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Substance P (SP)

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Gene Symbol: Tac1; PPTA ([Homo sapiens](#), [Mus musculus](#), [Rattus norvegicus](#))

1. General Information

Substance P (SP; CAS: [33507-63-0](#)) is an undecapeptide with an amino acid sequence of Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH₂. It was first identified by Ulf von Euler and John H. Gaddum as a substance that cause intestinal contraction (73). SP belongs to a family of structurally similar peptides called “tachykinins”, including neurokinin A (31, 48), neurokinin B (30, 32), neuropeptide K (70), and neuropeptide γ (29).

SP is encoded by the *tachykinin-1* (*Tac1*) (also commonly known as *preprotachykinin-A* (*PPTA*)) gene. It is widely distributed in the peripheral nervous system (54) and central nervous system (44), but also shown to be induced and expressed in other cell types such as monocytes (25), macrophages (25), lymphocytes (36), pancreatic acinar cells (34, 35, 69), Leydig cells (10) and various tumors (18, 20). A number of studies indicate control plasma SP levels in humans fall in the range between 30 pg/ml to 500 pg/ml (5, 39, 60). The endogenous receptor for SP is a G-protein coupled receptor called neurokinin-1 receptor (NK1R). SP can also bind and activate neurokinin-2 receptors and neurokinin-3

receptors, albeit with less affinity (59). Mechanisms that degrade SP and terminate its effects are also well known to be mediated by neutral endopeptidase (NEP) and/or angiotensin-converting enzyme (ACE) (65).

Physiological and pathological functions

Although the existence of substance P has been known for more than eighty years, the bulk of physiological and pathological roles of SP have been uncovered only in the past 20 years. Well known functions of SP are listed as follow.

i. Pain

One of the earliest physiological functions of substance P is described in its role in nociception. Substance P is one of the neurotransmitters that propagates pain. SP release from sensory afferents was detected from thermal (16), mechanical (15), and chemical (15) stimulation of the skin, increasing the SP concentration in the dorsal horn. Direct intrathecal injection of SP to the spinal cord induces pain-like behavior in rodents (43, 75). Clinically, substance P has been linked to pain disorders such as fibromyalgia (11) and arthritis (1, 63).

Interestingly, the skin of naked mole rats (*Heterocephalus glaber*) is naturally deficient in SP. When they are exposed to external pain stimuli such as capsaicin and acids, they showed negligible pain-like responses. (52)

ii. Vomiting

The vomiting center in the medulla controls the vomiting reflex. With appropriate stimuli, the vomiting center signals constriction of the stomach and expulsion of gastric contents through the esophagus. This region in the brain expresses high concentrations of neurotransmitters, which include substance P and its receptor NK1R. SP-NK1R interaction plays a major role in promotion of vomiting (61). Clinically, NK1R antagonists such as Aprepitant are commonly used drugs to manage chemotherapy-induced emesis (12).

iii. Inflammation

Substance P has also been linked with the pathogenesis of inflammatory disorders. Local release of pro-inflammatory mediators, such as substance P, from afferent neurons causes neurogenic inflammation. The involvement of SP was observed in various animal models of inflammation, including, but not limited to cecal ligation and puncture induced sepsis (23), burns injury (67), and colitis (68).

iv. Other functions of substance P

- Mood disorders, anxiety, stress (17). Substance P was suggested to have anxiogenic properties.
- Neurogenesis (51). Substance P promotes the proliferation of adult rat neural progenitor cells.
- Respiratory rhythm (6). Substance P increases respiratory rhythm and tidal volume.
- Vasodilation (50)
- Dermatitis (26)

2. Pancreatic Information

i. Substance P in acute pancreatitis

The role of substance P in acute pancreatitis and associated lung injury has been extensively studied. It was found that in normal mice, substance P and NK1R expression in the pancreas are both increased during caerulein-induced acute pancreatitis (3, 37). Genetic deletion of either *NK1R* or *PPTA* protected mice against experimental pancreatitis. This was demonstrated by the magnitude of hyperamylasemia, neutrophil sequestration in the pancreas, and pancreatic acinar cell necrosis were significantly reduced in *NK1R*^{-/-} mice and *PPTA*^{-/-} mice, when compared with their wild type controls. Moreover, pancreatitis associated lung injury was almost completely abolished when *NK1R* or *PPTA* were knocked out, as shown by reduced intrapulmonary sequestration of neutrophils and pulmonary microvascular permeability (3, 4). Similar protective effects were observed with hemorrhagic pancreatitis induced by feeding mice a diet deficient in choline, supplemented with ethionine (CDE diet) in NK1 receptor knockout mice (42). These results showed that *PPTA* gene products, as well as NK1R, are critical pro-inflammatory mediators in acute pancreatitis and the associated lung injury. SP-NK1R interaction is also a determinant of inflammatory edema in acute interstitial pancreatitis (21). Furthermore, mice treated with CP96,345, a specific NK1R antagonist, either prophylactically or therapeutically, were significantly protected against caerulein-induced acute pancreatitis (38). These results point to a key role of SP-NK1R interaction in acute pancreatitis and associated lung injury.

Primary sensory neurons that innervate the tissues contain an abundance of neurotransmitters, including substance P. Transient receptor potential vanilloid type 1 (TRPV1) channels located on these neurons, when activated, causes neuronal release of stored substance P. It was demonstrated *in vivo*

that capsazepine, a TRPV1 antagonist, significantly reduced inflammation and pancreatic injury in caerulein-induced acute pancreatitis (47). On the other hand, activation of TRPV1 by capsaicin caused release of substance P, and exaggerated caerulein-induced acute pancreatitis (28). Pre-treatment of capsazepine or CP96,345 before administration of capsaicin showed reduced severity of acute pancreatitis, highlighting the importance of TRPV1 and NK1R (28). High doses of Resiniferatoxin caused disruption of the celiac ganglion and inhibited substance P release, and showed protective effects against caerulein-induced pancreatitis in rats (49). A detailed review of the role of TRPV1 in acute pancreatitis is available (40).

The effects of substance P can be terminated through enzymatic degradation by neutral endopeptidase (NEP). Genetic deletion of NEP exacerbates pancreatic damage and associated lung injury, and also increased mortality rate in CDE diet induced acute pancreatitis (42). NEP is also a determinant of pancreatic elastase associated lung injury (13).

Besides pro-inflammatory effects of substance P in acute pancreatitis, it also mediates nociception in animal models of acute pancreatitis. Induction of necrotizing pancreatitis by L-arginine caused a large increase in c-fos expressing spinal neurons, suggesting activation of nociceptive pathways. Intrathecal administration of SR140333, a specific NK1R antagonist, was shown to suppress pancreatitis pain (74). In another study, intraperitoneal injection of CP99,994, another specific NK1R antagonist, attenuated nociceptive behaviours in dibutyltin dichloride induced acute pancreatitis (72).

ii. Substance P in chronic pancreatitis

Surprisingly there has been little work evaluating the role of substance P in chronic pancreatitis. Substance P was identified as a mediator of pain responses in chronic pancreatitis. *NK1R* mRNA levels in chronic pancreatitis patients were

significantly correlated with the intensity, frequency and duration of pain (66). Similar correlations were also observed between *NK2R* mRNA levels and pain (46). A marked increase of substance P contained nerve endings was observed from the inflamed pancreatic tissue, when compared to healthy subjects (8). However, Intrapancreatic *PPTA* mRNA expression was not increased in these patients, suggesting that the location of substance P synthesis is outside of the pancreas (14).

iii. Substance P in pancreatic acinar cells

Gene and peptide expression of substance P has been detected in isolated pancreatic acinar cells. Expression of substance P can be induced by caerulein, but its physiological significance is unclear (34, 69). On the other hand, exogenous substance P is able to stimulate the expression of chemokines in isolated primary pancreatic acinar cells. Exposure of mouse pancreatic acini to substance P (1 μ M) significantly increased synthesis of monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 (MIP-1), as well as macrophage inflammatory protein-2 (MIP-2). The stimulatory effect of substance P was mediated through the NF- κ B pathway (55). Substance P, acting specifically through NK1R, induced the activation of protein kinase C- δ (PKC δ), ERK and JNK with a time-dependent manner in isolated pancreatic acinar cells (56, 57). Inhibition of PKC δ , ERK or JNK with their respective specific inhibitors attenuated substance P-induced chemokines production (56, 57). More recently, a critical role of SRC family kinases (SFKs) has been demonstrated. SFKs mediated the activation of mitogen activated protein kinases (ERK, JNK), transcription factors (NF- κ B, AP-1, STAT3), and production of chemokines in pancreatic acinar cells (58).

iv. Effects of substance P on pancreatic exocrine secretion

Substance P has also been shown to regulate

pancreatic secretion. Exogenous substance P dose-dependently inhibited cholecystokinin-induced amylase release and secretin induced juice flow via the pancreatic duct in isolated, perfused rat pancreas (33). The effects of SP were partially blocked by NK1R and NK2R receptors (33). These observations were suggested to be mediated by a neural pathway and involve activation of the neurokinin-1 receptor (33). In contrast, Schmidt et al. showed that substance P stimulation of the pancreas stimulates pancreatic exocrine secretion in isolated porcine pancreas, and was attenuated by NK1R antagonists (64). It is currently unclear whether the conflicting observations in these two studies are the result of species variation or methodological differences. The effect of substance P on pancreatic secretion was also investigated using pancreatic cells. In isolated guinea pig pancreatic acinar cells, substance P caused a twofold increase in amylase secretion (53). Experiments done on AR42J cells (a rat pancreatic acinar cells line) also showed evidence of increased exocrine secretion when these cells were treated with substance P (22). On the other hand, substance P inhibited bicarbonate secretion from guinea pig pancreatic ducts, probably by inhibition of a Cl⁻/HCO₃⁻ exchanger on the apical membrane of pancreatic duct cells (24).

3. Tools for study of Substance P

i. Knockout mice and transgenic cell lines

- a) PPTA knockout mice of BALB/c background (9). The mice were healthy and fertile. These mice were protected against caerulein-induced acute pancreatitis. (4)
- b) NK1R knockout mice (3, 7, 62). These mice were protected against caerulein-induced acute pancreatitis (3)
- c) NEP knockout mice. These mice showed potentiated effects of substance P. (42)

ii. Specific NK1R antagonists

- a) CP96,345 (Compound ID: [104943](#)). It has been used in several acute pancreatitis studies with success (28, 38, 41).
- b) L703,606 (Compound ID: [132629](#)). It has been used in acute pancreatitis with success. (2)
- c) SR140,333 (Compound ID: [5311449](#)). It was shown to suppress pancreatitis pain in L-arginine induced pancreatitis. (74)
- d) RP67,580 (Compound ID: [107686](#)). It was shown to block the inhibitory effect of substance P on exocrine secretion (33).
- e) CP99,994 (Compound ID: [5311057](#)). It was shown to suppress nociceptive behavior in dibutyltin dichloride induced acute pancreatitis (72).
- f) L-733,060 (Compound ID: [132846](#))
- g) MK869 (Aprepitant) (Compound ID: [6918365](#))
- h) GR-205171 (Compound ID: [122033](#))

iii. NK1R agonists

- a) GR73,632 (Compound ID: [119599](#))(45)
- b) [Sar(9),Met(O(2))(11)]-substance P (Compound ID: [16219961](#)) (71). It was shown to stimulate pancreatic plasma extravasation via NK1R activation (21).

iv. Exogenous substance P is available from Bachem.

v. Capsaicin (Compound ID: [1548943](#)) and capsazepine (Compound ID: [2733484](#)) targets neuronal release of substance P

Capsaicin acts by activating TRPV1 channels in the primary ganglia, causing a massive release of stored substance P and then followed by depletion of available substance P. Capsazepine is a structural analog of capsaicin. It acts by blocking the TRPV1 channels, thus blocking SP release from the nerve endings.

vi. Method of measuring substance P

Substance P ELISA kits for human, mouse and rat are available from Peninsula Laboratories, Bachem.

vii. Antibodies

There are several commercially available SP antibodies. It is recommendable to test out the antibodies before use.

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