Review Article

Can The Mucoactive Drug, Ambroxol, Be a Candidate Prophylactic Agent Against SARS-CoV-2 Infection Based on Its Action on The Transmembrane Serine Protease 2?

Abstract

Currently the world is facing a pandemic disease, namely Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As finding new drugs targeting COVID-19 will take a long time, so repositioning currently existing FDA approved drugs for treating this disastrous disease is an acceptable solution. It has been found that for SARS-CoV-2 to be infective, this necessitates cleavage of the viral spike glycoproteins by the serine protease "type II transmembrane serine protease TMPRSS2" that has been shown to be widely expressed in pulmonary tissues. Thus, TMPRSS2 has been suggested as a potential target for antiviral drug design against COVID-19. The mucokinetic drug "Ambroxol" has been reported to be a potent inhibitor of TMPRSS2, thus it could represent a therapeutic as well as a prophylactic candidate against SARS-CoV2. This review gives a brief summary about ambroxol's potential role against COVID-19's TMPRSS2.

Key Words:

Coronavirus disease 2019 "COVID-19" , Type II transmembrane serine protease "TMPRSS2", Ambroxol ,Mucokinetic drug

Abbreviations

COVID-19 :Coronavirus disease 2019 , TMPRSS2: Transmembrane protease serine 2,

SARS-CoV: Severe acute respiratory syndrome-related coronavirus, MERS:Middle East respiratory syndrome , ACE2: Angiotensin-converting enzyme 2 , AR: Androgen receptor,

IECs: Intestinal epithelial cells,GI:Gastrointestinal ,PSA: Polar surface area ,

PRAC :Pharmacovigilance Risk Assessment Committee , EMA:European Medicines agency,

RTIs :Respiratory tract infection

Introduction

Pathogenic microorganisms have always been a major threat to human health[1]. Currently the whole world is facing a pandemic disease, namely Coronavirus disease 2019 (COVID-19) caused by the RNA virus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Along with the highly infectious power of the virus, the mortality rates have been reported to range from 1% to more than 5% [2]. Up till now neither a definite treatment nor a vaccine has been established for this virus.

Attempts to develop new antiviral drugs are concentrating on elements that can impact virus replication or host factor(s) that are critical to virus replication [3]. Transmembrane protease serine 2 (TMPRSS2) is one of the promising targets that when inhibited can slow or stop replication of viruses[4]. Cleavage of theviral spike glycoproteins by serine protease causes their activationand facilitates virus-cell membrane fusions leading to host cell entry, replication, and spread. A multidomain type II transmembrane serineprotease TMPRSS2 is one of the serine proteases essential for viral infectivity and it has been shown to be widely expressed in lung tissues[5,6].

TMPRSS2 has been suggested in new evidence to be involved in other known coronaviruses such as severe acute respiratory syndrome-related coronavirus (SARS-CoV) as well as Middle East respiratory syndrome (MERS) protein processing for infectionin a number of susceptible host cells from various organs[7]. Based on similarities between SARS-CoV-2 and SARS-CoVas well as the Middle East respiratory syndrome (MERS), TMPRSS2 was proposed as a potential target for antiviral drug design against COVID-19 [8].

As finding new drugs that can inhibit TMPRSS2 and target COVID-19 will take a long time so repositioning some of the existing FDA approved drugs for treating this disastrous disease is an acceptable solution. Drug repurposing is a quick answer to the urgent need for a treatment for COVID-19 as it screens through a limited number of drugs that have already been proven safe for human use and are readily accessible in the market. The FDA approved mucokineticdrug, ambroxol is

the active form of another mucokinetic drugbromhexine, either drug is a well-known potent inhibitor of TMPRSS2 [9]. Thus, inhibiting pulmonary TMPRSS2 with ambroxol could represent a therapeutic as well as prophylactic strategy against the airborne transmission of SARS-CoV2. Given the relative safety profile of this drug, it seems that this TMPRSS2 inhibitor could be regarded as a prophylactic agent against SARS-CoV-2 infection.

2. TMPRSS as a potential target in our fight against COVID-19

Attachment of SARS-CoV-2 to the target cell is initiated by interactions between the spike glycoprotein (S) and its cognate receptor, angiotensin-converting enzyme 2 (ACE2)[10]. Following receptor engagement, SARS-CoV-2 S is processed by a plasma membrane–associated type II transmembrane serine protease, TMPRSS2that is essential to release the viral contents into the host cell cytosol[11].Corona virus S proteins are typical class I viral fusion proteins, and protease cleavage is required for activation of the fusion potential of S protein[12].CoV S proteins may be cleaved by one or several host proteases, transmembrane protease serine protease-2,-4 (TMPRSS-2), (TMPRSS-4) depending on virus strains and cell types[13]. Availability of these proteases on target cells largely determines whether CoVs enter cells through plasma membrane or endocytosis[14]. However, whether any of these proteases could promote virus entry of SARS-CoV-2 remains elusive.

Other aspects of TMPRSS and COVID-19 interrelationship

Another interesting point in the context of TMPRSS and COVID-19 is that TMPRSS2 has been found to be androgen-regulated[15] and so we are wondering, whether there is any relationship between TMPRSS2 and the male to female discrepancy in COVID-19given the fact that COVID-19 requires TMPRSS2 to enter into the lung cell. Is there more TMPRSS2 in the male lung as a result of androgen versus the female lung?!Separate from viral infections, TMPRSS2, in fact, has a widely recognized role in prostate cancer pathogenesis[16]. In part, because of its oncogene-driving function, TMPRSS2 now serves as a canonical readout of androgen receptor (AR)-dependent transcription in prostate cancer models and tissues[17]. Up till now, it is not known if TMPRSS2 expression in the normal human lung is regulated by androgens in physiological settings. If the answer is yes, thenTMPRSS2 expression in lung tissue might account for male preponderance of COVID-19.

TMPRSS2 is also expressed in a number of different cells, including not only the lung but also the gastrointestinal system. TMPRSS2 is expressed highly in the gastrointestinal (GI) tract, in particular by intestinal epithelial cells (IECs), the predominant target cells for many human enteric viruses[18]. Notable GI symptoms including abdominal pain and diarrhea have been observed in 20 to 50% of patients with COVID-19 and sometimes precede the development of respiratory illness[19].Does this expression vary between individuals and could it account for variability in clinical presentations of COVID-19?!Expression of TMPRSS in the enterocytes has been proved where it has been found to facilitate SARS-CoV-2 spike fusogenic activity and promote virus entry into host cells[20].

Pharmacology of ambroxol

Ambroxol (2-amino-3,5-dibromo-N-[trans-4-hydroxycyclohexyl] benzylamine), is the active N-desmethyl metabolite of the prodrug bromhexine, and both are widely approved as over the counter mucoactive agents. It has been used widely to treat both acute and chronic respiratory diseases associated with viscid mucus since 1978 with excellent records of safety[21].

Ambroxol has a bioavailability of 79% when administered orally [22]. It is metabolized in the liver by cytochrome P450 3A4 and has a terminal elimination half-life of approximately 10 h, with a total clearance of 660 ml/min [22,23]. It has a good lipophilicity (cLogP = 2.8) and low polar surface area (PSA 58 Å2), predicting good CNS penetration [24].On distribution from blood to tissue, the highest concentration of ambroxol is found in the lungs.In human lung tissue, ambroxol has been detected at concentrations 15- to 20-fold higher than those in the blood [21]. Furthermore, age and gender have not been shown to affect the pharmacokinetics of ambroxol to a clinically relevant extent, therefore dose adjustment is not indicated [23].The normal expectorant dose in adults is in the range of 75–100 mg/day,while doses of 1000 mg IV are used in pregnant women experiencing premature delivery to aid fetal lung maturation, and doses of 30 mg/kg in neonates for fetal respiratory distress syndrome [24].

Clinical experience accumulated from randomized clinical trials and observational studies and suggests that ambroxol is a safe and well-tolerated treatment of bronchopulmonary diseases, with a well-balanced and favorable benefit-risk profile in adults as well as in the pediatric population. The

most common adverse events are mild and self-limiting GIT disturbances. The risk of serious cutaneous adverse reactions reported by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines agency (EMA) with ambroxol is extremely low [21,23].As a mucolytic it reduces mucus crosslinking and viscosity by disruption of polymer networks in the secretions through severing disulfide bonds, depolymerizing mucopolysaccharides, liquefying proteins, and degrading DNA filaments and actin [25].

Ambroxol is thought to stimulate surfactant and mucus secretion, yet promote normalization of mucus viscosity in viscid secretions. However, recent systematic reviews provide evidence of a generalized benefit using ambroxol for a range of parameters, including secretolytic activity (promoting mucus clearance), anti-inflammatory (through inhibition of the generation of pro-inflammatory mediators by leukocytes) and antioxidant activity(due to direct scavenging of reactive oxygen species) as well as local anaesthetic effect (through inhibition of the neuronal sodium channels) [21,24,26]. In addition, antiviral, antibacterial and antifungal properties for ambroxol have recently been described and published.Direct and indirect anti-infectious properties of ambroxol have been concluded such as; increasing bioavailability of antibiotics,increasing the concentrations of immunoglobulins A and G and its ability to suppress virus multiplication [27-29]. It is worth to mention that there is a special interest for ambroxol as an adjuvant in treatment of respiratory tract infection (RTIs) with biofilm-producing pathogens such as Pseudomonas aeruginosa and Candida albicans [29].This explains its usefulness in the prevention and treatment of upper and lower RTIs associated with abnormal mucus secretion or impaired mucus transport. Its efficacy has been shown in more than 100 clinical observational, uncontrolled, or randomized, controlled, double-blind trials on more than 15.000 adult and pediatric patients with various forms of acute and chronic diseases of the upper and lower respiratory tract [24,30].

5. Use of ambroxol as a prophylactic and/or therapeutic agent against Covid19

Since the entry of the COVID 19 virus into cells was reduced by camostatmesilate, Hoffman et al., suggested that TMPRSS2 could be a potential therapeutic target for COVID-19[11].Camostatmesilate, a TMPRSS2 inhibitor, is currently only approved for treatment of chronic pancreatitis in Japan, with very little available data on the drug's risk profile and no experience with use in children, pregnant women, multimorbid, and other high-risk patients. In addition, being a non-selective TMPRSS2 inhibitor, means that it has greater and more severe side effects [31]. The FDA-approved mucokinetic agent ambroxol, the active form of bromhexine hydrochloride, is a well-known potent selective inhibitor of TMPRSS2 with IC50 equal to 0.75 μM [13]. Typically bromide compounds, especially aromatic bromide compounds, show a relatively high binding affinity for serine-containing peptide sequences, proteins, and enzymes and this effect is due to a selective inhibition of TMPRSS2 by bromhexine [32]. Since epithelisin is expressed primarily in the apical surface of airway epithelial cells, inhibiting pulmonary TMPRSS2 with ambroxol could represent a prophylactic&/ therapeutic strategy against the COVID19 transmission [13].

6. Studies assessing potential role of ambroxol as a TMPRSS2 inhibitor in COVID-19

An "*in vitro*" study showing that a TMPRSS2 inhibitor Camostatinhibited SARS-CoV-2 from entering cells[14], encouraged conducting studies on ambroxol and its prodrug" bromhexine". Indeed, Ambroxol has beenshown to inhibit rhinovirus infection in human tracheal epithelial cells cultures by a number ofmechanisms[33]. One of these mechanisms (reducing acidic endosomes) might apply against SARS-CoV-2. According to researches from IBM, computer simulations indicate that ambroxolmight inhibit SARS-CoV-2's main protease[34].Ambroxol has been alsoshown to up-regulate endogenous protease inhibitors .Ambroxol's up-regulation of these defensive molecules has been shown to increase the survival of mice exposed to influenza virus[35]. The daily dosage reported to be most effective was found to be 10mg/kg, which for humans would be equivalent to 0.8 mg/kg[36].Ambroxol may be also an ACE2 binding agent according to an artificial intelligence drug target screening done by researchers at the School of Basic Medicine Sciences at Peking University[37].Ambroxol has been also found to inhibit SARS-CoV-2 replication in an *in vitro* screening of a number of approved drugs, according to a pre-print paper released several days ago [38]. The concentration of ambroxol found to inhibit SARS-CoV-2 replication falls in the range that can be achieved in lung tissue with therapeutic doses [39]indicating that ambroxol may have antiviral effects against SARS-CoV-2 at concentrations achievable with normal dosages. Currently, there is an epidemiologic study underway in China evaluating ambroxol's potential in the treatment of COVID-

19, sponsered by Boehringer Ingelheim [40]. Clinical trials assessing the possible antiviral effect of ambroxol'sprodrug , namely bromhexine, in COVID-19 patients are also currently going on in a number of countries[41,42] and we are waiting for results to be released. These clinical trials are based on preliminary promising results of bromhexine in inhibiting SARS-CoV-2 [43,44]. The use of ambroxol at the dose adequate to selectively inhibit the TMPRSS2, resulting in preventing of viral entrance via TMPRSS2-specific pathway, could be a new hope for an effective treatment of Covid-19.

7. Conclusion

As the world witnesses the alarming levels of spread and severity of COVID-19, strategies to combat this outbreak are in great need. Drugrepurposing is an attractive alternative drug discovery strategy because there is the advantage of accesability, decreased cost of development, availability of toxicity data and the availability of options for combination studies. The background pharmacological knowledge available for such compounds may also reduce concerns regarding adverse effects in patients. Using ambroxol that selectively inhibits TMPRSS2 thus inhibiting TMPRSS2-specific viral entry is likely to be effective against SARS-CoV-2. We propose the use of ambroxol as a prophylactic and treatment. Furthermore, a combination with hydroxylchloroquine, that is considred an effective endosomal protease inhibitor, inhibiting cathepsin B/L, could be a favorable combination for the treatment of COVID-19 cases. On the basis of this review it seems thatTMPRSS2couldbe a potential and attractive target to be seriously considered forSARS-CoV-2 antiviral therapy. Ambroxol (or bromohexine)could be a promising candidate forimmediate use as either drug is a TMPRSS2 inhibitor already approved by the FDA.The scientific testing ofambroxol is deeply encouraged.

8. Declarations:

The authors declare that:
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9. References

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