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# NK1 (substance P) receptor

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Neurokinin-1 receptor (NK1R), or substance P receptor, is a G protein-coupled receptor (GPCR) that transmits the signal of substance P (SP) and other tachykinins. Upon stimulation by its agonist SP, NK1R has been shown to interact with multiple G proteins, including Gs, Gq/11, Gi/o, G12, and G13. NK1R undergoes a rapid agonist-dependent desensitization, which is mediated by members of G protein receptor kinases (GRKs) and β-arrestins. NK1R is widely distributed in the central and peripheral nervous systems, as well as in the gastrointestinal tract, immune system, and skin. NK1R plays a key role in many physiological and pathophysiological processes, including pain, inflammation, cancer, brain edema, traumatic brain injury, nausea and vomiting, affective disorders, and obesity. Several pharmaceutical companies are actively developing compounds to target NK1R for its therapeutic potential. The first FDA approval for a NK1R antagonist was obtained in 2003 for aprepitant, which is indicated for chemotherapy-induced nausea and vomiting.

**KEYWORDS**
Neurokinin-1 receptor; NK-1 receptor; NK1 (substance P) receptor; NK1-R; NK1R; SPR; Substance P receptor; Tachykinin NK1 receptor; Tacr1

**IDENTIFIERS**
Molecule Page ID:A000045, Species:Mouse, NCBI Gene ID: 21336, Protein Accession:NP_033339.2, Gene Symbol:Tacr1

**PROTEIN FUNCTION**
Neurokinin-1 receptor (NK1R), which has been given the name Tachykinin Receptor 1 (TACR1) by Human Genome Organization (HUGO) gene nomenclature committee , is a G protein-coupled receptor (GPCR) that mediates the action of substance P (SP) and other tachykinins (Douglas and Leeman 2011, Otsuka and Yoshioka 1993). In most tissues, NK1R is coupled to Gq family of G proteins and its activation leads to the hydrolysis of membrane phosphoinositides, resulting in the formation of two second messengers: inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG) (Kwatra et al. 1993, Raddatz et al. 1995). Formation of IP3 triggers the release of calcium from intracellular stores and formation of DAG leads to the activation of protein kinase C (PKC). Together, these third messengers cause a cascade of protein phosphorylation/dephosphorylation reactions culminating in altered gene expression and cell function. SP is involved in several physiological and pathophysiological processes, the best-studied of which are its roles in pain transmission and inflammation (Basbaum 1999, Krause et al. 1995, Payan 1989). Several lines of evidence corroborate a key function for SP in pain transmission; for example, mice lacking NK1R have been shown to have reduced pain perception (De Felipe et al. 1998). Stimulation of NK1R by SP activates nuclear factor-kappaB (NF-kB) and leads to the production of inflammatory cytokines such as interleukin-6 (IL-6) and IL-8 (Koon et al. 2005, Lieb et al. 1997). Cross-talk between NK1R and neurokinin-2 receptor (NK2R) has been reported in hematopoietic functions (Klassert et al. 2010).

Recent studies indicate a role for SP and NK1R in the pathophysiology of several diseases, including emesis (Diemunsch et al. 2009, Reddy et al. 2006), affective disorders (Herpfer and Lieb 2003), cancer (Munoz and Covenas 2010, Palma 2006), pruritis (Wallengren 2005), acute pancreatitis (Lau et al. 2005), alcoholism (George et al. 2008, Thorsell et al. 2010), brain edema (Donkin et al. 2009), hematologic disorders (Liu et al. 2007), traumatic brain injury (Vink and van den Heuvel 2010), and obesity (Karagiannides and Pothoulakis 2009).

Involvement of NK1R has been implicated in several forms of cancer (Munoz and Covenas 2010, Munoz et al. 2010, Palma 2006). Considerable data supports a role for NK1R is glioblastomas (GBM) (Akazawa et al. 2009, Lazarczyk et al. 2007). The significance of NK1R in GBM was first suggested in 1995, when Hennig et al. showed that NK1R is expressed in 9 out of 12 astrocytomas and 10 out of 10 GBM. This study also found that the expression of NK1R correlates with the degree of malignancy, with aggressive GBM expressing more receptors than grade I-III astrocytomas (Hennig et al. 1995). Based upon our discovery of a constitutively active form of NK1R in GBM (Akazawa et al. 2009), we believe that the blockade of NK1R, either alone or in combination with other targets, could be effective in halting the growth of GBM.

SP is a known mediator of pruritus (itching), and recent studies also indicate involvement of NK1R in this pathophysiology (Wallengren 2005). In 2009, a report was published on the effectiveness of NK1R antagonist aprepitant in reducing pruritus in patients with Sezary syndrome (Duval and Dubertret 2009). Since then, several studies have demonstrated the effectiveness of NK1R antagonist aprepitant to reduce itching in cancer patients (Booken et al. 2011, Stander et al. 2010, Vincenzi et al. 2010).

Several lines of evidence support a role for NK1R in affective disorders, such as stress and anxiety (Ebner and Singewald 2006, Herpfer and Lieb 2003). Disruption of NK1R signaling, either via genetic or pharmacological approaches, decreases anxiety-related behavior (Santarelli et al. 2001). Indeed, initial clinical trials of NK1R antagonists in humans revealed significant anti-depressant activity (Kramer et al. 2004, Kramer et al. 1998). These interesting results, however, were not substantiated by larger clinical trials (Keller et al. 2006, Tauscher et al. 2010).

Several studies suggest a potential role for NK1R and SP in acute pancreatitis through mediation of neurogenic



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inflammation (Bhatia et al. 1998, Bhatia et al. 2005, Grady et al. 2000). In a mouse model of acute pancreatitis, selective NK1R antagonist CP-96,345 was shown to reduce downstream proinflammatory signaling, thereby slowing disease progression and associated lung injury (Lau 2005).

Emerging research suggests a potential therapeutic application for NK1R antagonists in alcoholism (Thorsell et al. 2010). After initial successful preclinical studies in mice, NK1R antagonist LY686017 was found to suppress spontaneous alcohol cravings in a relatively small inpatient study of recently detoxified alcoholics (George et al. 2008).

Other human disease areas in which NK1R appears to play a key role include emesis (Diemunsch et al. 2009, Reddy et al. 2006), traumatic brain injury (Vink and van den Heuvel 2010), brain edema (Donkin et al. 2009), and obesity (Karagiannides and Pothoulakis 2009, Karagiannides et al. 2008).

**REGULATION OF ACTIVITY**

A main mechanism by which the activity of NK1R is regulated involves agonist-induced receptor desensitization, a process in which the receptor's response is decreased in spite of the continued presence of the stimulus. Many GPCRs are known to undergo a two-step process of agonist-dependent desensitization (Gainetdinov *et al*. 2004, Reiter and Lefkowitz 2006). First, the agonist-occupied GPCR is phosphorylated at serine/threonine residues by G protein receptor kinases (GRKs), which prime the receptor to bind β-arrestins. Binding of β-arrestin to the phosphorylated receptor disrupts receptor coupling to G proteins. This paradigm of agonist-dependent receptor desensitization in NK1R has been demonstrated in live cells (Barak *et al*. 1999). In addition to GRK/β-arrestin-mediated desensitization, NK1R also undergoes desensitization via protein kinase C (Dery *et al*. 2001). TGF-β enhances the activity of NK1R in T-cells by delaying SP-induced NK1R internalization (Beinborn *et al*. 2010). NK1R activity is also regulated by N-linked glycosylation at its N-terminus (Tansky *et al*. 2007). Furthermore, regulating the concentration of substance P, which is degraded by neutral endopeptidase (EC3.4.24.11), can also have an impact on NK1R function (Sturiale *et al*. 1999).

**INTERACTIONS**

The endogenous ligands of NK1R are three mammalian tachykinins, including SP, neurokinin A (NKA), and neurokinin B (NKB) (Patacchini *et al*. 2004; Severini *et al*. 2002). These tachykinins are produced from two genes: preprotachykinin-A (*PPT-A*), which encodes SP and NKA, and preprotachykinin-B (*PPT-B*), which encodes NKB. The new names given to *PPT-A* and *PPT-B* by the Human Genome Organization (HUGO) Gene Nomenclature Committee are *TAC1* and *TAC3*, respectively. Recently, a third tachykinin gene, preprotachykinin-C (*PPT-C*), also called *TAC4*, was cloned from hematopoietic cells of both mice and humans (Kurtz *et al*. 2002; Zhang *et al*. 2000). The *TAC4* gene encodes for hemokinin 1 (HK-1), which binds and activates NK1R similar to SP (Bellucci *et al*. 2002; Berger and Paige 2005).

Several NK1R antagonists have been developed. The first non-peptide high affinity antagonist of NK1R was reported in 1991 (Snider *et al*. 1991). Since then, a large number of compounds in different chemical classes have been found to block NK1R with high affinity (Alvaro and Di Fabio 2007). In 2003, the NK1R antagonist aprepitant was approved by the FDA for chemotherapy-induced nausea and vomiting (CINV), and it remains the only NK1R antagonist approved for clinical use in humans (Quartara and Altamura 2006; Quartara and Maggi 1998). An injectable formulation of aprepitant (fosaprepitant dimeglumine) has also been approved for CINV and postoperative nausea and vomiting (Huang and Korlipara 2010). An NK1R antagonist, maropitant citrate, has been approved for vomiting in dogs (Huang and Korlipara 2010; Ramsey *et al*. 2008).

To transmit its signal, NK1R interacts with several G proteins, including Gαs, Gαi/o, Gαq/11, Gα12, and Gα13 (Barr *et al*. 1997; Roush and Kwatra 1998). NK1R also undergoes agonist-dependent phosphorylation by GRK2 and GRK5, and binds to β-arrestin1 and 2 (Barak *et al*. 1999; Kwatra *et al*. 1993; Nishimura *et al*. 1998; Warabi *et al*. 2002). Furthermore, NK1R forms heterodimers with mu-opioid receptor (Pfeiffer *et al*. 2003). Upon chronic stimulation with SP, NK1R undergoes ubiquitination (Cottrell *et al*. 2006).

**PHENOTYPES**

Mice lacking the gene for NK1R show alterations in adaptive response to stress, nociception, and a decrease in anxiety-related behavior (De Felipe *et al*. 1998; Santarelli *et al*. 2001).

**MAJOR SITES OF EXPRESSION**

The NK1R is widely distributed throughout the body (Quartara and Maggi 1998), including the brain (Saria 1999; Tooney *et al*. 2000), spinal cord (Dietl *et al*. 1989; Palma *et al*. 1997), stomach (Gates *et al*. 1988; Holzer and Holzer-Petsche 2001), skin (Bianchi *et al*. 1999; Deguchi *et al*. 1989), and immune system (Douglas and Leeman 2011; van Hagen *et al*. 1999).

**SPLICE VARIANTS**

A truncated splice variant (NK1RΔ311) that lacks 97 amino acids at the C-terminus and ends at amino acid 311 has been reported (Fong *et al*. 1992). NK1RΔ311 appears to be oncogenic, and its expression is controlled by NF-kB (Patel *et al*. 2005; Ramkissoon *et al*. 2007). While the full-length NK1R is the form found most often in the human brain, NK1RΔ311 has been demonstrated to be more prevalent throughout the peripheral nervous tissues (Caberlotto *et al*. 2003). A recent study, however, has reported that truncated NK1R is the predominant form of NK1R in various regions of human brain (Lai *et al*. 2008).

**REGULATION OF CONCENTRATION**

At the protein level, the concentration of NK1R at the plasma membrane is regulated by agonist-induced internalization, recycling, and down-regulation by ubiquitination (Cottrell *et al*. 2006). Down-regulation of NK1R has been reported in human astrocytoma cells in response to tumor necrosis factor and interleukin-1 (Johnson and Johnson 1991). Down-regulation of NK1R has also been reported in the spinal cord dorsal horn of morphine-treated neonatal rats (Thomson *et al*. 2008). The expression of mRNA of NK1R has been shown to increase by three-fold in bone marrow-derived dendritic cells in response to lipopolysaccharide (Janelsins *et al*. 2009).

**ANTIBODIES**

Antibodies against NK1R have been developed (Nishimura *et al*. 1998; Vigna *et al*. 1994). They are available from Santa Cruz Biotechnology, Inc (Santa Cruz, CA) and several other vendors.

## Table 1: Functional States

| STATE DESCRIPTION | LOCATION | REFERENCES |
|---|---|---|
| native Tacr1 | integral to plasma membrane | |
| Tacr1-gly | integral to plasma membrane | Tansky MF *et al.* 2007 |
| Tacr1-SP | integral to plasma membrane | Cascieri MA and Liang T 1983 |
| Tacr1-NKA | integral to plasma membrane | Bremer AA *et al.* 2001 |
| Tacr1-HK1 | integral to plasma membrane | Bellucci F *et al.* 2002 |
| Tacr1-SP/Galpha q | integral to plasma membrane | Roush ED and Kwatra MM 1998 |
| Tacr1-SP/Galpha o | integral to plasma membrane | Roush ED and Kwatra MM 1998 |
| Tacr1-SP/Galpha 12 | integral to plasma membrane | Barr AJ *et al.* 1997 |
| Tacr1-SP/Galpha 13 | integral to plasma membrane | Barr AJ *et al.* 1997 |
| Tacr1PGRK2 | Unknown | Nishimura K *et al.* 1998 |
| Tacr1PGRK5 | Unknown | Warabi K *et al.* 2002 |
| Tacr1PGRK2/bARR1 | Unknown | Barak LS *et al.* 1999 |
| Tacr1PGRK2/bARR2 | Unknown | Barak LS *et al.* 1999 |
| Tacr1Ubi | Unknown | Cottrell GS *et al.* 2006 |
| Tacr1/muOR | integral to plasma membrane | Pfeiffer M *et al.* 2003 |

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This molecule exists in 15 states , has 14 transitions between these states and has 0 enzyme functions.(Please zoom in the pdf file to view details.)