



Is research on the regulatory neuropeptide “substance P” experiencing a renaissance?

Riffat Mehboob (Lahore), Peter Oehme (MLS) and Gerhard Pfaff (MLS)

(Corresponding author: Gerhard Pfaff)

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Abstract

This article provides a condensed presentation of the authors' activities in the field of “substance P” research from the 1970s to the present day. This period includes the corona pandemic with its various facets up to the current post-corona syndrome. In this article, a link is established between this development and research into the neuropeptide “substance P” (SP). Selected current results, such as the defense function in the respiratory tract, as well as results from several decades ago are considered. These include the role of SP in stress events. Finally, thoughts on the perspective of research on “substance P” are presented.

Resümee

Der vorliegende Beitrag gibt eine komprimierte Darstellung von den Aktivitäten der Autoren auf dem Forschungsgebiet “Substanz P” von den 1970er Jahren bis zum jetzigen Zeitpunkt. In diesen Zeitraum fällt die Coronapandemie mit ihren verschiedenen Facetten bis hin zum aktuellen post-Corona-Syndrom. In dem Beitrag wird eine Verbindung hergestellt -zwischen dieser Entwicklung und den Forschungen zum Neuropeptid “Substanz P” (SP). Dabei werden sowohl ausgewählte aktuelle Ergebnisse wie die Abwehrfunktion im Respirationstrakt berücksichtigt als auch Resultate, die bereits einige Jahrzehnte zurückliegen. Hierzu zählt u. a. die Rolle von SP im Stressgeschehen. Abschließend werden Gedanken zur Perspektive der Forschung an der “Substanz P” aufgezeigt.

Keywords/Schlüsselwörter

Substance P, regulatory peptide, defense and repair function, corona disease, NIH, perspective substance P research

Substanz P, regulatorisches Peptid, Abwehr- und Reparaturfunktion, Coronaerkrankung, NIH, Perspektive der Substanz-P-Forschung

1 Introduction: On the defense function of “substance P” (SP)

In our previous contribution in Leibniz Online “On the role of ‘substance P’ in the respiratory tract in corona infections to the causes of corona-related brain destruction” (see Mehboob et al. 2023a), we had already described the genesis of the present publication. The starting point for it was a scientific event of the Leibniz Society of Sciences in Berlin on October 29, 2021 in Schloss Biesdorf. The speaker there was Wolf-Dieter Ludwig, Chairman of the Drug Commission of the German Medical Profession. His topic was “Drug therapy of COVID-19 and vaccines against SARS-CoV-2: expectations, current results and

uncertainties”. His important closing statement was: “... the next battle against corona is to be waged in the nose.” (see Pfaff/Oehme 2021).

Based on this statement, literature research was carried out, which led to an interesting publication from 2021 with the title “Neurokinin-1 receptor as a potential drug target for COVID-19 treatment” (see Mehboob 2021). The focus of this article was on the attack of coronaviruses in the respiratory tract and the involvement of the neuropeptide “substance P” in the disease process.

A team headed by Peter Oehme had worked on “substance P” in Berlin for many years (see Oehme 1987, 2022; Oehme/Hecht 2017, 2022). It was obviously appropriate to contact the author of the article Riffat Mehboob (founder and CEO of Lahore Medical Research Center LLP, Lahore, Pakistan and known for numerous publications on molecular pathology and neurobiology).

Mehboob started her research on SP in 2011 with Anna Maria Lavezzi, when she studied the cardiorespiratory role of SP in Sudden Infant Death Syndrome (SIDS), sudden perinatal death and still birth (see Lavezzi et al. 2011). Mehboob and Lavezzi examined the immunohistochemical expression of SP in the brainstems of these victims. The caudal trigeminal nucleus region showed SP positivity by immunohistochemistry, and throughout normal development from fetal life to the first postnatal months, there was a gradual rise in the density of SP-positive fibers of the corresponding tract. The morphologic and functional evolution of the human trigeminal nucleus was greatly aided by the delineation of its structure, which had not been extensively studied before. Rather, a large fraction of SIDS victims had a negative or low SP expression in these tract fibers, but a large fraction of abrupt fetal deaths had a high SP-expression. It was concluded that SP has a functional role in the control of autonomic functions and in the early stages of the development of the central nervous system. Furthermore, they proposed a close relationship between the absorption of cigarette smoke in utero and a decreased functional activity of the trigeminal nucleus, which can cause sudden death of the fetus during pregnancy or of the infant in the first months of life. This was supported by the observation of a significant correlation between altered SP staining, sudden unexplained death, and maternal smoking (see Lavezzi et al. 2011).

Later in 2014, some important studies were done on computational analysis of oncogenic properties of Tachykinin-1 gene, which is the gene that encodes SP (see Mehboob et al. 2014). In 2015, she worked on the role of SP in oral squamous cell carcinoma in terms of its diagnostic, prognostic and a possible therapeutic biomarker (see Mehboob et al. 2015). The role of SP in respiratory infections and COVID-19 was not studied much until 2020 when Mehboob and colleagues conducted a clinical trial of NK1R antagonist (Aprepitant) along with a corticosteroid (Dexamethasone) in COVID-19 patients (see Mehboob et al. 2020a). The trial was a huge success and later in 2020 this trial was included in WHO guidelines for the treatment of COVID-19 (see World Health Organization 2020). This treatment was also reported in Thailand News in 2021 (see Thailand Medical News 2021). NK1R, which is the receptor of SP, was also studied in miscarriages in 2020 (see Alwazzan et al. 2020). In 2021, a theory was proposed by Mehboob and Lavezzi, to explain a possible neuropathological explanation of less severity of COVID-19 infection in children on the basis of SP involvement (see Mehboob/Lavezzi 2021). The role of SP in human dental pulp inflammation, pain and breast cancer biopsies was also studied and a strong association was observed between SP/NK1R and disease mechanism (see Mehboob et al. 2020b, 2021). All these series of studies lead to an important study in understanding the respiratory roles of SP including the identification of NK1R antagonist as a promising drug target for COVID-19 treatment (see Mehboob 2021).

Oehme and Mehboob published some more perspectives along with Gerhard Pfaff and Jens Peter von Kries on in-depth exploration of the role of endothelial cells and angiotensin-converting enzyme-II in COVID-19 and associated brain damages (see Mehboob et al. 2023c). These findings shed light into the role of SP in the respiratory tract's defense line and neurological manifestations following COVID-19 infection (see Mehboob et al. 2023a). In addition, the investigation into the role of SP in corona infections and its implications for corona-related brain destruction supports the contention that the SP/NK1R pathway is intricately involved in respiratory viral infection (see Mehboob et al. 2023b).

Research findings and evidences of Mehboob's work in support of this theory of SP involvement in respiratory tract infections including COVID-19 were the symptoms in COVID19 infection and SP nociception, airway hypersensitivity and asthma in both phenomena, variable patterns of COVID-19 disease severity in different age groups, which is also addressed by SP theory, high death rate in COVID-19 patients having comorbidities of diabetes, hypertension and cardiac disorders, viral load correlates with SP secretion. Therefore, it is proposed that SP may be the trigger for cytokine storming during such inflammation (see Mehboob et al. 2023a). SP may be responsible for the initiation of inflammatory pathways and should be explored further. It aggravates the condition due to its over secretion by TG neurons which affects the immune cells as well as other cells in the respiratory tract to release the mediators for cytokine storming, which may be responsible for further complications. The ventilatory role of SP is well-established (see Szereda-Przestaszewska/Kaczyńska 2020).

During the subsequent dialog between Oehme and Mehboob, it became increasingly clear that there are numerous similarities between their fields of work, especially with regard to the function of “substance P” in the respiratory tract. It made sense, therefore, to combine the two areas of work and draw conclusions for the current coronavirus pandemic. With this in mind, the above-mentioned publication in Leibniz Online was published in 2023 (see Mehboob et al. 2023a).

2 Next steps: From the defence function of “substance P” to efficacy in post-corona syndrome

Important parts of her work have been published in the well-known international journal “Frontiers in Neurology” (see Mehboob et al. 2023b). After the publications focusing on the acute symptoms of corona infection and the acute defense function of SP in the respiratory tract, post-corona symptoms increasingly became the focus of public interest.

It seemed, therefore, advisable to compile an up-to-date overview of this subject area. This was taken up in another paper in “Frontiers in Neurology” with the title “Role of endothelial cells and angiotensin converting enzyme-II in COVID-19 and brain damages post-infection” a few months later (see Mehboob et al. 2023c). The work focused on the effect of coronaviruses on endothelial cells – especially in the brain. In connection with this, the post-corona symptoms were discussed, such as abnormal fatigue, significant disturbances of the sleep-wake rhythm, muscle weakness, pulmonary dysfunction, cardiovascular disorders, etc. The mechanism of this post-corona syndrome, the attack of the coronaviruses on angiotensin-converting enzyme II (ACE), was also discussed.

Both publications, which appeared in 2023, met with a great international response. The first paper in “Frontiers in Neurology” was placed on the website of the National Library of Medicine soon after publication, an official website of the United States government.

As feedback on the activities mentioned here, the authors received an invitation from the organizer of the “3rd Edition of World Congress on Virology & Infectious Diseases (WVID 2024)” in June 2024 in Prague for a presentation entitled “The role of Substance P in the

defense line of the respiratory tract and neurological manifestations post COVID-19 infection”.

3 The outlook: Projects for the fight against corona disease

However, competition soon arrived on the scene. Three months after the publication of the first paper in “Frontiers in Neurology”, a paper entitled “Tachykinins and the potential causal factors for post- COVID-19 condition” appeared in one of the most renowned international scientific journals “Lancet Microbe” (see Janket et al. 2023). This paper focused on “substance P”, which belongs to the group of tachykinins. On the other hand, it was a challenge to develop new perspectives.

Therefore, a third project was started. It was entitled “Substance P (SP) – a regulatory peptide with defense and repair functions. Results and projects for the fight against COVID-19”. In December 2023, a paper was submitted to “Frontiers in Neurology” (see Mehboob et al. 2024). The content of the article was no longer just about the acute defense function of SP, but also about repair processes after corona infection. This additional function of SP is based on the concept presented by Oehme as early as 1976 at the Nobel Symposium 37 on “substance P” in Stockholm. It has been shown already at this presentation that the SP-molecule carries various functions and that these functions are encoded in different parts of this peptide consisting of 11 amino acids (see Oehme et al. 1977). The ideas derived from this knowledge led to the working model of “substance P” as a regulatory peptide or regulide (see Oehme et al. 1980a).

Such a regulide has the task of securing homeostasis, i.e., maintaining or restoring disturbed functions. This also includes the restoration of disturbed microcirculation by formation of new blood vessels. Target cells are endothelial cells. The Institute for Drug Research (Institut für Wirkstoffforschung = IWF) of the Academy of Sciences of the GDR in Berlin has worked intensively on this subject. This can be read in detail in the anniversary brochure published in 1986 (see Axt 1985). This work formed the basis for the European patent “Process for the production of wound-healing preparations and such preparations” (see Patent 1984). The patent concerned a modified N-terminal substance P-dipeptide, certainly still interesting for future investigations.

Cultured endothelial cells are suitable for such preparations. Von Kries from the Leibniz Research Institute for Molecular Pharmacology in Berlin, was involved with his staff. This team has an open access technology platform for automated High Throughput Screening (HTS) of cell morphology alterations in response to cell function perturbations either by drug application or by RNA-interference or by Crispr-Cas9 gene editing.

A characteristic of post-corona symptoms is pronounced sleep disturbances. Together with the group of Karl Hecht at the Institute of Pathophysiology of the Charité in Berlin, intensive work was carried out at the IWF on the relationship between SP, stress and sleep. This was certainly pioneering work. The extensive results can be found in summarized form in the “Reflections on Substance P-Research” published by Oehme and Hecht in 2017 and 2022 (see Oehme/Hecht 2017, 2022). Supplementary information can be found in the meeting report published by Akademie-Verlag in 1987 with the lecture by Oehme “Aktuelle Probleme der Peptidforschung”. This meeting report was republished in 2022 by De Gruyter (see Oehme 1987, 2022).

In the opinion of the authors, two aspects should be taken into account in future work on the significance of “substance P”:

Firstly, the coronavirus, or other pathogens, should not be viewed one-dimensionally. The pathogen (virus), transmission medium (vector; e.g., air) and recipient (human) interact and

influence each other. Therefore, all three must be considered for the development of the disease and not the pathogen alone. The leading variable is, therefore, the disease and not the infection.

Mehboob's group is challenging the traditional one-dimensional view of diseases by conducting extensive clinical studies to explore the complex relationships between viruses, transmission media, and human receivers. They want to redefine the main variable as the illness itself, instead of only concentrating on the infectious agent, by using a holistic approach. Recently a study was conducted by Mehboob's group on role of SP/NK1R in dengue patients which is a novel concept and has not been explored before. The results of this study confirmed the hypothesis that SP/NK1R pathway is only involved in respiratory viral infections but not in non-respiratory viral infections such as dengue. However, further studies are required on larger sample size to validate this pilot study (unpublished).

Some of the recent clinical studies that have not yet been published have also found interesting results in this context. In the investigation on the diagnostic and therapeutic potential of SP and Neurokinin-1 Receptor (NK1R) in primary dysmenorrhea, involving NSAIDs and NK1R antagonists, substantial influences on SP/NK1R levels, pain intensity, and severity in participants are detected. Additionally, psychological characteristics such as stress, anxiety, and depression were strongly linked with SP levels, providing valuable insights into the diagnostic role of these neuropeptides and highlighting the efficacy of NK1R antagonists, specifically Dexamethasone and Aprepitant, in alleviating dysmenorrhea-related discomfort. In the research of immunomodulation of the renin-angiotensin system via SP/NK1R in hypertension and cardiac patients, the study found large differences in SP/NK1R levels in hypertensive patients, indicating a possible link with hypertension. However, no significant variations were identified in SP/NK1R levels in cardiac patients compared to the control group. In the investigation of SP and NK1R in diabetes patients with insulin and cortisol, the research observed no significant variations in SP/NK1R levels between diabetic and control groups. NK1R levels varied considerably between men and females, but no apparent relationships were discovered between SP/NK1R and age, cortisol, insulin, or HbA1C levels in diabetes individuals.

Prior papers, particularly the one with NK1R as therapeutic target for COVID-19, demonstrated high associations between SP/NK1R and COVID-19 findings (see Mehboob 2021). These studies showed the intricate link between neuropeptides and viral infections, suggesting they may be key respiratory virus players.

COVID-19 clinical trials also examined SP and NK1R dynamics in infected persons, revealing how these neuropeptides are regulated during respiratory viral infections. These findings support the broader research and contribute to the expanding body of information concerning SP and NK1R in viral respiratory infections. The study on non-respiratory viral illnesses like dengue fever supports the finding that SP levels did not alter much. This dramatic contrast underscores SP and NK1R's distinct role in this situation and supports the idea that they may be involved in respiratory viral infections. This discovery highlights the pathway's particular participation in respiratory viral infections as opposed to its absence in non-respiratory viral conditions.

Mehboob's team is carefully recording its conclusions and learnings from these clinical investigations in order to prepare them for publication. It is anticipated that the upcoming studies will make a substantial contribution to the scientific community's comprehension of the complex linkages involved in the emergence and spread of infectious illnesses. These papers will provide insight into the particular approaches used, the designs of the experiments, and the most important findings discovered during the investigations.

Secondly, the virus should be seen as an external stressor with infectious potential. This makes it possible to make a mental connection with the extensive results of stress research. Here are a lot of links to the results of Oehme and Hecht (see Oehme/Hecht 2014).

Taking these two premises into account, it makes sense to investigate the relationship between

1. susceptibility to corona disease of infected persons,
2. SP levels in the blood, lavage and tissue,
3. chronic stress (e.g., immobilization).

4 A circle is beginning to close

In September 2023, Mehboob was selected as a Senior Research Fellow in NIH, Bethesda, United States and will retain her scientific work opportunities in Lahore. Therefore, a very good combination of experimental work and clinical studies is possible.

This news reminded Oehme of the year 1982. In that year he was invited to give lectures in the USA. The first stage was a lecture on April 12, 1982 at the NIH as part of a seminar¹ on the topic “Modulatory function of substance P”. The chairman of this event was Nobel Prize winner Julius Axelrod.² Among the participants was also William A. (Bill) Krivoy from NIDA's Addiction Research Center in Lexington. Together with him, Oehme published a year later in the journal “Trends in Pharmacological Sciences” essential results of his lecture (see Oehme/Krivoy 1983).

The lecture at the NIH was not the end of the trip to the USA. Afterwards, there was a meeting with the neurophysiologist Robert C. A. Frederickson at Eli Lilly&Co in Indianapolis. Frederickson had published a paper on the effect of SP on the pain threshold in “Science” in 1978 (see Frederickson et al. 1978). In other words, similar results to those published by Oehme's group in “Science” in 1980 (see Oehme et al. 1980b). The presentation in Indianapolis entitled “Substance P as a regulatory peptide” was, therefore, based on both papers.

The third stop during the USA trip of Oehme was the 66th Annual Meeting FASEB³ in New Orleans. He gave a lecture there entitled “Action of Substance P (SP) on stress- induced disorders of behavior and vegetative functions of rat in relation to catecholamine metabolism”.

In summary, it was a very useful stay in the USA with a variety of positive feedback for the research work at the IWF and also for the organization of the scientific life there.

Overall, it is certainly correct in the perspective of SP research not to limit the view only to the relationship of SP to the coronavirus. Such results are relevant for other viruses, other

¹ The NIH Neuroscience Seminar Series features lectures and discussions with leading neuroscientists. Sponsored

by NINDS, NIMH, NIA, NIDCD, NIDA, NICHD, NEI, NIAAA, NIDCR, NHGRI and NC CIH, the series offers seminars on aspects of molecular, cellular, developmental and cognitive neuroscience as well as neuroscience related topics in disease, pain, and genetics.

² Axelrod was an American pharmacologist and neurochemist who, in 1970, received together with U. S. von Euler and Bernard Katz the Nobel Prize in Physiology/Medicine for their work on neurotransmitters. He was elected a Foreign Member of the Academy of Sciences of the GDR in 1984.

³ The Federation of American Societies for Experimental Biology (FASEB) is a non-profit organization of scientific societies in the United States. With a focus on the biological and biomedical sciences, the federation represents scientists in such fields as anatomy, physiology, immunology, biochemistry, molecular biology, toxicology, genetics, and nutrition.

germs or other stressors (e.g., nanoparticles) that enter the respiratory tract and other organs, including the brain, via the airborne vector. Such an approach could lead to a renaissance of SP research. Increasing usability for diagnostics, therapy and prevention in therapy is to be expected.

In her time in the NIH, Mehboob wants to start research on defining the function of heavy chain of mouse class V myosin (Va) in the brain and will make use of new myosin Va conditional knock out (KO) mouse recently developed by the research group of John Hammer. These are actin-based motors that mediate the proper intracellular localization of diverse organelles, mRNAs and proteins. Myosin-Va is encoded by Dilute (*Myo5a*), one of the three class V myosin genes present in mammals (see Sellers/Weisman 2008).

While the earlier work of Hammer’s group used the straight myosin Va knockout mouse revealed a role of myosin Va in synaptic plasticity/motor learning in the cerebellum (see Wagner et al. 2011), those findings cannot explain most of the profound neurological phenotype exhibited by these mice, which includes tonic-clonic seizures, opisthotonos and severe ataxia, resulting invariably in death at ~P21. Mehboob will use a variety of approaches (e.g., crossing the new myosin Va cKO mouse with cre drivers for various neuron and interneuron populations in an effort to zero in those neurons/interneurons most affected by the loss of myosin Va. She will then use a variety of techniques to define in mechanistic terms what myosin Va does in those neurons/ interneurons, and what goes wrong when it is missing. Here future scientific work at the powerful NIH in the USA offers good opportunities for the perspective development in the SP research.

There are now ongoing clinical studies at LMRC, Lahore that are focused on SP. The aim of these studies is to improve the understanding and application of SP to a variety of medical questions and problems.

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E-Mail-Adresse des korrespondierenden Verfassers: pfaff.pigmente@gmx.de