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Neurokinin-1 Receptor as a potential drug target for COVID-19 treatment

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ABSTRACT

Novel Coronavirus infection (COVID-19) has become a pandemic in these days. It is an acute respiratory and infectious disease with no known etiology and treatment. It is continuously causing losses of precious lives and economy at a global scale on daily basis. It is the need of the hour to find more treatment strategies by either developing a drug or to boost the immune system. This opinion article aims to provide Substance P (SP) as a possible cause of the initiation of cytokine storm developed in COVID-19 infection and to suggest Neurokinin-1 Receptor (NK-1R) antagonist, Aprepitant, as a drug to be used for its treatment. This perspective will provide directions to the Biomedical scientists to explore SP and NK-1R and prepare a drug to alleviate the symptoms and cure the disease. It is very important to work on this perspective at earliest to reach to some conclusion regarding the therapeutic intervention. Clinical studies may also be conducted if proven successful. SP is a neurotransmitter and neuromodulator, released from the trigeminal nerve of brainstem as a result of nociception. It is directly related to the respiratory illness as in COVID-19 infection. It is responsible for the increased inflammation and the signature symptoms associated with this disease. It is the main switch that needs to be switched off by administering Aprepitant along with glucocorticosteroid, dexamethasone.

1. Introduction

Coronavirus infection (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), appeared to have high infectious rates and relatively high mortality [1]. It was reported in Wuhan, China in December 2019. Since then it is spreading globally by human to human transmission and declared as "Pandemic" by WHO on 11th March, 2020 [2]. It has caused more than 100 thousand mortalities worldwide in just initial 4 months. In most complicated cases of COVID-19 infection, the clinical manifestations included fever, cough, fatigue, muscular pain, sputum production, loss of smell, shortness of breath, joint pain, sore throat, head ache, vomiting and pink eyes [3,4]. In severe cases it may lead to respiratory failure, organ failure, and eventually death [5].

Whole world is in locked down, in a state of fear, facing a biggest pandemic of 21st century and economical losses. Different clinical trials are undergoing to evaluate the anti-viral and anti-inflammatory effects of certain drugs. Here, we propose that SP via its tachykinin receptor, NK-1R is responsible for inflammation in COVID-19 infection. It is actually the main trigger which further activates the immune system. If blocked by Aprepitant, it may stop the cascade of inflammation and hence, the infection too (graphical abstract). The virus itself is not causing mortality but the respiratory failure, organ failure or heart attack due to cytokine storming. There are certain evidences discussed below to support this idea.

1.1. Substance P and Neurokinin-1 Receptor

SP was first discovered by V Euler and Gaddum in 1931 as a brain-gut hormone [6]. It is an undecapeptide which has role as neurotransmitter, neuromodulator and neurohormone, encoded by Tachykinin-1 gene (TAC-1) [7]. It is released from the fifth cranial nerve, the trigeminal nerve (TrN) and gives innervation to the orofacial region. SP and NK-1R are highly expressed in the enteric, central [8] and peripheral nervous system as well as cardiovascular system. It can also be expressed by immune cells such as leukocytes, lymphocytes, monocytes and macrophages [9,10]. SP has autocrine, paracrine and endocrine functions and can affect the distant cells e.g. smooth muscle cells, fibroblasts, endothelial cells and muscle cells. It is a chemokine that regulates the immune and endocrine system and stimulates them to release cytokines in respiratory tracts after binding with NK-1R [11]. It is involved in several pathological conditions and inflammation [12].

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NK-1R is a 7-transmembrane domain, G-protein coupled receptor with highest affinity for SP. Its full length form has 407 amino acids. It is present on many cell types in the body including the vascular endothelium and lymphatics, fibroblasts, white blood cells, neurons, cardioventilatory regulatory centers and phrenic nuclei controlling the diaphragm and respiration after binding to SP [7]. It is localized in brainstem nuclei controlling the rhythmic control [13]. SP/NK1-R complex, once formed, initiates a signaling cascade and produces inositol 1,4, 5-trisphosphate (IP3) and diacylglycerol (DAG) [14]. Importantly, the macrophages and other immune cells produce inflammatory mediators by activation of NF-kB and releases the pro-inflammatory cytokines [15].

1.2. Evidence of possible involvement of substance P/ Neurokinin 1-Receptor in COVID-19 infection

1.2.1. Common orofacial symptoms in COVID-19 infection and SP nociception

Common and initial symptoms of COVID-19 infection includes sore throat, loss of sense of smell and taste, pain in eyes, headache and flue [3] and similar functions are carried out by SP once it is released from trigeminal ganglion via TrN. It provides somatosensory innervation to the orofacial region and has three branches: ophthalmic (V1), maxillary (V2) and mandibular (V3). So any alteration in its secretion in response to viral infection may result in symptoms in orofacial region [16] (Fig. 1).

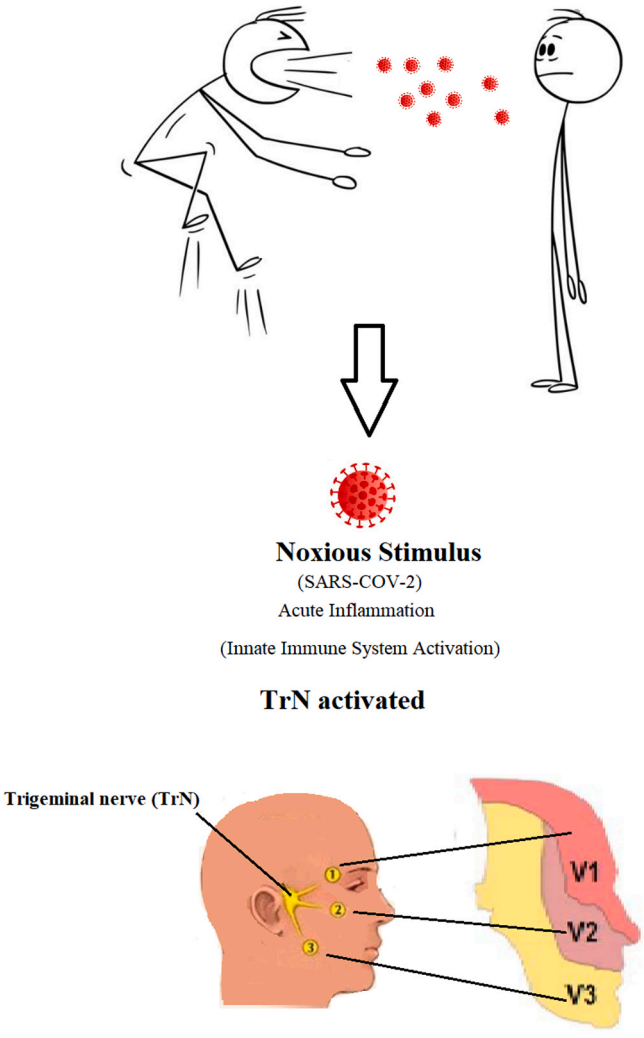

Fig. 1. Schematic representation of Trigeminal nerve innervation in orofacial region. Noxious stimulus such as Corona virus enters through nose, mouth and eyes and reaches the trigeminal ganglion where it initiate the release of Substance P.

1.2.2. Involvement of SP in cough/airway hypersensitivity/asthma which are symptoms of COVID-19 infection as well

Vagal C fibers in larynx and upper airways secrete SP and cause cough. NK-1R antagonists are found to be helpful in reducing the refractory cough frequency [17,18]. A study was conducted to assess the role of SP in clinical cough in humans. Serum SP levels were observed to be elevated in patients with persistent cough as compared to healthy controls. It was attributed to airway sensitivity in asthmatic cough [19].

1.2.3. Differential severity of COVID-19 infection in different age groups as addressed by the SP perspective

The mean age of COVID-19 patients was 45 years in a study conducted in China in which 161 patients were enrolled. Disease severity was found to be associated with older age [3] between 70 and 80 years and above [5]. So far, only few cases have been reported in children but with no complications, disease severity and deaths. In my previous studies related to sudden death [16,20], I have reported that SP expression, if raised before birth may lead to fetal death, if decreased after birth may cause sudden infant death while in adults, higher SP expression may cause death [21]. Keeping this in view, higher SP may be fatal for older age groups which may be the case in COVID-19 patients. While children are found to be protective, because if SP is raised in them, they have no serious concerns.

1.2.4. SP/NK-1R theory addresses the high mortality rate in COVID-19 patients with hypertension, blood pressure and diabetes

Most affected patients with COVID-19 infection are observed to be those who already had co-morbidities such as hypertension (HTN), diabetes mellitus (DM), renal, hepatic and cardiovascular conditions [3, 22]. DM and HTN patients have increased risk of cardiovascular diseases. They use medicines such as Dipeptidyl peptidase-4 (DPP4) and Angiotensin-converting enzyme (ACE) inhibitors to reduce the cardiac conditions by vasodilating the vessels and lowering the blood pressure (BP) [23]. ACE is usually located in lung capillaries, renal and endothelial cells [24]. It may act as the receptor for SARS-COVID-19 [25]. SP also causes vasodilation. Elevated SP levels as a consequence of COVID-19 infection may further dilate the vessels, hence, more blood will be pumped by heart and more cardiovascular risk, leading to heart attack in complicated cases. It may also cause a lowering in BP, resulting in organ failure in severe cases [26]. It may explain, one of the possible underlying mechanism for mortalities due to COVID-19 infection.

1.2.5. Viral load correlates with the SP secretion

SP is secreted by the immune cells and is positively correlated with the viral load. SP may facilitate the replication of viruses by upregulation of CC Chemokine Receptor 5 (CCR5), necessary for HIV infection [15,27]. If there is more infection, there will be more inflammation and elevated levels of SP. It can be used as a diagnostic and prognostic marker for COVID-19 infection.

1.2.6. SP initiates cytokine storming during inflammation-a possible mechanism in COVID-19 infection too

SP has immunomodulatory role and is an important link between nervous and immune systems [28]. SP initiates the release of all cytokines which in turn, further stimulates SP and the NK-1R [29]. SP boosts the inflammation in all three possible ways: First, by vasodilation and increasing the vascular permeability, Second, by leukocyte extravasation and third, by directly acting on native cells and the foreign invaders to activate their immune characteristics (Figs. 2,3) [30]. During inflammation, SP is secreted by immune system such as macrophages, dendritic cells, lymphocytes and neutrophils as well as other cells such as endothelial cells [11]. SP activates the immune cells to produce

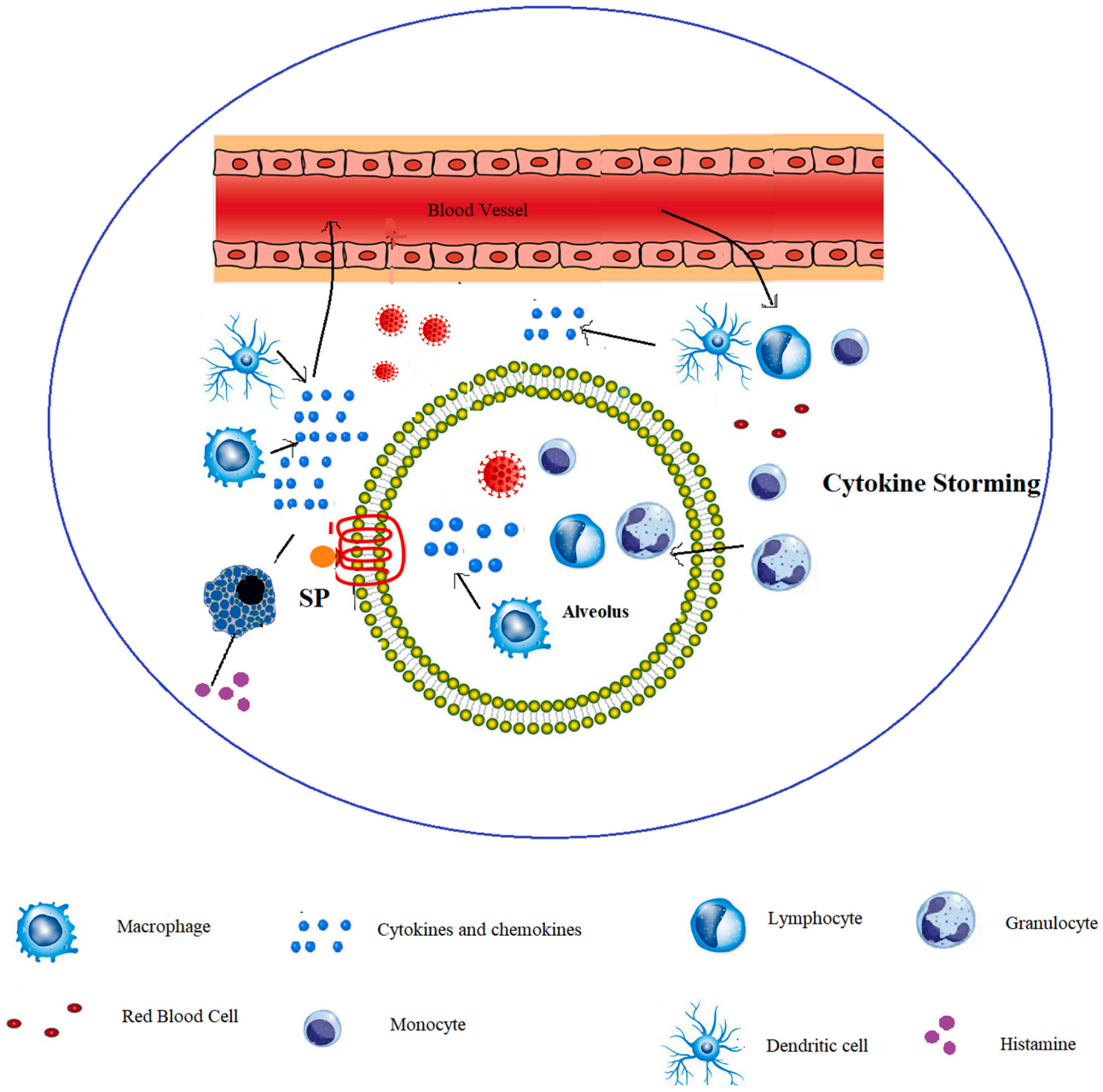

Fig. 2. Possible SP/NK-1R mediated Cytokine storming after COVID-19 infection.

cytokines, chemokines and histamines by mast cells [31]. It inhibits the cytokine TGF-β1, which is an immune-suppressor, released by macrophages [32] and thus promotes inflammation. It also induces the proliferation of T-lymphocytes, B-lymphocytes and natural killer cells, resulting in immunoglobulin secretion [33]. IFN-γ and TNF-α can activate the upregulation of NK-1R in macrophages like IL-4 [34].

SP is the first to react in response to a noxious stimulus. It is a rapid, immediate defense and survival system. In experimental studies, NK-1R deficient mice exhibited reduced pulmonary inflammation as compared to controls [35]. The immune response prevents the host cells by fighting against the pathogen but if it continues uncontrolled, it may be fatal. This phenomenon is known as "cytokine storming" (Figs. 2,3). Inflammatory mediators continue to be secreted by immune cells and can cause acute respiratory distress syndrome (ARDS) in COVID-19 infected patients. So, it is not actually the pathogen that is fatal, but the cytokine storming. If prevented or reversed, it may save the infected patients from further complications [36,37].

1.3. Neutral Endopeptidase (NEP) reduces inflammation by degrading SP

NEP or 'Enkephalinase' degrades SP and reduces the inflammation in respiratory tracts and associated conditions such as cough, edema and bronchoconstriction. It is localized in nerves, smooth muscle, trachea, and epithelium. In a study conducted on rats with respiratory infections caused by rat corona virus, parainfluenza type virus 1 and *Mycoplasma pulmonis*, had greater inflammation, reduced NEP activity and higher SP as compared to the pathogen free rats. NEP modulates the functionalities of SP. Respiratory tract infections may increase the airways responsiveness, cause inflammation, leading to bronchoconstriction due to raised SP (graphical abstract) [38]. Hence, the respiratory tract infections may be treated by elevating the NEP by its agonists. This is another possible treatment strategy.

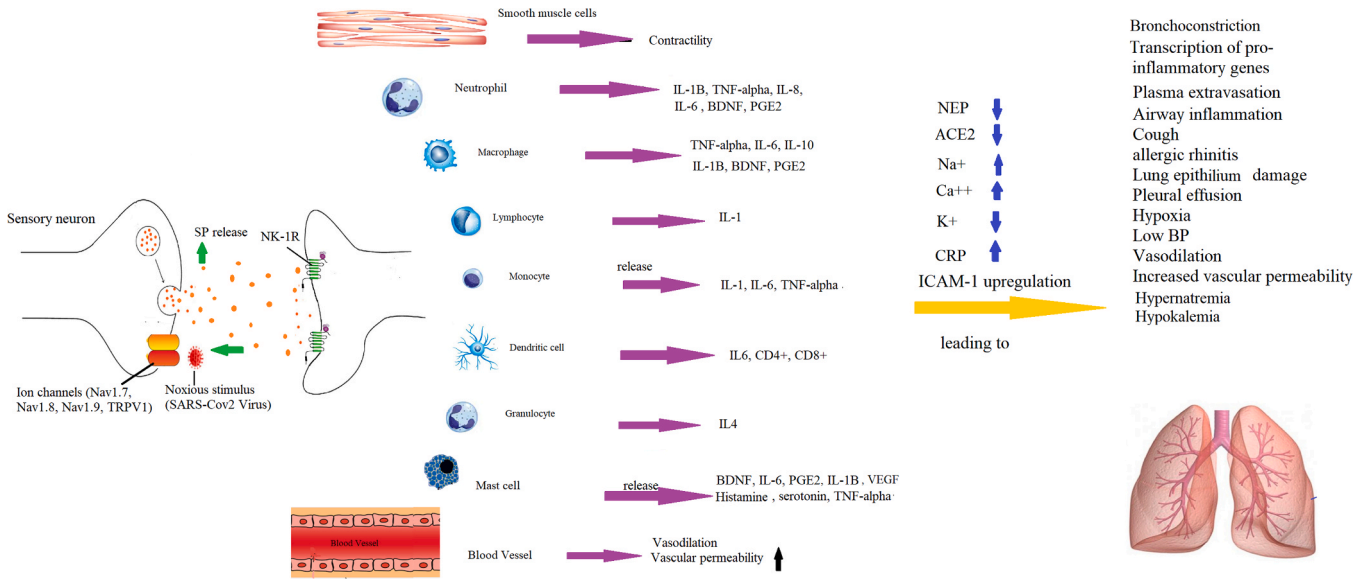

Fig. 3. Mechanisms by which SP-induced inflammation is implicated in the pathogenesis of COVID-19 infection. SP binds to NK-1R on endothelial cells to increase BBB permeability and release of cytokines by immune cells.

1.4. NEP and ACE inhibitors increase the muscle inflammation via decreased SP degradation

SP may also induce muscle inflammation or myositis. NEP and ACE may degrade the endogenous SP and hence the inflammation. NEP and ACE inhibitors administered intravenously along with SP, was found to cause muscle inflammation in rabbit after one week while only minimal changes were observed in the control group. Levels of SP and NK-1R was high in the inflamed muscles [39].

1.5. Involvement of SP/NK-1R in ventilatory response-evidence from past studies

SP is a most common neuropeptide in the airways and located in bronchopulmonary C fibers and protect the lungs against any injury from inhaled irritants. CNS responds to the noxious stimulus by cough, bronchoconstriction, hypotension, sleep apnea, and secretions from mucous glands in lungs, release of Nitric Oxide, prostaglandins and SP from airway epithelium [40]. In a study conducted on asthmatic patients, NK-1R mRNA was higher in broncho-alveolar lavage fluid [41], sputum samples [42] and lung tissue [43]. SP/NK-1R interaction is also required for the mediation of airway hyper responsiveness (AHR) [44]. SP is also a regulatory neuropeptide that control the ventilatory responses in humans. They are expressed in several brainstem nuclei where they regulate the respiratory rhythm at central or peripheral level as well as within the airways and lungs [45,46].

SP/NK-1R may be controlling the breathing activity in neonates as evident from the raised immunohistochemical SP expression in the brainstem tissues after postmortem studies in control infants as compared to Sudden Infant Death Syndrome (SIDS) victims in my previous study at Centro Lino Rossi, University of Milan, Italy [16,20]. SP expression was higher in sudden fetal deaths [20] and sudden death in adults [21]. SP and NK-1R regulates the breathing and cardiovascular control in medulla as a consequence of hypoxia. In another study conducted on SIDS victims, a significant decrease in NK-1R binding within medullary nuclei was observed as compared to controls. Alteration in SP secretions and modulation may disturb the autonomic functionalities leading to failure of arousal from sleep and leading to SIDS [47]. We may correlate these findings as a possible mechanism of complications and mortality in elderly patients due to COVID-19. As a neuromodulator, SP dilates the vessels, smooth muscle contractions in the respiratory walls, increases the excitatory potential by neurons, increased vascular permeability [48] and saliva production. Under pathological conditions, it may cause bronchoconstriction [45]. My another study highlighted the fact that SP encoding gene TAC-1 has unconventional networking properties: being singleton, small protein interaction network and the members of tachykinin family have conserved aminoacyl sequences, which make it vulnerable to be a causative agent for various diseases including fatal ones and death too [49].

1.6. SP as a predictor for mortality and disease severity

SP was found to be raised in serum samples of non/surviving patients of traumatic brain injury (TBI) as compared to surviving on Day 1. It was also found, that elevated SP levels during the first week of TBI was a predictor of increased mortality [50]. SIDS and cancer studies also support SP as a predictor of poor prognosis and mortality [51–53]. In COVID-19 patients, SP may be used as a biomarker for disease severity and prognosis.

1.7. SP/NK-1R involvement in physiology and pathophysiology of cardiac conduction system

SP/NK-1R complex is widely distributed through cardiac conduction system and involved in its regulation at various levels. SP nerves usually surround the coronary vessels, so that it may sense any change in the surrounding environment [54]. It may lead to fibrosis in hypertensive rat heart [55] which is an underlying mechanism for heart failure due to diastolic dysfunction. It increases the number of mature mast cells in hypertensive heart by activating and releasing more stem cell factor (SCF) [56]. It regulates the cardiac frequency, BP, stress response mechanisms, angiogenesis, pain transmission and inflammation [57]. A rise in SP levels in heart has been observed after viral infections [57]. It causes hypertrophy of cardiac cells and cytokine mediated apoptosis [58]. Mice deficient in TAC-1 gene were protected against the damaging effects of cardiac inflammation [59]. COVID-19 infected patients also undergo cardiac system malfunctioning or heart failure in severe cases.

1.8. SP as a nociceptive peptide, involved in pain mechanisms

SP is a nociceptive hormone involved in pain perception [60] including neuropathic pain [61], headache and migraine [62]. It was

also found to be the mechanism in chronic muscle pain in animal model [63]. SP in conjunction with glutamate in primary afferents carry out the transmission of pain stimulus [60,62]. Trigeminal ganglion releases SP which activates the satellite glial cells leading to the release of inflammatory factors or cytokines such as IL-1β and TNF-α and causes orofacial pain [64]. It is released from the sensory nerve fibers in skin, muscles and joints [65]. We may also relate this pain transmission phenomenon to COVID-19 infection.

1.9. SP/NK-1R involvement in vomiting

Area postrema is the emesis or vomiting center in the medulla and has an increased localization of SP and NK-1R. It stimulates and activates the vomiting reflex. SP/NK-1R appears to be the main anti-emetic pathway and NK-1R antagonists inhibit this reflex. The association of SP with vomiting was established in 1950s. SP/NK-1R antagonist is widely used to treat chemotherapy induced [66] and post-operative vomiting [67].

1.10. Role of SP/NK-1R in inflammation

SP has been associated with various pathogenic diseases. Its role in HIV-AIDS has also been reported [28]. SP binds to NK-1R and cause an augmented HIV infection in macrophages via CD163 receptor [68]. NK-1R antagonists such as Aprepitant show antiviral activities against HIV and may be used as a therapeutic strategy [27]. SP has also been reported in viral myocarditis which is a leading factor for heart failure. It is caused by encephalo-myocarditis virus. Use of NK-1R antagonist may block the SP signaling pathway and serve as a drug for treatment [69,70]. It was also observed to have inflammatory role in infected rats with rat corona virus and parainfluenza virus 1 [38].

Herpes simplex virus type 1 (HSV-1) causes an infection of muco-epithelial tissues of the eye and orofacial region. Virus passes through axons, reach the trigeminal neurons and its nuclei and establishes a lifelong latent infection where it encodes latency associated transcript (LAT) as shown in Fig. 2. In an experimental study involving transfected primary cultures of trigeminal neurons with LAT expressing plasmids, it was observed that LAT caused an increase in SP immunoreactivity by two thirds. These cultures were then transfected with bone-morphogenetic protein (BMP-7) which is a cytokine of TGF- β group. It has inhibitory effects against SP. It reversed the effects of LAT on increased SP in trigeminal neurons. We may imagine a similar mechanism and pathology in COVID-19 infection as well [71].

1.11. SP/NK-1R as vasodilatory peptides

SP induces vasodilation in response to inflammation via nitric oxide release [72]. SP has broncho-constrictive properties like other vasodilators. NEP and ACE degrade SP in normal physiological conditions and cause vasoconstriction. However, if their inhibitors are administered, it may reduce the SP degradation that will continue its vasodilatory effects [38,73]. Hypoxia also induces a downregulation and decreased function of NEP by histone modification. As a result, SP will continue to be released and causing vasodilation [74]. Controlled and well-regulated NEP is necessary for SP release, vasodilation and prevention from low BP, organ failure and cardiac arrest.

2. Treatment and management of COVID-19 infection

Passive immunization technique or the use of convalescent plasma was a transitionary management. It may boost the immune system to fight with viral infection but it is not the ultimate treatment. There is an urgent need to develop and discover more therapeutic strategies to control and contain this pandemic. NK-1R antagonists are a new class of drugs with anxiolytic, antidepressant, and antiemetic properties. Some examples of the NK-1R inhibitors are Aprepitant, Rolapitant, casopitant, Netupitant, Maropitant, and Fosaprepitant [75]. First NK-1R antagonist, Sprepitant got FDA approval in 2003 [76]. It may be used as a treatment regimen for respiratory viral diseases. Orvepitant use for the treatment of chronic refractory cough is in phase 2 trial (VOLCANO-1) and it has significantly improved the symptoms [18]. It is known that both SP and the NK-1Rs are upregulated during the inflammation processes and that, in rats, NK-1R antagonists exert an anti-inflammatory action [77]. Pharmacological inhibition of SP-signaling may be beneficial in COVID-19 infection. NK-1R antagonists may be recommended for the treatment of SP induced symptoms. SP-receptor antagonism may also be used as a therapeutic strategy in patients with viral-myocarditis [69].

In a recent randomized clinical trial conducted by our team, we have found very promising results for COVID-19 treatment in patients. There were 2 arms, one received normal management and care while the other received NK-1R antagonist, Aprepitant, in addition. Dexamethasone, was also administered to both the groups. 119 patients were randomly allocated in both arms, having 52 patients in control group A and 67 patients in interventional group B. Biochemical and hematological parameters were analyzed in both the groups before and after the intervention. Patients who received a combination therapy of Aprepitant and Dexamethasone showed improved clinical outcomes, laboratory findings and reduced C-reactive protein which is an inflammatory marker [78].

I suggest here that SP/NK-1R is associated with the pathogenesis of COVID-19 infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). It may be caused by aggravating the inflammatory mechanisms via cytokine storming as in other airway infections. A combined therapeutic approach including corticosteroids, antibiotics, purified intravenous immunoglobulins and anti-cytokinic therapy should be recommended [79].

3. Conclusions

Actually it is not the virus that is fatal and causing mortalities but the cytokine storming activated and initiated by SP is bringing the disaster. If we switch the SP off by its inhibitor or NK-1R antagonist or activate the enzyme NEP that degrades SP, cytokine storming may be stopped and hence the disease progression. Based on these findings, it may be speculated that therapeutic intervention with NK-1R antagonists may prove to be a potential drug for this viral infection but further studies are required in lab. Clinical trials with Apreitant and dexamethasone should be done on urgent basis, so that it may be implemented as a treatment for COVID-19 infection. These evidences support the use of NK-1R antagonists for the treatment of COVID-19 infection.

Aim

This study aims to provide Substance P as a possible cause of the initiation of cytokine storming developed in COVID-19 infection and to suggest Neurokinin-1 Receptor antagonist as a drug to be used for its treatment.

Scope

This review will provide directions to the Biomedical scientists to explore Substance P and Neurokinin-1 Receptor and prepare a drug to alleviate the symptoms and cure the disease. It is very important to work on this perspective at earliest to reach to some conclusion regarding the therapeutic intervention. Clinical studies may also be conducted if proven successfully.

Relevance of the study

Substance P is a neurotransmitter and neuromodulator, released from the trigeminal nerve of brainstem as a result of nociception. It is directly related to the respiratory illness as is in COVID-19 infection. It is

responsible for the increased inflammation and the signature symptoms associated with this disease. It is the main switch that need to be switched off at urgent basis by using the Neurokinin-1 Receptor antagonist which is the receptor of Substance P and responsible for its functionality.

Conflict of interest statement

Novel Coronavirus infection (COVID-19) has become a pandemic in these days. It is an acute respiratory and infectious disease with no etiology and treatment known. It is continuously causing losses of precious lives and economy at a global scale on daily basis. It is the need of the hour to find some treatment strategy by either preparing a vaccine or medicine or to boost the immune system.

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