

## Review Article

# The Potential Impact of the Orexinergic System on the Symptoms of Coronavirus-Infected Patients

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## Abstract

Coronavirus disease in 2019 (COVID-19) is a pandemic declared by the World Health Organization after its appearance in the Chinese city of Wuhan in late 2019. It has infected more than 30 million people worldwide and led to the death of nearly one million of them. Orexin-A (OXA), a neuropeptide produced by the lateral hypothalamic area and several peripheral tissues, regulates appetite, reproduction, and other physiological functions. There are many symptoms associated with infection with the coronavirus, such as a cytokine storm, narcolepsy, impaired senses of smell and taste, and loss of appetite, usually are associated with high or low levels of OXA in the infected people. Moreover, some chronic diseases such as cancer, diabetes, and obesity, generally referred to as risk factors for the disease, increase the severity of infection or even lead to death and they are associated with either an increase or a decrease in OXA levels. Moreover, some factors, such as a high testosterone level, facilitate the entry of a virus into the cells, which OXA controls. In this review, we described for the first time the potential impact of high or low levels of OXA on the severity of the symptoms of COVID-19 or the death due to this disease.

**Keywords:** COVID-19, Orexin-A, Hypersecretion, Hyposecretion, Severe symptoms

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## Introduction

Orexin-A (OXA) and Orexin-B (OXB) (also called hypocretin 1 and 2); are two neuropeptides discovered with their receptors in the lateral hypothalamic area (LHA) and have received widespread attention because of their diverse and vital functions. Both of them are derived from the precursor prepro-orexin (130 amino acids)<sup>1,2</sup>. There

are two types of orexin receptor type 1 (OX1R), type 2 (OX2R), G protein-coupled receptors, and their structure is highly conserved in mammals<sup>2</sup>. OX1R is selective for OXA, but OX2R has an almost equal affinity for both of them<sup>3,4</sup>. Despite many studies showing that orexins and their receptors just spread in the brain<sup>5,6</sup>; the subsequent studies, by using immunostaining, confirmed the presence of OXA also in various peripheral tissues, including myenteric

plexuses, ganglion cells of the sympathetic thoracic trunk, the islet cells of the pancreas, endocrine cells of the gastrointestinal tract, and both of syncytiotrophoblasts and decidual cells of the placenta. In addition, the prepro-orexin's mRNA is expressed in the colon, kidney, pancreas, stomach, adrenal gland, placenta, ileum, and colorectal epithelial cells of human<sup>7</sup>. Orexins have many biological functions such as reproduction<sup>8, 9</sup>, appetite<sup>10</sup>, sleep/wake states<sup>11</sup>, development<sup>12</sup>, smell and taste<sup>13,14</sup>, and regulate the immune response<sup>15</sup>, in addition, his disorders are accompanied by many diseases such as cancer<sup>16</sup>, diabetes<sup>17</sup>, obesity<sup>18</sup>, and hypertension<sup>19</sup>.

Coronavirus disease in 2019 (COVID-19), which first appeared in the city of Wuhan in central China's Hubei province at the end of 2019 and spread rapidly in many countries of the world, caused by a novel coronavirus known as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)<sup>20</sup>. On the 11th of March 2020, the World Health Organization (WHO) had declared COVID-19 a pandemic threatening the world<sup>21</sup>. Clinical symptoms of COVID-19 include fever, dry cough, shortness of breath, sore throat, sneezing, loss of smell, conjunctivitis, and rarely diarrhea<sup>22</sup>. WHO has reported similarities in clinical symptoms between the different strains of coronavirus, which include SARS-CoV-2, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS), which cause a respiratory syndrome with symptoms caused by influenza virus A (H1N1)<sup>23</sup>. Previous studies have indicated that the H1N1 causes narcolepsy, which results from the infection of the orexin-producing neurons in the hypothalamus<sup>24</sup>. From this standpoint and because of the possibility that either high or low levels of OXA and their receptors could be associated with the increase in the strength of symptoms in patients and the increased likelihood of death; we discussed in this review the

correlation between high or low levels of OXA with increased severity of symptoms or a chance of death, this could be a new approach towards understanding the causes that result in the severity of the infection and finding appropriate solutions to address it.

### **Orexin-A hypersecretion and COVID-19**

Hypersecretion of OXA is related to many factors that cause severe symptoms of COVID-19 or death, including high androgen levels and hypertension, besides some of the symptoms of COVID-19 like delirium (fig. 2).

#### **• Androgens**

OXA has a direct impact on the testis to stimulate it in order to increase its production of testosterone<sup>25,26</sup>. For example, in dogs, when the incubated fresh testis slices were treated with OXA, the synthesis of testosterone was stimulated in the normal and cryptic gonad, while this effect disappeared when OX1R antagonist SB-408124 was added<sup>27</sup>. The same result was obtained in the South American camelid alpaca (*Vicugna pacos*) and male Wistar rats so that OXA caused an increase in testosterone production by the testes or its fresh slices in a dose-dependent manner within a specific concentration range<sup>28-30</sup>. Furthermore, in primary rat Leydig cells, activation of OX1R by OXA had up-regulated testosterone production by extracellular signal-regulated protein kinase (ERK1/2) and mitogen-activated protein kinase (p38) signalling pathways<sup>31</sup>. On the other hand, OXA down-regulates aromatase mRNA, which transfers androgens to estradiol in the hypothalamus of the androgenized female rats<sup>32</sup>. However, radioimmunoassay in another study showed that OXA decreases the mean serum level of testosterone in male Wistar rats; and the treatment with OXA antagonists<sup>8,33</sup> cancelled this effect. As for OXB we had a regulating effect on the secretion and production of testosterone by both myometrium and endometrial slices during early pregnancy and the oestrous cycle in the porcine uterus<sup>34</sup>.

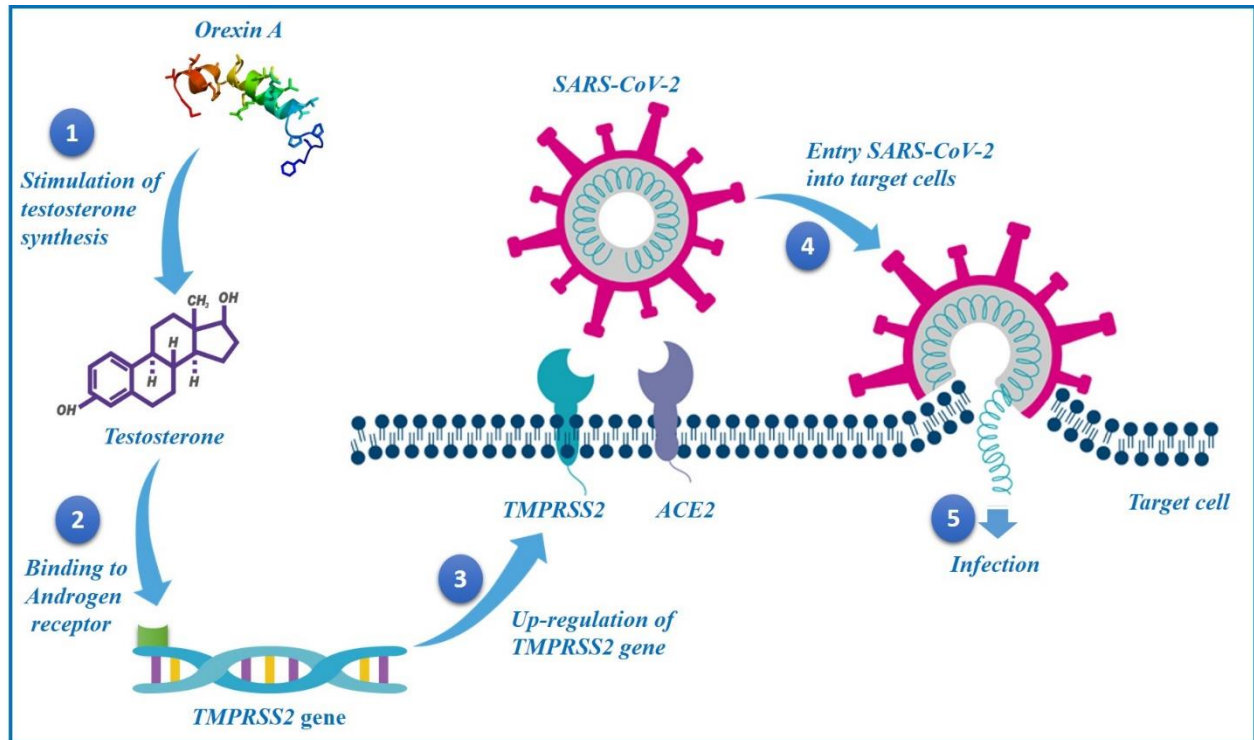


Figure 1. The potential mechanism by which OXA helps SARS-CoV-2 to enter the target cell.

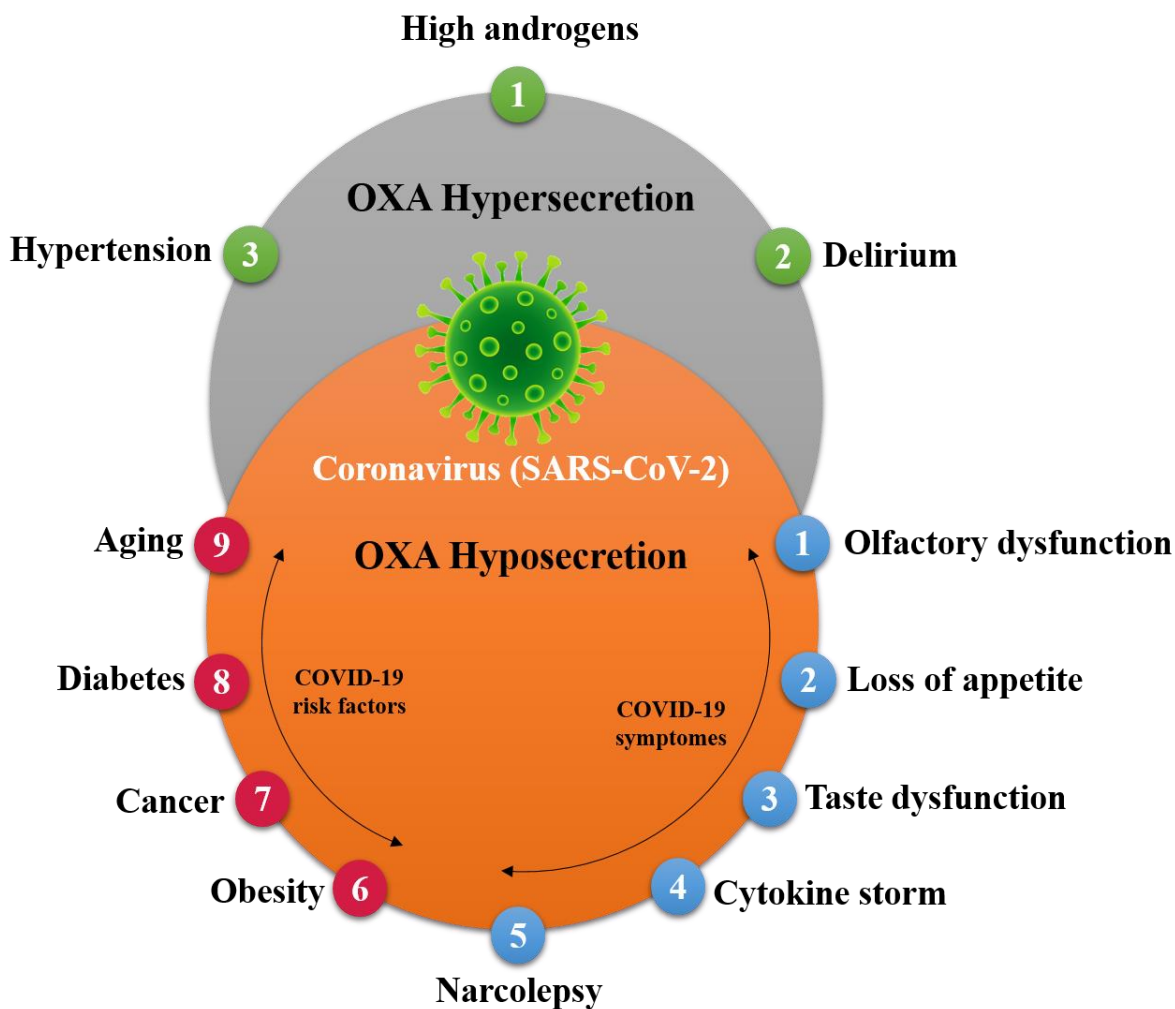
Recently, several studies have been published that have correlated testosterone levels in males to the likelihood of infection COVID-19 or even the severity of symptoms<sup>35,36</sup>. A study showed that prostate cancer patients with high testosterone levels are more likely to be infected with COVID-19 than non-cancer patients<sup>37,38</sup>. In addition, a clear relationship between androgenic alopecia and male patients hospitalized with COVID-19 has been reported<sup>39,40</sup>. Moreover, European countries severely affected by COVID-19; have a high frequency of the adrenal-permissive allele that encodes *Hydroxy-Delta-5-Steroid Dehydrogenase, 3 Beta- And Steroid Delta-Isomerase 1 (HSD3B1)* that increases testosterone synthesis<sup>41</sup>. Not only high testosterone level could be a cause an increase in the risk of infection with COVID-19 or causing severe symptoms, but also the low levels of it; in other words, an increase in the mortality rate of the infected elderly have been observed, and this has been explained that those with lower levels of testosterone had a greater predisposition for the thrombosis, endothelial dysfunction, and a defective immune response<sup>42,43</sup>. Moreover, a high rate of hospitalized male COVID-19 patients with a high

rate of hair loss was observed<sup>44</sup>.

Many studies have indicated that regulation of *transcription transmembrane protease serine 2 (TMPRSS2)* is mediated by androgen receptor<sup>45,46</sup>. Furthermore, TMPRSS2 receptor is largely accused, alongside angiotensin-converting enzyme 2 (ACE2), of helping the coronavirus enter the target cells<sup>47, 48</sup>. Remarkably, it has been observed that the males exhibit COVID-19 severe symptoms compared to children who were more resistant to infection. This has been explained that the androgen receptors are responsible for regulating transcription of *TMPRSS2*, which is required for entry SARS-CoV-2 to the target cells<sup>49</sup>. An overbalance in the number of infected and deaths among males compared to females due to the greater expression of *ACE2*, the critical receptor for virus entry into cells, has been reported<sup>50,51</sup>. In addition to the help provided by high testosterone levels in the entry of the coronavirus into target cells, it suppresses the immune system<sup>52,53</sup> (Fig. 1).

#### • Hypertension

Using animal models of hypertension, several studies have shown that hypertension is associated with hyperactivity of the orexin neurons and the overexpression of orexin and its receptors<sup>54,55</sup>. To



**Figure 2.** The relationship between OXA and the symptoms and risk factors of COVID-19. This figure shows the accompaniment of some symptoms of COVID-19 and risk factors, causing severe symptoms and death, with hyper or hypo OXA secretion.

some extent, patients with high blood pressure are more likely to develop severe symptoms of COVID-19 and are more likely to die<sup>56,57</sup>. This may suggest that there could be a relationship between orexinergic system activity and severity of the symptoms of COVID-19 in hypertensive patients infected by the virus.

• **Delirium**

Delirium is one of the symptoms resulting from the effect of coronavirus on the central nervous system in COVID-19 infected patients, which is caused by the arrival of the virus to the nervous system and the occurrence of infections in it or hypoxia<sup>58</sup>. A positive correlation was found between death and severity of infection with COVID-19 on the one hand and access to delirium on the other hand, so that; it was clear

that patients who had reached the stage of delirium were more likely to die<sup>59</sup>. Although the non-significant difference in plasma OXA levels between the delirium patient and non-patient had been reported<sup>60</sup>, the Suvorexant, an orexin receptor antagonist, is a recommended medication for treating delirium<sup>61,62</sup>.

• **Orexin-A hyposecretion and COVID-19**

Some of the symptoms of COVID-19 include defects in the sense of smell and taste, loss of appetite, and narcolepsy besides risk factors that increase the severity of infection or even death, such as cytokine storm, ageing, cancer, diabetes, and obesity, are associated with a decrease in serum OXA levels (fig. 2).

• **Cytokine storm**

The "cytokine storm", which is a hyperinflammatory

response, causes serious complications such as respiratory distress syndrome and thromboembolic diseases, one of the factors causing the increase in symptoms and the death rate in COVID-19<sup>63,64</sup>. A few studies have demonstrated the anti-inflammatory properties of OXA. In mice, peripheral administration of OXA reduced the levels of several proinflammatory cytokines and chemokines<sup>65</sup>. Additionally, OXA had relieved the inflammatory manifestations by inhibiting the NF- $\kappa$ B pathway in the murine model of experimental colitis<sup>66</sup>. Furthermore, pre-treatment of BV2 cells *in vitro* with OXA decreased the production of IL-6 and TNF- $\alpha$ <sup>67</sup>. Moreover, the endogenous orexin system alleviated the brain damage in the murine focal cerebral ischemia model, accompanied by a decline in IL-6 and TNF- $\alpha$ <sup>68</sup>. Thus, from previous studies, low levels of OXA can increase the severity of inflammation.

#### • Olfactory dysfunction

Immunological detection of OXA and its receptors in different regions of the olfactory system, especially the olfactory bulb, indicated its potentially important role in the sense of smell in mice and rats<sup>69,70</sup>. It was hypothesized in a previous study that the impairment of smell in narcolepsy patients may be due to the loss of OXA in the central nervous system. This olfactory dysfunction has been remedied by administering OXA nasally<sup>71</sup>. It has become known that infection with COVID-19 may cause a defect in the sense of smell that can sometimes persist even after recovery<sup>72,73</sup>.

#### • Loss of appetite

Although orexins have been implicated in various physiological functions since its initial discovery, it has been known as an appetite-regulating peptide<sup>2</sup>. Outcomes indicated that OXA increases food intake by delaying the onset of a behaviourally normal satiety sequence<sup>10</sup>, and destruction of the lateral hypothalamus area, which is responsible for producing orexins, also led to underfeeding<sup>74</sup>. Loss of appetite is one of the symptoms of COVID-19<sup>75,76</sup>.

#### • Taste dysfunction

Inactivation of OXRs in the central nucleus of the amygdala, which is responsible for flavour-taste preference, by SB-334867 antagonist, caused a malfunction in the flavour-taste preference<sup>77</sup>, and blocked taste preference learning in the rats<sup>78</sup>.

COVID-19 infection is significantly associated with impaired taste function and is considered an indication of infection<sup>79,80</sup>.

#### • Ageing

Although there is research indicating a positive correlation between plasma OXA concentration and age in humans and that in both sexes, OXA levels in the plasma of people under 40 years old are lower than those of 60 years old or over<sup>81, 82</sup>. However, many of the behavioural, cognitive, and sleep disturbances seen in the elderly have been associated with decreased hypothalamic production of orexins<sup>83,84</sup>. In aged animal models, these animals had lower orexin-producing neurons in the hypothalamus and other regions of the brain<sup>85, 86</sup>. Moreover, immunoreactivity has indicated a decrease in the expression of orexins in the hypothalamus in older humans compared with younger adults, which leads to sleep disturbances<sup>87</sup>. Also, significantly decreased OX1R expression in the orexinergic systems was reported in the elderly rats compared to the young<sup>88</sup>. This confirms the role of orexin in ageing; in the case of stimulation of orexin, neuronal activity by designer receptors exclusively activated by designer drugs alleviates the impairments associated with ageing, such as anxiety-like behaviour in young and middle-aged mice<sup>89</sup>. Furthermore, intranasal OXA was able to diminish the age-related cognitive dysfunction in the aged rats<sup>13</sup>. The elderly, especially those with chronic diseases, are at high risk of developing severe symptoms of COVID-19 or even death<sup>90,91</sup>.

#### • Cancer

Although there are studies that have indicated the negative role of OXA and OX1R in some types of cancers, such as the pancreas and BGC-823 gastric cancer cells, by increasing proliferation and viability of cells and inhibiting apoptosis<sup>92, 93</sup>. However, orexins have had an anti-cancer role in more than one cell line derived from prostate cancer, LNCaP and DU145, accompany with OX1R overexpression that plays a role as an apoptotic regulator<sup>94-96</sup>. Also, in colon cancer, orexins had an inhibitory role for cancer cells and induced apoptosis dramatically even in cells resistant to 5-fluorouracil<sup>97</sup>. Ultimately, orexins tend to drive different types of cancers to apoptosis and prevent their proliferation. Therefore they could be promising therapies<sup>16</sup>. Studies have indicated that

cancer patients have a higher chance of dying with COVID-19, in addition to showing more severe symptoms and admission in the intensive care unit and mechanical ventilation<sup>98, 99</sup>.

- **Narcolepsy**

Studies have indicated that narcolepsy is associated with decreased orexin levels and receptors or a loss of its producing neurons<sup>100,101</sup>. The relationship between narcolepsy and COVID-19 has been mentioned<sup>102, 103</sup>.

- **Diabetes**

Type 2 diabetes mellitus is associated with decreased levels of OXA because of the inverse correlation between insulin resistance and plasma OXA levels<sup>104</sup>. Furthermore, in pregnant women with gestational diabetes mellitus, OXA levels are significantly lower than control<sup>17</sup>. This could be explained by a study that indicated that a decrease of OXA causes stress in the endoplasmic reticulum in the liver, which causes the failure of the hepatic insulin signaling<sup>105</sup>. People with diabetes have been reported to be more likely to have more severe symptoms of COVID-19, need for mechanical ventilation, and death compared to non-diabetic people<sup>106, 107</sup>.

- **Obesity**

In a study, plasma OXA levels and orexin receptor activity in adipose tissue negatively correlated with body mass index (BMI) in obese subjects<sup>108, 109</sup>. Orexin via spontaneous physical activity and energy expenditure induces obesity resistance<sup>110</sup>. Also, mice that loss orexin-containing neurons acquired obesity despite consuming less food<sup>111</sup>. Furthermore, injection of OXA into the brain led to weight loss and thus played a dampening role in the rise of obesity<sup>112</sup>. In addition, mice deprived of orexins through a knockout or treatment with an ataxin toxin postnatal caused the emergence of obesity in later stages<sup>113</sup>. Reports indicate that COVID-19 patients who are already obese have more severe symptoms of COVID-19 and are at a higher risk of death<sup>114, 115</sup>.

## Conclusion

High levels of OXA increase the severity of COVID-19 infections by raising testosterone levels, which contributes to facilitating the entry of larger numbers

of the coronavirus into target cells. In addition, some chronic diseases that increase the severity of the infection and the likelihood of death, such as hypertension, are associated with a rise in the levels of OXA. Also, COVID-19 infection is associated in some cases with delirium, accompanied by high levels of OXA. On the other hand, some factors causing the possibility of death with COVID-19, such as cytokine storm, ageing, obesity, cancer, diabetes, and clinical symptoms of COVID-19 such as loss of smell, taste, and narcolepsy, are associated with a decrease in the levels of OXA. All this prompts us to pay attention to this neuropeptide to investigate its involvement in the pathogenesis of this disease.

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## Conflict of interest

The authors further declare that they have no conflict of interest.

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