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On the role of "substance P" in the respiratory tract in corona infections to the causes of corona-related brain destruction

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Abstract
The present work establishes the connection between the neuropeptide "substance P" (SP), which belongs to the group of neurokinins, the COVID-19 infection, and air and environmental pollution on the basis of historical developments and current research results. For this purpose, older studies on the role of SP as an important responder in stress events and in the defense line of the respiratory tract are used in conjunction with recent results on the function of this neuropeptide in corona infection. It will be shown how SP has been successfully used as start point for therapeutic approaches. In further pursuing this therapeutic approach, an opportunity is seen for preventive concepts as well. For this purpose, the classification of SP as a regulatory peptide (regulide) offers promising approaches.

Zusammenfassung
Die vorliegende Arbeit stellt anhand von historischen Entwicklungen und aktuellen Forschungsergebnissen den Zusammenhang zwischen dem zur Gruppe der Neurokinine gehörenden Neuropeptid „Substanz P" (SP), der Covid-19-Infektion sowie der Luft- und Umweltverschmutzung her. Dazu werden ältere Untersuchungen zur Rolle von SP als wichtiger Responder im Stressgeschehen und in der Abwehrfunktion des Atmungstraktes in Verbindung mit neueren Ergebnissen zur Funktion dieses Neuropeptides bei der Corona-Infektion herangezogen. Es wird aufgezeigt, wie SP bereits erfolgreich als Ausgangspunkt für therapeutische Ansätze genutzt wurde. Im weiteren Verfolgen dieses therapeutischen Ansatzes wird eine Chance gesehen, auch zu präventiven Konzepten zu gelangen. Dazu bietet die Einordnung von SP als ein regulatory peptide (regulide) erfolgversprechende Ansätze.

Keywords/Schlüsselwörter
substance P (SP), neuropeptide, COVID-19 infection, corona infection, coronavirus, stress responder, defense line in the respiratory tract, ventilatory response, brain damage, regulatory peptide, regulide
Substanz P, Neuropeptid, Covid-19-Infektion, Corona-Infektion, Coronavirus, Stress-Responder, Defense-Line im Atmungstrakt, Atemwegsreaktion, Hirnschädigung, regulierendes Peptid, Regulid

On October 29, 2021, at the invitation of the Leibniz Sozietät der Wissenschaften zu Berlin, an evening event was held at Schloss Biesdorf in Berlin with a lecture of Wolf-Dieter Ludwig, Chairman of the Drug Commission of the German Medical Profession, on the topic of "Drug therapy of COVID-19 and vaccines against SARS-CoV-2: expectations, current results and uncertainties". Together with the Leibniz Sozietät, the Berliner Medizinische Gesellschaft, the Campus Berlin-Buch GmbH and Schloss Biesdorf had invited to the event. A statement by Wolf-Dieter Ludwig, "that the next battle against corona is to be waged in

the nose" was the reason to consult the literature (see Pfaff/Oehme 2021). One result was the recent work of Riffat Mehboob that the neuropeptide "substance P" (hereafter abbreviated SP), which is present in the sensory fibers of the respiratory tract, plays a role in COVID disease etiology (see Mehboob 2021). From this, a close collaboration developed between authors, which also led to this work: What is the role of "substance P" in the respiratory tract?

1. Historical background

In 1930/31, the Swedish postgraduate student Ulf Svante von Euler isolated a biological extract from animal intestinal material in H. H. Dale's laboratory in London (see von Euler, Gaddum 1931; von Euler 1977). The extract was available for pharmacological studies as a "stable dry powder". The P from the word "powder" was used to identify the substance. It has remained part of the name "substance P" to this day. The peptide chemistry team of Susan E. Leeman isolated the substance from the hypothalamus and in 1971 determined the structure to be an undecapeptide with the sequence Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH2 (see Chang, Leemann 1970). Total synthesis was also carried out by the Leeman team (see Tregear et al. 1974).

1976 was a special year for substance P researchers. The meanwhile world famous physiologist/pharmacologist and Nobel Prize winner von Euler had invited to a Nobel Symposium in Stockholm. The symposium covered the current state of knowledge of "substance P": from history, chemistry, mechanisms, distribution, to pharmacology. One focus was on the effect of SP on sensory nerve endings and pain. Pioneering work on this had been done by Fred Lembeck, who investigated the effect of SP-powder on afferent systems as early as in 1953. His paper in Stockholm, and other papers, confirmed the hypothesis that SP is a transmitter in primarily sensory afferent neurons and plays an important role in the pain process (see Lembeck et al. 1977). Two papers at the symposium concerned the effect of SP on the tracheobronchial tissue (see Nilson et al. 1977; Sundler et al. 1977). In these, the presence of SP was demonstrated in both nerve fibers and endocrine cells of guinea pig tracheobronchial tissue. At the same time, a strong effect on bronchial tone was found for SP, in vivo as well as in vitro, 45 times stronger than the effect of histamine.

Peter Oehme, also invited by von Euler, hypothesized in his contribution that different information is encoded in the SP molecule (see Oehme et al. 1977):

- a direct effect on smooth muscle, sensory nerves, and others
- an indirect effect through modulation of other transmitter systems, e.g., acetylcholine

For both effects, different parts of the SP sequence were discussed (Figure 1).

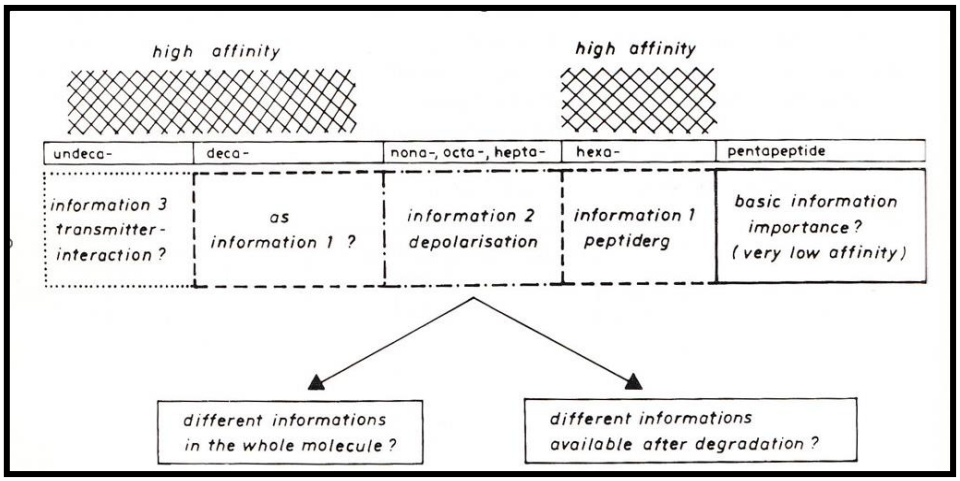

Fig. 1: Hypothesis for the different information in the substance P molecule (see Oehme et al. 1977).

2. Pharmacological effects of "substance P"

2.1 "Substance P" and pain

After returning from Stockholm, Oehme started investigations on the "action of SP on pain threshold" in the Institute for Drug Research (IWF) of the Academy of Sciences in Berlin-Friedrichsfelde, which he founded in 1976. His investigations using the "hot plate technique" on mice yielded surprising results (see Oehme et al. 1980/1). It was shown that the SP effect depends on the initial condition of the test animals. SP has an analgesic effect on mice with a short reaction time to pain stimuli, whereas it has a hyperalgesic effect on mice with a long reaction time. Both led to a normalization of reaction time. Subsequent studies revealed that the analgesic effect component is assigned to the C-terminal SP domain, whereas the hyperalgesic effect component is assigned to the N-terminal SP domain (see Görne et al. 1982). This dual effect of SP was in accordance with the model presented by Oehme at the Stockholm SP Congress in 1976.

2.2 "Substance P" and stress

Interesting findings also followed from the studies on "SP-action on behavior" carried out jointly by Oehme and Karl Hecht's team. In a series of stress models (immobilization, noise, electric footshocks, etc.), it was found in rats that SP is able to normalize the disturbances such as "decrease in learning", "loss of deep sleep and REM sleep", "increase in blood pressure and heart rate" (see Hecht et al. 1980; Oehme et al. 1980/2). Clinical studies conducted by Hecht and his team on patients with stress-induced sleep disorders with nasal SP application also showed positive results.

Overall, it appeared that the N-terminus was relevant for the "anti-stress effect", whereas the C-terminus was relevant for acute effects, such as the spasmogenic effect. Therefore, the term "regulatory peptide" ("regulide" was proposed for SP (see Oehme et al. 1980/2).

2.3 "Substance P" and catecholamines

Since there is an increase of catecholamines in plasma under stress, the "interaction of SP with the aminergic system" was investigated. In adrenal slices, which contain chromaffin cells as well as endings of the splanchnic nerve, the electrically stimulated release of acetylcholine was investigated in addition to the release of noradrenaline. SP inhibited both electrically

stimulated acetylcholine release and nicotinic release of norepinephrine (see Nieber, Oehme 1987). "Substance P" thus has both a presynaptic and a postsynaptic target.

For a more in-depth investigation of postsynaptic attack, studies were performed on isolated chromaffin cells (see Cheung et al. 1987). These studies showed that SP has two effects. First, it inhibits cholinergically induced catecholamine release, and second, it counteracts nicotine-induced desensitization of catecholamine release. Thus, SP can both inhibit excessive release and counteract too rapid depletion of release. Two separate points of attack are, therefore, provided. Overall, SP is thus able to modulate synaptic transmission and act in the sense of the above-mentioned "regulide" (see Oehme/Krivoy 1983). It is the N-terminal tetrapeptide that inhibits both presynaptic acetylcholine release and postsynaptic norepinephrine release, thus modulating synaptic transmission in multiple ways. This is consistent with its role as an "essential nucleus for the 'anti-stress effect' of SP". These effects are independent of the NK 1 receptor. Apparently, the target for this modulation are the polyphosphoinositides (see Minenko/Oehme 1987).

2.4 "Substance P" and mast cells

Since it was known from the literature that SP can release histamine from peritoneal mast cells and that SP is released from sensory nerves upon antidromic stimulation, Oehme and his team, in cooperation with the Pharmacological Institute of the University College in London (UCL), started studies on mast cells. First, SP, SP fragments and analogues were injected into the forearms in self-experiments. Later, volunteers from UCL were added. As expected, there was dose-dependent redness and swelling on the forearms in these experiments. This was to be suppressed by antihistamines. N- and C-terminal SP fragments were ineffective. This implied that the entire SP molecule was necessary for histamine release from mast cells (see Foreman et al. 1983). Identical structure-activity relationships were shown on isolated peritoneal mast cells (see Renner/Oehme 1983). These results were considered significant for understanding the role of SP in the pathophysiology of inflammatory processes in various tissues; particularly in the bronchial tract.

3. "Substance P" actions in the respiratory tract

The "action of Substance P in the respiratory tract" played only a minor role at the "Substance P symposia" following the Stockholm SP conference. At the 1983 SP conference hosted by David Powell in Dublin, local release of SP in the bronchial tract of guinea pigs by various chemical irritants was reported (see Lundberg et al. 1983). This SP release was associated with mucosal edema and bronchospasm.

In 1984, the symposium on "Substance P - metabolism and biological actions", in conjunction with the 9th IUPHAR International Congress of Pharmacology, was held in Maidstone (UK). In the review lecture by Bengt Pernow on "Substance P: present status and future prospects", the function of SP in sensory nerves was discussed in detail. However, a crucial statement was, "Although there is now strong evidence that SP is an important factor in the development of neurogenic inflammation, the mechanism by which SP exerts its biological effects is not clear" (see Pernow 1985).

Starting in 1987, Oehme focused his group's work in this area and formed a joint research group with the Research Institute for Lung Diseases and Tuberculosis (FLT) in Berlin Buch. The research group's first interest was the known bronchospastic effect of SP. As expected, SP_{1-11} showed a pronounced dose-dependent constrictor effect at the basal tone of isolated guinea pig trachea (see Schreiber et al. 1990/1). The C-terminal heptapeptide SP_{5-11} also caused a dose-dependent contraction of the isolated tracheal preparation. In contrast, the N-

terminal tetrapeptide SP_{1-4} showed no constrictor effect. The contraction triggered by acetylcholine was significantly attenuated.

Thus, the picture was the same as in other pharmacological studies. The C-terminal has a direct effect; mediated via the NK 1 receptor. The N-terminal tetrapeptide has an indirect protective effect against the acetylcholine effect. This is mediated via a different target.

Since SP also acts on immunocompetent cells in the bronchial tract, it was of interest to determine whether differences also exist between the N- and C-terminal SP fragments. The studies were performed on spleen cell cultures from mice and mononuclear cells from rat lymph nodes (see Paegelow et al. 1989). SP and the N-terminal sequences SP_{1-4} and SP_{1-7} were capable of secreting lymphokines with chemotactic properties for granulocytes and lymphocytes. The maximum of the dose-response curves was between 10^{-11} and 10^{-10}, but the C-terminal fragments SP_{6-11}, SP_{7-11}, SP_{8-11}, and SP_{9-11} cannot induce lymphokines to be expressed.

Therefore, investigations were planned with both antagonists for the NK-1 receptor and N-terminal SP sequences for their therapeutic or preventive utility, primarily for the respiratory tract. In addition, capsaicin was of interest because of its influence on bronchial hyperreactivity (see Schreiber et al. 1990/2).

However, things were to turn out differently. With German unification, there were serious changes for both the Institute for Drug Research of the Academy of Sciences and the FLT. The research work oriented on SP and the bronchial tract was finished in both institutes at the beginning of the 1990s (see Nieber et al. 1992).

A summary on pharmacological effects of SP can be found in Sitzungsberichte der Akademie der Wissenschaften der DDR, newly edited and published by de Gryuter in 2022 (see Oehme 1987) and in the "Reflections on Substance P-Research" (see Oehme/Hecht 2017/2021).

4. Role of "Substance P" in the first defense line of the respiratory tract

The main focus of the above-mentioned current work of Mehboob was on the investigation of the NK 1 receptor in the therapy of COVID-19 (see Mehboob 2021). In particular, this work reported on the use of the NK-1 antagonist aprepitant, in combination with dexamethasone, for the therapy of severe COVID courses. Mehboob proposed SP as a possible factor responsible for initiation of cytokine storming after getting infected with any foreign agent such as coronavirus. Neurokinin-1 receptor (NK-1R) antagonist, aprepitant, was suggested as a potential drug for the treatment by inhibiting the receptor. Some evidences and commonalities were provided supporting the idea of SP involvement in respiratory tract infections including COVID-19, e.g.,

- symptoms in COVID-19 infection and SP nociception
- airway hypersensitivity/asthma in both phenomena
- variable patterns of COVID-19 disease severity in different age groups
- high death rate in COVID-19 patients having co-morbidities of diabetes, hypertension and cardiac disorders
- viral load correlating with SP secretion
- cytokine storming during inflammation triggered by SP

Aprepitant is a NK-1R antagonist that has been approved for the treatment of chemotherapy-induced vomiting for a number of years (see Mehboob 2021).

The immune reaction kills the virus to protect the host cells, but if it is continued unchecked, it is known as cytokine storming, which may be lethal (Figure 2). Patients with COVID-19 infection may develop acute respiratory distress syndrome (ARDS) because immune cells continuously release inflammatory mediator. Therefore, the pathogen itself is not doing much damage, but cytokine storming is the main offender. On the other hand, if restricted, illness severity could be reduced (see Sarzi-Puttini et al. 2020; Leng et al. 2020). The immune system stimulating effects of SP could cause a cytokine storm. The inflammatory pathways and, hence, the cytokine storming may both be stopped if its receptor is suppressed by aprepitant. When exposed to toxic stimuli, SP is the first to react and acts as a quick defense mechanism to ensure survival. Comparing them to controls, NK-1R defective mice were shown to exhibit less pulmonary inflammation (see Bozic et al. 1996). Immune cells secrete SP, which has endocrine, paracrine, and autocrine effects (see O'Connor et al. 2004). It can activate cells that are far away, such as smooth muscle cells, endothelium cells, lymphatics, white blood cells and fibroblasts. It interacts with NK-1R, stimulates the immunological and endocrine systems to produce inflammatory mediators in the airway tracts (see Graefe, Mohiuddin 2022). It is also found on the cardio-ventilatory regulatory centers and phrenic nuclei, which regulate the diaphragm and respiration. It is concentrated in the brainstem nuclei that mediate respiratory regulation (see Mazzone, Geraghty 2000). Once formed, the SP/NK1-R complex starts a signaling chain that results in the production of IP3 and diacylglycerol (DAG) (see Ramkissoon et al. 2006). The activation of NF-kB by macrophages and other immune cells results in the production of inflammatory mediators and the release of pro-inflammatory cytokines (see Bost 2004).

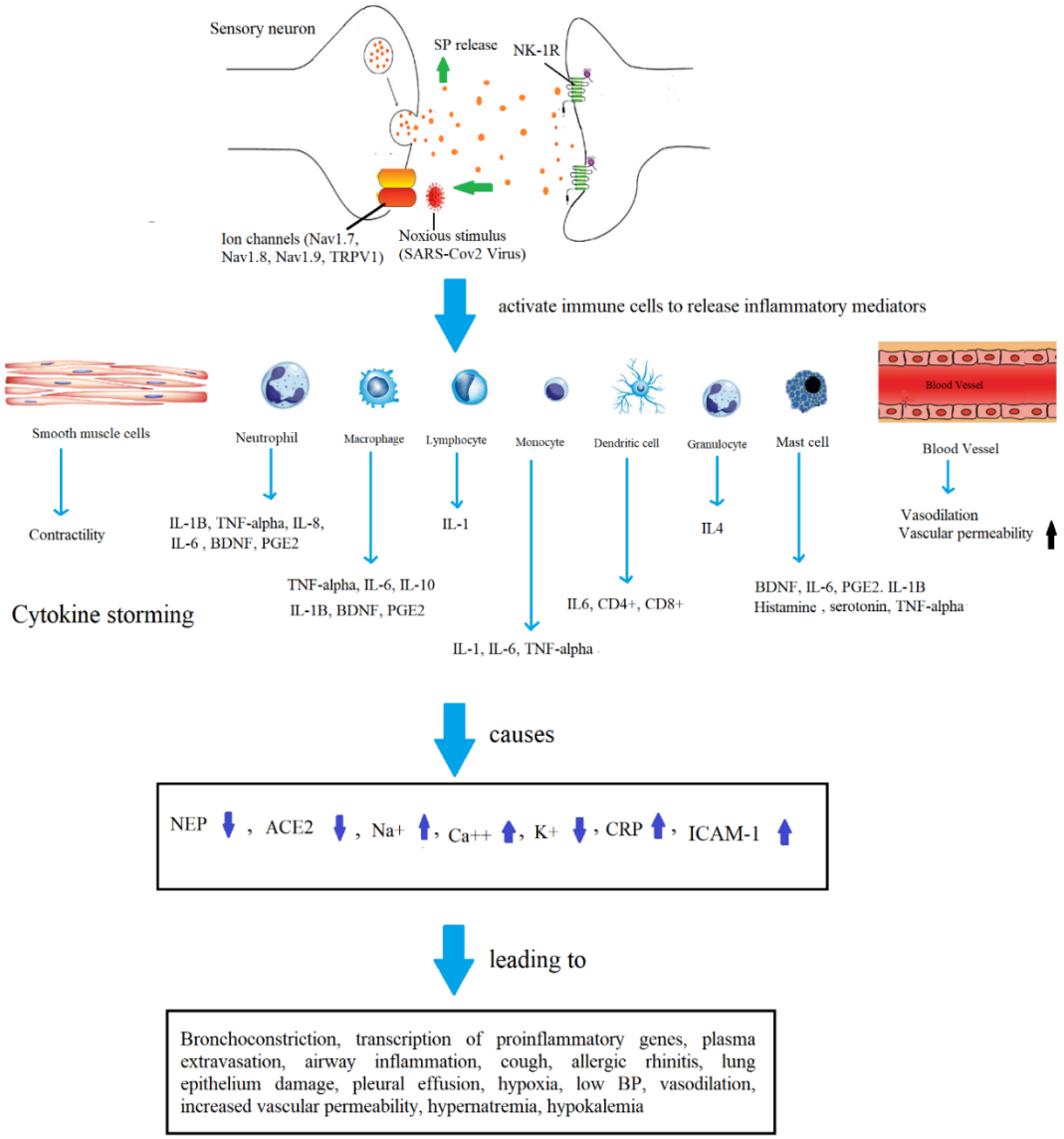

Fig. 2: Mechanisms involved in the development of COVID-19 infection by which SP-induced inflammation is implicated. Increased BBB permeability and immune cell cytokine release are caused by SP's binding to the NK-1R on endothelial cells (see Mehboob 2021).

5. "Substance P" in ventilatory responses

SP has a major role in cardio-respiratory rhythm generation and control evidenced through previous study (see Mazzone/Geraghty et al. 2000; Lavezzi et al. 2011; Mehboob et al. 2014; Mehboob 2017; Kaczyńska et al. 2018; Mehboob/Lavezzi 2021). It has an impact on how people react to ventilation since they are expressed in several brainstem regions. In a previous study, Mehboob and Anna Maria Lavezzi found that the increased expression of SP in the brainstem tissues of control infants compared to infants who had experienced sudden infant death syndrome (SIDS) shows that SP/NK-1R may be regulating the ventilatory regulation in newborns (see Lavezzi et al. 2011). In a related investigation, the brainstem nuclei of victims showed a marked reduction in SP and NK-1R binding. Due to a failure in cardiorespiratory regulation brought on by this altered SP expression, SIDS may result (see

Scholle et al. 1990). In unexpected fetal fatalities, SP expression was increased (see Lavezzi et al. 2011; Mehboob 2017) as well as in sudden adult death (see Hayashi/Sakuma 2016).

These findings may be correlated with mortalities in COVID-19 patients due to respiratory complications. SP also serves as a neuromodulator and vasodilator and leads to contractions of smooth muscles in upper airways, increased excitatory potential by neurons, enhanced saliva production and a higher vascular permeability (see Kaczyńska et al. 2018; Mehboob et al. 2017). It may also lead to bronchoconstriction in pathological conditions (see Mehbob et al. 2017; Mehboob 2021). Another study of Mehboob has discussed the fact that the gene encoding SP, TAC-1, has unconventional networking properties (see Mehboob et al. 2014). It is a singleton gene, has a small protein interaction network and the members of tachykinin family have conserved aminoacyl sequences. These properties are responsible for vulnerability of the TAC-1 gene and show that it is a very important gene, any mutation in this gene may lead to fatal consequences as there will be no other gene copy to compensate its functions. These fatal outcomes may be sudden death due to respiratory failures. The other members of these gene pathway should also be explored (see Mehboob et al. 2014).

SP and serotonin innervate the medullary motoneurons involved in the upper respiratory tract (see Szereda-Przestaszewska/Kaczyńska 2020) and in the laryngeal afferent system (see Kaczyńska et al. 2018). In the bronchopulmonary C fibers of the respiratory tracts, SP, the most prevalent neuropeptide and neurotransmitter, is found. It guards the lungs against any harm from irritating substances that are inhaled. The central nervous system (CNS) reacts to nociceptive stimuli by releasing nitric oxide, prostaglandins, and SP from the respiratory epithelium, as well as bronchoconstriction, cough, hypotension, sleep apnea, and mucus secretions in the lungs (see Geppetti et al. 1993). NK-1R mRNA was found to be raised in broncho-alveolar lavage fluid (see Nieber et al. 1992), sputum samples (see Tomaki et al. 1995), and lung tissue (see Adcock at al. 1993) in a study conducted on asthmatic patients. SP/NK-1R binding and the resulting interactions are also vital for the regulation of airway hyper responsiveness (AHR) (see Bertrand, Geppetti 1996).

An example of extreme hypersensitivity of the bronchial tract is SIDS when exposed to irritants, e.g., the cigarette smoke of the mother (see Lavezzi et al. 2011; Bright et al. 2017). In this regard, immunohistochemical studies were published in 2011 and 2017 (see Lavezzi et al. 2011; Mehboob 2017). These showed downregulated SP expression for SIDS-risk newborns in such brainstem areas that are important for respiratory regulation. This confirms earlier research results on infants at increased risk of SIDS, where a correlation between mean respiratory failure and low SP plasma levels was shown in the first five months of life (see Scholle et al. 1989; Scholle et al. 1990). This has been discussed as an indication of delayed maturation of respiratory control mechanisms. Vice versa, Mehboob and Lavezzi questioned whether the minimal probability of healthy neonates and infants to become ill after corona infection is also related to the SP system (see Mehboob, Lavezzi 2021). It was also discussed that the abnormalities in the brainstem nuclei may be responsible for cardiorespiratory failure and hence SIDS (see Bright et al. 2017, Bright et al. 2018/1; Bright et al. 2018/2). According to Mehboob, a fetus's brainstem exhibits very little SP expression. On the other hand, it is increased for newborns and lowered for kids and adults in controls (see Mehboob 2017).

6. SP/NK-1R and its relation to trigeminal ganglion, latency during coronavirus infection

Another innovative idea for coronavirus latency during infection was put out by Mehboob (see Mehboob et al. 2021). If it is assumed that the SARS-CoV-2 virus is operating through

the trigeminal ganglion (TG), which is the principal location for other latent viruses, there should be the possibility of latency of a SARS-CoV-2 virus infection. The SP/NK-1R pathway is obviously the key player in inflammation during COVID-19 infection as it may directly affect the ventilatory responses (see Szereda-Przestaszewska, Kaczyńska 2020). The immune cells, along with other cells in the airways and the lung's epithelial lining, are impacted by the excessive secretion of SP by TG neurons (see Mehboob 2021). The coronavirus may have a less unlikely chance of going latent and controlling the release of different TG peptides, including SP, by entering the TG via the trigeminal nerve in the eyes, nose, and mouth but the possibilities cannot be ruled out. The coronavirus might be latent or quiescent in the TG and could be reactivated at any time. As a result, it can happen that the patient does not develop an infection and, therefore, does not show symptoms. After the initial infection, a virus' latency may be broken within the cell (see Villareal 2008). Despite blood antibodies to the virus being present, the viral genome may stay in the host cell after primary infection and may be reactivated by any stressor (see Dimmock et al. 2007).

The mesencephalic trigeminal nucleus and the TG in the brainstem both include some of the primary afferent neurons of the trigeminal nerve. The ocular (V1), maxillary (V2), and mandibular (V3) nerves are the three branches that make up the trigeminal nerve. Each branch gives innervation to their distinct head regions (see Bista, Imlach 2019). The nociceptors, which are the free nerve ends of the trigeminal sensory afferents, are activated by pain or any other unpleasant stimulus, such as SARS-CoV2. These C-fiber sensory nerve fibers can be myelinated or not, and their cell bodies are found in the trigeminal ganglion (see Mehboob et al., 2017; Bista/Imlach 2019). The trigeminal spinal caudalis (Vc) nucleus of the brainstem receives these impulses via afferent fibers. Here, they connect with the second order neurons that send signals to the thalamus and the limbic and somatosensory cortices. Trigeminal afferent neurons' activity can be altered by inflammation of orofacial tissues that the TrN innervates, leading to ectopic firing and increased sensitivity to painful stimuli. Numerous mediators, including neurotrophic factors or neuropeptides at nerve ends, such as SP, CGRP (calcitonin gene-related peptide), and serotonin, induce sensitization. TG and TrN's SP and CGRP levels rise in response to painful stimuli, including nerve damage (see Goto et al. 2017).

7. Penetration of coronaviruses into the brain and brain destruction

At the end of this contribution, the penetration of coronaviruses into the brain will be briefly discussed. Coronaviruses can enter the brain via several pathways. On the one hand, they take the route via the olfactory bulbar zone (axonal transport along the olfactory nerve) and may reach the temporal lobe and the olfactory area of the cerebral cortex, which can result in brain infection. Transsynaptic transmission allows the virus to reach the brain stem and thalamus. The virus produces acute respiratory problems in the respiratory tract.

The second, more typical method is known as the "hematogenous route", which involves blood brain barrier (BBB) breaching and vascular endothelium destruction brought on by a coronavirus. The virus may damage the capillary endothelium by interacting with the ACE2 protein, causing endotheliitis, which makes it easier for the virus to enter the brain. ACE2 downregulation and increased activity of cathepsin L and transmembrane protease serine 2 (TMPRS2) may lead to increased expression of proinflammatory mediators that trigger blood barrier disruption and neuroinflammatory responses (Figure 3). Also, dysregulation of neurotransmitter signaling and hormones are important elements in the neuropathogenesis of SARS-CoV-2 infection. The RNA of SARS-CoV also interacts with or activates the molecular signaling pathways controlled by cell suicide molecules, pattern recognition

receptors, and complement cascades thus, affecting central nervous system functions by humoral and neural pathways (see Welcome/Mastorakis 2021).

Low oxygen levels and high cytokines in brain tissue may lead to brain damages. The consequential effects may occur in the form of psychological symptoms such as mood changes, anxiety, depression and many others that need to be investigated.

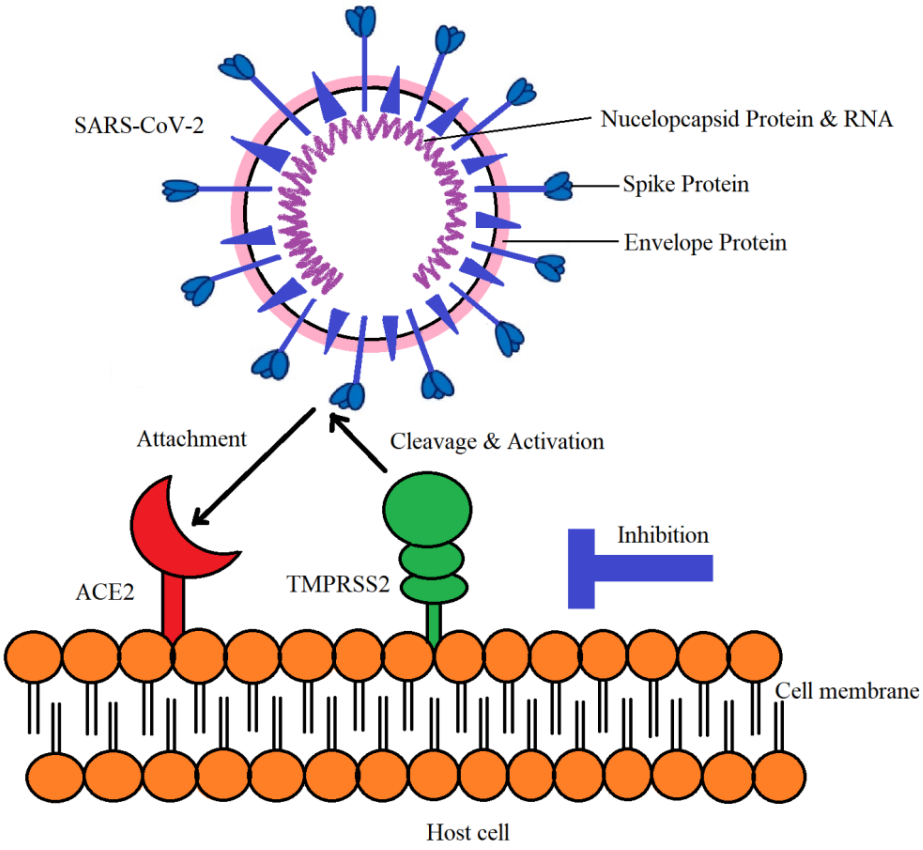

Fig 3: Interaction of SARS-CoV-2 with ACE2 and TMPRSS2 in host cell (see Mehboob/Ehsan in preparation).

The effect of coronaviruses in and on the brain is characterized by Gomazkov with the term neurotropism (see Gomazkov 2022). The scientific study of it is certainly an important perspective field of work

8. Future focal points

The statement of Mehboob "Actually it is not the virus that is fatal and causing mortalities but the cytokine storming activated and initiated by SP is bringing about the disaster" (see Mehboob 2021) recalls historical discussions of Rudolf Virchow, Robert Koch, Max von Pettenkofer and Oscar Liebreich on the proper control of epidemics (see Labisch 2004; Oehme/Pfaff 2022). Summarizing these discussions that were held in the context of the cholera epidemics of the time, it can be stated that the germ is not the disease and that the disease germ, the vector and the human interact and, therefore, must be considered equally (see Labisch 2004; Oehme/Pfaff 2022).

While contaminated water was the main vector for the cholera epidemics in the 19th century, air is the main vector for the Corona pandemic today. The vector air is certainly a multi-faceted problem. In addition to viruses as pathogens, the air today contains a large number of pollutants that must be taken seriously. It is significant for the discussion here that air and the respiratory tract are closely related. The findings presented here show that the neuropeptide SP has a defense function in the respiratory tract. Therefore, some perspective thoughts follow here with the intention of linking research on "substance P" more closely with research on corona diseases.

A first idea is that the viruses (or pollutants) invading via the respiratory tract are to be understood as stressors. The respiratory tract has the task of recognizing these stressors as such, organizing the local defenses, impeding or blocking further penetration and, if possible, destroying the stressors. In this context, the respective state of the defenses is certainly decisive for the subsequent outcome. It appears that the different rates of COVID-19 infections or the frequencies of "sudden death infant syndromes" correlate with the SP plasma level (see Scholle et al. 1989; Scholle et al. 1990; Mehboob 2017; Mehboob, Lavezzi, Anna 2021). In addition, the experience of the current corona epidemic indicates that children are equally infected with corona but contract corona much less than adults. From the experimental studies with animals and humans described in section 2.2, there is a clear relationship between stress sensitivity and SP levels: Low SP levels = high stress sensitivity (see Hecht et al. 1980; Oehme et al. 1980/2). These findings should be followed up to investigate in adult corona-infected individuals whether the frequency of transition from infection to disease correlates with SP levels in plasma or bronchial lavage.

A second idea derives from the work on aprepitant. As shown above, this SP antagonist, in combination with dexamethasone, is able to improve symptomatology in severe coronary events (see Mehboob 2021). This finding is explained by a reduction in cytokine storming triggered by SP in the deeper pulmonary alveoli. However, the primary response to coronavirus occurs in the upper nasopharynx. Here, SP (antidrome) is also released to trigger defense processes. Since these local processes determine to a large extent the further course of the infection, they should be investigated in depth. Of particular interest would be whether N-terminal dipeptides, in particular Lys-Pro, are cleaved during this local SP release by enzymatic cleavage from $SP_{1\text{-}11}$. For this dipeptide, both stress-protective effects (see sections 2.2 and 2.3) and positive effects in the respiratory tract (see section 3.) have been demonstrated. In addition, Lys-Pro was found to stimulate nerve fiber growth in tissue culture (Kaczyńska et al. 2018).

The third important field of future research for the role of "substance P" in corona infection is probably the role in the penetration of coronaviruses into the brain and the processes then triggered there. The function of SP as a regulatory peptide ("regulide") should be taken as a basis (see section 2. 2). On the one hand, this involves the destruction processes in the brain described briefly in section 7. Here, the NK1 receptor plays a role. The positive results described in the paper with the NK1 antagonist aprepitant can certainly be further extended. However, the N-terminus of the "substance P" molecule, with the opposing effects described in the work, must also be taken into account here – certainly not an uncomplicated but important "new territory".

Overall, a closer connection of research on "substance P" with corona research would most certainly be enriching and could contribute to a closer connection of medical research with environmental research.

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