NTSR1 (neurotensin receptor 1 (high affinity))

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Abstract
Review on NTSR1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: NTR
HGNC (Hugo): NTSR1
Location: 20q13.33

Note
Neurotensin receptor 1 is the high affinity receptor for neurotensin, a 13 amino acid peptide with neurotransmitter and hormone functions. Neurotensin binds 3 known receptors. Two of them belong to the superfamily of G-protein coupled receptors (GPCR): NTSR1 the high affinity receptor for neurotensin and NTSR2 its low affinity receptor, both belonging to GPCR class A (Mazella et al., 1996). The third receptor is NTR3 or sortilin, a member of VPS10 family (Petersen et al., 1997; Mazella et al., 1998).

NTSR1 through neurotensin binding is implicated in several functions, the modulation of dopaminergic systems, analgesia, and inhibition of food uptake, hypothermia, hypotension, intestinal motility and digestive secretions.

DNA/RNA

Description
The length of NTSR1 gene is 53.93 Kb, including 4 exons and 3 introns.

Transcription
Two transcripts are identified, a 4132 bp coding for a protein of 418 aa. The second contains 2950 bp but without yet identified coding protein.

Protein

Description
NTSR1 (418 aa in human) belongs to the GPCR family containing 7 TM domains. Its structure contains 4 extracellular and intracellular loops, the N terminal amino acid extracellular part located in extra cellular region. Four glycosylation sites (extracellular) are reported as essential for the functions. The binding of neurotensin is depending on 6 aa of the 4th extracellular loop of the protein (Vincent et al., 1999).

Expression
In central nervous system, NTSR1 is expressed in substantia nigra, ventral tegmental area, amygdal nucleus, striatum and entorhinal and prefrontal cortices (Kanba at al., 1986; Nicot et al., 1994).

In extra cerebral region, NTSR1 was detected in small intestine (Seybold et al., 1990; Mendez et al., 1997), fundus of stomach (Huidobro-Toro et al., 1985), pancreas (Wang et al., 2000), fetal liver (Ehrenfried et al., 1994), colon (Mendez et al., 1997) uterine tissue (Rodriguez et al., 2010) and prostate (Swift et al., 2010).

NTSR1 expression in human cells was reported in prostatic cells (Swift et al., 2010), colonic epithelial
cells (Martin et al., 2002), lymphocytes (Evers et al., 1994) including T (Magazin et al., 2004) and B lymphocytes (Saada et al., 2012).

**Localisation**
In the cell membrane: Activation of NTSR1 through neurotensin binding needs some post translational events including glycosylation and palmitoylation to downstream heterotrimeric G protein subunits effectors. This lipidation allows its localization within cell membrane microdomains and enhances the interaction with Gαq /11 which mainly reside within structured microdomains. This NTSR1-mediated MAPK signaling and cellular proliferation was demonstrated in breast cancer cells (Heakal et al., 2011).

Endocytosis: After activation by neurotensin, NTSR1 is desensitized through its internalization in endosomal vesicles in association with β-arrestin. This event requires phosphorylation depending on the C terminal region of NTSR1. Intracellular trafficking leads to NTSR1 degradation in lysosomes (Mazella and Vincent, 2006).

**Function**
NTSR1 is activated by neurotensin binding through autocrine or paracrine mechanism. Several signalizations were described depending on cell lines.

Indeed, neurotensin induces Erk phosphorylation colonic HT29 cells through PLC activation leading to Inositol phosphate formation (Massa et al., 2011).

The recruitment of G protein was described through NTSR1 activation in microdomains (Heakal et al., 2011). In other cell types, cell proliferation, migration and invasion are depending on a transactivation of EGFR by NTSR1 (Amorino et al., 2007; Moody et al., 2014) or act through the increase of expression and activation of EGFR, HER2, HER3 (Younes et al., 2014; Dupouy et al., 2014).

**Homology**
The NTSR1 gene is conserved in Rhesus monkey, dog, cow, mouse, rat, chicken, zebrafish, and frog. 81 organisms have orthologs with human gene NTSR1.

Conservation during evolution: NTSR1 gene is retrieved in jaw vertebrates (Gnathostomes) from the australian ghostshark, (Callorhinichus milii) to man, including most vertebrate groups (Teleosts, Coelacanth, the Amphibian Rana catesbeiana (Hwang et al., 2009), reptiles (python and lizard), birds and mammals. The duplication giving rise to NTSR1 and NTSR2 occurred probably in early vertebrates via the genome doubling (R2) events but details are unknown, as genes clearly encoding neurotensin receptors are doubtfully present in more basal vertebrates such as lampreys and hagfishes. Unlike its paralogue gene, NTSR1 was subject to positive selection in mammals, as numerous genes involved in chemosensory perception (Kosiol et al., 2008).

**Implicated in**

**Breast cancer**
NTSR1 is associated with the tumor grade and is a candidate risk factor involved in ductal breast cancer progression (Dupouy et al., 2009). Its functions in oncogenesis depend on EGFR, HER2 and HER3 expression in breast cancer cells (Dupouy et al., 2014).

**Lung cancer**
NTSR1 is overexpressed in lung cancer (Alifano et al., 2010b).

Its activation enhances HER2, HER3 and EGFR expression in lung cancer (Younes et al., 2014). Pharmacological NTSR1 inhibitor (SR48692) inhibits EGFR activation (Moody et al., 2014).

**Malignant pleural mesothelioma**
In malignant pleural mesothelioma, neurotensin and NTSR1 are significantly overexpressed in patients (Alifano et al., 2010a).

**Head and neck squamous cell carcinomas**
NTSR1 contributed to cancer cell invasion and migration and is highly expressed in patients with metastasis (Shimizu et al., 2008).

**Prostatic cancer**
NTSR1 is overexpressed in malignant prostatic tumors and malignant cell lines (Swift et al., 2010).

**Pancreatic cancer**
An increase of NTSR1 expression is detected in human ductal pancreatic adenocarcinoma (Reubi et al., 1998; Wang et al., 2000) as well as in PANC-1 cell line (Wang et al., 2011).

**Colorectal cancer**
NTSR1 is associated with human cell proliferation (Massa et al., 2011), promotes tumor development in mouse colon cancer model (Bugni et al., 2012) and is overexpressed in colorectal cancer progression (Gui et al., 2008).

NTSR1 activates miR-21 and miR-155, via Akt and NFkB, to down-regulate PTEN and SOCS1 and promote growth of tumors in mice.

NTR1, miR-21, and miR-155 levels are increased in human colon tumor samples and correlate with tumor stage (Bakirtzi et al., 2011).
Glioblastoma
Neurotensin through NTSR1 activation is implicated in maintaining glioblastoma stem, depending on IL-8 and Stat3 pathways (Zhou et al., 2014).

Melanoma
SR48692 through NTSR1 inhibition decreases melanoma cell proliferation and induces melanoma cell apoptosis (Zhang et al., 2014).

Neurodegenerative and psychiatric diseases
Schizophrenia and Parkinson disease (Ferraro et al., 2014) and addiction (Ma et al., 2013).

Inflammation
NTSR1 is overexpressed in colonic epithelial cells during inflammatory bowel diseases (Castagliuolo et al., 1999; Gui et al., 2013)

References
Gui X, Guzman G, Dobner PR, Kadok SS. Increased neurotensin receptor-1 expression during progression of colon adenocarcinoma. Peptides. 2008 Sep;29(9):1609-15
Mazella J, Botto JM, Guillemer E, Coppola T, Sarret P, Vincent JP. Structure, functional expression, and cerebral


Swift SL, Burns JE, Maidland NJ. Altered expression of neurotensin receptors is associated with the differentiation state of prostate cancer. Cancer Res. 2010 Jan 1;70(1):347-56


Wang JG, Li NN, Li HN, Cui L, Wang P. Pancreatic cancer bears overexpression of neurotensin and neurotensin receptor subtype-1 and SR 48692 counteracts neurotensin induced cell proliferation in human pancreatic ductal carcinoma cell line PANC-1. Neuropeptides. 2011 Apr;45(2):151-6


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