, NK1Rs are located in a wide range of brain regions involved in the regulation of affective behaviors and addiction, including the striatum, extended amygdala, hippocampus, and brainstem monoaminergic nuclei (Quirion et al., 1983; Mantyh et al., 1984; Shults et al., 1984; Yip and Chahl, 2000).

Another well known neuropeptide, corticotropin-releasing hormone (CRH), has been considered by many to be the prototypical stress-responsive signaling molecule, and much research supports its role in stress and drug-seeking behaviors, especially through activation of CRH type-1 receptor (CRH-R1) (for review, see Heilig and Koob, 2007; Koob, 2010; Koob and Zorrilla, 2010). Generally, inhibition of CRH-R1 function can suppress escalated self-administration in dependent animals and can suppress stress-induced reinstatement of drug seeking without affecting baseline self-administration or cue-induced reinstatement of drug seeking. This pattern of effects holds for most drugs of abuse. As described in detail in this review, the SP/NK1R system appears to have a similar stress-specific impact in drug-seeking behaviors, with some exceptions that are discussed here. This review outlines the role for the SP/NK1R system in these phenomena and describes its role in primary reward and reinforcement for some classes of drugs. It also describes the promising clinical findings that suggest that the NK1R may be a useful target in the development of medications for the treatment of addiction, comparing this along the way with findings pertaining to CRH and CRH-R1.

SP and CRH: Siblings in Behavioral, Neurochemical, and Endocrine Stress Responses

Substance P is released in stress-sensitive brain regions in response to acute stressors (Ebner et al., 2004, 2008b; Singewald et al., 2008), and exogenous SP infusion induces anxiety-like
behavior in rodents that is NKIR-dependent (Teixeira et al., 1996; Duarte et al., 2004; Ebner et al., 2004). In addition, mice with genetic deletion of the NKIR show decreased anxiety in the elevated plus maze, novelty-suppressed feeding paradigm, and ultrasonic vocalization during maternal separation, three commonly used measures of anxiety-like behavior in rodents (Santarelli et al., 2001). Interestingly, NKIR antagonists also have anxiolytic properties under basal conditions (Teixeira et al., 1996; Santarelli et al., 2001; Ebner et al., 2008a), in contrast to the effects that are typically observed with CRH-R1 antagonism. CRH-R1 inhibitors generally show anxiolyis only under conditions in which anxiety has been elevated, such as after stress, drug withdrawal, or genetic selection for increased anxiety (Heilig and Koob, 2007; Rotzinger et al., 2010).

Thinking in terms of receptor-specific pharmacotherapies, this finding may argue for a more general effect of NKIR antagonists on anxiety disorders; however, clinical results have not been particularly promising in this regard (Tauscher et al., 2010; Michelson et al., 2013).

To mediate stress- and anxiety-related effects, the NKIR may act via modulation of monoaminergic neurotransmission and neuroendocrine responses. For example, NKIR antagonism promotes active coping behavior and prevents suppression of septal serotonin release after forced swim stress (Ebner et al., 2008b). NKIR activation generally suppresses the output of the dorsal raphe nucleus (Valentino et al., 2003; Guiard et al., 2007), and inhibition of the NKIR can increase serotoninergic activity (Santarelli et al., 2001; Conley et al., 2002; Gobbi et al., 2007). Also, NKIRs are found on the noradrenergic cell bodies of the locus coeruleus (LC) (Chen et al., 2000; Ma and Bleasdale, 2002) and influence the output of these neurons, although the direction of this influence is unclear. Most studies suggest that SP can increase LC firing and that NKIR antagonists attenuate stress-induced norepinephrine (NE) release (Guyenet and Aghajanian, 1977; Cheeseman et al., 1983; Renoldi and Invernizzi, 2006); however, there has been some suggestion that NKIR antagonists themselves can increase NE in some terminal fields (Millan et al., 2001; Maubach et al., 2002). When considering the regulation of behaviors that lie at the intersection of stress and addiction, the ability of NKIR to modulate NE transmission is especially intriguing because the NE system has been shown to mediate stress-induced reinstatement and escalated self-administration of multiple drugs of abuse (Erb et al., 2000; Shaham et al., 2000; Leri et al., 2002; Gilpin and Koob, 2010; Mantsch et al., 2010; Vranjkovic et al., 2012). Although it is known primarily as a reward-related neurotransmitter, dopamine activity is increased during exposure to some stressors. NKIR antagonists can prevent immobilization stress–induced dopamine release in the prefrontal cortex (Hutson et al., 2004; Renoldi and Invernizzi, 2006), which is of particular interest for the NKIR’s targeted role in stress-elicited drug seeking (see later discussion). The effect of the NKIR on monoamine signaling is a major mechanism of overlap with the functions of CRH receptors, which can influence the activity of the monoaminergic systems (Dunn et al., 2004; Valentino and Commons, 2005; Valentino et al., 2010).

The NKIR can also mediate hypothalamic-pituitary-adrenal (HPA) axis responses to environmental stressors. For example, anxiety-like behavior and elevations in cortisol during exposure to the elevated-plus maze are attenuated in mice with genetic deletion of the NKIR (Santarelli et al., 2001). The paraventricular nucleus of the hypothalamus, a region that drives HPA axis activity and endocrine responses to stress, is innervated by SP-positive fibers (Kawano and Masuko, 1992; Womack and Barrett-Jolley, 2007; Womack et al., 2007), and NKIR antagonists attenuate stress-induced neuronal activation (as measured by c-fos expression) in this region (Ebner et al., 2008a). CRH is a major player in the HPA axis, as it is the biochemical intermediary that is produced in the hypothalamus and activates adrenocorticotropic hormone release from the pituitary via activation of the CRH-R1. The HPA axis is one point of convergence in which NKIR could influence stress responses in a manner similar to the actions of CRH. However, a large body of evidence has demonstrated that many CRH effects that regulate affective function occur in extrahypothalamic regions of the brain, such as the extended amygdala. In addition, evidence for direct interactions between SP and CRH are rather sparse (but see Hamke et al., 2006). Taken together, these findings suggest that the CRH and SP systems play similar roles and function in parallel to affect drug seeking behavior, as opposed to directly interacting.

**Preclinical Findings in Rodent Models of Drug Addiction**

There is a large body of literature, and many excellent reviews, outlining the role of CRH in drug-seeking and drug-taking behaviors, and those are not outlined in detail here (see, for example, Sarnyai et al., 2001; Heilig and Koob, 2007; Koob, 2010; Koob and Zorrilla, 2010; Shalev et al., 2010). Given its role in stress responses, monoaminergic signaling, and neuroanatomic pathways that mediate drug reward and reinforcement, much research has focused on the impact of NKIR manipulations on stress-induced drug seeking. The preclinical findings for the NKIR system with three major classes of drugs of abuse are outlined below, followed by a conclusion relating this to the effects of CRH.

**Opiates.** Likely owing to a purported role of SP in pain processing, there has been much interest in the role of the NKIR in opiate reward and reinforcement, and some of the earliest studies using mice with a genetic deletion of the NKIR explored these behaviors. For example, morphine reward is absent in NKIR−/− mice, as evidenced by a complete lack of conditioned place preference (CPP) for the drug (Murtra et al., 2000). Morphine-induced locomotor activation, psychomotor sensitization, and Fos B immunoreactivity are also attenuated in these animals (Murtra et al., 2000; Ripley et al., 2002); however, the analgesic properties of opiate drugs are unaffected. Further studies focused on outlining the neuroanatomy of NKIR mediation of morphine reward used a targeted lesion approach, where a saporin neurotoxin linked to SP was used to selectively ablate NKIR containing cells. Lesions using this method identified the amygdala (AMG) as a major anatomic locus for NKIR effects on morphine reward but found no effect of targeted lesions in the nucleus accumbens (Gadd et al., 2003). In support of a role of the SP/NKIR system in motivational properties of opioids, it was recently reported that NKIR antagonism attenuates the ability of morphine to lower intracranial self-stimulation thresholds (Robinson et al., 2012), a method largely believed to assess the rewarding properties of pharmacologic agents, with a lowering of stimulation thresholds believed to indicate increased reward processing.
These assessments of opiate reward are consistent with decreased morphine reinforcement that has been observed in NK1R−/− mice (Ripley et al., 2002). Specifically, NK1R−/− mice show decreased self-administration rates for morphine, with no effect on cocaine self-administration. Accordingly, NK1R antagonism suppresses heroin self-administration in rats in both short- and long-access sessions (Barbier et al., 2013). It is largely believed that long-access sessions (longer than 6 hours) lead to escalated drug self-administration that, in part, is driven by the recruitment of stress systems (for review, see Specio et al., 2008; Wee et al., 2008, 2009). The effects of CRH-R1 on drug reinforcement are observed only during such long-access sessions. However, the evidence suggests a more general role for the NK1R in primary reward and reinforcement for opiates that may not involve stress interactions.

On an intracellular level, an intriguing interaction between the NK1R and μ-opioid receptor (MOR) has been described. Specifically, coadministration of SP prevents morphine-induced internalization and acute desensitization of the MOR (Yu et al., 2009), a result of sequestering of β-arrestin by NK1Rs, which are internalized following activation by SP, thereby depleting the available cytoplasmic pool of β-arrestin necessary for MOR internalization. This in vitro effect was also observed in dissociated AMG and LC neurons, some of which endogenously coexpress NK1R and MOR. This intracellular interaction may explain in part why the NK1R mediates reward and reinforcement for opiates but not for other drugs. In addition, it has been reported that chronic morphine administration leads to upregulation of the NK1R in vitro (Wan et al., 2006), further suggesting an important functional interaction between NK1R and MORs.

Cocaine. Some of the earliest studies exploring the role of the NK1R in drug-related behaviors investigated the influence of this receptor on cocaine-induced locomotion and DA release in the dorsal striatum. It was found that inhibition of the NK1R attenuated both of these responses (Kraft et al., 2001a,b; Noailles and Angulo, 2002; Loonam et al., 2003). However, NK1R deletion did not affect locomotor sensitization to cocaine in mice (Ripley et al., 2002). Furthermore, in contrast to its role in opioid-related behaviors, genetic deletion of NK1R does not affect cocaine CPP (Murtra et al., 2000). In agreement with this finding, lesions targeted specifically to NK1R-containing neurons of the AMG had no effect on cocaine CPP (Gadd et al., 2003). However, the effect of NK1R-targeted lesions of the nucleus accumbens on cocaine reward was not assessed.

When considering the results from operant self-administration experiments, the picture becomes more complex. First, cocaine self-administration rates were not affected by NK1R deletion in mice (Ripley et al., 2002) or NK1R antagonism in rats (Placenza et al., 2006; Schank et al., 2014). However, Placenza et al. (2004, 2005) showed that extinguished cocaine seeking can be reinstated by infusion of specific NK1R agonists into the lateral ventricles or ventral tegmental area but found that an NK1R-specific antagonist was unable to prevent reinstatement of cocaine seeking induced by noncontingent cocaine injection. This finding suggests that the NK1R is involved in reinstatement of cocaine seeking triggered by some stimuli but not that induced by drug priming.

Because of the role of SP/NK1R in stress responses, reinstatement induced by stress was therefore examined by our group. We found that yohimbine-induced reinstatement of cocaine-seeking is attenuated by treatment with a specific NK1R antagonist. Yohimbine is an antagonist of α2-adrenergic autoreceptors that increases NE output and is considered a pharmacologic stressor. Yohimbine injection, like intermittent footshock stress, can trigger a reactivation of drug seeking after extinction of operant self-administration.

Thus, NK1R antagonism is ineffective at suppressing baseline self-administration of cocaine in short-access sessions, demonstrating a lack of effect of NK1R on baseline cocaine reinforcement. An intriguing question for future studies is whether NK1R antagonism might influence cocaine self-administration during long-access sessions, which promote escalated cocaine self-administration rates, potentially through recruitment of stress-related systems, as mentioned already.

Alcohol. In the last several years, a series of studies has indicated that the SP/NK1R system is involved in alcohol-related behaviors. Similar to morphine, NK1R−/− mice on a C57/BL6 background exhibit a complete lack of CPP for alcohol (Thorsell et al., 2010). Also, these animals consume less alcohol in voluntary two-bottle choice drinking over a range of pharmacologically active concentrations (George et al., 2008). Decreased alcohol consumption in NK1R−/− mice was replicated by NK1R antagonist administration in wild-type C57/BL6 mice (Thorsell et al., 2010). In this study, there appeared to be an interaction between genotype and NK1R antagonist efficacy, with wild-type mice responding to lower doses of the antagonist than heterozygotes. These effects did not result from off-target action of the antagonist since NK1R−/− mice were insensitive to its effects. Consistent with decreased alcohol consumption observed as a result of genetic or pharmacologic inhibition of the NK1R, microRNA silencing of NK1R expression using intracerebroventricular infusions also suppressed alcohol consumption in mice (Baek et al., 2010). Thus, both pharmacologic blockade of NK1Rs and transient knock-down of their expression mimic the effects of constitutive NK1R gene inactivation. Thorsell et al. (2010) further demonstrated that NK1R−/− mice do not escalate their voluntary alcohol consumption after repeated cycles of deprivation, suggesting that the SP/NK1R system may be involved in neuroadaptations that influence the development of escalated alcohol seeking.

In pharmacologic studies using rats, the specific NK1R antagonist L822429 [(2S,3S)-N-[2-cyclopropoxy-5-(5-trifluoromethyl)tetrazol-1-yl]benzyl]-2-phenylpiperidin-3-amine dihydrochloride] (Singewald et al., 2008) was found to suppress stress-induced reinstatement of alcohol-seeking (Schank et al., 2011, 2014). This effect was observed for reinstatement induced by both pharmacologic (yohimbine) and physical/environmental (intermittent footshock) stressors. In these studies, L822429 was used at doses that had no effect on operant self-administration of sucrose, cue-induced reinstatement of alcohol seeking, or novel environment-induced locomotion. L822429 also had no effect on baseline alcohol self-administration rates. In agreement with these findings, Steensland et al. (2010) also did not observe a suppression of alcohol self-administration or two-bottle choice consumption in rats after NK1R antagonism with ezlopitant until doses were reached that also suppressed sucrose consumption, indicating nonspecific suppression on consummatory behavior at these doses. Thus, similar to the effects of CRH on alcohol consumption and the effects of NK1R antagonists on...
cocaine seeking, it appears that the effects of the NKIR on operant responding for alcohol in rats are specifically targeted to stress-elicited drug seeking.

As stated already, the behavioral profile of L822429 to suppress stress-induced reinstatement of alcohol seeking without affecting baseline self-administration or cue-induced reinstatement is similar to compounds that target the CRF-1R (Koob and Zorrilla, 2010; Shalev et al., 2010). Importantly, these compounds also attenuate escalated alcohol consumption that results from the induction of alcohol dependence or where increased alcohol preference is achieved by genetic selection (Heilig and Koob, 2007). In other words, compounds that act on the CRH system are selectively effective under conditions where stress systems have been hypersensitized. A hypothesis that remained to be addressed, therefore, was whether NKIR antagonists, while leaving basal alcohol intake unaffected, could suppress escalated alcohol consumption. In support of this idea, NKIR antagonists suppress alcohol consumption in a high alcohol preferring line of mice (C57/BL6J, see preceding) and attenuate escalated alcohol self-administration in alcohol-preferring (P) rats but do not affect alcohol self-administration in nondependent, nonpreferring rats (Thorsell et al., 2010; Schank et al., 2011, 2013). It was also demonstrated that P rats show an upregulated NKIR system, as evidenced by increased transcript levels of the Tacr1 gene, as well as increased receptor binding in specific brain regions. Of the regions explored, NKIR upregulation was specific to the central nucleus of the AMG (CeA), and direct infusion of NKIR antagonists into this region mimicked the effect of systemic treatment in P rats. A similar upregulation of CRH-R1 has been observed in the CeA of a different alcohol preferring rat line, the Marchegian Sardinian Alcohol Preferring rat (Hansson et al., 2006). Altered CeA function is especially intriguing, as this structure is an important part of the extended amygdala stress circuitry. This network is thought to be recruited to influence drug reinforcement under conditions of stress or dependence, when negative reinforcement to alleviate drug-withdrawal–related dysphoria plays a major role in motivating drug seeking (Koob, 2003, 2009a,b; Koob and Le Moal, 2008).

The heightened NKIR function in P rats described above was associated with increased transcription factor–binding potential at a region of the Tacr1 promoter that shows single nucleotide variation between P rats and the founder Wistar strain. Specifically, approximately 20% of Wistar rats were CC homozygous at position –1372 from the transcriptional start site of the Tacr1 gene, whereas P rats were 100% CC homozygous at this location. CC homozygosity was associated with increases in transcription factor binding potential (as measured by gel shift assays) and promoter activity (as measured by luciferase expression assays). We have observed that P rats are generally more sensitive to the effects of NKIR antagonists, suggesting a potential pharmacogenetic interaction that is mediated by this locus.

Summary

As outlined here, the NKIR system has many similarities but also some important differences compared with the effects of CRH on drug seeking (for summary of NKIR effects, see Table 1). For cocaine and alcohol, the effects of NKIR antagonism on drug seeking and drug taking seem to overlap entirely. NKIR and CRH-R1 antagonists suppress stress-induced reinstatement of drug seeking and escalated drug self-administration without affecting baseline self-administration or cue-induced reinstatement. One aspect of this relationship that still requires exploration is whether NKIR antagonists can suppress escalated cocaine self-administration during long-access self-administration sessions. For opioids, there appears to be a divergence between the effects of CRH-R1 and NKIR inhibition in that the NKIR mediates baseline reward and reinforcement for opioids in addition to escalated self-administration rates, whereas CRH-R1 effects are selective for the latter. Although this has not yet been examined, it is hypothesized that NKIR antagonism would attenuate stress-induced reinstatement of opiate seeking due to the influence of the NKIR system on stress-induced reinstatement for other drugs and to its more general effects on responding for opiates. One issue that has not been discussed is drug withdrawal. CRH systems have also been demonstrated to have an important role in drug withdrawal symptoms, but this has not yet been explored with NKIR antagonists.

The SP/NKIR System as a Promising Therapeutic Target

The NKIR was the first neuropeptide receptor for which a potent, highly selective nonpeptide antagonist was developed (Snider et al., 1991), and early studies focused on developing treatments for analgesia and inflammation. Another physiologic role of the NKIR is the mediation of emesis, and a potent, highly selective nonpeptide antagonist was developed (Snider et al., 1991), and early studies focused on developing treatments for analgesia and inflammation. Another physiologic role of the NKIR is the mediation of emesis, and a potent, highly selective nonpeptide antagonist was developed (see, for example, Keller et al., 2006). However, more recent studies have suggested the possibility that NKIR antagonists may in fact have antidepressant properties but require near-complete receptor occupancy to produce these effects reliably.

TABLE 1

<table>
<thead>
<tr>
<th>Effect of NKIR Inhibition</th>
<th>Cocaine</th>
<th>Ethanol</th>
<th>Opiates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline self-administration</td>
<td>No effect</td>
<td>No effect</td>
<td>↓</td>
</tr>
<tr>
<td>Conditioned place preference (mouse)</td>
<td>No effect</td>
<td>l*</td>
<td>↓</td>
</tr>
<tr>
<td>Drug-primed reinstatement</td>
<td>No effect</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Locomotor sensitization</td>
<td>No effect</td>
<td>?</td>
<td>↓</td>
</tr>
<tr>
<td>Cue-induced reinstatement</td>
<td>?</td>
<td>No effect</td>
<td>?</td>
</tr>
<tr>
<td>Stress-induced reinstatement</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

*Experiment was performed in high alcohol-consuming C57/BL6 mouse strain.
(Ratti et al., 2011; Zamuner et al., 2012). Indeed, a retrospective assessment of clinical trials for depression suggests that greater than 95% receptor occupancy is required for efficacy, whereas occupancy even up to 90% is ineffective (Ratti et al., 2013; Trist et al., 2013). These observations may also be relevant for clinical research aimed at developing NK1R antagonists for addiction pharmacotherapy as well as for treatment of chronic pain. The findings outlined above suggest that a reassessment of recent pessimism concerning clinical efficacy of NK1R antagonists should be reconsidered (Borsook et al., 2012).

The preclinical findings indicating a role for NK1R in alcohol-related behaviors have translational value when considered in light of clinical studies where alcohol-dependent inpatients were treated with an NK1R antagonist (George et al., 2008). This compound decreased spontaneous alcohol craving as well as craving triggered in response to a combined social stressor and alcohol-associated cue challenge. NK1R antagonist treatment also suppressed cortisol release during cue/stress exposure, supporting a role of the NK1R in regulation of HPA axis function (see preceding). In this study, prescreening selected for alcoholics with high anxiety. This selection based on anxiety phenotype may have inadvertently selected for a genetically defined subpopulation of alcoholics. Genetic analyses of alcoholic patients has suggested an association of specific TacR1 gene (which encodes the NK1R) polymorphisms with increased risk for alcohol dependence (Seneviratne et al., 2009) and increased sensitivity to alcohol-related cues (Blaine et al., 2013). This is especially intriguing in light of the pharmacogenetic interactions that we have observed in our preclinical studies using P rats (see preceding) and suggests that genetically defined subgroups of patients may therefore be particularly responsive to NK1R antagonist treatment. This genetic variation may need to be taken into account in the course of clinical development. A lack of consideration for this potential interaction may underlie the mixed results of clinical trials for psychiatric conditions, including alcoholism. Whether TacR1 polymorphisms (or another genetic factor) may influence the efficacy of NK1R-based treatments, the human and animal data support the prediction that NK1R antagonists would be effective only in a subpopulation of alcoholics, namely, those that have increased anxiety or stress reactivity. Attempts to target patient populations heterogeneous for important determinants of treatment response combined with a failure to achieve adequate central receptor occupancy may have led to termination of NK1R antagonist programs. Recent identification of the factors mentioned here suggests that carefully designed clinical studies will be more successful. Given that prior failures of NK1R programs limit the willingness of the pharmaceutical industry to further invest in this mechanism, public-private partnerships may be needed going forward.

It is important to highlight again the fact that NK1R antagonists specifically mediate stress-elicited drug seeking for most drugs of abuse studied in preclinical settings. Although this seems to suggest a promise of clinical efficacy for addiction, it is unclear whether this targeted effect would translate into beneficial pharmacotherapy when given alone. A recent clinical trial (ClinicalTrials.gov Identifier: NCT00835718) explored the effect of the NK1R antagonist serlopitant on alcohol consumption but was terminated prematurely; thus, conclusions cannot be drawn from this study. Ultimately, it may be that NK1R antagonists will serve as useful medications when given in combination with a drug that acts on other facets of the addictive process, such as naltrexone. Naltrexone has a more targeted effect on cue-elicited drug seeking with no effect on stress-elicited drug seeking. The fact that NK1R antagonists influence a restricted set of drug seeking behaviors may underlie negative results from clinical trials and may have a more important impact than receptor occupancy (as mentioned already herein). On the other hand, the stress-selective effect of NK1R antagonists may suggest efficacy in only a portion of the population with specific psychiatric comorbidities. Future studies would benefit from taking these issues into consideration.

When comparing the effects of NK1R antagonism to the body of literature examining CRH effects on drug seeking, NK1R antagonists may hold greater promise as addiction pharmacotherapies for a number of reasons. First, the existence of safe, well tolerated NK1R-targeted pharmacotherapies is perhaps the most important advantage of the NK1R over the CRH system as a target of drug development. Even though CRH-R1 antagonists have shown promise in small clinical trials, the compounds that have been tested have side effects that prohibit their development for use in medical treatment. In addition to aprepitant, which is approved by the FDA, several NK1R antagonists have been developed by the pharmaceutical industry and tested for efficacy in anxiety, mood disorders, and alcohol cravings in humans (see preceding description). Second, NK1R antagonists suppress opiate reward and reinforcement in preclinical studies, which would suggest that these agents would have utility for treating opiate dependence. Third, NK1R antagonists have anxiolytic properties in animal models under baseline conditions, suggesting that these drugs would be effective at preventing alcohol abuse in patients with high levels of anxiety, which can increase the risk of problematic alcohol consumption as a means to alleviate elevated anxiety states. Finally, clinical trials for alcoholism have shown efficacy of NK1R antagonists in alleviating cravings and neural processing abnormalities in detoxified, anxious alcoholics.

The preclinical and clinical findings reviewed here suggest that NK1R antagonists hold promise as potential addiction pharmacotherapies. However, no clinical trials pertaining to drugs of abuse other than alcohol have been performed, and future efforts should address this gap in the literature. One exception is a recent clinical trial in prescription opiate abusers. Unexpectedly, however, NK1R antagonism seemed to heighten the effects of these drugs (Walsh et al., 2013). How this relates to voluntary use of prescription opioid medications or illicit opiate drugs is unknown and will need to be addressed in future studies. Recent findings also suggest that NK1R antagonists could have utility for the treatment of cocaine abuse, especially in cases with increased risk of stress-induced relapse in abstinent cocaine addicts, but this also has not been examined clinically.

Conclusions

Taken together, the findings outlined here would predict that NK1R antagonists could be potentially useful treatments for some subpopulations of substance abusers such as those with certain genetic variants of the Tacr1 gene, patients that are especially sensitive to stress-triggered craving, anxious alcoholics, and those that abuse opiates alone or in combination with other drugs. The recent development of new, more...
potent NK1R antagonists will likely stimulate a reimagining of the pharmaceutical utility of this class of drugs and it is hoped will lead to clinical trials for addiction, anxiety, and depression. Some considerations to acknowledge going forward are the apparent need to tailor dosing to achieve nearly complete receptor occupancy and the potential for pharmacogenetic interactions that are influenced by polymorphisms of the Tac1 gene.

Acknowledgments
The author thanks Dr. Markus Heilig (National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD) for valuable comments in the revision of this manuscript.

Authorship Contributions
Wrote or contributed to the writing of the manuscript: Schank.

References