Nasal Air Conditioning and SARS-CoV-2

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as with the influenza virus, has been shown to spread more rapidly during winter. Severe coronavirus disease 2019 (COVID-19), which can follow SARS-CoV-2 infection, disproportionately affects older persons and males as well as people living in temperate zone countries with a tropical ancestry. The available data are consistent with optimal warming and humidifying of inspired air by the nose (nasal air conditioning) being essential for minimising SARS-CoV-2 infectivity of the upper respiratory tract (URT) and, as a consequence, severe COVID-19.

Keywords: COVID-19 ; gender ; genetic factors in SARS-CoV-2 susceptibility ; innate immunity ; nasal conditioning of inspired air ; SARS-CoV-2 infectivity ; upper respiratory tract immunity

1. SARS-CoV-2 Infection in the Upper Respiratory Tract

Recent molecular studies demonstrate that SARS-CoV-2 viral load and the expression of host proteins needed for infection, are higher in the nasal epithelium than the lower respiratory tract, and therefore that the nasal epithelium is the probable initial infection site followed by infection of the pharynx as a result of mucociliary clearance of virus towards the nasopharynx and later the likely seeding of the lower respiratory tract and lungs by aspiration [1][2][3], as is the case with influenza viruses [4].

2. Innate and Adaptive Immune Response in the Upper Respiratory Tract in Protection against SARS-CoV-2 Infection

Innate immune mechanisms, analogous to those characterised in influenza virus infections [5][6][7], that can also protect against infection by SARS-CoV-2 in the URT are summarised in **Table 1**.

Table 1. Innate immune mechanisms that can protect against SARS-CoV-2 infection in the upper respiratory tract.

Induction	Effector Cell or Molecule	Effector Mechanism
-	Naturally occurring mucins, defensins and collectins	Bind virion and prevent cell binding and entry
Altered surface of the virion and virus-infected cells	Complement	Activation through the alternate or lectin pathway to promote lysis and opsonisation, inflammation
Pathogen associated molecular pattern (PAMP) recognition by pattern recognition receptors (PRRs)	Type 1 (α,β) and Type 3 (λ) interferons (IFNs)	Induction of anti-viral state in infected and neighbouring cells through inhibition of protein synthesis and mRNA degradation. Activation of phagocytic cells and dendritic cells
PRR	Inflammasome in macrophages and dendritic cells	Production of IL-1, IL-6 and TNF that promote an inflammatory response in tissue, fever and the synthesis of acute phase proteins
PRR	Macrophage and dendritic cell synthesis of IL-12, IL-18	Activation of NK cells to lyse virus infected cells and enhancement of adaptive immune response
Stress molecules expressed by infected cells	γδT cells secreting Type 2 IFNγ	Activation of NK cells, phagocytes, dendritic cells and the adaptive immune response

An adaptive or antigen-specific immune response follows soon after an innate or non-antigen-specific immune response and the principal adaptive immune mechanisms that can protect against infection by SARS-CoV-2 in the URT are summarised in **Table 2**.

Table 2. Adaptive immune mechanisms that can protect against SARS-CoV-2 infection in the upper respiratory tract.

Effector Molecule or Cell	Mechanism of Action
Secreted IgA antibodies in mucus	Prevention of virion binding to epithelial cells by agglutination and neutralization of virions
IgG and IgM antibodies in mucosa and blood, including anti-A and anti-B blood group antibodies	Prevention of virion binding to host cells through agglutination and neutralization, activation of complement through the classical pathway, promoting opsonisation and phagocytosis, assisting NK cell killing through Fcγ receptors
CD4+ T_H lymphocytes	Activation of B cells, promoting immunoglobulin class switching and affinity maturation, secretion of cytokines like IFNγ that activate phagocytes and NK cells and upregulate major histocompatibility complex molecules.
CD8+ cytotoxic lymphocytes	Apoptosis of virus-infected cells by granzyme, perforin, etc.

3. Humidity of Inspired Air and Protection against SARS-CoV-2 Infection

The multiple ways in which humidity may affect the stability of respiratory viruses and the mucosal barrier function have been recently reviewed [8] and may be summarized as follows for the URT: (i) airborne enveloped viruses may be more stable at low and high humidities and less stable at intermediate humidities, (ii) mucoepithelial integrity is decreased by inspired air of low humidity, and (iii) mucocilary clearance, which removes virions trapped in the mucus from the airway, is reduced at low humidity. Inadequate humidification of inhaled air of relatively low moisture content that is characteristic of winter may, therefore, be expected to enhance infection of the URT epithelium by SARS-CoV-2.

4. Temperature of Inspired Air and Protection against SARS-CoV-2 Infection

Low temperature affects the stability of respiratory viruses in the environment and also compromises mucosal barrier function [8][9]. There is evidence to suggest that SARS-CoV-2 survives better at lower temperatures in human nasal mucus and sputum [10], which is pertinent to both airborne and fomite transmission. Essentially, it can be surmised that lower than optimal temperatures in the URT: (i) may improve the stability of the lipid bilayer in enveloped viruses, (ii) reduce the mucociliary clearance of viruses, (iii) compromise URT-epithelium repair during infections [8][9], and (iv) adversely affect the Type 1 and 3 interferon dependent early innate immune responses in the URT [11][12][13][14].

Colder-than-normal inspired air in winter may be expected to produce temperatures in parts of the nasal cavity that are lower than its usual 33-34°C, thereby, likely further facilitating the infectivity of SARS-CoV-2 in the nasal epithelium and nasopharynx. The relationships between the temperature of inspired air, intranasal temperatures, and nasal air conditioning have not been systematically studied to date. However, modelling studies showed that the anterior nasal cavity is responsible for most of the warming of inspired air [15].

5. Nasal Air Conditioning and Genetic Differences in Susceptibility to SARS-CoV-2 Infection

Defects in specific genes involved in the Type 1 and 3 interferon pathway increase the risk of developing severe COVID-19 and this may likely be due to a failure to control SARS-CoV-2 infection in the URT [13][14]. Additionally, recent GWAS have identified large segments of human chromosomes inherited from Neanderthals that are associated with a major risk for susceptibility [16] or protection [17] against severe COVID-19. These two studies did not identify specific genes responsible for susceptibility or protection but demonstrated a variable distribution of the relevant chromosomal regions in different parts of the world.

The differential susceptibility and resistance to a variety of human infectious diseases are governed by genetic factors [18] and are particularly well studied in malaria [18][19][20][21]. However, genetic factors that specifically affect the initial infectivity of SARS-CoV-2, in contrast to the severity of ensuing COVID-19, have not been clearly established. The nearest experimental approach to investigate this difference recently examined SARS-CoV-2 RNA test positivity separately from

disease phenotype in a US-based GWAS [22]. The results showed that blood group O was significantly associated with reduced SARS-CoV-2 test positivity and an association between some types of tropical ancestry and SARS-CoV-2 test positivity [22]. It is possible to hypothesise that the blood group O association is due to protection conferred in the URT by natural anti-A and anti-B antibodies universally present in blood group O individuals acting against infecting virions carrying membrane A and B antigens derived from infecting individuals of blood groups A and B.

Variations in nasal structure between human populations living in geographically disperse locations with different climates have been correlated with the greater need to humidify and warm inspired air during cold and dry winters on one hand and the correspondingly reduced need for this in warm and humid climates of the tropics on the other [23][24][25]. It is reasonable to postulate that selection by respiratory viral infections in temperate zones in ancient times may have been a factor that contributed to such nasal variations. SARS-CoV-2 may, therefore, be more infectious in temperate zone countries to persons with a tropical ancestry [22] due to a weaker nasal air conditioning ability, and that this may contribute, in addition to socio-economic factors, to their observed propensity to develop more severe COVID-19 [26][27].

6. Differences in Nasal Air Conditioning and the Age and Gender Differences in Susceptibility to SARS-CoV-2 Infection

Intranasal air temperature and humidity are lower in elderly in comparison with younger persons, and this is associated with the atrophy of the nasal mucosa with increasing age [28]. Many nasal parameters also display a pronounced gender dimorphism in diverse populations [24]. Through possible differential nasal air conditioning, these variations may contribute in some small measure to age- and gender-related differences in the susceptibility to infection with SARS-CoV-2, which can then, in turn, impact the frequency of severe COVID-19 [29][30][31].

An increase in the basal level of immune activation or inflammation, reduced innate responses in the airway epithelium, deterioration of the quality of adaptive immune responses involving B and T lymphocytes with age, are additional immunological factors [30] that, together with a possibly reduced nasal air conditioning ability, may permit better replication of SARS-CoV-2 in the nasal epithelium and nasopharynx of older persons and, thereby, facilitate severe lower respiratory tract disease and increased mortality [29][30][31].

There are also gender-related differences in the innate and adaptive immunity [32] that can play a role in limiting SARS-CoV-2 infection of the URT epithelium, with an attendant impact on the severity of any ensuing COVID-19 [29]. The relative contributions of these other factors and possibly altered nasal air conditioning ability toward the age and gender-related differences in the susceptibility to COVID-19 merit further investigation. It is encouraging, however, that age and gender do not affect the efficacy of early licensed vaccines [33][34][35][36][37][38], which also augurs well for immunity generated after recovery from a primary SARS-CoV-2 infection.

7. Other Factors Influencing Susceptibility to SARS-CoV-2 Infection

Air pollution can potentially play a role in the susceptibility to SARS-CoV-2 infection by providing air-borne particles to transport virions and affecting the barrier and innate immunity functions of the respiratory epithelium [39]. Available evidence also suggests that the relatively common URT conditions of allergic rhinitis and chronic rhinosinusitis do not increase the risk of COVID-19 [40]. Rhinitis can, however, promote the transmission of SARS-CoV-2 from infected to uninfected persons as a result of increased nasal mucus production and sneezing. Another likely confounding factor is that prior infection with common cold coronaviruses may generate a degree of cross-reactive protective immunity against SARS-CoV-2 infection in the URT. Cross-reactions between common cold coronaviruses and SARS-CoV-2 have been documented at the level of CD4+ T_H cells and CD8+ cytotoxic lymphocytes [41][42]. Vaccination against COVID-19 and previous resolved infections with SARS-CoV-2 augment adaptive immune responses in the URT and will, therefore, reduce the susceptibility to infection. In contrast, the emergence of SARS-CoV-2 variants with a higher affinity of binding to human cells and reduced binding to neutralizing antibodies [43], as well as potential other mechanisms to evade protective immunity in the URT, will increase the susceptibility to infection. The contribution of the nasal air conditioning ability on reducing SARS-CoV-2 infectivity in the URT has to be considered in the context of such additional factors.

Figure 1 summarizes different aspects of the relationship between nasal conditioning of inhaled air and SARS-CoV-2 infectivity in the URT.

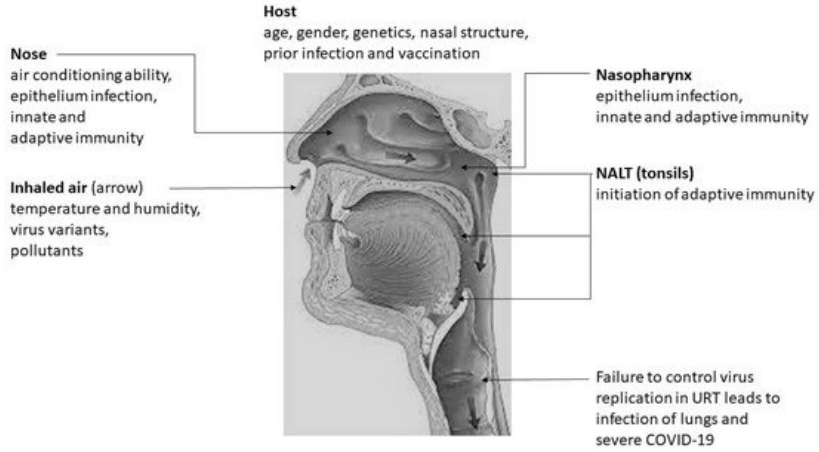

Figure 1. Relationship between the nasal conditioning of inhaled air and SARS-CoV-2 infectivity in the upper respiratory tract.

8. Conclusions

The importance of nasal air conditioning in SARS-CoV-2 infectivity remains poorly explored experimentally. The determination of SARS-CoV-2 infection rates and viral loads in the nasal cavity and nasopharynx in relation to the inhaled air temperature and humidity, age, gender, and genetic background is warranted. A better understanding of this may help to develop more effective measures to reduce infections and control the pandemic. Clinical studies on whether safe induction of type 1 and 3 IFNs in the URT reduces SARS-CoV-2 infection rates may be helpful to health personnel working in high risk situations.

The importance of nasal air conditioning predicts that simple measures, like minimizing exposure to cold air and keeping the nose warm with a scarf wrapped around the face and neck or a face mask may help to promote more efficient nasal air conditioning to reduce infections. Keeping the nose warm in cold temperatures is an ancient and common practice to protect against respiratory illnesses in many parts of the world. While infectivity and immune protection in the URT is connected with the subsequent development of serious or even critical illness involving the lungs, many more factors, including comorbidities, come into play in the development of severe COVID-19.

It is reasonable to conclude, however, that taking appropriate simple precautions to keep the nose warm to promote better nasal air conditioning in cold temperatures, particularly by more infection-susceptible persons, could minimise the initial infectivity of SARS-CoV-2 and other respiratory viruses. These measures promote more effective innate and adaptive immune responses in the URT. In the case of SARS-CoV-2, they supplement vaccination and previous infection with SARS-CoV-2 to further enhance adaptive immunity in the URT. The added advantage of using face masks and face scarves is that they also help reduce the person-to-person transmission of SARS-CoV-2 as well as other respiratory viruses.

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