Tachykinins and the potential causal factors for post-COVID-19 condition

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The most prevalent symptoms of post-COVID-19 condition are pulmonary dysfunction, fatigue and muscle weakness, anxiety, anosmia, dysgeusia, headaches, difficulty in concentrating, sexual dysfunction, and digestive disturbances. Hence, neurological dysfunction and autonomic impairments predominate in post-COVID-19 condition. Tachykinins including the most studied substance P are neuropeptides expressed throughout the nervous and immune systems, and contribute to many physiopathological processes in the nervous, immune, gastrointestinal, respiratory, urogenital, and dermal systems and participate in inflammation, nociception, and cell proliferation. Substance P is a key molecule in neuroimmune crosstalk; immune cells near the peripheral nerve endings can send signals to the brain with cytokines, which highlights the important role of tachykinins in neuroimmune communication. We reviewed the evidence that relates the symptoms of post-COVID-19 condition to the functions of tachykinins and propose a putative pathogenic mechanism. The antagonism of tachykinins receptors can be a potential treatment target.

Introduction

SARS-CoV-2 caused COVID-19, resulting in an unprecedented global health emergency. After 3 years of concerted efforts worldwide, the acute phase of COVID-19 is transitioning towards a subacute or chronic form of multisystem pathology termed post-COVID-19 condition or long COVID. Approximately 30–50% of patients suffer persistent symptoms that can manifest after 4 weeks or several months later. Although symptoms vary according to cohort characteristics, the most prominent post-COVID-19 condition symptoms among non-hospitalised patients are ageusia and anosmia, and the most common symptoms among previously hospitalised patients are fatigue and dyspnoea. Among the non-hospitalised patients with post-COVID-19 condition, the most common symptoms are respiratory insufficiency, followed by neurocognitive dysfunction, and metabolic, cardiovascular, and gastrointestinal diseases. In a short follow-up study, the most common symptoms of post-COVID-19 condition 30 days after infection were shortness of breath (37·5%) and fatigue (37·5%), followed by brain fog (30·8%) and anxiety (30·8%).[1] Meanwhile, a large UK biobank study reported that anosmia, hair loss, and sexual dysfunction were the most prevalent PASC symptoms,[2] implicating dysautonomia.[3] A systematic review of 57 studies reported that the most prevalent findings were chest imaging abnormalities (62·2%), general functional impairments (44·0%), fatigue or muscle weakness (37·5%), generalised anxiety disorder (29·6%), and difficulty in concentrating (23·8%).[4] Pulmonary insufficiency, neurological dysfunction, and autonomic impairments were evident in post-COVID-19 condition. On the basis of these reports, we conclude that the common symptoms among moderate to severe COVID-19 cases are pulmonary dysfunction and fatigue, while among mild cases anosmia, brain fog, and anxiety are more pronounced. Most viral infections can cause post-acute sequelae; however, the risk factors or the pathophysiological mechanisms of post-COVID-19 condition are not well delineated.[5] Herein, we summarise the evidence connecting post-COVID-19 condition and tachykinins, propose a theorem that this association might be causal, and present a potential mechanism.

Overview of tachykinins

Tachykinins are a family of small neuropeptides that can rapidly defend the host against noxious stressors,[6] from which the name tachykinin was derived.[7] The nervous system communicates with immune cells so that they can respond quickly and appropriately if invading pathogens are detected. Substance P, the most widely researched of the tachykinins, and neurokinin A are synthesised and released from the peripheral and enteric nerves,[8] and are also expressed by immune cells such as macrophages, eosinophils, lymphocytes, and dendritic cells.[9] Thus, tachykinins are at the nexus between the immune and nervous systems providing cellular communication.[6] Indeed, tachykinins are neurotransmitters and their actions are mediated by binding to three G protein-coupled receptors—namely, neurokinin 1 receptor (NK1R), NK2R, and NK3R. Substance P has the strongest affinity to NK1R, neurokinin A exhibits the highest affinity for NK2R, and neurokinin B for NK3R.[8] However, some cross-reactivities between specific peptides and less favoured receptors have been reported. Additionally, other tachykinins have been identified—namely, neuropeptide K, neuropeptide γ, haemokinin-1, and endokinins. Tachykinin neurokinin 1 receptors are widely distributed in both CNS and peripheral nervous systems.[10] In the CNS, NK1Rs regulate cardiovascular and respiratory functions; in the spinal cord, they regulate nociception and autonomic reflexes.[10]

A study suggested that substance P was synthesised in the cell bodies of vagal sensory ganglia and transported bidirectionally toward the CNS and thoracic and abdominal viscera nerves that are involved in nociception, inflammation, anxiety, and depression.[11] Of note, post-COVID-19 condition displays all of these symptoms and

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it is worth evaluating the evidence that connects tachykinins to post-COVID-19 condition syndromes. Once the causative molecules are identified, then successful prevention or treatment strategies are possible.

Tachykinin functions

Tachykinins are broadly involved in many human physiological and pathological processes in the nervous, immune, gastrointestinal, respiratory, urogenital, and dermal systems.[7] Tachykinins initiate inflammation, nociception, smooth muscle contraction, epithelial secretion, and cell proliferation.[7] They also contribute to multiple disease processes including acute and chronic inflammation, pain, fibrosis, infection, and cancer.[6] Tachykinins are known to be involved in haematopoiesis, venous thromboembolism, and taste perception.[11] Moreover, in the CNS, neurokinin B signalling in the hypothalamus plays an important role in gonadotropin secretion.[12]

NK1Rs are found in the peripheral nervous system, especially in the tissues controlling pain transmission, vasodilation, and cell proliferation. Substance P and its receptor NK1R are present in the brain regions that control the vomiting reflex, the nucleus tractus solitarius, and the area postrema. Subsequently, antagonism against NK1R has been developed for the treatment of chemotherapy-induced nausea and vomiting.[13] NK1R also acts as the regulator of brain homoeostasis and sensory neuronal transmission associated with depression, stress, and anxiety.[13] In a randomised crossover trial, substance P evoked significantly worsening mood and sleep disturbances.[14]

Substance P activation generates pro-inflammatory reactions modulating immune cell proliferation and cytokine production to destroy invading pathogens or noxious stimuli. In these processes, substance P enhances production of interferon-induced protein-10,[15] which is predictive of poor outcomes in acute COVID-19. Furthermore, NK1R and NK3R are present on platelets and substance P binding to these receptors stimulates platelet aggregation.[16] Thus, we can speculate that substance P might be directly involved in the thrombo-inflammation associated with COVID-19. In the context of post-COVID-19 condition, we will discuss the role of tachykinins on pulmonary dysfunction, fatigue, and dysautonomia including anosmia, dysgeusia, depression, and sexual dysfunction, individually.

Tachykinins and pulmonary dysfunction in post-COVID-19 condition

It is well established that sensory nerve stimulation in the bronchial airways causes broncho-constriction and inflammation as observed in asthma. When unmyelinated, C fibre endings in the peripheral nerves are stimulated by allergens, ozone, leukotriene B4, prostaglandin D2 and histamine, neuropeptides, substance P, and other neurokinins and calcitonin gene-related peptide (CGRP) release.[9,17] These peptides trigger vasodilation, oedema, mucus secretion, and leukocyte chemotaxis resulting in pulmonary dysfunction that is observed in post-COVID-19 condition. Notably, both bradykinin and substance P increase vascular permeability and pain responses.[18] Bradykinin has been investigated as a cause for acute respiratory distress syndrome in COVID-19, but substance P has not. However, it has been reported that substance P and NK1R binding correlate with acute lung damage in burn injuries because of increased microvascular permeability, oedema, and neutrophil recruitment. Also, substance P binding increased IL-1β, TNF-α, and IL-6 mRNA expression. More importantly, treatment with NK1R antagonist L703606 disrupted substance P and NK1R signalling and reversed pulmonary inflammation and injury.[19] Additionally, chronic activation of NK1R induced pulmonary hypertension in rats whereas administration of the specific NK1R antagonist CP-96345 significantly attenuated substance P-induced pulmonary hypertension.[20] These lines of evidence suggest the potential role of substance P in pulmonary dysfunction associated with post-COVID-19 condition, and NK1R antagonism might block this pathology.

Bradykinin is an important component of the kallikrein-kinin system and the renin-angiotensin-aldosterone system that plays a crucial role in blood pressure control. As for the cause of impaired pulmonary function associated with post-COVID-19 condition, we postulate that decreased angiotensin converting-enzyme 2 (ACE2) availability due to COVID-19 entry causes insufficient catabolism of Des_Arg9-Bradykinin and increases effector bradykinin. Excess bradykinin increases substance P expression,[21] which compounds inflammation, dysautonomia, and pulmonary dysfunction. Furthermore, sensory nerve activation independently expresses substance P and other tachykinins generating neuroinflammation.[18] Substance P and NK1R are naturally expressed on many inflammatory cells such as mast cells, macrophages, eosinophils, neutrophils, lymphocytes, and dendritic cells when sensory nerves in the lung are stimulated. Indeed, human peripheral monocytes and sputum macrophages might be a major source of the expression of substance P and NK1R in inflammatory airway diseases.[22] Activated substance P releases leukotrienes, increases phosphorylation of protein kinase C and mitogen activated protein kinases, and upregulates E-selectin, P-selectin, IL-1β, and TNF-α.[9] Moreover, substance P and NK1R binding promotes expression of ICAM-1 and VCAM-1 on endothelia and secretion of pro-inflammatory cytokines such as TNF-α and IFN-γ.[23] Several trials of bradykinin receptor inhibition among patients with COVID-19 did not improve the clinical outcomes. The reason could be because substance P also exerts potent pro-inflammatory actions such as increasing pulmonary vascular permeability and oedema, which

results in influx of protein rich fluid in the alveoli leading to acute respiratory distress syndrome independent of bradykinin.[24] Therefore, blocking bradykinin alone might not be sufficient to prevent respiratory dysfunction in COVID-19.

Tachykinins and fatigue in post-COVID-19 condition

Fatigue after viral infections has been well recognised; however, the mechanism is not clearly defined. It was suggested that fatigue following viral infection was due to neuroinflammation and expression of IFN-α, which causes fatigue-like symptoms by suppressing the serotonergic system.[25] Additionally, substance P is coexpressed with serotonin[26] and both can counter-balance each other.[26] Both serotonin and substance P modulate breathing, which explains their coexistence in numerous respiratory tissues including the lungs.[27]

The extreme fatigue in post-COVID-19 condition could also be due to dysautonomia, which causes lower heart rate and poor oxygen saturation during peak exercise.[28] Nevertheless, the mechanism of how dysautonomia develops is unclear. We postulate that substance P expressed in the peripheral nervous system and its action potential propagates antidromically to the CNS.[29] Notably, NK1Rs are widely distributed in both the central and peripheral nervous system.[10] Furthermore, reports show that substance P targets sympathetic neurons in the paraventricular nucleus while sympathetic nerve fibres are innervated into all lymphoid organs (bone marrow, thymus, spleen, and lymph nodes) providing a communication link between the CNS and immune responses.[30] Thus, it is possible that immune responses in the periphery stimulate substance P and other tachykinins that can lead to dysautonomia.

Tachykinins and dysautonomia in post-COVID-19 condition

The high prevalence of anosmia among patients with COVID-19 is well documented and estimated at approximately 38% and dysgeusia at 36·5%. Anosmia and dysgeusia are innate immune-related and not adaptive immune-related as previously reported. Tachykinins are involved in innate immune defence by mobilisation of immune cells to the site of inflammation and by enhancing the expression of cytokines.[9] Cytokines and inflammation have been implicated in the development of depression and anxiety.[31]

Substance P, neurokinin A, and neurokinin B are active partners in neurological functions. Substance P and neurokinin A are present in nociceptive sensory fibres expressing transient receptor potential cation channel, subfamily V, member 1.[32] These sensory fibres are found in close proximity to the taste buds. Thus, anosmia and dysgeusia could be related to the presence of substance P and neurokinin A.

Corticotropin releasing factor and substance P coexist in the bed nucleus of the stria terminalis and neurons, which might be a part of the amygdaloid nucleus lower-brainstem pathways.[33] Substance P inhibits adrenocorticotropin release in vivo in rats[34] and spinal NK1R modulates autonomic reflexes in humans.[10] These facts support our rationale that tachykinins regulate dysautonomia in post-COVID-19 condition.

Tachykinins and sexual dysfunction in post-COVID-19 condition

The UK Biobank report of hair loss and sexual dysfunction in post-COVID-19 condition[2] might be attributable to substance P. In an earlier organ culture study, substance P was shown to be responsible for hair loss via mast cell degranulation on the hair follicle connective tissue sheath.[35] In another study, women who reported changes to their menstrual cycle were more likely to report fatigue, headache, body aches, and shortness of breath.[36] These are well recognised post-COVID-19 condition symptoms and the menstrual cycle disturbance could be referable to neurokinin B dysfunction. Indeed, the loss-of-function mutations in the genes encoding either neurokinin B (NKB) or its receptor NK3R result in hypogonadotropic hypogonadism.[37] Several studies have implicated NKB and NK3R as essential elements of the human reproductive axis.[37] Some neurons in the hypothalamic infundibular (arcuate) nucleus form an important reproductive regulatory circuit and are steroid-responsive. Additionally, NKB, NK3R, and oestrogen receptor-α are coexpressed.[37] Other studies show that 97% of all neurokinin B neurons were immunoreactive for oestrogen receptor-α and that neurokinin B-immunoreactive fibres were found in close proximity to gonadotropin-releasing hormone neurons and fibres.[38] Essentially, all neurokinin B neurons express oestrogen receptors.[38] These observations further support the hypothesis that tachykinins are associated with post-COVID-19 condition and might explain the female dominance in post-COVID-19 condition. Another study observed lower cortisol levels in the post-COVID-19 condition group than in the control group, which further confirms our rationale that substance P dictates autonomic dysfunction in post-COVID-19 condition.[39]

Tachykinins at the neuroimmune junction in post-COVID-19 condition

In several studies, a predominance of non-traditional or non-standard monocytes that are $CD14^-$ and $CD16^+$ was reported.[39] Traditional monocytes mainly engage in phagocytosis and show almost no inflammatory action. In contrast, non-standard monocytes display inflammatory characteristics upon activation.[40] CD16 is an Fcγ III receptor and is a marker of infected monocytes.[41] CD16 positivity in monocytes suggests that the host immune system might not adequately respond to viral infections.[41] It has been reported that monocytes opsonised with SARS-CoV-2 virus died of pyroptosis. This form of programmed cell death is highly inflammatory and occurs most frequently in intracellular

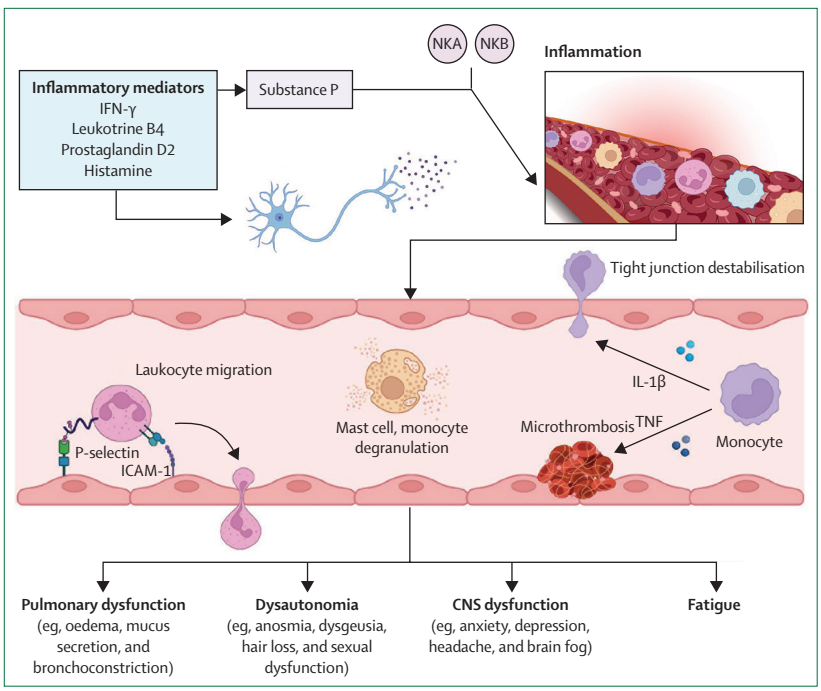

Figure: **Tachykinins, neuroinflammation, and vascular inflammation in potential post-COVID-19 condition pathogenesis**
NKA=neurokinin A. NKB=neurokinin B.

pathogens such as viral, fungal, or protozoan infections. Pyroptosis generates abundant IL-1β, IL-1RA, and IL-18. Indeed, it has been reported that infected monocytes aborted SARS-CoV-2 infections while expressing multiple antiviral and pro-inflammatory cytokines including INF-α, INF-β, TNF-α, IL-1β, IL-6, and IL-10.[42]

Monocytes and tachykinins appear to be involved in SARS-CoV-2-related inflammation. Substance P enhances CCL5-induced chemotaxis and intracellular signalling in human monocytes,[43] and substance P stimulated production of inflammatory cytokines IL-1β, IL-6, and IL-8 in vitro.[44] With COVID-19, substance P and other tachykinins cause increased microvascular permeability, oedema, and pain, which are the cardinal signs of inflammation. Sensory neurons in damaged tissue release substance P and the neuropeptide CGRP that lead to degranulation of mast cells, vasodilation, and chemotaxis of immune cells. These are the examples of neuroinflammation, which is the collaboration between nervous and immune systems.

Additionally, elevated levels of non-traditional monocytes might be a sign of increased inflammation as non-traditional monocytes have been described as the main producers of pro-inflammatory cytokines IL-1β and TNF-α.[40] COVID-19-related cytokine release syndrome is characterised by IFN-γ, not type I interferons, which strongly suggests that IFN-γ is pro-inflammatory. Several in-vitro studies have shown that substance P induces IFN-γ expression. Together, these data indicate that endogenous substance P might be an important molecule that links together neurohormonal stimuli, inflammation, and immunity (figure).

Tachykinins in nociception

Although the peripheral nervous system and CNS can express substance P by nociceptor activation, the causes of substance P expression from infection are not well delineated. In an in-vitro study, primary human nasal cells were treated with TLR7 agonists to mimic viral insults, which resulted in substance P release from the sensory neurons within 15 min.[45] This study suggests that viral infection can release substance P.[45]

Headache that is associated with post-COVID-19 condition might be attributable to CGRP and substance P. These neuropeptides are simultaneously released from nociceptive C-fibres and collaborate in pain perception via complex interactions.[17] Neurokinin A was also observed in C-fibres and small neurons where it colocalises with substance P. Thus, CGRP, substance P, and neurokinin A all appear to contribute to nociception and headache associated with post-COVID-19 condition.[46]

Substance P can induce smooth muscle contraction and inflammation in the gut and plays a crucial role in diarrhoea, nausea, abdominal pain, and vomiting in post-COVID-19 condition, as a key neurotransmitter in the brain–gut axis.[47] Earlier studies reported that substance P was implicated in inflammatory bowel disease,[9] and others have suggested that gut microbiome might be involved in post-COVID-19 condition. However, dysbiosis occurs during inflammation. We have assembled the prevalent symptoms of post-COVID-19 condition and the evidence that links them to the function of tachykinins in table 1.

Risk factors for post-COVID-19 condition symptoms

Obesity is associated with substance P expression. Indeed, high BMI was one of the factors observed in neurological symptoms in post-COVID-19 condition and elevated substance P levels.[48] Numerous studies reported that obesity is a strong risk factor for acute COVID-19 and post-acute COVID-19. In obesity, adipose tissue becomes the site of pathological immune cell activation, causing chronic low-grade systemic inflammation.[49] Obesity also induces hypercoagulability and contributes to thrombotic outcomes in COVID-19.[50]

Immunologically, obesity induces natural killer cell proliferation and IFN-γ production, which in turn triggers differentiation of pro-inflammatory macrophages and promotes insulin resistance.[51] Specifically, obesity pushes normally homoeostatic adipose tissue to the type I inflammatory state characterised by IFN-γ.

In a 3-year-long clinical intervention, successful weight loss showed significantly reduced insulin, triglycerides, low-density lipoprotein cholesterol, and leukocyte count. Moreover, IL-1β, IL-6, and urinary 8-epi-prostaglandin F2α were also reduced.[52] This study shows that obesity induces

cytokines and inflammatory mediators, which exacerbate COVID-19-related symptoms. Moreover, the substance P and NK1R complex was reported to alter adipose tissue responses to a high-fat diet and insulin action in a murine model.[53] Mesenteric fat from NK1R knockout mice fed with a high-fat diet has reduced stress-activated protein kinase compared with wild-type mice. Also, when challenged with glucose, NK1R knockout mice removed glucose from their circulation more efficiently than wild type.[53] These results suggest that substance P and its receptors regulate obesity-related energy metabolism.

Another lifestyle factor that increases substance P expression is cigarette smoking. Chronic smoking enhances tachykinin synthesis and airway responsiveness.[9] Not only current smoking, but also second-hand tobacco smoke exposure in children increases the risk of asthma and sudden infant death syndrome.[54] In primates, tachykinin and NK1R-related neuroplastic dysfunction was observed after second-hand tobacco smoke exposure in the neurons of the nucleus tractus solitarius.[54] Taken together, obesity and smoking both affect substance P expression and might also have an effect on post-COVID-19 condition symptoms.

Next, endogenous factors can increase the risk of substance P expression and post-COVID-19 condition. Angiotensin (1–7) attenuates nociceptive action by substance P.[55] With COVID-19 there is reduced ACE2 availability due to COVID-19 entry and angiotensin (1–7) levels are lower. The reason could be that ACE2 cleaves angiotensin 1–8 (AT II) to produce angiotensin (1–7). In addition, neprilysin also cleaves angiotensin I (AT 1–10) and angiotensin 1–9 and generates angiotensin (1–7). Low levels of neprilysin will decrease angiotensin (1–7) while increasing its substrate substance P, which has strong nociception and pro-inflammatory actions. In this regard, neprilysin can be considered anti-inflammatory as we have reported.[56] Notably, smoking decreases neprilysin levels as do cardiac medications called angiotensin receptor and neprilysin inhibitors.

	Role of tachykinins	References
Pulmonary dysfunction	Substance P releases histamine, prostaglandins, and leukotrienes, and promotes E-selectin, P-selectin, IL-1β, TNF-α, and IFN-γ expression leading to vascular permeability, oedema, and mucus secretion; substance P induces bronchoconstriction	9, 16, 19, 20, 22–24
Fatigue	IL-1β and INF cause fatigue-like and depression-like symptoms; dysautonomia leads to low heart rate and pO_2, resulting in fatigue and muscle weakness	10, 25, 26, 28, 73
Anosmia and dysgeusia	Substance P and neurokinin A in olfactory and taste sensory fibres might contribute to anosmia and dysgeusia; related to dysautonomia	9, 32, 33, 73
Anxiety, depression, and the inability to concentrate	Tachykinins are distributed widely in CNS and peripheral nervous system causing nociception, inflammation, anxiety, and depression; immune activation (IL-1β) causes depression	9–11, 14, 31, 94
Sexual dysfunction, hair loss, and other dysautonomia symptoms	Tachykinins leads to dysautonomia then sexual dysfunction and hair loss; all neurokinin B neurons express oestrogen receptors that lead to female dominance	33–38
Nociception, headache, and gastrointestinal pain	Substance P, neurokinin A, and calcitonin gene-related peptide contribute to nociception and are co-released from nociceptive C-fibres; angiotensin (1-7) attenuates the nociception by substance P; low neprilysin will increase nociception by substance P; smoking and some cardiac medicines lower the neprilysin level	7, 10, 11, 12, 32, 33, 17, 46, 47, 55, 56

Table 1: **Prevalent post-COVID-19 condition symptoms and correlated tachykinin functions**

Potential mechanisms of post-COVID-19 condition related neurological symptoms

Several theories have been proposed to describe the pathogenic mechanisms of post-COVID-19 condition-related neurological symptoms. The first line of thought is that infected monocytes transmit the virus to the CNS. However, numerous studies have reported that SARS-CoV-2 viral invasion of the CNS is rare.[57,58] The second theory is that autoimmune responses due to molecular mimicry between pathogen and host proteins cause post-COVID-19 condition. However, reports on prototypical antinuclear antibody are conflicting. Further studies investigating COVID-19-specific autoantibodies might be necessary to establish the autoimmune aetiology for post-COVID-19 condition.

Rather than autoimmunity, what Hewitt[59] proposed previously seems more plausible. It was suggested that viruses generate proteins that can interfere with antigen presentation by MHC class I molecules. Viruses utilise tactics such as peptide translocation that use the transporter involved in antigen processing or by degradation or translocation of the molecules in MHC class I. More importantly, viruses achieve this subversion with the host's own proteins or trafficking mechanism. This seemingly autoimmune-like process can cause antigen presentation failure leading to chronic inflammation.[59]

We and others consider that immune dysregulation following impaired resolution of inflammation from acute COVID-19 generates lingering inflammation at the peripheral nerve endings and might spread to the CNS. This is the basic underpinning of neurological symptoms in post-COVID-19 condition.[60,61] This theory is supported by the fact that patients with HIV are reported to have higher substance P in plasma than people without HIV[62] and that they also experienced neurogenic inflammation, neurological disorders (pain, depression, and anxiety), and platelet aggregation similar to patients with post-COVID-19 condition. Meanwhile, the use of specific NK1R antagonists such as aprepitant alleviated the symptoms caused by substance P and NK1R binding.[63]

Mechanisms of lingering inflammation in post-COVID-19 condition

Normal viral clearance requires a sequence starting with viral recognition[49] then destruction by the innate immune system, which responds rapidly by expressing type I interferons and other cytokines including IL-1, IL-18, and

IL-6 to suppress viral replication.[64] IFN-γ, in collaboration with type I interferons, also participates in viral suppression by generating nitric oxide, which not only inhibits virus replication, but also induces vasodilation and inflammation. Moreover, IFN-γ plays a crucial role in antigen presentation to ensure that the adaptive immune

	Study design and sample size (n)	Predictors of post-COVID-19 condition	Biomarker correlation to tachykinins	Supporting references
Al-Jassas et al (2022)[74]	Patients with COVID-19 (n=60) *vs* healthy controls (n=30)	IL-6, IL-10, CRP, and low SpO_2 were associated with depression, anxiety, and myalgic encephalomyelitis/chronic fatigue syndrome	Study supports the neuroimmune collaboration; substance P contributes to neuroimmunity	9–11, 25, 28
Barthélémy et al (2022)[75]	Self-reported survey of Twitter users (n=956)	Never been hospitalised (95% of the cohort), female, and smokers	Predictors are related to females and smoking, which increase substance P expression	9, 37, 38, 54
Bizjak et al (2022)[76]	Inpatients (n=151) *vs* controls (n=302)	Kyn related to IL-6 and CRP; in long COVID, Kyn was a significant predictor, but CRP was not	Substance P promotes IL-6 expression and can increase Kyn	23, 44, 67
Captur et al (2022)[77]	Nested case-control study; cases (n=54) *vs* controls (n=102)	ICAM-1 and E-selectin were higher in patients with obesity	Obesity upregulates substance P; substance P promotes ICAM and E-selectin expression	9, 49–53
Crudele et al (2022)[78]	In-vitro study of respiratory, intestinal, and liver epithelial cells	Smoking leads to inflammation, which remains after viral clearance; this might cause long COVID-19	Smoking elicits substance P expression and inflammation	9, 54
Daitch et al (2022)[79]	Prospective cohort study (n=2333)	Fatigue, dyspnoea, female, and obesity	All predictors correlated with substance P	9, 28, 36–38, 49, 53
Freedberg and Chang (2022)[80]	Review	ANA positivity predicted long COVID; heartburn, constipation, diarrhoea, and abdominal pain	Diarrhoea and abdominal pain can be attributable to substance P	8–10, 47
García-Abellán et al (2022)[81]	Prospective follow-up (n=154)	ANA positivity was not significant; women and smokers were significant predictors	Females and smoking are associated with substance P expression	9, 36–38, 54
Kruger et al (2022)[82]	Post-COVID-19 condition of 1 year duration; cases (n=99) *vs* controls (n=29)	IL-6, D-dimer, fibrinogen, and plasma kallikrein	Substance P promotes IL-6 expression; substance P releases renal kallikrein	44, 17, 53, 68
Liang et al (2022)[83]	Review	IL-6 leads to blood–brain barrier disruption; IL-1β leads to depression; unresolved inflammation can cause post-COVID-19 condition	Substance P leads to IL-6 expression resulting in blood–brain barrier permeability; substance P promotes IL-1β expression leading to depression; we concur with Liang that unresolved inflammation is the cause for post-COVID-19 condition	14, 18, 44, 50, 52, 55
Maes et al (2022)[84]	Cases (n=86) *vs* controls (n=39)	IL-1β, IL-18, and SpO_2	Substance P promotes IL-1β expression and decreases SpO_2 via dysautonomia	28, 31, 44, 50, 67
Margalit et al (2022)[28]	Nested case-control study; cases (n=66) *vs* controls (n=75)	Lower heart rate, low O_2 consumption during exercise, depression, and insomnia	Substance P lowers blood pressure, lowers O_2 consumption, low mood, and causes depression via dysautonomia	9, 28, 31, 54
Menezes et al (2022)[85]	Cases (n=108) *vs* controls (n=112)	No comorbidities predicted long COVID-19 except obesity	Obesity increases substance P expression	48–53
Novak et al (2022)[86]	Cases (n=30) *vs* controls (n=11)	Small fibre neuropathy, dysautonomia, pain, and IL-1β	Small fibre neuropathy, pain, dysautonomia, and IL-1β are all associated with substance P	18, 44, 54, 67
Patel et al (2022)[5]	Cases (n=23) *vs* controls (n=69)	Angiopoietin-1, P-selectin, female, and no treatment for COVID-19	Substance P promotes P-selectin expression and induces angiogenesis; substance P colocalises with oestrogen receptor	9, 36–38, 90, 91
Schultheiß et al (2022)[87]	Cohort study (n=318)	No autoantibodies; IL-1β, IL-6, and TNF	SP promotes IL-1β, IL-6, and TNF expression	44, 50, 54, 67
Son et al (2022)[88]	Cases (n=34) *vs* controls (n=22)	Detectable autoantibodies; TNFα, D-dimer, and IL-1β strongest markers at 12 months	SP promotes TNF-α and IL-1β expression	23, 44, 50, 67
Zis et al (2022)[89]	Cross-sectional study; cases (n=57) *vs* controls (n=33)	Female dominance; pain in the lower back, joints, and neck	Tachykinins promote oestrogen receptor expression and nociception	11, 12, 36–38

ANAs=antinuclear autoantibodies.CRP=C reactive protein. Kyn=kynurenine. SpO_2=oxygen saturation.

Table 2: **Studies identifying predictors of post-COVID-19 condition attributable to tachykinins**

system will take over the task of eliminating residual viruses and develop memory to safeguard against future infection. Once adaptive immunity is adequately activated, T cells eliminate remaining virus-infected cells, B cells induce memory, and innate immunity is downregulated.[65] Due to viral evasion tactics,[59] if this transition is less than optimal, hyperinflammation persists and tissue damage can occur by persistent innate immune activation.[65] We theorise that post-COVID-19 condition is an example of this suboptimal transition from innate to adaptive immunity leading to subsequent immune dysregulation and inflammation. Following acute responses, incomplete resolution of inflammation can lead to chronic inflammation, scarring, and eventual loss of tissue function.[66]

Another example of suboptimal clearance of infection causing chronic inflammation is granuloma formation. In granulomas, substance P increases IFN-γ release and neuroinflammation.[61] IFN-γ is the primary activator of macrophages and natural killer cells. Natural killer cells are involved in antigen presentation in viral infection; therefore, IFN-γ and substance P are the linking molecules between innate and adaptive immune transition. Moreover, substance P and haemokinin-1 upregulate IFN-γ production by human memory $CD4^+$ T cells and trigger IL-1β, IL-6, and TNF-α production.[67] Notably, these cytokines are highly pathognomonic in COVID-19 and post-COVID-19 condition. Conversely, cytokines IL-4 and IFN-γ upregulate substance P receptor expression.[68] These results suggest the reciprocal relationship between substance P and IFN-γ, which may be associated with post-COVID-19 condition.

IFN-γ induces Fc gamma RIII (CD16) expression.[69] We postulate that substance P stimulates immunocytes towards pro-inflammatory phenotypes and produces neurogenic inflammation. This neuroinflammation can propagate via the CNS and cause neurological pathologies of post-COVID-19 condition. The propagation of peripheral neuroinflammation to the CNS takes several pathways. One pathway is that SARS-CoV-2 virus enters the human body via the oral and nasopharyngeal mucosa and reaches the trigeminovascular system and expresses substance P, neurokinin A, and other neuropeptides.[11] These neuropeptides are released from the trigeminovascular system directly into the cranial circulation[70] and cause CNS inflammation. Another pathway is that SARS-CoV-2 viruses damage the olfactory nerve-endings causing anosmia and inflammation on the olfactory nerve. This olfactory inflammation is propagated to the CNS via the olfactory bulb, which is the gateway to the CNS.[71] Moreover, substance P and CGRP are highly expressed in the nasal epithelium and trigeminal ganglion cells with sensory endings in the nasal epithelium and their branches reaching directly into the olfactory bulb.[72] The entry receptor for SARS-CoV-2 ACE2 facilitates neurotropism, which enhances dysautonomia in patients with long COVID. Patients with anosmia persisting over 3 months after COVID-19 diagnosis showed extensive destruction of the olfactory epithelium leading to dysautonomia and expression of ACE2 antibodies, which enhances a persistent immune activation.[73] These two pathways appear to offer a patent access for inflammation to reach the CNS.

Recent developments and future directions

To confirm our hypothesis that tachykinins are a potential cause for post-COVID-19 condition, we searched PubMed with search terms: "post covid" OR "long covid" or "post-acute sequelae of covid" and combined this with a separate search with the terms "substance P" OR "neurokinin A" or either "neurokinin B" OR "tachykinins" OR "calcitonin gene related protein". We retrieved only two references, which we already had found. So, we searched with terms: "blood markers" OR "biomarkers" or either "serum markers" OR "predictors" combined with post-COVID-19 condition search results. Among the results we reviewed the 100 most relevant references and evaluated whether the biomarkers presented were related to tachykinins (table 2). The results were consistent with what we have reported in this review—namely, obesity, female sex, IL-1β, IL-6, and TNF-α were predictive of post-COVID-19 condition, all of which are highly correlated with substance P. Additionally, angiogenesis markers angiopoietin 1 and P-selectin, were reported to be significant predictors of long COVID.[5] This study indirectly supports our theory that substance P can be the causal factor for post-COVID-19 condition because previous studies have shown that substance P induces angiogenesis.[9,90] Additionally, it has been reported that substance P stimulates neovascularisation in vivo and also in cultured endothelial cells whereas NK1R antagonism blocked angiogenesis by substance P.[91]

Future longitudinal studies that could establish a causal relationship between antecedent substance P levels and expectant post-COVID-19 condition should be conducted. If causality is established, a randomised trial of tachykinin inhibition as the post-COVID-19 condition treatment target would be a reasonable next step. A recent case report showed promise indicating that the NK1R antagonist aprepitant administered for 4 days can alleviate the symptoms of pain, asthenia, and psychomotor retardation in post-COVID-19 condition.[92]

Contributors

S-JJ, IP, DDF, and EPD were responsible for researching data for this Personal View. The study was designed by S-JJ, FT, HAC, and EPD. S-JJ, DDF, AEB, DS, FT, IP, and EPD wrote the article. S-JJ, DDF, AEB, DS, FT, IP, HAC, and EPD contributed to the report of the content, reviewed and edited the manuscript before submission, and approved submission for publication.

Declaration of interests

EPD holds an advisory and consultant role with Abbott Diagnostics and Imaware Diagnostics. All other authors declare no competing interests.

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