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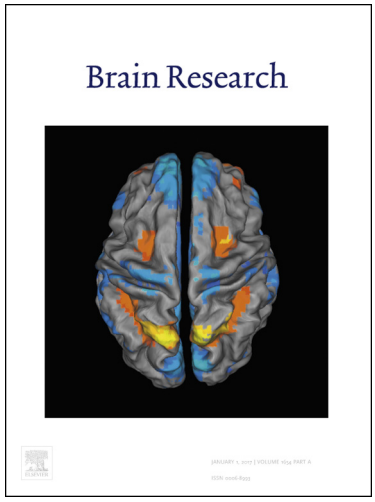


Review

# Neurokinin Receptors in Drug and Alcohol Addiction

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**Neurokinin Receptors in Drug and Alcohol Addiction**

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**Abstract**

The neurokinins are a class of peptide signaling molecules that mediate a range of central and peripheral functions including pain processing, gastrointestinal function, stress responses, and anxiety. Recent data have linked these neuropeptides with drug-related behaviors. Specifically, substance P (SP) and neurokinin B (NKB), have been shown to influence responses to alcohol, cocaine, and/or opiate drugs. SP and NKB preferentially bind to the neurokinin-1 receptor (NK1R) and neurokinin-3 receptor (NK3R), respectively, but do have some affinity for all classes of neurokinin receptor at high concentrations. NK1R activity has been shown to influence reward and reinforcement for opiate drugs, stimulatory and neurochemical responses to cocaine, and escalated and stress-induced alcohol seeking. In reinstatement models of relapse-like behavior, NK1R antagonism attenuates stress-induced reinstatement for all classes of drugs tested to date. The NK3R also influences alcohol intake and behavioral/neurochemical responses to cocaine, but less research has been performed in regard to this particular receptor in preclinical models of addiction. Clinically, agents targeting these receptors have shown some promise, but have produced mixed results. Here, the preclinical findings for the NK1R and NK3R are reviewed, and discussion is provided to interpret clinical findings. Additionally, important factors to consider in regards to future clinical work are suggested.

**Introduction**

There are three primary neurokinin peptides, Substance P (SP), Neurokinin A (NKA) and Neurokinin B (NKB). The neurokinin class of peptides is part of the tachykinin family and the associated nomenclature is influenced by this classification (see below). SP and NKA are produced by the preprotachykinin-a (PPTA) propeptide and NKB is produced by preprotachykinin-b (PPTB) propeptide. Other tachykinin peptides including Neuropeptide K and Neuropeptide γ are formed by alternative splicing of the PPTA mRNA, but will not be discussed in this review[1]. Neurokinin systems play a diverse role in physiological processes including regulation of pain processing, cardiovascular function, intestinal motility, and complex behaviors such as stress responses and drug seeking. Genetic association studies have implicated a role of neurokinin receptors in alcohol abuse, attention deficit hyperactivity disorder, and bipolar disorder[2-4]. Also, medications targeting these receptors have been tested for the treatment of depression, substance abuse, and menopausal hot flashes[5-11]. One FDA-approved medication, the neurokinin-1 receptor antagonist aprepitant, is currently in use to treat chemotherapy-induced nausea.

There are three neurokinin receptor subtypes: neurokinin-1 receptor (NK1R; TACR1 gene), neurokinin-2 receptor (NK2R, TACR2 gene), and neurokinin-3 receptor (NK3R; TACR3 gene). At sufficient concentrations, all neurokinin peptides can activate each neurokinin receptor, but each receptor has a preferred high affinity endogenous ligand. Specifically, SP prefers the NK1R, NKA preferentially binds the NK2R, and NKB targets the NK3R[12]. Very little research has been done in regards to the NK2R in responses to drugs of abuse, and it will not be covered in detail here. This review will focus exclusively on the NK1R and NK3R, two tachykinin receptors that are widely distributed in the regions of the brain that mediate motivated

behavior and drug responses, and have been studied fairly extensively in addiction models. These receptors are most commonly coupled to the Gαq mechanism, which stimulates phospholipase C activity to cleave PIP2 into the intracellular signaling molecules IP3 and diacylglycerol. The end result of activation of this pathway is calcium mobilization from endoplasmic reticulum stores and stimulation of protein kinases including calcium/calmodulin kinase and protein kinase C. In general, both NK1R and NK3R activation has a positive, stimulatory effect on dopaminergic signaling in the mesolimbic pathway. This pathway, which originates in the ventral tegmental area (VTA) of the midbrain and sends dopaminergic innervation to the striatum and other limbic regions, is thought to underlie the rewarding and reinforcing properties of drugs and natural rewards. Additionally, both NK1R and NK3R influence the activity of other monoamine neurotransmitters including norepinephrine (NE) and serotonin (5HT). These neurotransmitters can influence drug seeking directly as well as through their interactions with the mesolimbic DA system.

In this review, the role of the NK1R and NK3R in monoamine function and drug seeking behavior will be described in detail. This will be followed by a commentary on the state of clinical research for neurokinins in addiction to date, and will highlight important aspects that should be considered in this realm of research going forward. While the research on the NK3R in drug responses is not quite as extensive as that for the NK1R, some interesting effects have been reported for this receptor over the last few decades.

**Monoamine Signaling**

The NK1R is expressed widely throughout brain regions that mediate affective behaviors, including in the amygdala, striatum, hippocampus, and brainstem[13-16]. Administration of SP

into the VTA increases locomotor activity, suggesting a psychostimulatory effect[17]. NK1R activation has also been shown to modulate neurophysiological and neurochemical measures in the mesolimbic pathway. Specifically, peripheral administration of SP increases DA release in the striatum[18], intra-VTA infusion of the SP analog DiMe-C7 increases DA content in multiple terminal regions of the VTA[19], and local application of the NK1R agonist GR73632 causes electrophysiological excitation of the VTA in anesthetized rats[20]. Taken together, these results indicate that SP and the NK1R influence the activity of dopaminergic projections that originate in the VTA and mediate drug reward and reinforcement, although it has been suggested that the effect of neurokinins in the VTA could be mediated through the NK3R. Specifically, it was shown that in *ex vivo* brain slices containing the VTA, application of the NK3R agonists senktide or NKB increase neuronal firing rates more strongly than agonists of other neurokinin receptor subtypes[21]. This is intriguing because the NK3R is expressed more highly than the NK1R in the rodent VTA; however, retrograde tracing studies show that the NK1R seems to be expressed more strongly in VTA neurons projecting to the NAC, whereas NK3R is more prominent in VTA neurons that project to the frontal cortex[22].

Like the NK1R, the NK3R is expressed widely throughout the brain in regions that mediate affective and motivated behaviors, including in the olfactory bulb, amygdala, multiple cortical regions, hypothalamic subnuclei, hippocampus, locus coeruleus, VTA, and interpenduncular nucleus, among others [23-26]. Overall, NK3R activation has very similar effects to NK1R stimulation on mesolimbic DA function. For example, NK3R stimulation increases the firing rate of dopaminergic neurons of the substantia nigra pars compacta and VTA [17, 20, 21, 27]. In agreement with this, NK3R activation in dopaminergic cells of the midbrain

induces transmitter release in the striatum, an effect that is also observed for acetylcholine release in from septal inputs to the hippocampus[17, 28].

The NK1R and NK3R also regulate the activity of the monoamines NE and 5HT. In general, reduction of NK1R signaling in the raphe nuclei, either by genetic deletion of the receptor or pharmacological antagonism, increases serotonergic function[29-33]. Also, activity of the NK1R in the septal nuclei regulates coping behavior during stress exposure and modulates the release of 5HT in this region[34]. For NE, NK1R signaling seems to facilitate the activity of NE neurons in the locus coeruleus[35-37]. Some evidence suggests that the NK3R also regulates 5HT and NE signaling. Specifically, NK3R agonism increases the firing rate of locus coeruleus neurons and induces NE release in the cortex[38, 39]. Additionally, it is thought that NK3Rs stimulate 5HT neuron activity in the dorsal raphe via indirect effects on local glutamate terminals[40].

One prominent function of the NK1R is the regulation of stress responses. Following exposure to stressors, SP is released and activates the NK1R in regions such as the lateral septum and the amygdala[34, 41]. Another neurochemical effect of stress exposure is the release of monoamine transmitters into the cortex, and this has been shown to be NK1R-dependent. Specifically, the NK1R antagonist GR205171 reduces the stress-induced increase in DA metabolites the prefrontal cortex (PFC) following immobilization stress in rats[42]. This NK1R antagonist also suppresses immobilization stress-induced release of DA and NE in the PFC of both rats and gerbils, as measured by *in vivo* microdialysis[43]. It is important to note one study which observed increased DA release and VTA neuronal activity following systemic administration of GR205171[44]. However, this finding runs counter to the stress effects

outlined above, and the effect of NK1R agonists on VTA/DA function described earlier in this section.

Taken together, these findings suggest that the NK1R and NK3R can both positively regulate DA signaling in the mesolimbic pathway. Additionally, these receptors influence the activity of other monoaminergic systems. There appears to be an important role of the NK1R in stress-induced transmitter release; however, the role of the NK3R in stress-induced monoamine release has not been studied.

**Reward Behavior**

Functionally, neurokinin receptor stimulation itself can induce reward responses. SP or peptide analogs (for example DiMe-C7) can induce place preference when administered either systemically or directly into the nucleus basalis magnocellularis (a cholinergic nucleus of the basal forebrain, also called nucleus basalis of Meynert), or the lateral hypothalamus (a hypothalamic subregion involved in motivated behavior and a transit point for the median forebrain bundle) [45-48]. The place preference model is a commonly used rodent behavioral test that pairs a drug or stimulus with a novel environment. A subsequent preference to spend time in the drug paired environment is thought to be indicative of rewarding properties of that drug. NK1R/SP-induced place preference was subsequently suggested to be dependent upon μ opioid receptor (MOR) signaling[46]. This is intriguing in light of data demonstrating a cellular interaction between NK1R and MORs[49]. Specifically, concurrent NK1R activation prevents agonist-induced MOR internalization through the sequestration of intracellular arrestins. In general, opioid receptors and the SP/NK1R system have complex interactions in the brain and spinal cord in the regulation of drug reward and pain sensitivity (for review see[50]). Similar to

the NK1R, intracerebroventricular (ICV) infusion of a NK3R agonist induces a place preference to an environment paired with the drug [51]. While these experiments demonstrate individual roles of the NK1R and NK3R in reward development, it is important to note that some agonists (for example the endogenous ligands SP and NKB) have affinity for both receptor types, albeit at varying affinities. Thus, depending on the concentration and specificity of the compounds used, it is difficult to clearly dissect the individual roles of the NK1R and NK3R under these conditions. It is likely that both receptors contribute to the development of reward responses, given their anatomical distribution and common facilitation of DA signaling in the mesolimbic pathway.

**Opiate Reward and Reinforcement**

There is a quite extensive literature demonstrating a role of the NK1R in opiate reward and reinforcement. For example, morphine administration induces SP release in the VTA [52], and NK1R antagonism attenuates DA release in the nucleus accumbens (NAC; a ventral region of the striatum and terminus for mesolimbic DA projections) following morphine injection[52]. Inhibition of NK1R function by genetic deletion or pharmacological antagonism attenuates self-administration of morphine or heroin[53, 54], suppresses morphine-induced locomotion[55], and blunts the rewarding properties of these drugs[56, 57]. The latter effect has been localized at least in part to NK1R expressing cells in the amygdala using a NK1R targeting neurotoxin[58]. For operant self-administration, it is important to note that NK1R antagonism attenuates drug intake under both short access and long access schedules[54]. Long access self-administration (operant sessions longer than 6 hours) typically leads to escalation of intake compared to short access self-administration (1-2 hour operant sessions) and is thought to recruit additional stress-

related signaling systems[59-62]. This suggests that NK1R signaling is involved in baseline reward/reinforcement, as well as escalated consumption, of opiate drugs. An exciting recent study used CRISPR-Cas9 methods to selectively delete NK1R expression in VTA neurons. It was found that this manipulation prevented morphine place preference and DA release in the NAC, suggesting a specific locus of action for the role of the NK1R in opiate reward[52].

The role of the NK1R in opiate reward and reinforcement is one of the most consistent findings from the addiction literature on neurokinin systems and represents a highly significant target in medication development. There is no evidence to date of a role of the NK3R in opiate reward or reinforcement, and more research is needed in this area.

**Cocaine-Induced Behaviors**

Several early studies indicated that cocaine administration alters SP/NK1R function. Specifically, cocaine injection increases c-fos expression (immediate early gene that indicates neuronal activation) preferentially in SP-expressing cells of the striatum[63]. Also, repeated cocaine injection increases expression of the propeptide for SP in multiple subregions of the striatum including the dorsal striatum and NAC core, whereas acute cocaine injection tended to increase SP expression primarily in the dorsal aspects of the striatum[64, 65]. The findings described above refer to the effects induced by non-contingent (experimenter delivered) cocaine administration; however, contingent (voluntary operant self-administration) cocaine administration also effects SP expression. For example, chronic cocaine self-administration increases the expression of SP in the striatum of rats[66, 67]. Behaviorally, NK1R antagonism has been shown to prevent both the acute stimulatory effects of cocaine as well as the locomotor sensitization response following repeated cocaine injections[68, 69].

While the NK1R may mediate some behavioral effects of cocaine, most studies on cocaine-related behaviors indicate that the NK1R is not involved in primary reward or reinforcement for this drug, as evidenced by a lack of effect of NK1R manipulations in cocaine self-administration or place preference[53, 55, 57, 70]. However, the NK1R may have a functional role in reinstatement of cocaine seeking following extinction[70-72], a preclinical animal model of relapse-like behavior (see below). Also, the effect of NK1R antagonism on escalated cocaine self-administration following long access sessions has not been examined. Given the role of the NK1R in stress responses in general, and the ability of long access drug self-administration to recruit stress signaling systems, it is possible that NK1R antagonism would attenuate escalated cocaine intake following exposure to long access sessions.

There is a substantial literature describing the role of the NK3R in cocaine responses. For example, NK3R antagonist treatment reduced, and NK3R agonists enhanced, the locomotor activating effects of cocaine in rats, and these effects were sensitive to the specific doses of NK3R acting drugs administered[73, 74]. Acute NK3R antagonism also reduces cocaine-induced stereotypical behaviors[75], as well as the development and expression of locomotor sensitization following repeated cocaine injections[76]. Chronic treatment with NK3R antagonist in this study also revealed increased sensitivity to cocaine-induced stereotypies, suggesting DA hypersensitivity following chronic antagonist administration, an effect that was confirmed using D1 receptor binding assays. In non-human primates, decreased methylation state of the TACR3 promoter (which generally correlates with increased expression) following repeated cocaine administration has been observed [77]. Paradoxically, DA levels in the NAC were increased by systemic pretreatment of rats with either an agonist or antagonist of the

NK3R[73, 74]. Similar to this, both NK3R antagonists and agonists attenuate some behavioral responses to cocaine in marmosets[78, 79].

Taken together, these findings indicate a complex role of the NK1R and NK3R in cocaine-induced behaviors. While there seem to be substantial effects of these receptors on the locomotor stimulating effects of cocaine, for example, there is no data demonstrating a role of the NK1R or NK3R in cocaine reward or reinforcement in standard rodent models used to measure these behaviors. However, these receptors may be involved in relapse-like behavior or escalated drug seeking, and may still have promise for the development of pharmacotherapies for cocaine abuse.

**Alcohol Reward and Reinforcement**

For alcohol, the effect of the NK1R appears to be specific to stress-induced alcohol seeking and escalated consumption. For example, NK1R inhibition, either by genetic deletion, viral vector mediated knockdown, or pharmacological means, attenuates alcohol consumption in C57BL6/J mice, which consume high amounts of alcohol[9, 80, 81]. In this strain of mice, exposure to chronic social defeat increases NK1R expression and alcohol consumption[82]. Also, in a recent study, NK1R levels were found to positively correlate with the strength of alcohol place preference, and a NK1R antagonist reduced the expression of this reward behavior[83]. In agreement with this, NK1R knockout mice show a complete lack of place preference for alcohol[80].

Alcohol consumption in high preferring rats is also dependent on NK1R signaling. For example, inhibition of the NK1R reduces escalated alcohol consumption in specific rat lines bred for high alcohol preference including alcohol preferring P rats and Marchegian-Sardinian alcohol

preferring rats[84, 85]. Intermittent alcohol access (Monday/Wednesday/Friday access to 20% v/v alcohol) is another exposure that induces escalated alcohol intake in rodents[86]. Intermittent alcohol access alters NK1R expression in the striatum, and the NK1R plays a functional role in the escalated intake that is induced by this access schedule[87, 88]. In operant models, escalated alcohol self-administration can be induced by yohimbine injection, and this is also sensitive to NK1R antagonism[87]. Escalated alcohol self-administration has also been induced by upregulation of the NK1R in the central nucleus of the amygdala (CeA) using viral vector methods [89]. This is particularly intriguing because this particular brain region shows increased NK1R expression in the P rat. While there is strong evidence for a role of the NK1R in escalated and stress-induced alcohol intake, it has been repeatedly demonstrated that NK1R antagonism does not reduce alcohol intake under baseline (non-escalated) conditions[84, 85, 90-92].

ICV infusion of NK3R agonists acutely suppress alcohol consumption in alcohol preferring rats but do not affect food/water intake, alcohol metabolism, or alcohol-induced conditioned taste aversion [51, 93-95], and this effect is mimicked by systemic injection [96]. This effect of NK3R action has been suggested to be localized to the nucleus basalis magnocellularis, a cholinergic nucleus of the basal forebrain[97], and the lateral hypothalamus, a major subregion of the hypothalamus that is involved in motivated behavior[98]. Intriguingly, these two regions have also been found to play a role in SP effects on DA function and reward behavior (see above) [47, 99]. Infusion of NK3R agonist into the lateral ventricles or the paraventricular nucleus of the hypothalamus also attenuated motivation for alcohol access[100]. Since NK3R activation has rewarding properties by itself as described above, NK3R agonists

may reduce alcohol intake by contributing in part to the hedonic response when alcohol is consumed. The role of the NK3R in stress-induced alcohol intake has not been assessed.

Taken together, these complex roles of the NK1R and NK3R in alcohol-related behaviors argues for the further investigation of compounds targeting these receptors in the treatment alcohol use disorder. Given that the NK1R tends to affect stress-induced alcohol intake and the NK3R influences baseline consumption may argue for the development of dual NK1R/NK3Rs as potential treatments.

**Nicotine-Related Behaviors**

One study has examined the role of neurokinin receptors in neural responses to nicotine and is of interest to include here. It was found that NK1R (and NK3R) on neurons of the medial habenula (MHb) are involved in acute excitability, neuroadaptations, and withdrawal processes following exposure to nicotine[101]. In this study it was hypothesized that nicotinic receptors on neurokinin terminals that innervate the MHb have a stimulatory role in acute release, but chronic nicotine exposure desensitizes this response and contributes to withdrawal. Given this functional role of neurokinins in nicotine responses and its expression within critical circuits that mediate the response to this drug, additional research is needed in this area.

**Reinstatement of Drug Seeking**

Reinstatement is a preclinical rodent model that is used to study relapse-like behavior. In this behavioral protocol, an animal is first trained to self-administer a drug. Next, drug delivery is removed during the extinction phase and operant responding gradually subsides. Next, reactivation, or reinstatement, of responding is triggered by exposure to specific stimuli

including stress exposure, drug priming, or presentation of drug-paired cues. NK1R antagonism has repeatedly been shown to reduce the reinstatement of alcohol seeking that is triggered by footshock stress exposure or yohimbine (often considered a pharmacological stressor) injection, but not that which is induced by presentation of an alcohol-paired cue[70, 85, 89, 91, 102]. Increased sensitivity to yohimbine-induced reinstatement is exhibited by alcohol preferring P rats, which express high levels of the NK1R in the CeA (see above), and intra-CeA infusion of a NK1R antagonist attenuates this response[89]. Overexpression of the NK1R using viral vector infusion in control rats produces a behavioral response similar to that observed in P rats (increased yohimbine-induced reinstatement). The NAC shell appears to be another critical site of NK1R action in stress-induced reinstatement, as NK1R activity in this NAC subregion mediates stress-induced reinstatement of alcohol seeking in an outbred control strain of rats (Wistar)[102]. Overall, this suggests that the NK1R in the CeA and the NAC shell, two critical nodes of the extended amygdala stress circuitry that influences drug seeking behavior, mediates stress-induced reinstatement of alcohol seeking [84, 89, 102].

The role of the NK1R in reinstatement for other drugs of abuse has also been examined to some extent and the effect of NK1R antagonism in stress-induced reinstatement seems to be a consistent effect across drug classes. Early work examining the role of the NK1R in reinstatement of cocaine seeking demonstrated that infusion of a NK1R agonist, either intracerebroventricularly or directly into the VTA, induced reinstatement of extinguished cocaine seeking[71, 72]. However, pretreatment with a specific NK1R antagonist did not attenuate cocaine-primed reinstatement. Importantly, stress-induced reinstatement was not examined in these studies. It has more recently been shown that NK1R antagonism attenuates reinstatement of cocaine seeking that is triggered by yohimbine injection, which is often considered to be a

pharmacological stress stimulus (see above)[70]. Only one study has examined the role of the NK1R in reinstatement of opiate seeking. Specifically, a very recent study reported an attenuation of stress-induced reinstatement of oxycodone seeking by NK1R antagonism[103]. Taken together with the findings for alcohol reinstatement described above, it seems likely that the NK1R is involved in stress-induced reinstatement for all classes of drugs, but not reinstatement that is induced by other classes of stimuli (cues, for example). However, drug-primed reinstatement for opiate drug seeking has not yet been assessed, and given the role of the NK1R in most opiate responses examined to date suggests that it may have a role in this behavior as well. Additionally, it is unknown if the neurocircuitry that mediates the NK1R effect on stress-induced reinstatement to cocaine and opiate seeking is identical to that which has been identified for alcohol seeking.

The role of the NK1R in stress-induced reinstatement of drug seeking following extinction is one of the most consistent findings in the preclinical literature on this topic, and may represent the most valuable behavioral target for testing NK1R antagonists in the clinic. This affect appears to hold for all classes of drug tested thus far. However, there is no literature reporting any test of the NK3R in this behavior, and these experiments would be of great interest.

**Summary of Preclinical Findings**

Overall, a survey of the literature suggests that neurokinin receptors are strong candidates for development of pharmacotherapies for addiction. However, there seems to be stronger evidence in support of a role of the NK1R in drug-related behaviors, with the NK3R less represented in the preclinical findings, especially when considering opiate-related behaviors and relapse-like behavior for all classes of drugs. There is a considerable support for both receptors

in alcohol-related behaviors, with the NK3R being more associated with baseline intake and the NK1R being more involved in escalated and stress-induced intake. Alcohol use disorder is an area where much attention should be focused in the testing of neurokinin receptor antagonists. Additionally, the NK1R seems to have prominent effects on opiate reward and reinforcement. Given the magnitude of opiate use disorder and its related health risks in our current world, this is an additional area where more extensive clinical testing of NK1R antagonists should be focused.

Given the highly overlapping expression patterns and behavioral effects of the NK1R and the NK3R, and the diverse role that the NK1R plays in drug seeking behaviors, additional research on the role of the NK3R in stress-induced drug seeking, opiate reward/reinforcement, and escalated alcohol self-administration is needed. Testing of combined antagonists also holds potential as a novel pharmacological approach. Finally, more research on nicotine is needed given the one intriguing study described above and the scope of that health issue.

**Therapeutics & Clinical Research**

Human studies have supported a role of neurokinin receptor genetic polymorphisms in drug and alcohol dependence. Single Nucleotide Polymorphisms (SNPs) in the gene for the NK1R (TACR1 gene) influences risk of alcohol abuse and other related comorbid disorders [2, 3]. Additionally, similar SNPs contribute to the sensitivity to alcohol associated cues as measured by the magnitude of functional activation in critical brain regions during cue presentation[104]. For the NK3R, multiple SNPs in the human TACR3 gene are associated with the incidence of alcohol and cocaine dependence[4]. For both the NK1R and NK3R receptor, several clinical trials have been performed for conditions such as depression, anxiety, pain, and

drug abuse. Testing NK1R pharmacotherapies for novel indications is aided somewhat by the existence of a FDA-approved drug that targets this receptor: aprepitant, which is prescribed for chemotherapy induced nausea. In general, the results of clinical trials using NK1R or NK3R antagonists have produced mixed results, but these systems continue to hold great promise in pharmaceutical development. Future research should consider several key factors which will be discussed below including polymorphisms in neurokinin receptor genes, comorbidity with other psychiatric conditions, dosing/receptor occupancy, the use of combined NK1R/NK3R antagonists, and the viability of NK1R antagonist/MOR agonist formulations.

As stated above, SNPs in the genes for both the NK1R and NK3R associate with increased risk of alcohol and drug dependence. While these SNPs may influence functional response of the receptor to stressful stimuli or drug exposure, it is important to consider that these SNPs may also affect the efficacy of antagonists that target these receptors. Such pharmacogenetic interactions should be considered in clinical trials as a potential factor that influences the viability of these drugs in diverse patient populations. As such, it is possible that NK1R or NK3R acting agents may be indicated for a genetically defined subpopulation of patients that should be screened to identify such predictive factors. This personalized approach to medicine is commonly thought to be a major direction in which health care and pharmaceutical development will move.

NK1R antagonists gained much attention 2 decades ago when they were shown to have clinical efficacy in the treatment of depression[5]. However these results were not replicated in subsequent studies[105]. While most pharmaceutical companies halted NK1R-related research on this receptor system for psychiatric indications, newly developed, high potency NK1R antagonists have been developed and this new generation of drugs has shown considerable

promise in depression pharmacotherapy. It is now thought that early negative findings resulted from insufficient occupancy of NK1Rs with the compounds and doses used. Indeed, when very high NK1R occupancy is achieved, antidepressant effects are typically observed[7, 8, 106, 107]. In the future, clinical trials for depression, anxiety, addiction, and other related conditions should be performed with this in mind, and high potency receptor occupancy should be confirmed at the doses used in these experiments.

One notable trial for alcohol dependence produced highly promising results, with NK1R antagonism reducing craving and other physiological responses in treatment seeking detoxified alcoholics with comorbid anxiety[9]. However, a subsequent study using aprepitant showed no efficacy on behavioral outcomes in alcoholics with comorbid post-traumatic stress disorder[10]. This negative result may have been due to insufficient receptor occupancy by aprepitant at the dose used (see discussion above). In regards to opiate drugs, pretreatment with a NK1R antagonist increased the subjective effects of oxycodone administration[108]. However, it is unclear where on the dose-response function for oxycodone and/or aprepitant the specific doses administered lie for these individuals. In these unexpected and somewhat confusing results, another factor that should not be overlooked is that the sample population in the initial alcohol study was selected for alcoholics with comorbid anxiety. This suggests that substance dependent patients with specific comorbidities may be the most responsive to neurokinin targeting treatments. Whether these specific comorbidities associate with identifiable genetic signatures is unknown and should be examined in more detail.

Of potential benefit to the clinical field, new dual acting antagonists of NK1R and NK3R have shown safety, tolerability, and high receptor occupancy, but have yet to be tested in addiction[109, 110]. NK1R and NK3R have overlapping expression distributions, behavioral

effects, and affinity for the same endogenous ligands. For example, combined effects of the NK1R and NK3R have been shown to modulate nicotine responses and withdrawal effects, specifically in the MHb (see above)[101]. Preclinically, few studies have examined both NK1R and NK3R in the same experimental preparations and behavioral protocols, and additional research in this realm is needed. These receptors may act in concert, or may compensate for one another when one is inhibited with an antagonist. In either case, combined NK1R/NK3R antagonists may be a quite valuable strategy to implement in pharmaceutical development.

Another exciting avenue that has been introduced in the last decade is the development of combined MOR agonists/NK1R antagonist compounds. New generation compounds that agonize opioid receptors while concurrently inhibiting NK1Rs have been reported to have beneficial analgesic properties without developing tolerance following chronic administration, triggering increased DA release in the NAC, or inducing place preference; however, these compounds have yet to be tested in humans[52, 111]. These agents hold great promise as treatments for chronic pain, but also for opiate addiction.

**Conclusions**

As described in detail above, the NK1R and NK3R have notable effects on drug responses and drug seeking behavior. One of the most consistent findings has been an effect of NK1R antagonism on stress-induced drug seeking for multiple classes of drugs, an effect that is likely mediated by the extended amygdala stress circuitry. Considering these findings together, neurokinin receptor targets hold great promise in pharmaceutical development, and additional clinical studies would help to advance this field. Previously reported results and negative

findings should be considered in the context of the specific drugs/doses used, the impact of pharmacogenetic interactions, and comorbid psychiatric conditions.

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**Highlights**

-Neurokinins are stress-related neuropeptides that mediate drug-related behaviors

-NK1 receptors are primarily involved in opiate reward and stress-induced relapse for most drugs

-NK3 receptors mediate cocaine-induced behaviors and alcohol consumption

-NK1R and NK3R are valuable targets in medication development for addiction