INTRODUCTION:
Drugs of abuse such as opioids, cocaine, amphetamines, alcohol, and nicotine affect the reward pathway in unique ways leading to the potential of addiction. In the United States the cost of drug abuse to society is over $700 billion per year necessitating new strategies in management of addiction. Particularly alarming is the rate of deaths due to heroin overdose which has skyrocketed since 2010. The National Institute on Drug Abuse (NIDA) and Centers for Disease Control and Prevention (CDC) attribute this increase in heroin usage and mortality to an inadvertent consequence of reducing the availability of prescription painkillers. While abstinence from drugs of abuse seems like the most logical strategy, this has proven to be only an illusory goal. Therefore, the FDA and NIDA have planned to change the requirements for new therapies designed as deterrents for drugs of abuse; a reduction in the use of drugs of abuse over the long-term may be the more appropriate requirement for FDA approval. Neurokinins are a family of peptide transmitters involved in the reward pathway for each of the drugs of abuse, giving researchers a target to design new medications aimed at reducing the addictive profile of said drugs of abuse.

Substance P (SP) was the first member of the neurokinin family of peptides to be isolated, initially from equine intestine and brain in 1931 and shown to act as a vaso-depressor. The subsequent decades of research implicated SP and its neurokinin relatives as neurotransmitters involved in the modulation of the reward pathway. Here, we review the neurokinin literature giving a brief historical perspective of neurokinin pharmacology, localization in various brain regions involved in addictive behaviors, and the functional aspects of neurokinin pharmacology in relation to reward in preclinical models of addiction that have shaped the rational drug design of neurokinin antagonists that could translate into human research. Finally, we will cover the clinical investigations using neurokinin antagonists and discuss their potential as a therapy for drug abuse.

Historical Overview of Neurokinins
In 1931, Ulf Von Euler and John Gaddum were on an expedition of the nervous system (CNS) disorders including anxiety, depression, migraine, schizophrenia, and addiction. Here, we review the basic and clinical science of the last 80 years that have helped shape our current understanding of how neurokinins specifically alter the neuronal pathway involved in addiction. We will then introduce potential neurokinin directed therapies that may have efficacy in clinical practice relating to addiction.

ABSTRACT: Addiction is a chronic disorder in which consumption of a substance or a habitual behavior becomes compulsive and often recurrent, despite adverse consequences. Substance P (SP) is an undecapeptide and was the first neuropeptide of the neurokinin family to be discovered. The subsequent decades of research after its discovery implicated SP and its neurokinin relatives as neurotransmitters involved in the modulation of the reward pathway. Here, we review the neurokinin literature giving a brief historical perspective of neurokinin pharmacology, localization in various brain regions involved in addictive behaviors, and the functional aspects of neurokinin pharmacology in relation to reward in preclinical models of addiction that have shaped the rational drug design of neurokinin antagonists that could translate into human research. Finally, we will cover the clinical investigations using neurokinin antagonists and discuss their potential as a therapy for drug abuse.

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rons in the VTA, but how was SP signaling to the postsynaptic neuron and were there other ligands of the same family in humans?

**Basic Neurokinin Pharmacology**

The ensuing era of neurokinin research revolved around the characterization of two more human neuropeptidases and their receptors. In 1983, neurokinin A and neurokinin B (NKA and NKB respectively) were discovered and characterized, putting them in the same family as SP (the tachykinin family) based on similar -CO₂ terminal sequences. By 1984, all three neurokinin receptors had been proposed followed by the permanent nomenclature: neurokinin-1 receptor (NK₁), neurokinin-2 receptor (NK₂), and neurokinin-3 receptor (NK₃) in 1986. Each ligand can bind and activate each receptor, however all they have their preference owing to a graded affinity: SP preferentially activates NK₁, NKA preferentially activates NK₃, and NKB preferentially activates NK₂ (Table 1). Cellular and molecular experiments linked neurokinin receptor activation to inositol phospholipid hydrolysis (later referred to as Gq coupling). Following receptor activation, the NK₂ is rapidly internalized leading to visual NK₂⁺ endosomal varicosities in the dendrites and somata of neurons, disappearing an hour later. This discovery made future cellular investigations into neurokinin pharmacology easier to trace.

Receptor localization is important in determining how the pharmacology affects a local neuronal circuit. Unfortunately for neuroscientists, the reward circuitry and accompanying pharmacology is quite complex. Further complicating the picture, G-protein coupled receptors (GPCRs) like the neurokinin family of receptors can act in both rapid (Ca⁺ or Na⁺ induced cell activation) and delayed (transcriptional) ways. Validating this notion, the activation of the neurokinin family of receptors will ultimately lead to an increase in [Ca⁺]intracellular, thus potentiating neuronal mechanisms of firing an action potential, in addition to activating the nuclear translocation of certain transcription factors including NF-kB. Additionally, recent evidence implicates swift activation of a Na⁺ leak channel, NALCN, as well as the closure of G-protein-linked inwardly rectifying K⁺ (GIRK) channels in the rapid SP-induced activation of neuronal action potentials.

For years, neurokinin antagonists studies were made very difficult by the lack of penetration of the available ligands (ie. only peptidergic antagonists were available). The breakthrough came in 1991 when scientists at Pfizer discovered the first nonpeptide molecule with classical competitive antagonism at the NK₁. The identification of this compound led to the discovery of even more selective, structurally diverse, nonpeptidic NK₁ antagonists at other pharmaceuticals, namely Merck’s MK-869, which later became known in the clinic as the antiemetic Aprepitant (EMEND). While considerable time and money went into the possibility of Aprepitant working as a stand-alone analgesic and/or antidepressant (without much success), the prospect of an NK₁ antagonist for the treatment of addiction still remains viable. The rest of this review will cover the specifics of neurokinin pharmacology in addiction.

**Neurokinins in the Reward Pathway**

While SPergic cell bodies have been found in a number of CNS cofi including the septal complex, nucleus tractus diagonalis (diagonal band of Broca), nucleus accumbens and habenula, with projections to various regions including the nucleus basalis magnocellularis, VTA, and interpeduncular nucleus, each constituent seems to have a unique function in the limbic loop. A recent report links NK₁ receptor activation to µ-opioid receptor recycling, offering direct evidence for a neurokinin mediated opioid resensitization. In fact, the neurokinin system is consistently found co-localized in or in other ways affecting endogenous opioid, dopamine, and serotonergic signaling, thereby exerting its effect on affective and drug seeking behavior.

**VTA**

Important to the reward pathway and the study thereof, the VTA most notably sends dopaminergic projections to the NAC where dopamine release triggers euphoria or positive reinforcement. Critically, intra-VTA injections of both an NK₁ agonist and NK₁ agonist facilitate dopamine release in the NAC. Indeed, autoradiographic studies using the radiolabeled NK₁ agonist [³H]5-enkiside confirmed the presence of NK₁Rs in the VTA in addition to the IPN and Hb. This complemented the previously studied NK₁ localization in the VTA amongst other CNS locations. While in vitro electrophysiologic studies in the VTA demonstrated NK₁Rs may mediate more of the excitory effects of dopaminergic neurons while leaving a role for SP out, in vivo electrophysiologic recordings in the VTA confirmed that systemic administration of an NK₁ agonist was sufficient to block dopamine cell firing. In addition, studies demonstrated an increased firing rate of VTA dopaminergic neurons due to the application of SP. These apparent discrepancies in dopaminergic activity and neurokinin pharmacology may be in part due to the marked receptor heterogeneity of the VTA.

The expression of various neurokinin receptor subtypes is rather diverse. For example, while there is somatodendritic expression of the NK₁R in the cell membrane of dopaminergic and non-dopaminergic neurons of the VTA, NK₂Rs are often found in the cytoplasm of dopaminergic and non-dopaminergic neurons of the VTA. Additionally, the NK₁Rs found in the plasma membrane are frequently extrasynaptic. Furthermore, VTA glia exhibit substantially more NK₁Rs than NK₂Rs, suggesting the importance of the immune cells in the reward pathway (more on glia later). Overall, the expression of NK₁Rs in the VTA is twice that of NK₂Rs. Interestingly, NK₂Rs, but not NK₁R or NK₃Rs, were found within the nuclear envelope of projection neurons of the VTA. This suggests the possibility of direct NK₁R involvement in gene transcription. Indeed, ligand-dependent and independent nuclear translocation of the NK₁R in the VTA has been observed. The significance of these nuclear events in the reward pathway has not been fully elucidated.

The literature on the NK₁R in the VTA is sparse, however it has been shown that i.v. infusion of the selective NK₁R antagonist SR-48968 did not alter basal dopaminergic firing rate in rats. Peculiarly, the acute administration of SR-48968 i.p. increased the number of spontaneously active VTA DA neurons, however this may be due to dosing differences or possible pharmacologically active metabolites. The intracellular interaction between neurokinin receptors has also been studied. When expressed by the same cell, NK₁R activation sequesters β-arrestins in endosomes impeding ligand-dependent NK₁R endocytosis. The pau-

| Endogenous Ligand | Receptor |
|-------------------|----------|
| **Substance P**   | **NK₁R** |
| 0.19 ± 0.02 nM    | 100 ± 39 nM |
| 20 ± 7 nM         | 0.32 ± 0.07 nM |
| 63 ± 13 nM        | 5.5 ± 3.7 nM |
| **Neurokinin A**  | **NK₂R** |
| 0.19 ± 0.02 nM    | 100 ± 39 nM |
| 20 ± 7 nM         | 0.32 ± 0.07 nM |
| 63 ± 13 nM        | 5.5 ± 3.7 nM |
| **Neurokinin B**  | **NK₃R** |
| 0.37 ± 0.03 nM    | 100 ± 39 nM |
| 28 ± 3 nM         | 100 ± 39 nM |

Table 1: **SP** has the greatest functional activity at the **NK₁R**, **NKA** at the **NK₂R**, and **NKB** at the **NK₃R**. **IC₅₀**, half maximal inhibitory concentration; **NK₁R**, neurokinin receptor 1; **NK₂R**, neurokinin receptor 2; **NK₃R**, neurokinin receptor 3; **SP**, substance P; **NKA**, neurokinin A; **NKB**, neurokinin B.

Reproduced with permission from Ingi T, Kitajima Y, Minamikata Y, Nakanishi S. Characterization of ligand-binding properties and selectivities of three rat tachykinin receptors by transfection and functional expression of their cloned cDNAs in mammalian cells. J Pharmacol Exp Ther. 1991;259(3):968–975.
city of information regarding how heterologous interactions between neurokinin receptors affects the reward pathway indicates the necessity of future research in addiction.

Some of the earliest investigations into neurokinin’s ability to functionally impel the reward pathway came in 1983 when Staubli and Huston showed that injection of SP into the medial forebrain bundle, the neuronal tract that connects the VTA to the NAc, resulted in positive conditioned place preference (CPP).43 In regards to specific drugs of abuse, microinjection of the SP analog DMe-C7 induced reinstatement of cocaine seeking behavior which could be significantly reduced by the D1 receptor antagonist SCH23390.44

Nucleus Accumbens
The NAc is often regarded as the limbic-motor interface receiving inputs from the VTA and amygdala among other regions and sending projections to the cortex, ventral pallidum, globus pallidus, and reciprocal projections to the VTA and amygdala.45 One study provided evidence that the NAc required input from both the VTA and the basolateral amygdala for excitation of NAc efficients.46 SP injected into the NAc by itself increases concentrations of extracellular DA but does not induce positive CPP.47 A SP antibody injected into the NAc prevents AMPH induced increase of extracellular DA in the NAc.48 Likewise, NAC administration of the NK1 antagonist L-733,060 significantly diminishes cocaine induced DA release.49

Nucleus Basalis Magnocellularis-Substantia Innominata
Evidence for SPergic fibers projecting to the nucleus basalis magnocellularis (nucleus basalis of Meynert) comes from simple light microscopic images and immunohistochemical staining.50 Accordingly, the injection of SP or the C-terminal fragment of SP into the nucleus basalis magnocellularis resulted in a positive CPP, which the authors attributed to the positive reinforcing effects of the specific C-terminal sequence of SP.51 Of course the C-terminal fragment is shared amongst all tachykinin ligands so releasing which receptor subtype responsible was an obvious next step. With the use of selective agonists they went on to show that this effect was mediated by both NK1 and NK2 activity.52 Further, SP injection into the nucleus basalis magnocellularis increased extracellular dopamine content in the NAc, 53 a barometer of positive reinforcement. The fact that injection of the NK2 agonist amino-sentkide into the nucleus basalis magnocellularis inhibits alcohol intake at first glance contradicts the aforementioned positive reinforcement.54 The authors speculated that alcohol may actually be mediating its effects on the reward pathway via NK2R, thereby rendering an NK2R agonist a substitute for the rewarding properties of alcohol.55 Whether or not alcohol engages the NK2R system in the nucleus basalis magnocellularis remains to be investigated.

NK1 fibers have been traced from the dorsal AND ventral striatum to the substantia innominata.56 Pre-protachykinin-B, the mRNA for NK1, has also been found heavily concentrated in fibers from the lateral stripe of the striatum, a region just lateral to the shell of the NAc, to the nucleus basalis magnocellularis.57 The importance of these projections in reward is not well understood, however it should be remembered that NK1 is the most efficacious endogenous ligand for the NK1R in mammals.

Habenula
The habenula is an understudied brain region let alone the role neurokinins play in its function. What is known is that the habenula white matter tracts tie it extensively to other regions of the limbic pathway including the ventral pallidum and ventral midbrain. Moreover, SPergic and NK2ergic cell bodies are indeed found in the medial habenula with axons projecting to the VTA and the adjacent interpeduncular nucleus.64,65 The role of the VTA in reward is well described; the interpeduncular nucleus also seems to contribute to positive reinforce-
silencing with a microRNA directed at the receptors' transcript reduced alcohol consumption in mice. The study noted that the NK-R antagonist reduced expression in the hippocampus, the only subcortical area they examined for proof of action. To the contrary, Ezlopitant, the NK-R antagonist developed for chemotherapy induced nausea and vomiting (CINV), exhibited little to no efficacy in reducing operant self-administration of alcohol in Long-Evans rats. The aforementioned inconsistency raises a valid point about nonconserved regions of the neurokinin receptors. While stress has been shown to increase extracellular SP in the amygdala, it should be mentioned that SP and NKA have been found to co-localized in neurons of the infundibulum of the CNS and myenteric plexus of enteric nervous system, a possibility that hasn't been specifically investigated in neurons of the amygdala. In fact, NK-Rs do appear in a significant concentration in the amygdala, and the NK-R antagonist SR142808 was sufficient to block stress induced behaviors in mice and central neuronal markers of stress in rats.

An analogous pathway observed in the alcohol reward system in relation to neurokinin pharmacology is that observed with corticotropin releasing factor (CRF). There is extensive research into the effects of CRF and other neuropeptides on addiction that are out of the scope of this review. In general, it is accepted in the addiction field that the stress response is mediated by several neurotransmitter systems including CRF and SP, thus precipitating undesirable outcomes as relapse.

Frontal Cortex
The literature on neurokinins in the cortex is more scant than other brain regions; nevertheless cortical neurokinins seem to play an important role in the limbic system. As one of the terminal sites of mesencephalic dopaminergic projections, the frontal cortex has been shown to have increased dopamine metabolites (DOPAC) in response to stress (ie. footshock). This increase in cortical dopamine is correlated to periods of intoxication and craving, particularly with cocaine abuse. Pretreatment with the selective NK-R antagonist (S)-GR205171 i.p. was sufficient to prevent footshock induced dopamine release in the cortex. In addition to stress, morphine injections i.p. increased SP levels in the cortex which subsequently significantly decreased due to the administration of the opioid antagonist, naloxone. The relative importance of the frontal cortex in neurokinin mediated addiction is not well understood and warrants further exploration.

Involvement of the Immune System in Addiction
The role of the resident immune cells in the brain, the glia (astrocytes, microglia, oligodendrocytes), has been emerging in the last 20 years as critical for normal neuronal signaling. Importantly, microglia and astrocytes have recently been implicated in addictive processes as activated microglia release “proinflammatory” cytokines that act at the neural synapse, strengthening the signal. Expanding on this notion, alcohol, cocaine, morphine, and amphetamines have all been indicted for their role in microglial activation with microglial activation proven to be critical to the maintenance of addictive behaviors. Critically, NK-Rs are located on microglia and inducible by IL-1β in astrocytes. SP has been shown to activate NF-κB in microglia which has a strong, yet neglected role in the progression of addiction. In astrocytes, SP application induces a complex depolarization by modulating Cl- and K+ currents. Astrocytes are probably most notorious for their role in glutamate homeostasis so there is a high likelihood of the neurokinin system modulating extracellular glutamate in brain regions including those of the limbic system. There is substantial information on both neurokinins and glia in the reward pathway, yet a dearth of information on the interaction between the two. It may end up representing one of the more promising avenues in addiction research.

Neurokinin in the Clinic
We have outlined the neural and pharmacological basis for the use of neurokinin antagonists in addiction. To summarize, SP appears to be overexpressed after chronic administration of drugs of abuse and mediates some of the negative effects such as CPP and reinstatement. Here the focus will be on the use of neurokinin antagonists specifically in humans and the potential success as a therapeutic. While SP has long been infamous as one of the primary pronociceptive neurotransmitters, an NK-R antagonist did not achieve appreciable analgesia as a standalone medication in patients suffering from pain. However, one of the first investigations into neurokinins in human disease with positive results demonstrated elevated cerebrospinal fluid levels of SP in psychiatric patients with depression or schizophrenia. With the development of radiolabeled substance p antagonists (SPAs), imaging of receptor localization and saturation in humans became possible with positron emission tomography (PET). (18F)-SPA-RQ was taken up in the brain of healthy male volunteers in regions described earlier that are involved in reward including the VTA, amygdala, habenula, and ventral striatum. The most notable differences from rats were the high density of NK-Rs in the cortex of humans and a greater NK-R/NK-R ratio in the VTA of humans.

Functionally, the NK-R antagonist Aprepitant has an effect on positive incentive in humans. In an experiment enlisting healthy volunteers of both genders, monetary incentive delay was the paradigm used to determine if the NK-R antagonist could prevent NAc activation typical of incentive anticipation. Indeed, when subjects expected a monetary reward for completing a task in the study, Aprepitant reduced NAc blood oxygenation-level-dependent (BOLD) contrast compared to control as seen on fMRI, indicating the attenuation of NAc activation.

An association between various NK-R gene (TACR1) single nucleotide polymorphisms (SNPs) and alcoholism may exist. In a large sample of heavy drinkers (> 7 drinks per day on average), 5 SNPs of the TACR1 gene were predictive of BOLD activation as assessed by fMRI in response to alcohol cues. In a separate study, 1 SNP and 2 haplotypes (a specific combination of alleles on the same chromosome) of the TACR1 gene were associated with alcohol dependence. The significance of these studies isn’t well understood, however they point to a link between a specific neurokinin genotype and alcohol dependent phenotype that may have potential as a drug target. Of course, the NK-R is not the only SNP found to dysregulate the reward pathway as OPRM1 (μ-opioid receptor) has also been highlighted as a troublesome gene of interest. Much like carriers of certain OPRM1, SNPs are more sensitive to the effects of naltrexone on reducing alcohol cravings, so too should NK-R antagonists on specific TACR1 SNP related addictions.

Unexpectedly in a clinical study examining the role of Aprepitant on oxycodone abuse liability, the authors found the NK-R antagonist actually increased the abuse potential of oxycodone in patients who were already opioid drug abusers. Several explanations for the unanticipated outcomes were proposed including the pharmacokinetic interaction between the two drugs. That is, Aprepitant and oxycodone compete for metabolism by the enzyme CYP3A4, rendering higher concentrations of serum oxycodone than expected. The unfortunate pharmacokinetic profiles of many drugs have hindered their success in the past, despite promising pharmacodynamic actions on the biology of the system. Future studies on opioid dependence may require a novel neurokinin antagonist that is not involved in CYP3A4 metabolism, a requirement that will surely prove challenging though not impossible.

In alcohol dependent humans that were recently detoxified, LY686017, a brain penetrant NK-R antagonist with high bioavailability, was efficacious in suppressing spontaneous alcohol cravings as assessed by the Alcohol Urge Questionnaire. When the alcohol dependent subjects were then provoked with a combined stress test and alcohol-cue
challenge, the treatment group still had reduced cravings for alcohol compared to controls. To the contrary, psychiatric patients with comorbid posttraumatic stress disorder (PTSD) and alcoholism experienced no reduction in symptoms of alcohol craving after administration of an NK\(_R\) antagonist.\(^{10}\) This may point to the fact that comorbidity with PTSD complicates the syndrome by adding another “stress” related illness.

**Neurokinin Prospects for Therapy**

The neurokinin field indeed does seem poised to produce significant contributions to addiction research and therapy. We have outlined the role neurokinins play in the reward pathway, particularly via NK\(_R\)s and NK3Rs. Accordingly, GlaxoSmithKline has a dual NK\(_R\)/NK3 antagonist, GSK1144814, in the pipeline for future clinical trials for psychiatric disorders.\(^{10}\) Vanda Pharmaceuticals acquired world-wide licensing for LYB68017 (now called VLY-686) from Eli Lilly after the proof of concept studies in alcohol cravings mentioned above. Vanda is now attempting to commercialize and develop this compound “for all human conditions” including an indication for substance abuse. Our pharmacology/chemistry group has created several opioid agonist/NK\(_R\) antagonist compounds that have efficacy in antinociception and do not produce CPP or increase extracellular dopamine content in the nucleus accumbens.\(^{11-15}\)

In addition to the new compounds in the pipeline, the original gold standard NK\(_R\) antagonist is still under investigation for its effects on substance abuse potential since it already has FDA approval for the clinic. A brief ClinicalTrials.gov search reveals that Aprepitant is currently undergoing clinical trials for the evaluation of its effects on cannabis cravings in cannabis dependent outpatients, co-morbid alcoholic and cannabis dependent patients, and in opioid dependent patients. More compounds that selectively block the neurokinin system will undoubtedly materialize in the drug pipeline as preclinical and clinical studies further identify the role of the neurokinin system in drug addiction.

**REFERENCES:**

1. Trends and Statistics. 2015. http://www.drugabuse.gov/related-topics/trends-statistics.
2. Volkow N. What is the Federal Government Doing to Combat the Opioid Abuse Epidemic? NIDA. NIDA: NIH; 2015.
3. US VE, Gaddum JH. An unidentified depressor substance in certain tissue extracts. The Journal of physiology. 1931;72(1):24-37.
4. Gaddum JH, Schild H. Depressor substances in extracts of intestine. The journal of physiology. 1934;83(11):1-14.
5. Pernon B. Distribution of substance P in the central and peripheral nervous system. Nature. 1953;171(4357):476.
6. Yaksh TL, Jessell TM, Gamez R, Mudge AW, Leeman SE. Intrathecal morphine inhibits substance P release from mammalian spinal cord in vivo. Nature. 1980;286(5786):155-157.
7. Chang MM, Leeman SE. Isolation of a sialogogic peptide from bovine hypophysial tissue and its characterization as substance P. J Biol Chem. 1970;245(8):4784-4790.
8. Aroz EO, Brownstein MJ, Leeman SE. Evidence for substance P in the habenulo-interpeduncular tract. Brain research. 1976;111(3):597-599.
9. Kanazawa I, Emson PC, Cuello AC. Evidence for the existence of substance P-containing fibres in striato-nigral and pallido-nigral pathways in rat brain. Brain research. 1977;119(3):447-453.
10. Naper TC, Mitrovic I, Churchill L, Kittenick MA, Lu XY, Kalivas PW. Substance P in the ventral pallidum: projection from the ventral striatum, and electrophysiologic and behavioral consequences of pallidal substance P. Neuroscience. 1995;64(1):59-70.
11. Cuello AC, Jessell TM, Kanazawa I, Iversen LL. Substance P localization in synaptic vesicles in rat central nervous system. Journal of neurochemistry. 1977;29(4):747-751.
12. Kelly PH, Iversen SD. Selective 60HDA-induced destruktion of mesolimbic dopamine neurons: abolition of psychostimulant-induced locomotor activity in rats. European journal of pharmacology. 1976;40(1):45-56.
13. Spyriak C, Fibiger HC, Phillips AG. Attenuation of heroin reward in rats by disruption of the mesolimbic dopamine system. Psychopharmacology. 1983;78(2-3):278-283.
14. Baik JH. Dopamine signaling in reward-related behaviors. Frontiers in neural circuits. 2013;7:152.
15. Stinus L, Kelley AE, Iversen SD. Increased spontaneous activity following substance P infusion into Avo dopaminergic area. Nature. 1978;276(5688):616-618.
16. V. Erspreer AM. Polypeptides active on plain muscle in the amphibian skin. Paper presented at: Proceedings of the International Symposium: Hypotensive Peptides; October 25-29, 1965, Florence, Italy.
17. Kimura S, Okada M, Sugita Y, Kanazawa I, Munekata E. Novel Neuropeptides, Neurokinin-Alpha and Neurokinin-Beta Isolated from Porcine Spinal Cord. Jpn Acad B-Phys. 1985;61(4):101-104.
18. Burk SH, Burcher E, Shults CW, Loveryen W, O’Donoghue TL. Novel pharmacology of substance P-binding sites: a third type of tachykinin receptor. Science. 1984;226(4677):987-989.
19. Henry JL. Substance P and Neurokinins. Paper presented at: Proceedings of “Substance P and Neurokinins-Montreal ’86” A Satellite Symposium of the XXX International Congress of The International Union of Physiological Sciences (96), Montreal, Canada.
20. Regoli D, Drapeau G, Dion S, O’Dorleans-Juste P. Pharmacological receptors for substance P and neurokinins. Life Sci. 1987;40(2):109-117.
21. Manthyp PW, Pinkow RD, Downes CP, Goedert M, Hunt SR. Correlation between inositol phospholipid hydrolysis and substance P receptors in rat CNS. Nature. 1984;310(5977):795-797.
22. Manthyp PW, Allen CJ, Chilardi JR, et al. Rapid endo- cytosis of a G protein-coupled receptor: substance P-evoked internalization of its receptor in the rat striatum in vivo. Proceedings of the National Academy of Sciences of the United States of America. 1995;92(1):622-626.
23. Steinhoff MS, von Mentzer B, Geppetti P, Pothoulakis C, Bunnell NW. Tachykinin and their receptors: contributions to physiological control and the mechanisms of disease. Physiol Rev. 2014;94(1):265-301.
24. Lu B, Su Y, Das S, et al. Peptide neurotransmitters activate a cation channel complex of NALCN and UNC-80. Nature. 2009;457(7230):741-744.
25. Koike-Tani M, Collins JM, Kawano T, et al. Signal transduction pathway for the substance P-induced inhibition of rat Kir3 (GIRK) channel. The journal of physiology. 2005;554(1):P289-500.
26. Iversen L, Leslie Iversen. In: Squire LR, ed. The History of Neuroscience in Autobiography. Vol 6: Oxford University Press; 2009:190-225.
27. Snider RM, Constantine JW, Lowe JA, et al. A potent neuropeptide antagonist of the substance P (NK1) receptor. Science. 1991;253(4992):425-427.
28. Kramer MS, Cutler N, Feighner J, et al. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. Science. 1998;281(5383):1640-1645.
29. Hill R. NKS (Substance P) receptor antagonists—why are they not analgesic in humans? Trends in pharmacological sciences. 2000;21(7):244-246.
30. Ljungdahl A, Hockfeld T, Nilsson G. Distribution of substance P-like immunoreactivity in the central nervous system of the rat—Cell bodies and nerve terminals. Neuroscience. 1978;1(6):861-943.
31. Bowram SL, Soothoo AL, Shiwasaki DJ, Schulz S, Pradhan AA, Puthenveedu MA. Cell-Autonomous Regulation of Mu-Opioid Receptor Recycling by Substance P. Cell reports. 2015.
32. Santarelli L, Gobbii G, Biler P, Hen R. Behavioral and physiologic effects of genetic or pharmacologic inactivation of the substance P receptor (NK1). The journal of clinical psychiatry. 2002;63 Suppl 11:17-17.
33. Mantyh PW. Neurobiology of substance P and the NK\(_R\) receptor. The journal of clinical psychiatry. 2002;63 Suppl 11:6-10.
34. Wise RA, Koob GF. The development and maintenance of drug addiction. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2014;39(1):232-262.
35. Elliott PJ, Mason GS, Stephens-Smith M, Hagan RM. Behavioural and biochemical responses following activation of midbrain dopamine pathways by receptor selective neurokinin antagonists. Neuropeptides. 1991;19(2):119-126.
36. Dam TV, Escher E, Quirion R. Visualization of neurokinin-3 receptor sites in rat brain using the highly selective ligand [3H]entendine. Brain research. 1990;506(1):173-179.
37. Mantyh PW, Gates T, Manthy CR, Maggio JE. Autoradiographic localization and characterization of tachykinin receptor binding sites in the rat brain and peripheral tissues. The journal of neuroscience: the official journal of the Society for Neuroscience. 1989;9(3):258-279.
38. Seabrook GR, Bowrey BJ, Hill RG. Pharmacology of tachykinin receptors on neurons in the ventral tegmental area of rat brain slices. European journal of pharmacology. 1995;273(1-2):113-119.
39. Minabe Y, Emori K, Toor A, Stutzmann GE, Ashby CR, Jr. The effects of the acute and chronic administration of CP 96,345, a selective neurokinin receptor antagonist, on midbrain dopamine neurons in the rat: a single unit, extracellular recording study. Synapse. 1996;21(3):33-45.
40. Korotkova TM, Brown RE, Sergeeva OA, Ponomarenko AA, Haas HL. Effects of arousal- and feeding-related neuropeptides on dopaminergic and GABAergic neurons in the ventral tegmental area. The European journal of neuroscience. 2006;23(10):2677-2685.
Aims: To evaluate the role of the neurokinin-1 (NK1) receptor expressed on non-dopaminergic dendrites in the rat substantia nigra and ventral tegmental area. 

Subjects and methods: Neurokinin-1 receptor agonist SR142801 prevents the apomorphine-evoked surface but not nuclear NK1 receptor redistribution in dopaminergic neurons of the rat ventral tegmental area. Synapse. 2009;63(6):484-501.

Results: A differential targeting of neurokinin-1 receptors to mesocortical and mesolimbic projection neurons and to neuronal nuclei in the rat ventral tegmental area. Synapse. 2013;127:124-24.

Conclusions: In vivo extracellular single cell study.

Implications: This study provides novel insights into the role of the NK1 receptor in reward-related neuronal circuits.

Keywords: Neurokinin-1 receptor; Ventral tegmental area; Dopaminergic neurons; Striatum; Substantia nigra; Mesolimbic projections.

References:

1. Lessard A, Gajewski CA, Bunnett NW, Pickel VM. Subcellular distribution and pharmacology of neurokinin-1 receptors in the rat substantia nigra and ventral tegmental area. Neuroscience. 2005;135(4):1309-1323.

2. Hasenohrl RU, Gerhardt P, Huston JP. Positively reinforcing effects of neurokinin substance P in the basolateral forebrain: mediation by its C-terminal sequence. Experimental neurology. 1992;11(2):282-291.

3. Gadd CA, Muttra P, De Felipe C, Hunt SP. Neurokinin-1 receptor-expressing neurons in the amygdala modulate morphine reward and anxiety behaviors in the mouse. The journal of neuroscience: the official journal of the Society for Neuroscience. 2003;23(2):827-835.

4. Placenza FM, Fletcher PJ, Vaccarino FJ, Ebbs E. Effects of central neurokinin-1 receptor antagonism on cocaine- and opiate-induced locomotor activity and self-administration behaviour in rats. Pharmacology, biochemistry, and behavior. 2006;84(1):94-101.

5. Placenza FM, Vaccarino FJ, Fletcher PJ, Ebbs E. Activation of central neurokinin-1 receptors induces reinstatement of cocaine seeking behavior. Neuroscience letters. 2005;390(1):42-47.

6. Yang AR, Yi HS, Marcamz J, June HL, Jr., Hwang BH, June HL, Jr. Distinct deficiencies in substance P mRNA levels in the CeA are inversely associated with alcohol-motivated responding. Synapse. 2009;63(11):972-981.

7. L. Lumeng TD, T.K. Li. New Strains of Rats with Alcohol Preference and Nonpreference. In: Ronald G. Thuman JRi, Henry Drott, Britton Chance, ed. Alcohol and Adrenergic Metabolizing Systems: Intermediary Metabolism and Neurochemistry. Vol 3: Academic Press, Inc., 1977:537-544.

8. Higley AE, Koob GF, Mason BJ. Treatment of alcohol dependence with drug antagonists in the stress response. Alcohol research: current reviews. 2012;34(4):916-921.

9. Sinha R. How does stress lead to risk of alcohol re-lapse? Alcohol research: current reviews. 2012;34(4):432-440.

10. Eben B, Rupniak NM, Saria A, Singewald N. Substance P in the medial amygdala: emotional stress-sensitive release and modulation of anxiety-related behavior in rats. Proceedings of the National Academy of Sciences of the United States of America. 2004;101(2):4280-4285.

11. Schank JR, Pickens CL, Rowe KE, et al. Stress-induced reinstatement of alcohol-seeking in rats is selectively suppressed by the neurokinin-1 (NK1) antagonist LB124299. Psychopharmacology. 2011;218(1):111-119.

12. Thorsell A, Schank JR, Singley E, Hunt SP, Heilig M. Neurokinin-1 receptors (NK1-R), alcohol consumption, and alcohol reward in mice. Psychopharmacology. 2010;205(1):103-111.

13. Baek MN, Jung KH, Halder D, et al. Artificial microRNA-based nanorobots as tools to silencing alcohol reduces alcohol consumption in mice. Neuroscience letters. 2010;475(3):124-128.

14. Steensland P, Simms JA, Nielsen CK, Holgate J, Bito-Ono JJ, Bartlett PS. A selective neurokinin-1 receptor antagonist, eltoprazin, reduces appetitive responding for sucrose and ethanol. PloS one. 2010;5(9).

15. Jensen CJ, Gerard NP, Schwartz TW, Gether U. The species selectivity of chemically distinct tachykinin nonpeptide antagonists is dependent on common divergent residues of the rat and human neurokinin-1 receptors. Molecular pharmacology. 1994;45(2):294-299.

16. Bravosky E, Borsay BA, Razz K, et al. Substance P immunoreactivity exhibits frequent colocalization with kisspeptin and neurokinin B in the human infundibular region. PloS one. 2011;8(1):e57266. silencing prevents alcohol consumption in mice. Neuroscience letters. 2010;475(3):124-128.

17. Deacon CF, Agoston DV, Nau R, Conlon JM. Conversion of neuropeptide K to neurokinin A and vesicular colocalization of neurokinin A and substance P in neurons of the guinea pig small intestine. Journal of neurochemistry. 1987;48(1):141-146.

18. Nagano M, Oishi T, Suzuki H. Distribution and pharmacological characterization of primate NK1 and NK2 tachykinin receptors in the central nervous system of the rhesus monkey. Neuroscience letters. 2001;312(1):23-26.

19. Steinberg R, Alonso R, Griebel G, et al. Selective blockade of neurokinin-2 receptor produces antidepressant-like effects associated with reduced corticosterone-releasing factor function. The Journal of pharmacology and experimental therapeutics. 2001;293(2):449-458.
47. Hargreaves R. Imaging substance P receptors (NK) in the living human brain using positron emission tomography. J Clin Psychi. 2002;63:18-24.

51. Hietala J, Nyman MJ, Eskola O, et al. Visualization and quantification of neurokinin-1 (NK1) receptors in the midbrain dopamine neurons. The Journal of comparative neurology. 1997;382(3):394-400.

53. Okumura M, Arakawa R, Ito H, et al. Quantitative analysis of NK1 receptor in the human brain using PET with 18F-FE-SPA-RQ. J Nucl Med. 2008;49(11):1749-1755.

55. Saji K, Ikeda Y, Kim W, et al. Acute NK(1) receptor antagonist administration affects reward incentive anticipation processing in healthy volunteers. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum. 2013;16(7):1461-1471.

57. Blaine S, Claus E, Harlaar N, Hutchison K. TACR1 genotypes predict fMRI response to alcohol cues and level of alcohol dependence. Alcoholism, clinical and experimental research. 2013;37 Suppl 1:S125-130.

59. Seneviratne C, Ait-Daoud N, Ma JZ, Chen G, Johnson BA, Li MD. Susceptibility locus in neurokinin-1 receptor gene associated with alcohol dependence. Neupropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2009;34(11):2442-2448.

61. Heilig M, Goldman D, Berrettiini W, O’Brien CP. Pharmacogenetic approaches to the treatment of alcohol addiction. Nature reviews. Neuroscience. 2011;12(11):670-684.

63. Anton R, O’rossi G, O’Malley S, et al. An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. Archives of general psychiatry. 2008;65(2):135-144.

65. Walsh SI, Heilig M, Nuazzo RA, Henderson P, Lofwall MR. Effects of the NK1 antagonist, aripiprazole, on response to oral and intranasal oxycodone in prescription opioid abusers. Addiction biology. 2013;18(2):332-343.

67. George DT, Gilman J, Hersh J, et al. Neurokinin 1 receptor antagonist as a possible therapy for alcoholism. Science. 2008;319(5869):1536-1539.

69. Kwako LE, George DT, Schwartz ML, et al. The neurokinin-1 receptor antagonist aripiprazole in co-morbid alcohol dependence and posttraumatic stress disorder: a human experimental study. Psychopharmacology. 2015;232(1):293-304.

71. Ridler K, Gunn RN, Searle GE, et al. Characterising the plasma-target occupancy relationship of the neurokinin antagonist GSK144184 with PET. Journal of psychopharmacology. 2014;28(3):264-272.

73. Largent-Milnes TM, Yamamoto T, Nair P, et al. Sinal or systemic YF005, a peptide opioid agonist/neurokinin 1 antagonist, attenuates pain with reduced tolerance. British journal of pharmacology. 2010;161(5):1009-1018.

75. Yamamoto T, Nair P, Jacobsen NE, et al. The importance of micelle-bound states for the bioactivities of bifunctional peptide derivatives for delta/mu opioid receptor agonists and neurokinin 1 receptor antagonists. Journal of medicinal chemistry. 2008;51(20):6334-6347.

77. Sandweiss A, Stark J, Largent-Milnes TM, et al. An Opioid Agonist/NK1 Antagonist Inhibits Nociception in an Animal Model of Neuropathic Pain while Lacking Accumbs Dopamine Release. International Narcotics Research Conference 2015; Phoenix, AZ.

79. Ingi T, Kitajima Y, Minamitake Y, Nakashima S. Characterization of ligand-binding properties and selectivities of three rat tachykinin receptors by transfection and functional expression of their cloned cDNAs in mammalian cells. The Journal of pharmacology and experimental therapeutics. 1993;259(4):968-975.