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**Involvement of substance P and the NK-1 receptor in pancreatic cancer**

Muñoz M *et al*. SP/NK-1 receptor in pancreatic cancer

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**Abstract**

Pancreatic cancer is the fourth leading cause of cancer related-death for both men and women and the 1- and 5-year relative survival rates are 25% and 6%, respectively. Thus, it is urgent to investigate new antitumor drugs to improve the survival of pancreatic cancer patients. The peptide substance P (SP) has a widespread distribution throughout the body. After binding to the neurokinin-1 (NK-1) receptor, SP regulates biological functions related to cancer, such as tumor cell proliferation, neoangiogenesis, the migration of tumor cells for invasion, infiltration and metastasis, and it exerts an antiapoptotic effects on tumor cells. It is known that the SP/NK-1 receptor system is involved in pancreatic cancer progression: (1) Pancreatic cancer cells and samples express NK-1 receptors; (2) The NK-1 receptor is overexpressed in pancreatic cancer cells in comparison with non-tumor cells; (3) Nanomolar concentrations of SP induce pancreatic cancer cell proliferation; (4) NK-1 receptor antagonists inhibit pancreatic cell proliferation in a concentration-dependent manner,. At a certain concentration, these antagonists inhibit 100% of tumor cells; (5) This antitumor action is mediated through the NK-1 receptor, and tumor cells die by apoptosis; and (6) NK-1 receptor antagonists inhibit angiogenesis in pancreatic cancer xenografts. All these data suggest that the SP/NK-1 receptor system could play an important role in the development of pancreatic cancer; that the NK-1 receptor could be a new promising therapeutic target in pancreatic cancer, and that NK-1 receptor antagonists could improve the treatment of pancreatic cancer.

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**Key words**: Pancreas; Substance P; Neurokinin-1 receptor antagonists; Apoptosis; Antitumor; Angiogenesis; Metastasis

**Core tip:** The substance P (SP)/neurokinin-1 (NK-1) receptor system plays an important role in pancreatic cancer progression. Pancreatic cancer cells overexpress NK-1 receptors and SP promotes angiogenesis and the proliferation and the migration of pancreatic tumor cells. By contrast, NK-1 receptor antagonists, in a concentration-dependent manner, inhibit pancreatic cell proliferation (tumor cells die by apoptosis), have antiangiogenic properties in pancreatic cancer and block the migratory activity of pancreatic tumor cells. The antitumor action is mediated through the NK-1 receptor. Thus, the NK-1 receptor could be a new promising therapeutic target in pancreatic cancer and NK-1 receptor antagonists could improve pancreatic cancer treatment.

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**INTRODUCTION**

Pancreatic cancer is the fourth leading cause of cancer related-death for both men and women, with less than 5% survival at 5 years after diagnosis. In 2013, the American Cancer Society estimated 45220 new cases of pancreatic cancer in the United States and 38460 deaths from the disease. Treatment strategies have not succeeded in significantly extending patient survival, and neither have clinical outcomes improved substantially over the past 35 years; the overall 5-year survival rate remains dismal, at around 5%[1]. Pancreatic cancer remains a major unsolved health problem and conventional treatments having little impact on the course of the disease. Moreover, almost all patients with pancreatic cancer develop metastases, this being the primary reason for its lethality[2]. Accordingly, there is an urgent need to improve current therapies. Cytostatic drugs show a low safety profile and severe side effects, since they are not specific to tumor cells. Research should focus on drugs with the same or greater antitumor action but with fewer side effects. This can only be achieved if the drug is specific against pancreatic cancer cells and researchers are therefore seeking to identify novel molecular targets for blocking pancreatic cancer growth.

For some years, the expression and secretion of peptides by tumors has attracted increasing interest[3]. Substance P (SP) is an undecapeptide that is widely distributed throughout the body. It is derived from the preprotachykinin A gene and belongs to the tachykinin family of peptides. The biological actions of tachykinins (SP, neurokinin A, neurokinin B...) are mediated through the neurokinin-1 (NK-1), NK-2 and NK-3 receptors. SP has the highest affinity for the NK-1 receptor, which shows a widespread distribution throughout the body. This means that the biological actions (*e.g.,* pain, neurogenic inflammation, regulation of the cardiovascular system, mitogenesis...) exerted by the SP are mainly mediated by the NK-1 receptor[4,5]. Moreover, there are many data suggesting the involvement of the SP/NK-1 receptor system in cancer[5] (Figure 1 and Table 1). SP and NK-1 receptors have been detected in tumor cells and in intra- and peri-tumoral blood vessels[4-6]. SP induces mitogenesis in normal and tumor cells, protecting the latter from apoptosis, and controls the migration of tumor cells[4,7,8]. This is extremely important since the prevention of metastasis is a major goal in the treatment of tumors because over 90% of cancer deaths are derived not from the primary tumor but from the development of metastases. Moreover, it has recently been reported that the extravasation of tumor cells into the brain to form cerebral metastases may be an SP-mediated process[9]. More specifically, it has been reported that the SP/NK-1 receptor system is involved in pancreatic cancer by inducing pancreatic cancer proliferation, neoangiogenesis, and migration of pancreatic cancer cells (invasion, infiltration and metastasis). By contrast, NK-1 receptor antagonists inhibit pancreatic cancer cell proliferation (tumor cells die by apoptosis), angiogenesis and the migration of pancreatic cancer cells[10-14](Figure 1 and Table 1).

In sum, all the data reported above suggest that novel possibilities for translational research are emerging to improve the diagnosis and treatment of pancreatic cancer. Here, we review the involvement of the SP/NK-1 receptor system in pancreatic cancer and, specifically, the use of NK-1 receptor antagonists as antitumor drugs in pancreatic cancer (Figure 1 and Table 1).

**PANCREATIC CANCER CELLS AND SAMPLES EXPRESS NK-1 RECEPTORS**

The NK-1 receptor is synonymous with the SP receptor (SPR) and tachykinin receptor 1 (Tac1r). The NK-1 receptor is a G protein-coupled receptor (GPCR) that mediates the action of SP and other tachykinins[15,16]. The NK-1 receptor consists of 407 amino acid residues; it has a molecular weight of 58 kDa, and it is made of seven hydrophobic transmembrane (TM) domains with three extracellular and three intracellular loops, an amino-terminus and a cytoplasmic carboxy-terminus[17,18] (Figure 1). The loops have functional sites, including two cysteines amino acids for a disulfide bridge, Asp-Arg-Tyr, which is responsible for the association with arrestin and, Lys/Arg-Lys/Arg-X-X-Lys/Arg, which interacts with G-proteins[18,19]. The NK-1 receptor is coupled to the 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)[20,21]. The formation of IP3 triggers the release of calcium from intracellular stores and the formation of DAG leads to the activation of protein kinase C (PKC). Together, these messengers cause a cascade of protein phosphorylation/dephosphorylation reactions, culminating in altered gene expression and cell function.

SP is an undecapeptide widely distributed throughout the body and it is the natural ligand showing the highest affinity for the NK-1 receptor (Figure 1). In fact, the NK-1 receptor has been defined as a mediator of the biological activities encoded by the C-terminal sequence of tachykinins, for which SP is a more potent agonist than neurokinin A or neurokinin B[22]. After binding to the NK-1 receptor, SP regulates many biological functions (*e.g.,* pain, neurogenic inflammation, mitogenesis...)[4,5], although other NK receptors could also be involved (*e.g.,* NK-2) in these actions. After the binding of SP to the NK-1 receptor, both are internalized into endosomes; the undecapeptide induces a clathrin-dependent internalization of the receptor, after which SP is degraded and the NK-1 receptor is recycled to the cell surface[23-26]. SP-NK-1 receptor binding can generate second messengers (cAMP accumulation via stimulation of adenylate cyclase; stimulation, via phospholipase C, of phosphatidyl inositol turnover, leading to calcium mobilization; arachidonic acid mobilization via phospholipase A2), triggering numerous effectors mechanisms involved in cellular excitability and in the regulation of cell function[4,5,27].

It is known that pancreatic cancer cells and samples express the NK-1 receptor[10,13,14] (Table 1). This receptor has been also demonstrated in human cancer cell lines and/or in primary tumors (*e.g.,* glioma, astrocytoma, retinoblastoma, ganglioneuroblastoma, leukemia, neuroblastoma, carcinomas (larynx, gastric, colon, medullary thyroid, breast, oral...))[4-6,10,28-37]. In addition, in most tumors investigated NK-1 receptors have been found in intra- and peri-tumoral blood vessels. This is quite important regarding the involvement of the NK-1 receptor in angiogenesis[6]. NK-1 receptors have been located in both the plasma membrane and the cytoplasm of tumor cells and, occasionally, in the nucleus of these cells[31,34,38]. Moreover, several isoforms (33-38, 46, 54-58 and 75 kDa) of the NK-1 receptor have been reported in human cancer cells (*e.g.,* neuroblastoma, retinoblastoma, larynx carcinoma, gastric adenocarcinoma, leukemia, *etc.*)[33-36,38]. Regarding the pancreatic cancer, it has been reported that its tumor cells express several isoforms (36, 46, 58 and 75 kDa)[10,13,14].However, in order to clarify the functional roles of these isoforms, further research is needed. In humans, the presence of two subtypes of the NK-1 receptor has been reported: the full-length one and the truncated one. The former mediates a slow growth of tumor cells and the second enhances the growth of these cells to a considerable extent and stimulates the production of cytokines with growth-promoting functions[39]. It seems that these cytokines activate a transcription factor (NF-κB) that upregulates the truncated NK-1 receptor form and slightly increases the full-length form[40,41]. It is also known that the truncated form, an oncogenic isoform of the NK-1 receptor, mediates malignancy in tumor cells[39] and that the truncated NK-1 receptor is increased in colonic epithelial cells from patients with colitis-associated cancer[42].

In the first study in which NK-1 receptors were reported in pancreatic cancer (1 of 9 samples)[6], the authors applied an autoradiographic method. Later, in another study, NK-1 receptor expression was reported in 27% of the samples[43]. However, a third study compared 50-pancreatic human cancer samples obtained from pancreatoduodenoctomy (Whipple operation) with normal controls[10]. In these cases, the authors found the expression of NK-1 receptors in all the pancreatic cancer samples. Thus, by using *in situ* hybridization and immunohistochemistry techniques, in normal pancreas NK-1 receptor mRNA and NK-1 receptor immunoreactivity were occasionally weakly observed in acinar and ductal cells, but a moderate to strong NK-1 receptor mRNA signal and NK-1 receptor immunoreactivity were present in most of the cancer cells[10]. Moreover, the growth of the tumor mass, peritumoral infiltration and metastasis could be regulated by the SP/NK-1 receptor system, overexpressed in tumor cells and in tumoral and peritumoral tissue in pancreatic cancer (inflammatory cells, fibroblasts, blood vessels, nerves, ganglia, islet)[10].

The NK-1 receptor is also known to be involved in the viability of tumor cells. It has been reported that after a knockdown gene-silencing method (siRNA), the NK-1 receptor is involved in the viability of such cells[33,34,37]. Following the administration of the siRNA *TACR1* (tachykinin 1 receptor gene) to cultured tumor cells, more apoptotic cells were found in siRNA cells than in cells not transfected, and hence the number of siRNA tumor cells was significantly decreased in comparison with the number of non-transfected cells[33,34,37].

**NK-1 RECEPTOR IS OVEREXPRESSED IN PANCREATIC CANCER CELLS IN COMPARISON WITH NON-TUMOR CELLS**

It is known not only that the NK-1 receptor is expressed in tumor cells, but also that this receptor is overexpressed in such cells (*e.g.,* glioblastoma, breast cancer, retinoblastoma, larynx, pancreatic, gastric and colon carcinomas...)[4,5,10,30,33,34,37]. This is important, since the visualization of NK-1 receptors by immunohistochemistry for diagnostic or therapeutic purposes would facilitate the identification of tumors overexpressing this receptor[44]. It is known that normal cells express a lower number of NK-1 receptors than tumor cells (*e.g.,* human pancreatic cancer cell lines express more NK-1 receptors than control cells)[10]; that tumor samples from patients with advanced tumor stages exhibit significantly higher NK-1 receptor levels[10]; that *TACR1* mRNA is present in human acute lymphoblastic leukemia cell lines, with the highest levels in these cells and the lowest ones in normal cells[33]; that astrocytoma/glioma cell lines in culture shows a lower number of NK-1 receptors than astrocytoma/glioma primary tumors; that glioblastomas express more NK-1 receptors than astrocytomas, and that the most malignant phenotypes of tumors show a higher rate of NK-1 receptor expression and are associated with advanced tumor stages and a poorer prognosis[6,10,45].The data suggest that the number of NK-1 receptors could be correlated with the degree of malignancy. Thus, the overexpression of the NK-1 receptor in tumor cells suggests the possibility of finding a specific treatment against cancer using NK-1 receptor antagonists and, in this way, the side effects of the treatment could be decreased considerably. This strategy opens up new approaches for cancer treatment. Moreover, following the use of real-time quantitative RT-PCR methodology in 50 pancreatic human cancer samples obtained from pancreatoduodenoctomy (Whipple operation), NK-1 receptor mRNA levels were increased 36.7-fold in these samples in comparison with normal controls. Enhanced NK-1 receptor expression levels were not related to tumor grade but were associated with advanced tumor stage and a poorer prognosis. As reported above, NK-1 receptor mRNA levels and NK-1 receptor immunoreactivity are higher in human pancreatic cancer samples than in normal pancreas[10]. Moreover, using a Western blot analysis, the NK-1 receptor was found to be increased 26-fold in pancreatic cancer samples in comparison with normal controls. NK-1 receptor mRNA was detected in five pancreatic cancer cell lines by real-time quantitative RT-PCR, the highest levels being observed in CAPAN-1 cells and the lowest ones in ASPC-1 cells. SP and SP analog agonists stimulated pancreatic cancer cell growth, depending on the NK-1 receptor expression level, and this effect could be blocked by a selective NK-1 receptor antagonist in a concentration-dependent manner[10,13].

It has been suggested that chronic inflammation could be correlated with an increased risk of developing cancer. It is known that the risk of pancreatic cancer is very high in subjects with chronic pancreatitis and appears to be independent of sex, country, or type of pancreatitis[46] and that the up-regulation of the NK-1 receptor mRNA expression in chronic pancreatitis has a strong relationship with the pain syndrome that these patients experience[47]. Thus, overexpression of the NK-1 receptor could be involved in chronic pancreatitis-associated cancer. It has also been reported recently that the truncated NK-1 receptor is overexpressed in colonic epithelial cells from patients with colitis-associated cancer, whereas the full-length is not affected[42]. Thus, the overexpression of NK-1 receptors could be used as a diagnostic marker to identify patients at risk of neoplasms and may serve as a useful therapeutic target in the treatment of chronic inflammation-associated cancer.

**NANOMOLAR CONCENTRATIONS OF SP INDUCE PANCREATIC CANCER CELL PROLIFERATION AND THE MIGRATION OF TUMOR CELLS**

SP acts as a mitogen in normal and tumor cells (*e.g.,* neuroblastoma, astrocytoma, melanoma, retinoblastoma, glioma,melanoma, larynx carcinoma, gastric and colon carcinoma, lymphoblastic leukemia) via the NK-1 receptor, since the growth inhibition of many human tumor cells after the administration of NK-1 receptor antagonists is partially reversed by the administration of SP[4,5,33-38,48]. Regarding pancreatic cancer cells, nanomolar SP concentrations elicit the proliferation of the pancreatic cancer CAPAN-1, PA-TU 8902, BxPC-3 and MIA PaCa-2 cell lines[13,14]. By contrast, the mitogenic action of SP on these cell lines could be partially reversed by using NK-1 receptor antagonists such as L-733,060, L-732,138 or the drug aprepitant[12-14]. Many data indicate that SP in a universal mitogen in NK-1 receptor-expressing tumor cells. The undecapeptide can be synthesized and secreted by tumor and non-tumor cells and SP can be released from nerve terminal, and/or it can be released into blood vessels[4,5]. Through these paths, the peptide can exert a mitogenic action on tumor cells. The regulation of local tumor activity through sensory nerves containing SP is relevant, since the undecapeptide could modulate the growth of tumor cells, exerting a direct interaction between the nervous system and the tumor cells. Thus, SP could induce mitogenesis via the following mechanisms: (1) autocrine (SP is secreted from tumor cells); (2) paracrine (SP exerts a mitogenic action in endothelial cells); (3) SP is released from nerve terminals; (4) SP reaches the whole body through the bloodstream; this is regulated by the limbic system; and (5) endocrine (SP is released from the tumor mass into the blood vessels)[3-5].

There are multiple cell signaling pathways regulated by SP. After the activation of the NK-1 receptor by SP, an increase in DNA synthesis has been reported in tumor cells, and it seems that via the NK-1 receptor the undecapeptide activates members of the mitogen-activated protein kinase (MAPK) family, including extracellular signal-regulated kinases 1 and 2 (ERK1/2) and p38MAPK[45] (Table 1). Once activated, ERK1/2 is translocated into the nucleus, inducing proliferation and protecting the cell from apoptosis[5,7]. In tumor cells, SP increases the phosphorylation and activity of Akt or protein kinase B, a serine-threonine protein kinase that becomes activated via phosphatidyl-3-kinase (PI3K); the activation of Akt suppresses apoptosis[49,50]. By contrast, NK-1 receptor antagonists inhibit the basal activity of Akt[51] (Table 1). After it has bound to the NK-1 receptor, other effects are also exerted by SP in tumor cells: it activates phospholipase D and enhances forskolin-stimulated cyclic AMP-production; SP induces the release of interleukins, taurine and glutamate; it mobilizes intracellular calcium; it induces the formation of inositol phosphate; it stimulates glycogen breakdown; and it influences glutamate and K+ transport[5, 52-56]. The release of interleukins, taurine and glutamate by tumor cells induces an inflammatory process, increasing the levels of SP and hence increasing tumor cell proliferation. Moreover, it has been reported that after binding to the NK-1 receptor SP stimulates glycogen breakdown and increases the intracellular Ca2+ concentration in astrocytoma cells. Both effects occur in a concentration-dependent manner. These effects are completely blocked by the NK-1 receptor antagonist CP-96345[55]. In addition, one of the most prominent metabolic alterations in cancer cells is the increase in aerobic glycolysis and the dependency on the glycolytic pathway for ATP generation, known as the Warburg effect, because most cancer cells predominantly produce energy by means of a high rate of glycolysis followed by lactic acid fermentation[57]. Growing tumor cells typically have glycolytic rates up to 200 times higher than those of their normal tissues of origin; this occurs even if oxygen is plentiful. Thus, after binding to the NK-1 receptors located in tumor cells, SP causes glycogen breakdown and the glucose obtained would be used by tumor cells to increase their metabolism[55]. This mechanism could partly explain the Warburg effect. By contrast, NK-1 receptor antagonists block glycogen breakdown in tumor cells[55], and hence can counteract the Warburg effect[3] (Table 1). This new approach to the NK-1 receptor is very interesting because until now the main goal has been the inhibition of the glycolitic enzymes. However, this strategy has not provided any practical results. In cancer treatment, a reduction in glucose formation by blocking the NK-1 receptor may be possible and indeed easier using NK-1 receptor antagonists. Accordingly, without glucose the Warburg effect is not possible in cancer cells.

The migration of tumor cells is a crucial requirement for the development of metastasis and the progression of cancer. At present, over 90% of cancer deaths are derived not from the primary tumor but from the development of metastases[58]. Thus, a major goal in the treatment of cancer should be to inhibit the development of metastases. In this sense, it is known that tumor cell migration is induced by classical neurotransmitters (dopamine, noradrenalin) and peptides (*e.g.,* SP) and that such migration is inhibited after the administration of D2 receptor, adrenoceptor or NK-1 receptor antagonists[5,59]. It is also known that after binding to the NK-1 receptor SP induces a rapid change in cellular shape (including blebbing) and that membrane blebbing is important in cell movement, cell spreading, and cancer cell infiltration[60,61]. It has recently been reported that SP is involved in pancreatic cancer perineural invasion and that in pancreatic cancer cells SP induces cancer cell proliferation and invasion as well as the expression of matrix metalloproteinase (MMP)-2. SP also promotes neurite outgrowth and the migration of pancreatic cancer cell clusters to the dorsal root ganglia of newborns[14].

**NK-1 RECEPTOR ANTAGONISTS INHIBIT PANCREATIC CELL PROLIFERATION IN A CONCENTRATION-DEPENDENT MANNER. AT A CERTAIN CONCENTRATION, THESE ANTAGONISTS INHIBIT 100% OF TUMOR CELLS**

NK-1 receptors antagonists are a broad group of heterogeneous chemical compounds (Figure 1 and Table 1). There are two groups: peptide NK-1 receptor antagonists and non-peptide NK-1 receptor antagonists.

***Peptide NK-1 receptor antagonists***

Most of the work carried out on the design and preparation of antagonists of the NK-1 receptor has focused on the introduction of D-amino acids[18]. However, their affinity is several orders of magnitude lower than that of natural agonists, and the metabolic instability of peptide NK-1 receptor antagonists and their inability to gain access to the central nervous system through the blood-brain barrier limit their usefulness for *in vivo* studies. In addition, these substances generally have a number of drawbacks, such as poor potency and a lack of the ability to discriminate between tachykinin receptors, partial residual agonist activity, mast cell degranulating activity, and neurotoxicity after administration in the central nervous system[22]. Some of these peptide NK-1 antagonists are[18]: [D-Arg1, D-Trp 7,9, Leu11] SP (Spantide I). This antagonist is neurotoxic and a potent histamine releaser from mast cells; H-D-Lys (Nicotinoyl)-Pro-[3-(3-pyridyl)-Ala]-pro-D-Phe83,4-Cl2)-Asn-DTrp- Phe-D-Trp-Leu-Nle-NH2 (Spantide II). This antagonist is devoid of neurotoxicity; [D-Arg1, D-Trp5, 7, 9, Leu11] SP. This antagonist has anticancer effects in a variety of *in vitro* and *in vivo* models (*e.g.,* pancreatic cancer)[11, 62-65]; (D-Arg1, D-Phe5, D-Trp7, 9, Leu11) SP; (D-Arg1, D-Pro2, D-Trp 7,9, Leu11) SP; [Arg6, D-Trp7,9, MePhe8] SP (6-11); [D-Pro2- Trp7, 9] SP; [D-Pro4, D-Trp7, 9, 10, Phe11] SP (4-11) p-HOPA-DTrp-Phe-DTrp-Leu-Leu-NH2: NY-3238; DMePhe-DTrp-Phe-DTrp-Leu(CH2NH)Leu-NH2: NY-3460.

***Non-peptide NK-1 receptor antagonists***

Since non-peptide NK-1 receptor antagonists became available[66-68], an increasing number of papers describing new non-peptide antagonists have been published[69]. Thus, steroids (WIN- 51708, *etc.*), perhydroisoindolones (RP-67580, RP-73467, RPR-100893, *etc.*), benzylamino and benzylether quinuclidine (CP-96345, L-709210, *etc.*), benzylamino piperidines (CP-99,994, GR-203040, GR-205171, CP-122721, *etc.*), benzylether piperidines (L-733060, L-741671, L-742694, *etc.*) and tryptophan based (L-732138, L-737488, *etc.*) NK-1 receptor antagonists have been reported[22]. Investigation into non-peptide NK-1 receptor antagonists is a fast-developing field. Some of these peptide NK-1 antagonists have been used in clinical trials and found to be safe. Examples are the drug aprepitant (Figure 1)and its prodrug fosaprepitant, casopitant (GW-679769), vofopitant (GR-205171), L-759274, CP-122721, Ezlopitant (CJ-11974), Rolapitant, L-754030, Serlopitant and CJ-11974[70].

The binding sites for NK-1 receptor antagonists and SP are different[5]. SP is hydrophilic and binds to the extracellular ends of the transmembrane helices and especially to the extracellular loops of the receptor, whereas NK-1 receptor antagonists are lipophilic and bind more deeply between the transmembrane III-VII domains (Figure 1). After binding to the NK- 1 receptor, NK-1 receptor antagonists could block the functions of SP (Table 1). The pharmacologic effect is related to stereochemical features and is not linked to chemical composition. The action is concentration- and time-dependent manner. At higher concentrations, the beneficial effect in the host is summative. Thus, the pharmacologic effects of the NK-1 receptor antagonists are: anxiolytic, antidepressant, antiemetic, antimigraine, antialcohol addiction or neuroprotector effect in the central nervous system, and they also play a role in analgesic, antiinflammatory, and hepatoprotector processes, as well as in antivirus proliferation (Table 1). Regarding cancer, NK-1 receptor antagonists exert an antitumor action (inducing tumor cell death by apoptosis), and they have antiangiogenesis effects and inhibit the migration of tumor cells[3-5] (Table 1). Therefore, the NK-1 receptor antagonists could be considered a new generation of anticancer drugs[3-5, 71].

In 1993, Merck initiated studies on NK-1 receptor antagonists based on both CP-96,345 and CP-99,994. L-733060 (Figure 1) is one of the compounds developed from CP-99,994. It is a 3, 5- bistrifluoromethyl benzylether piperidine[72]. The administration of the NK-1 receptor antagonist L-733060 produces analgesia[73] and antidepressive effects[74,75]. The compound has been suggested for the treatment of anxiety and mood disorders[76] and in inflammatory liver disease, most likely owing to its ability to inhibit the effects of SP[77]. In addition, it has been reported that the NK-1 receptor antagonist L-733,060 acts as an antitumor agent in several human tumor cell lines[13,38,78-81]. In fact, this antitumor action has been reported against pancreatic cancer cell lines[13,14].

A morpholine nucleus that was introduced in the NK-1 receptor antagonist L-742694 was found to enhance NK-1 receptor-binding affinity[82]. This nucleus was kept in further modifications of the molecule. In order to prevent possible metabolic deactivation, several refinements such as methylation on the C alpha of the benzyl ring and fluorination on the phenyl ring were introduced. These changes afforded the compound MK-869, which showed high affinity for the NK-1 receptor. MK-869 is also called aprepitant (Figure 1) and it has been tested for the treatment of several disorders. Those studies led the FDA (Food and Drug Administration) to approve the drug Emend, which is indicated for chemotherapy-induced nausea and vomiting and is available for oral use[83]. A water-soluble phosphoryl prodrug for intravenous use, called fosaprepitant, is also available and is marketed as Ivemend[84]. It seems that aprepitant is effective for the treatment of depression[74,75], and it has recently been demonstrated that it is a broad-spectrum antitumor drug[12]. Moreover, the antitumor action of the drug aprepitant against pancreatic cancer cells has been reported. In fact, aprepitant inhibits 100% of pancreatic cancer cells in a concentration-dependent manner[12].

The NK-1 receptor antagonist L-732138 (N-acetyl-L-tryptophan3,5-bis (trifluoromethyl) benzyl ester) (Figure 1) shows a competitive and selective antagonism for the NK-1 receptor. It is approximately 1000-fold more potent in cloned human NK-1 receptors than in cloned human NK-2 and NK-3 receptors, and approximately 200-fold more potent in human NK-1 receptors than in rat NK-1 receptors[85]. The IC50 for the human NK-1 receptor expressed in Chinese Hamster Ovary (CHO) cells is approximately 2.3 nmol[86]. It is known that the administration of L-732,138 produces an attenuation of hyperalgesia[87] and that L-732138 is able to antagonize H(3) antagonist-induced skin vascular permeability. The antitumor action of the tryptophan-based antagonist L-732,138 against glioma, neuroblastoma and a larynx carcinoma cell lines has been also reported[80], as well as its antitumor action against pancreatic cancer cell lines[13,14].

The immunosuppressive cyclic undecapeptide cyclosporin A (CsA) is a naturally occurring fungal metabolite from *Tolypocladium inflatum Gams*.This molecule has been proposed to play a role in the treatment of human malignancies as an effective modifier of multidrug resistance. It is known that CsA has the pharmacological profile of an NK-1 receptor antagonist[88] and that CsA exerts an antitumor action due to its NK-1 receptor antagonist pharmacological profile in competition assay with SP. The antitumor action of CsA against pancreatic cancer cells occurs in a concentration-dependent manner and pancreatic tumor cells die by apoptosis[89]. However, in clinical practice this interesting therapeutic action of CsA is not possible because the high doses necessary to exert an antitumor action are associated with dangerous side effects, such as kidney failure.

Taking the above data together, it seems that the antitumor action of NK-1 receptor antagonists against pancreatic cancer cells would be due to stereochemical features and that it is not linked to the chemical composition of the antagonists[71] (Table 1),since different compounds (L-733060, a piperidine derivative; aprepitant, a morpholine derivative; L-732138, a tryptophane derivative ; CsA, a cyclic undecapeptide) exert an antitumor action (Figure 1). These compounds have only one thing in common: their affinity for the NK-1 receptor.

**ANTITUMOR ACTION OF THE NK-1 RECEPTOR ANTAGONISTS IS MEDIATED THROUGH THE NK-1 RECEPTOR AND TUMOR CELLS DIE BY APOPTOSIS**

As reported above, the NK-1 receptor antagonists (L-733060, L-732138, the drug aprepitant, *etc.*) exert an antitumor action[4,5,33-38] (Figure 1). In particular, these antagonists exert this action against human glioma, larynx carcinoma, neuroblastoma, rhabdomyosarcoma, leukemia, astrocytoma, osteosarcoma, lymphoma, retinoblastoma, melanoma, lung, breast, and gastric, and colon carcinoma cell lines[4,5,33-38,90,91], as well as against pancreatic cancer cell lines[13,14]. The antitumor action of L-733,060 against human cancer cell lines is more potent than that of aprepitant, and the antitumor action of aprepitant is more potent than that of L-732,138[4,5]. NK-1 receptor antagonists block the SP-induced mitogen stimulation of tumor cells, and they inhibit tumor cell growth in a dose-dependent manner[4,5] (Table 1).

After binding to NK-1 receptors overexpressed in tumor cells, NK-1 receptor antagonists activate the apoptotic machinery and these cells (*e.g.,* pancreatic cancer, *etc.*) die by apoptosis[4,5,12,33,34,38]. Thus, the induction of apoptosis represents a highly suitable approach to cancer treatment, although currently little is known about the mechanisms responsible for the induction of apoptosis in tumor cells. Despite this, it has been reported that the blockade of NK-1 receptors by NK-1 receptor antagonists inhibits the basal kinase activity of Akt. Tumor cells develop strategies to neutralize the multiple pathways leading to cell death, and it has been suggested that one of the most important of these is the expression of the NK-1 receptor[92]. This strategy renders tumor cells highly dependent on the SP stimulus, which provides a potent mitotic signal. This signal could counteract the different death signal pathways activated in tumor cells. The absence of the mitotic signal when the receptor is blocked with NK-1 receptor antagonists could tilt the balance within the cell to favouring apoptotic/death signals, and hence the cell would die[92]. The data reported suggest that NK-1 receptor antagonists could inhibit a large number of tumor cell types in which NK-1 receptors are overexpressed[3-5,33,34,37], and that NK-1 receptor antagonists could be candidates for broad-spectrum antineoplastic drugs including pancreatic cancer[3-5,13,14]. In general, NK-1 receptor antagonists are safe, since the administration of NK-1 receptor antagonists does not induce serious side effects[5,72,93-96], although headaches, hiccupping, vertigo and drowsiness have been reported in humans after their administration[71,95,96] (Table 1). The safety of aprepitant against human fibroblasts has been also demonstrated: the IC50 for fibroblasts is three times higher than the IC50 for tumor cells[12]. Moreover, the IC50 for non-tumor cells is 90 μM but the IC100 for tumor cells is 60 μM approximately[12].

Furthermore, it has been suggested that the co-administration of NK-1 receptor antagonists and microtubule-destabilizing agents (*e.g.,* vinblastine) could be useful in cancer, since these compounds have a synergic effect[5,98] (Table 1). This combination is synergistic for the growth inhibition of NK-1 receptor-possessing cancer cells, but not for normal cells. A better understanding of the mechanisms underlying this interaction is needed in order to assess the clinical relevance of this novel synergistic combination. It has also been reported that the use of chemotherapy and/or radiation therapy and NK-1 receptor antagonists affords a synergistic antitumor action and decreases the side effects of chemotherapy and radiation therapy[5,97,98] (Table 1).Moreover, synergism has been reported for the combination of L-733,060 with common cytostatic drugs (adriamycin, mitomycin, ifosfamide, cisplatin) in MG-63 human osteosarcoma cells, but not in non-malignant HEK293 cells[99]. Pretreatment of HEK293 with L-733,060 prior to exposure to cytostatic drugs partially protected HEK293 cells from inhibition by these drugs[99].

**NK-1 RECEPTOR ANTAGONISTS INHIBIT ANGIOGENESIS IN PANCREATIC CANCER XENOGRAFTS**

Neovascularization or neoangiogenesis is a sequential process, with early endothelial proliferation followed by new vessel formation and increased blood flow, accompanied by maturation of endogenous neurovascular regulatory systems occurring late in this process in inflamed tissues[100]. The growth of new vessels from a pre-existing vasculature is a common feature of chronic inflammation (early neoangiogenesis is a key step in the transition from acute to persistent inflammation) and wound healing. Neoangiogenesis, a hallmark of tumor development, has also been associated with increased tissue innervation and the expression of NK-1 receptors. In a large majority of tumors investigated, SP and NK-1 receptors are found in the intra and peritumor blood vessels[6]. These findings have been reported specifically in pancreatic cancer[10]. SP, a main mediator of neurogenic inflammation through the release of the peptide from peripheral nerve terminals, is involved in the growth of capillary vessels *in vivo* and in the proliferation of cultured endothelial cells *in vitro*. Additionally, it is known that the proliferation of endothelial cells by NK-1 receptor agonists (SP or SP analog agonists) increases in a concentration-dependent manner (NK-1 receptor antagonists block the proliferative action of SP), whereas the action of selective NK-2 and NK-3 receptor agonists has no significant effects on the proliferation of endothelial cells. These findings indicate that NK-1 receptor agonists (*e.g.,* SP) can stimulate the process of neovascularization directly, probably through the induction of endothelial cell proliferation[101], and that SP enhanced angiogenesis results from a direct action on microvascular NK-1 receptors. Thus, through such receptors found at high density in blood vessels SP may strongly influence vascular structure and function inside and around tumors by increasing tumor blood flow and by fostering stromal development[6]. By contrast, it has been reported that NK-1 receptor antagonists inhibit endothelial cell proliferation and angiogenesis in a concentration-dependent manner[101] (Table 1). It has also been reported that the [D-Arg1, D-Trp5,7,9, Leu11] SP analog antagonist (SPA, broad-spectrum GPCR antagonist, peptide NK-1 receptor antagonist) has an antitumor action[11]. It is known that in ductal pancreatic cancer cells expressing NK-1 receptors, NK-1 receptor antagonists induce the synthesis of proangiogenic chemokines and that in HPAF-II, a well-differentiated pancreatic cancer cell line, peptide NK-1 receptor antagonists inhibit Ca2+ mobilization and DNA synthesis[11]. These antagonists also significantly attenuated the growth of HPAF-II tumor xenografts in nude mice beyond the treatment period. Interestingly, one peptide NK-1 receptor antagonist (SPA, broad-spectrum GPCR antagonist) markedly increases apoptosis but moderately decreases the proliferation marker Ki-67 in tumor xenografts, implying additional mechanisms for the significant growth inhibitory effect[11].HPAF-II cells express ELR+ CXC chemokines, including IL-8/CXCL8, which bind to CXCR2 (a member of the GPCR superfamily) and promote angiogenesis in many types of cancer, including pancreatic cancer. A salient feature of these results is that peptide NK-1 receptor antagonists markedly reduced tumor-associated angiogenesis in HPAF-II xenografts *in vivo*. The data suggest that peptide NK-1 receptor antagonists (SPA, broad-spectrum GPCR antagonist) attenuate tumor growth in pancreatic cancer via a dual mechanism involving both antiproliferative and antiangiogenic properties[11]. Thus, the dual-inhibitory effect of peptide NK-1 receptor antagonists could be of significant therapeutic value in pancreatic cancer, when used in combination with other anticancer drugs. In sum, all these data indicate that the SP/NK-1 receptor system controls neoangiogenesis in pancreatic cancer and that, in addition, this system could also regulate the growth of the pancreatic tumoral mass, since NK-1 receptors are overexpressed in tumoral cells and in peritumoral pancreatic cancer tissues[10]. Thus, by using NK-1 receptor antagonists (peptide or non-peptide), the NK-1 receptor could be used as a target to inhibit both neoangiogenesis and the growth of pancreatic cancer (Figure 1 and Table 1).

Accordingly, targeted therapies for pancreatic cancer offer new ways to search for potentially more effective strategies. Thus, the use of NK-1 receptor antagonists in chronic pancreatitis could: (1) improve chronic inflammation; (2) improve pain; and (3) prevent the chronic pancreatitis associated with cancer. The use of NK-1 receptor antagonists in pancreatic cancer could exert: (1) an antitumor action, by inhibiting pancreatic cancer cell proliferation (tumor cells die by apoptosis); (2) antiangiogenic properties; and (3) inhibition of the migration of pancreatic cancer cells (preventing invasion, infiltration and metastasis). Thus, the antitumor action of NK-1 receptor antagonists in pancreatic cancer could be specifically for a single target: the NK-1 receptor (Figure 1). The mechanisms of action of NK-1 receptor antagonists are the opposite of those involved in classic chemotherapy. In addition, NK-1 receptor antagonists not only exert an antitumor action, but also elicit beneficial effects in the host such as anti-inflammatory, analgesic, anxiolytic, antidepressant, antiemetic, hepatoprotector and neuroprotector effects[4,5] (Table 1).

**SAFETY OF NK-1 RECEPTOR ANTAGONISTS IN HUMAN CLINICAL TRIALS**

As reported above, an upregulation of the SP/NK-1 receptor system occurs in human pancreatic cancer cells and hence the NK-1 receptor can be considered as an important target for the treatment of this disease. The overexpression of the NK-1 receptor in human pancreatic cancer cells suggests that the administration of NK-1 receptor antagonists is an excellent strategy for the treatment of this disease (these antagonists, after binding to NK-1 receptors, induce the apoptosis of tumor cells) and in addition fewer side effects should be expected after the administration of these drugs to patients, since NK-1 receptor antagonists are specific for a determined target, the NK-1 receptor, which is overexpressed in cancer cells and it is involved in the viability of tumor cells[3]. It should be noted that the IC100 for cancer cells is 60 µM approximately but the IC50 for non-tumor cells is 90 µM[12].

Many studies have reported the absence of serious side effects when non-peptide NK-1 receptor antagonists have been administered to humans[71]. It is known that the NK-1 receptor antagonist GR-205171 alleviated anxious symptoms in patients with social phobia[102]. Several non-peptide NK-1 receptor antagonists (*e.g.,* casopitant, orvepitant, vestipitant, vofopitant) have been also tested in human clinical trials for the treatment of depression, anxiety disorders, post-traumatic stress disorder, alcoholism, panic disorder and schizophrenia[103,104]. In some trials, these antagonists exerted an anxiolytic or an antidepressant action and in all the cases showed a low side effect profile. Moreover, the analgesic action of the NK-1 receptor antagonists aprepitant, lanepitant (LY-303870), AV-608 and CJ-11,974 has been tested in human trials and in all the cases the drug was ineffective in relieving pain (*e.g.,* neuropathic pain, visceral pain, osteoarthritis, fibromyalgia)[105]. However, the NK-1 receptor antagonist CP-99994 decreased postoperative dental pain[106]. NK-1 receptor antagonists have been also tested for the treatment of migraine. Thus, lanepitant was ineffective in migraine prevention and acute migraine; RPR-100,893 had no effects on migraine attacks; L-758,298 failed to abort migraine attacks, and GR-205171 was ineffective against the treatment of migraine[106]. Moreover, it has been reported that HIV-infected adults not receiving antiretroviral therapy, low (125 mg) and high (250 mg) doses of aprepitant (daily, for 14 d) were found to be safe[107]. Neurological adverse events (headache, hypersomnia, lightheadedness, dizziness) were observed in the 50% of the patients that received a higher dose of the NK-1 receptor antagonist, whereas insomnia was reported in those treated with 125 mg of aprepitant (11.1% patients). In both groups, the concentration of SP in plasma decreased. Gastrointestinal, ocular/visual, dermatological and systemic adverse events were also reported in the patients treated with aprepitant[107]. No changes in sleep quality, anxious mood, depressed mood or neurocognitive measures were found[108].

Despite the large number of non-peptide NK-1 receptor antagonists reported, the only NK-1 receptor antagonist used currently in clinical practice is the drug aprepitant (Emend, MK-869, L-754030) (oral) and its intravenously administered prodrug, fosaprepitant[3]. Fosaprepitant is rapidly converted to aprepitant via the action of ubiquitous phosphatases[108]. Both NK-1 receptor antagonists are used for the prevention of chemotherapy-induced nausea and vomiting and post-operative nausea and vomiting[70]. Many clinical human trials have reported the efficacy and safety of aprepitant/fosaprepitant for the treatment of emesis[70]. No serious adverse events were found. Aprepitant was well tolerated: no grade 3 or higher toxicities related to aprepitant were reported, whereas the adverse events mostly observed were nausea and vomiting, fatigue, diarrhoea, febrile neutropenia, headache, dyspnea, constipation and hiccups[109].

Accordingly, novel possibilities for translational research are emerging for improving the treatment of diseases in which the SP/NK-1 receptor system is upregulated and hence, in particular, the use of NK-1 receptor antagonists in oncology therapy is quite promising according to the data obtained from preclinical studies[3]. Aprepitant is an excellent candidate for testing its antitumor, antimigratory and antiangiogenic action in human clinical trials since a large part of the required safety and characterization studies for aprepitant have already been carried out (aprepitant is already available in clinical practice for the treatment of emesis)[70]. Moreover, aprepitant has been developed as a nanoparticle formulation to enhance exposure and to minimize food effects[111]. In humans, the nanoparticle formulation increased 3-4 times the bioavailability of this NK-1 receptor antagonist[110]. It has been also demonstrated in an *in vivo* study that fosaprepitant reduced significantly the tumor volume of MG-63 human osteosarcoma xenografts[99].

It seems that by increasing the number of days on which aprepitant is currently administered and using higher doses of aprepitant than those used in chemotherapy-induced nausea and vomiting this NK-1 receptor antagonist could be effective in cancer (*e.g,* pancreatic cancer)[3]. However, these issues should be investigate in depth. By increasing the dose of aprepitant, higher and undescribed side effects may occur, although it has been reported that in patients with depression a dose of 300 mg/day of aprepitant was well tolerated and no significant difference in the frequency of adverse events was observed as compared with placebo[3].

**CONCLUSION**

The SP/NK-1 receptor system plays an important role in the development of pancreatic cancer, neoangiogenesis and metastasis. It seems that SP acts as a mitogen for pancreatic tumor cells overexpressing NK-1 receptors and that NK-1 receptor antagonists also induce apoptosis in tumor cells. Research into the involvement of the SP/NK-1 receptor system in pancreatic cancer must continue in forthcoming years since it is necessary to explore new and effective therapeutic interventions in pancreatic cancer research. It is important to seek strategies targeting tumor-specific molecular derangements. This is the case of the NK-1 receptor, which is overexpressed in pancreatic tumor cells and tumor samples. NK-1 receptor antagonists induce the death of tumor cells by apoptosis. Accordingly, the NK-1 receptor is a promising target in the treatment of pancreatic cancer and NK-1 receptor antagonists could be considered as drugs for the treatment of this tumor. This conclusion is based on the following data: (1) After binding to the NK-1 receptor, SP induces pancreatic tumor cell proliferation, angiogenesis and the migration of pancreatic tumor cells (invasion, infiltration and metastasis); and (2) By contrast, NK-1 receptor antagonists inhibit pancreatic tumor cell proliferation (tumor cells die by apoptosis), have antiangiogenic properties in pancreatic cancer, and block the migratory activity of pancreatic tumor cells. Currently, in clinical practice there are few new drugs against the treatment of pancreatic cancer. However, it has been demonstrated *in vitro* and *in vivo* that NK-1 receptor antagonists exert an antitumor activity against pancreatic cancer cells. At the present, there are more than 300 NK-1 receptor antagonists[69] and this means that there are more than 300 potential drugs against the treatment of pancreatic cancer. Thus, it is crucial to test the antitumor action of NK-1 receptor antagonists in human clinical trials. In this sense, the antitumor action of NK-1 receptor antagonists already available in clinical practice for the treatment of emesis (*e.g.,* aprepitant) should be tested in clinical trials. It has previously been reported that the administration of aprepitant is well tolerated and is associated with minimal side effects. Indeed, at 300 mg/d of aprepitant was well tolerated and no significant difference in the frequency of adverse events were observed in comparison with placebo administration[71]. It is also known that, *in vitro*,aprepitant exerts an antitumor action against human pancreatic tumor cells[12]. In sum, all the data point to the notion that the NK-1 receptor could be a new and promising therapeutic target in pancreatic cancer and that NK-1 receptor antagonists could open the door to a new and promising generation of anticancer drugs against pancreatic cancer.

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**Table 1** **Technical features of NK-1 receptor antagonists**

|  |  |
| --- | --- |
| **NK-1 Receptor Antagonists** | |
| Therapeutic action | Linked to stereochemical features (receptor affinity) and not to  chemical composition |
| Cell specificity | Specific cytotoxicity against pancreatic cancer cells via the NK-1  receptor |
| Antitumor action | Mitogenesis inhibition  Cell death by apoptosis  Angiogenesis inhibition  Inhibition of the migration of cancer cells:  inhibit invasion, infiltration and metastasis |
| Beneficial effects | Central nervous system:  Antiemetic  Anxiolytic  Antimigraine  Anticonvulsant  Neuroprotector  Peripheral nervous system:  Neuroprotector  Liver:  Hepatoprotector  Kidney:  Nephroprotector  Systemic:  Analgesic  Antiinflammatory  Antiviral |
| Side-effects | Headaches, hiccupping, vertigo and drowsiness |
| Synergistic effect with cytostatic and radiation therapy | Vinblastine, adriamycin, mitomycin, ifosfamide, cisplatin |
| Decrease cytostatic and radiation therapy side-effects | Cisplatin, cyclophosphamide |
| Block multiple intracellular signaling  pathways | NK-1 receptor (G protein-coupled receptor):  Rho-Rock-pMLC: cell migration inhibition  PLC-IP3-Akt: apoptotic effect  PLC-DAG-TK-MAPKs: inhibition of tumor cell proliferation  PLC-DAG-PKC-MAPKs: inhibition of tumor cell proliferation  ATP-cAMP-PKA-Phosphorylation  PLA-Arachidonic acid-PGs  -TXAs  -LXs  Glycogen breakdown inhibition (counteract the Warburg effect) |
| Dosage | Act at μM in a concentration-dependent manner |

Akt: Protein kinase B; ATP: Adenosine triphosphate; cAMP: Cyclic adenosine monophosphate; DAG: Diacilglicerol; IP3: Inositol triphosphate; LXs: Leukotrienes; MAPKs: Mitogen- activated protein kinase; PGs: Prostacyclin; PKA: Protein kinase A; PKC: Protein kinase C; PLA: Phospholipase A; PLC: Phospholipase C; pMLC: Myosin regulatory light chain phosphorylation; TK: Tyrosine-kinase; TXAs: Thromboxanes.

**Figure 1** **SP and NK-1 receptor antagonists bind to different sites of the NK-1 receptor.** SP binds to the extracellular loops of the receptor, whereas NK-1 receptor antagonists (*e.g.,* L-733,060, aprepitant, L-732,138) bind more deeply, between the transmembrane segments.