Review article

Substance P and its receptors – a potential target for novel medicines in malignant brain tumour therapies (mini-review)

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Abstract

Tachykinins are excitatory neuropeptides synthesised in neuronal and glial cells of the human central and peripheral nervous system. They participate in both physiological and certain pathological conditions, i.e. synaptic transmission, nociception and neuroimmunomodulation. Tachykinins act as excitatory neurotransmitters and/or neuromodulators and induce DNA synthesis leading to stimulation of cell division and proliferation. Their biological responses are triggered via the well-established tachykinin receptors NK1, NK2 and NK3 that belong to the G protein-coupled receptor family (GPCRs).

Substance P is the most important member of the tachykinin family that constitutes the major endogenous ligand for the NK1 receptor type. The presence of functional NK1 receptors has been documented in malignant brain tumours of glial origin. It has been evidenced that SP-NK1 receptor communication is involved in glioma development and progression. It is possible because the tumour cells display SP-mediated autocrine activity, the ability of cytokines stimulation and MAP kinases activation. It has been suggested that SP receptor antagonists application might be useful in attempts directed at anti-cancer therapy.

Key words: substance P, NK1 tachykinin receptor, glioma malignancy.

Family of tachykinin compounds

Tachykinins are neuropeptides widely spread in various species from low invertebrates to mammals [55]. The family of these compounds is characterised by a common and strongly evolutionarily conserved, specific C-terminal sequence: Phe-X-Gly-Leu-Met--NH$_2$. This motif of each tachykinin allows entry to the important signal transduction pathways and generation of diverse responses to different external and internal stimuli. So far the sequences and enco- ding genes of several diverse tachykinins have been established (Table I).

Tachykinins are produced in neuronal and glial cells of the human central and peripheral nervous system. These substances participate in nociception, synaptic transmission (as excitatory neurotransmitters) and neuroimmunomodulation. Knockout mice with SP deficiency demonstrated less depression--related behaviour and decrease of anxiety level that confirmed the significant role of tachykinins in modulation of emotional responses. It is not a surprising

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Table I. Tachykinins: sequences and encoding genes [48]

Name	Sequence	Gene (alternative name)
substance P (SP)	Arg-Pro-Lys-Pro-Gln-Gln-**Phe**-Phe-**Gly-Leu-Met**-NH$_2$	*TAC-1 (PPT-A or PPT-I); human chromosome 7*
neurokinin A (NKA)	His-Lys-Thr-Asp-Ser-**Phe**-Val-**Gly-Leu-Met**-NH$_2$	*TAC-1*
neurokinin B (NKB)	Asp-Met-His-Asp-Phe-**Phe**-Val-**Gly-Leu-Met**-NH$_2$	*TAC-3 (PPT-B or PPT-II); human chromosome 12*
hemokinin-1 (hHK1) (human)	Thr-Gly-Lys-Ala-Ser-Gln-**Phe**-Phe-**Gly-Leu-Met**-NH$_2$	*TAC-4 (PPT-C); chromosome 17*
Endokinin A/B (EKA; EKB)	Gly-Lys-Ala-Ser-Gln-**Phe**-Phe-**Gly-Leu-Met**-NH$_2$	*TAC-4 (PPT-C)*
C14TKL-1 (chromosome 14 tachykinin-like peptide 1)	Arg-His-Arg-Thr-Pro-Met-**Phe**-Tyr-**Gly-Leu-Met**-NH$_2$	*?*
virokinin (VK)	Gly-Ile-Pro-Glu-Leu-Ile-His-Tyr-Thr-Arg-Asn-Ser-Thr-Lys-Lys-**Phe**--Tyr-**Gly-Leu-Met**-NH$_2$	

finding since high levels of SP and its receptor density have been detected in the limbic system of the brain, known as a source of emotional behaviour [5,39].

The presence of tachykinins has been documented also in non-neuronal cells, including endothelial, muscle and inflammatory cells [28]. Moreover, tachykinin expression was evidenced in different parts of the mouse female reproductive system [48]. It has been proved that tachykinins contribute to smooth muscle contraction (intestinal and airway muscle cells), control of respiration (*in vivo* SP administration causes rise of breathing frequency), cardiovascular function and emesis [50]. Substance P (SP) is also important for wound healing [9].

The well-established substance P (the greatest attention in the present overview is reserved for this peptide) is undecapeptide and was identified in 1971 by Chang (the "P" term of this neuropeptide is connected with the powder obtained after the extraction procedure). This tachykinin is produced by primary afferent neuronal endings of the central and peripheral nervous system. The conformation of SP depends on the environment (type of solvent or lipids presence). An extended chain structure is observed in water, whereas β-turn conformation is created in hydrophobic conditions, i.e. methanol [20].

SP is encoded by the pre-protachykinin A (PPT-A) gene, consisting of 7 exons. The PPT-A gene arose from a common ancestral gene (originated by duplication). The fact that PPT-A also encodes neurokinin

A, and neuropeptide K and γ, strongly supports this hypothesis. The PPT-A gene transcript may undergo alternative splicing that gives three distinct products: αPPT-A (without the 6th exon), βPPT-A (containing all seven exons of the PPT-A gene) and γPPT-A (without the 4th exon) mRNAs. All mentioned mRNAs encode for the SP precursor sequence, but only α and β PPT-A mRNAs encode for NKA. Neuropeptide K and NPγ are post-translational derivatives of processed NKA (N--terminally extended sequence of neurokinin A). The PPT-B gene, consisting of 7 exons, encodes for only NKB. The PPT-C mRNA (transcript derived from *TAC4* gene) is a common precursor for hemokinin-1 and endokinin A, B, C and D [20].

Several events take place during the period from gene to native peptide synthesis. The translation of mRNA from PPT-A, PPT-B or PPT-C generates prepropeptides. Each one possesses a signal sequence located at the N-terminus, one or more copies of an exact neuropeptide and one or several spacer parts. The signal element is cleaved off, allowing it to pass into the endoplasmic reticulum. The formed propeptide is transported to the Golgi apparatus where the spacer parts are cut off. Finally the peptides are packed in secretory granules and shifted along the axon to the nerve endings [48].

Another tachykinin family member, hemokinin-1 (HK-1), discovered for the first time in mice, plays a role in haematopoiesis regulation by control of pre-B cells maturation. However, as has been docu-

mented on astrocytoma U-251 MG cells expressing NK1 receptors, hemokinin-1 is also able to interact with the (seemingly exclusively reserved for SP) NK1 receptor and generate similarly responses, i.e. Ca^{2+} ions mobilization and stimulation of cytokine production as SP triggers [2]. Thus HK-1 may participate not only in processes as its name suggests.

Worth attention is the example of "molecular mimicry" concerning virokinin, being a converted derivative of the bovine respiratory syncytial virus (BRSV) fusion protein. Virus-infected cells release this peptide containing a typical tachykinin sequence that might be recognized by the NK1 receptor [65].

Tachykinin receptors and their properties

Tachykinins constitute endogenous ligands for tachykinin receptors, belonging to the G protein-coupled receptor family (GPCRs). So far only three types of tachykinin receptors, NK1, NK2 and NK3, have been identified in comparison to many kinds of its well-known agonists. Searching for more potentially existing receptors has failed. Up to now, only some isoforms have been revealed, for instance full-length (407 amino acids) and C-terminally truncated (311 amino acids; variant expressed by several glioma cell lines: U87 MG, T98G and CCF-STTG1) modifications of human NK1 receptor.

SP, NKA and NKB demonstrate the ability to interact with each kind of tachykinin receptor. However, these neuropeptides exhibit distinct preferences for target binding sites (Table II). The cross-talk between ligand and receptor type depends on receptor availability. Any given tachykinin concentration (elevated level) and low quantities of the rest of the competitive substances also facilitate the interaction with each receptor [20,52].

Tachykinin receptors have been detected using autoradiography (analysis of mRNA encoding for NK1 receptor protein) and immunohistochemistry [50]. There is a very high sequence homology of ta-

chykinin receptors between different species (for instance a 92% similarity between human and rat NK1 receptors).

The *TACR1* gene, encoding for the NK1 receptor, possesses a 5' untranslated region. This motif contains a cyclic adenosine monophosphate (cAMP) response element binding the protein (CREB)/calcium response element sequence (neighbouring the TATAA sequence). The existing element's role is regulation of gene transcription (enhancement) in response to increased level of calcium ions or cAMP [20]. This important motif enables control of NK1 trafficking: resensitization rapidly following desensitisation.

Tachykinin NK1 receptor protein consists of seven transmembrane domains, three extracellular and three intracellular loops. Carboxy-terminus is directed to cell cytoplasm. Heterotrimeric G-protein, consisting of α, β, γ subunits and GDP, is linked to one of the intracellular loops. It has been investigated that many GPCR receptors, i.e. tachykinin receptors, undergo endocytosis, after binding with appropriate ligands [24,60,54]. It is documented, using quantitative confocal microscope analysis, that SP may induce endocytosis of the NK1 receptor on myenteric neurons of the guinea pig ileum. Simultaneously, NK1 receptor antagonists (i.e. CP-99994, MEN-10581) are not able to generate the same process that allows maintenance of the membrane internalisation state of the NK1 receptor [24]. Endogenous ligands for the GPCR family usually cause receptors' desensitisation, translocation (together with β-arrestin 1 protein) into endosomes and degradation after its prolonged activity. As a signal for the beginning of this process is ubiquitin attaching to lysine residues, being a component of the receptor protein sequence. Therefore, chronic exposure to substance P mediates NK1 receptor downregulation [8].

The involvement of tachykinins in different pathological conditions of CNS

As the name of these substances indicates, tachykinins (*gr. tachys* means swift) are able to generate different biochemical pathways aiming at cell growth acceleration (DNA synthesis induction and cell proliferation). Following interaction between tachykinin and appropriate receptor, α subunit dissociates from β and γ subunits that activates phospholipase C (PLC) [59]. PLC hydrolyses phosphatidyl inositol to diacylglycerol (DAG) and inositol 1,4,5-

Table II. Tachykinin preferences for receptors

Tachykinin receptor	Affinity	Encoding gene
NK1 (neurokinin-1; SPR/ substance P receptor/)	SP>NKA>NKB	*TACR 1*
NK2 (neurokinin-2)	NKA>NKB>SP	*TACR2*
NK3 (neurokinin-3)	NKB>NKA>SP	*TACR3*

-trisphophate (IP_3). Formed products play a role as second messengers. IP_3 binds to a specific receptor ($InsP_3R$) located on the surface of the endoplasmic reticulum, generating Ca^{2+} ions depletion of this store. DAG leads to translocation of kinase C protein isozyme (PKCε) from the cytoplasm to the cell membrane, consequently making voltage-gated L-type Ca^{2+} channels open and leading to Ca^{2+} ions' influx from the extracellular space. A prolonged period of Ca^{2+} signalling (elevated calcium ion level) promotes cells growth [16].

Tachykinins are responsible for the origin of various pathological conditions such as inflammatory bowel syndrome, bronchial asthma, and psychiatric disorders [49]. It is suspected that tachykinins may be involved in development of Alzheimer's disease, Parkinson syndrome, sclerosis multiplex, anxiety and sudden infant death. In astrocytes, NK1 receptor expression normally occurs in their development, but could appear in mature "reactive" astrocytes, for instance neighbouring degenerated optical nerve [10].

Furthermore, apart from tachykinin involvement in neurodegenerative aetiology, these neuropeptides also are not "innocent" taking into consideration glial-derived tumours, particular glioma development and progression.

Role of tachykinins in cancer development

Tachykinins and their receptors are strongly considered to be involved in development and progression of various neoplasms.

The most recent investigations have implicated the crucial role of the PPT-1 gene and neurokinin receptors in breast cancer development. As it is supposed, the PPT-A gene may also be responsible for metastasis to bone marrow in advanced stage of the disease (by increase of SP expression). It is possible because of the presence of two binding sites for the Myc protooncogene (promoting proliferation) in the 5' flanking region in the PPT-1 gene [34,56].

Not only substance P and its cognate NK-1 receptors are associated with pathways related to cell proliferation, but also neurokinin A and the NK-2 receptor demonstrate such capacity [4]. Experiments made on the oestrogen receptor negative (ER-), but NK1 and NK2 receptor positive, human breast carcinoma cell line MDA-MB-231, using antagonists for NK1 (MEN 11,467) and NK2 (nepadutant: MEN 11,420) receptors showed the crucial role of these tachykinin

receptors in cancer cell growth (both antagonists limited the stimulating effect of SP and NKA *in vitro*). Additionally, the same tested compounds exhibited significant cytostatic activity *in vivo*. Antagonists' administration at a dose of 5 mg/kg every day for 2 weeks (in a nude mice model with MDA-MB-231 tumour cells xenografted s.c.) inhibited tumour growth effectively [4].

Tachykinins and the NK1 receptor seem to be particularly significant in development and progression of malignant gliomas. Gliomas constitute a heterogeneous group of brain tumours, displaying resistance to almost all current anti-cancer approaches: chemo- or radiotherapy and even to the induction of apoptosis [27]. According to the WHO classification, poorly differentiated GBM displays histological features characteristic for grade IV tumours: greater mitotic activity, nuclear atypia and polymorphism, endothelial proliferation and necrosis [45].

It has been evidenced that gliomas demonstrate NK1 receptor overexpression. The presence of NK1 tachykinin receptors has been documented in the human T98G glioblastoma cell line (Fig. 1, personal observation). Thus, it has been suggested that the NK1 receptor may be responsible for glioma progression. In addition, degree of tumour malignancy correlates with increased density of SPR receptor. Elevated NK1 receptor expression level has been revealed in malignant tumours in comparison to normal neighbouring brain tissue or benign neoplasms. Henning et al., using autoradiography, have confirmed SPR presence in 100% (10/10 cases) of glioblastoma biopsy specimens, and 75% (9/12) of cases of astrocyto-
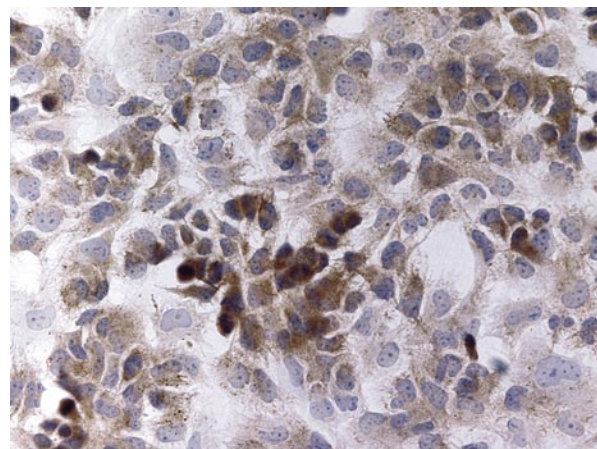

Fig. 1. NK1 tachykinin receptor expression in T98G cell line

ma. NK1 receptor overexpression was detected also in 83.3% (10/12) of cases of medullary carcinoma of the thyroid, 80% (4/5) of cases of ganglioneuroblastoma and 50% (8/16) of cases of breast carcinoma [21]. Independently of tumour grade and type, SPR expression is observed in blood vessels, with higher density in arteries than in veins. SP has angiogenic properties, and thus NK1 receptor presence in vessels probably facilitates tumour vascularization.

Biochemical reactions taking place following NK1 receptor activation, within the downstream agents cascade, are associated with glioma progression. Substance P–NK1 receptor dialogue leads to DAG accumulation that activates enzyme kinase C (PKC). Kinase C phosphorylates proteins c-Raf-1 and MEK-1, which stimulates Erk1 and Erk2 tyrosine of MAP kinases phosphorylation, transcription early genes *c-fos* and *c-myc*, induction of DNA synthesis and cell proliferation [42]. Another kinase that is probably activated by the NK1 receptor is PKCδ. Growth regulation through that PKC isozyme stimulation was noticed in human glioma cell line U373 MG [64].

Substance P, besides its mitogenic activity, is also able to stimulate release of cytokines [47]. Cytokines are a low-molecular weight soluble class of glycoproteins. These agents are involved in communication between cells, co-ordinate development during embryogenesis, cell growth and maturation, wound healing, immune response and contribute to neoangiogenesis [13]. Tumour cells can produce and secrete these molecules constitutively, supporting their own growth in an autocrine fashion and facilitating metastatic spread. Cytokines released by malignant cells also may induce normal cells to synthesise additional cytokines serving tumour progression [13].

Glioma cells exhibit the ability to produce the following substances: IL-1, IL-6, IL-8, TGF-β, arachidonic acid (prostaglandin E1 precursor), and cytokines responsible for gliomas' autocrine/paracrine activity: LIF (*leukaemia inhibiting factor*), GM-CSF (*granulocyte/macrophage colony stimulating factor*), GDNF (*glial cell line-derived neurotrophic factor*). Taurine is an additional molecule released as a consequence of NK1 receptor activation.

Glial cell line-derived neurotrophic factor (GDNF) was found for the first time in a growth medium cultured B49 rat glioma cell line [62]. Tumours of glial origin express GDNF at concentrations of even over five times higher than normal brain tissue [62]. This factor is secreted in greater amounts by high-gra-

de (for example C6) than low-grade (Hs683) glioma cell lines. GDNF, added to growth medium, supports cells migration. It takes place because of GDNF stimulating ability, providing mobilization of mitogen-activated protein kinases: c-JUN N-terminal protein kinase (JKN), extracellular signal- regulated kinases (ERKs) and p38 MAPK [57].

Granulocyte-macrophage colony stimulating factor (GM-CSF) is released following SP-mediated PKC activation. This molecule is responsible for macrophage aggregation, observed in malignant gliomas, and autocrine regulation of growth and migration [45]. GM-CSF, added to growth medium, triggers tumour cell proliferation. GM-CSF receptor blockage using antibodies causes mitosis suppression. It has been proved that many glioma cell lines (e.g. human glioblastoma T98G) retain the ability of GM-CSF production [13].

Leukaemia inhibiting factor (LIF) is a neuropoietin cytokine responsible for neurogenesis and neuronal differentiation. This glycoprotein is able to stimulate glioma proliferation by induction of substance P and NK1 receptor expression [45]. LIF is produced and released by neuronal cells following proinflammatory cytokines appearing, such as IL-1β, which leads to increased SP production and NK1 receptor formation [7].

Interleukin-1 (IL-1) could provoke glioma cells to VEGF production; it thus promotes angiogenesis and provides tumour vascularization [31,61]. The effect is generated through an autocrine/paracrine mechanism. Under the influence of IL-1, rapid activation of DAG and cytosolic Ca^{2+} influx usually appear in order to maintain a high level of VEGF, required for tumour growth.

Interleukin-6 (IL-6) plays an autocrine role in glioblastoma cell growth. IL-6 exhibits immunosuppressive and anti-inflammatory properties. IL-6 receptor activation leads to proliferation and phenotype changes (cell shape and GFAP expression) in normal astrocytes.

Another chemokin, interleukin-8 (IL-8), contributes to glioma progression probably by angiogenesis stimulation and tumour vascularization. IL-8 presence constitutes an attribute particularly in the case of high-grade gliomas [23,44,45].

Tumour growth factor β (TGF-β) is the agent involved in glioma progression [25]. It is secreted by human malignant gliomas *in vitro*, and is usually detected in the cerebrospinal fluid of patients suffering from gliomas. TGF-β displays mitogenic, angiogenic (through VEGF stimulation) and immunosuppressive

activities. Animals immunized s.c. with genetically modified rat C6 glioma cells (demonstrating silenced expression of TGF-β) have significantly higher chance of survival [45].

Arachidonic acid is a precursor of prostaglandin E1. This tissue hormone E1 decreases microglia function, i.e. phagocytosis in response to foreign antigens' recognition, also those expressed by malignant cells [45]. But on the other hand, this type of glia may induce glioma cell growth by secreting IL-1 or by decline of T cells activity [3].

Taurine is a molecule displaying osmoregulatory properties (modulation of ion transport) in the CNS [58]. This amino acid regulates cell volume, contributing to oedema, commonly observed in tumours and other pathological states [53].

Interleukin-1β (IL-1β) is an inflammatory cytokine, produced by immunological, gial or neuronal cells also following SP stimulation (SP-NK1R-mediated phosphorylation of p38 MAPK and/or JNK represents one mechanism leading to activation of IL-1β). This constitutive process is normally observed in gliomas. IL-1β plays a fundamental role in the immune response to various antigens, i.e. those expressed by malignant cells. Regulation of cytokine expression (i.e. IL-1β) is governed by nuclear factor κB (NFκB), a transcriptional agent that is a dimeric DNA binding protein attaching to a promoter gene sequence. *TACR1* gene promoter also possesses putative NFκB binding sites. It has been documented that SP as well as IL-1β can cause NFκB induction, which implicates NFκB involvement in NK1R gene upregulation. It has been evidenced that U87 MG glioma cells exposed to IL-1 β exhibited elevated expression level of NK1 receptors [30]. A similar effect was observed also by Lai et al. [29]. Incubation of U87 MG cells with IL-1 β (at a dose of 4 ng/ml) exhibited radically increased NK1 receptor mRNA expression (using Real-Time PCR), particularly after one-hour treatment that confirmed the regulatory function of this cytokine on enhancement of tachykinin receptor expression.

Substance P also provides NFκB activation in lung epithelial cells exhibiting NK1 receptor expression. Increased *TACR1* expression is often observed in pathological states of lungs (inflammation or respiratory syncytial virus infection). Functional NK1 receptor triggers a G_q protein response that generates an events cascade identified as the Ras/Raf/Erk signal pathway, involved in NFκB activation and inflamma-

tory cytokine production. Inhibition of any molecule of this signal transduction trail (Ras, Raf, MEK-1 proteins), using pharmacological agents, prevents NFκB activation. Thus, the mechanism underlying NFκB activation and consequently proinflammatory factor gene expression evidences tachykinins' involvement in inflammation propagation [63].

Furthermore, IL-1 β is also responsible for tumour angiogenesis. IL-1β contributes to VEGF production, usually secreted by malignant gliomas. Secretion of this angiogenic agent is especially high in U87MG, U373MG and T98G glioma cell lines. IL-1β receptor antagonists efficiently inhibit VEGF synthesis in U373 MG. An antagonist of the NK1 receptor (whose activation stimulates IL-1β production) also might break this additional track through which gliomas augment (via angiogenesis) their own growth.

Tachykinin receptor antagonists – their properties and clinical implications

Investigations *in vitro* or *in vivo* suggest that blockage of NK1 receptor activity, interrupting pathways related to mitogenesis, might be successfully done using selective antagonists [35]. An experiment carried out on a nude mice model (with glioma cells heterotransplanted subcutaneously) showed that NK1 receptor antagonists effectively inhibited tumour growth [37,45]. Until now, only one NK1 receptor antagonist (termed aprepitant) has been accepted for clinical usage by Food and Drugs Administration (since 2003). This compound serves as an anti-emetic remedy in chemotherapy.

So far a great amount of tachykinin receptor antagonists have been studied in different experimental models of pathological conditions [20]. A variety of their biological properties has been suggested:
a) anti-emetic
   - L-754 0303 (aprepriant) prevents patients' emesis after cisplatin treatment in chemotherapy [40]. It is used currently as an anti-nausea drug [18,41].
   - Tests carried out on ferrets indicate that CP99994, as a full receptor NK1 antagonist, prevents vomiting effectively [26]. CP99994 also attenuates emesis in copper sulphate gastric-irritated dogs [1].
b) anti-inflammatory
   - It is evidenced that CP96345 (as a non-peptide SP antagonist), added in medium cultured hu-

man astroglioma cells (U87 MG) and primary rat astrocytes, blocks SP-induced Ca^{2+} increased level leading to IL-1β release. IL-1 β is able to enhance NK1 receptor expression (at mRNA and protein level) *in vitro*. Thus NK1 receptor antagonists might be a useful tool in anti-inflammatory disease treatment of the CNS [19].

- SR140333, another NK1 receptor antagonist, exhibits anti-inflammatory properties in experimental autoimmune encephalomyelitis in mice. The data received by Reinke et al. [51] pointed out an additional therapeutic approach in multiple sclerosis treatment using this SP antagonist. SR140333 also triggers colitis reduction after focal ischaemia in rats [12]. It has been proved that this SP antagonist has a beneficial effect in suppression of food allergy symptom [33].

c) cytostatic (**potential novel antitumour drugs**)

- GR71251, a selective NK1 receptor antagonist, displays growth inhibition of human skin fibroblasts cultured *in vitro* [32].
- L733,060 demonstrates not only anti-inflammatory and analgesic properties, but also antitumoural activity against the human SKN-BE(2) neuroblastoma, COLO 679, COLO 858, MEL HO melanoma, WERI-Rb-1 and Y-79 retinoblastoma cell lines by blocking NK1 receptors. Growth suppression was documented on the basis of experiments *in vitro* and *in vivo* using small cell lung cancer and U373 MG glioma as material [14]. Antiproliferative ability of L-732138 was documented on a GAMG glioma cell line [14].

d) analgetic

- Administration of FK888, a selective NK-1 receptor antagonist, results in significant reduction of pain in mice treated with phorbol 12-myristate 13-acetate (PMA) – activator of protein kinase C (PKC) [15]. It is known that PKC participates in nociception through phosphorylation of various agents involved in pain transmission.
- CP99994 reduces post-operative pain after dental extraction in humans [11].
- RP67580 also annuls the nociceptive effect in mice and rats induced by phenylbenzoquinone and formalin administration [17].

e) other properties

- FR113680 treatment in case of airway constriction and oedema in guinea pigs results in inhibition of this response after SP-mediated neurokinin-1 receptor activation [38].

- RP67580, another SP antagonist, is able to inhibit plasmatic extravasation in rats (after SP-stimulated NK1 receptor activation) [17].
- GR205171 diminishes the effect of mechanically induced arthritis in rats [6].

It is necessary to mention that peptide or non-peptide NK-1R antagonists' concerning glioma therapy should fulfil distinct criteria such as easy blood-barrier overcoming and low neurotoxicity. Attempts are directed at obtaining more selectivity and effectiveness, to avoid species-related heterogeneity (differences in potency between various organisms) and to facilitate oral bioavailability.

The current knowledge evidences the important role of tachykinins in modulation of physiological and pathological conditions and gives opportunities to develop advanced experimental and therapeutic strategies, particularly regarding malignant gliomas.

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