

REVIEW

Correlation Between Nongenomic Action of C19-Steroids and COVID-19 Severity

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Summary

The recent COVID-19 pandemic is the defining global health crisis of our time and little is known about this disease. It has been reported that advanced age is considered a major risk factor for COVID-19 complications, and data suggest that this disease is deadlier for men than women but these observations are currently unclear. Regarding androgen action, it has been shown that certain smooth muscles are a target for androgens by inducing an acute relaxing effect in airway and vascular tissues that is nongenomically mediated; likewise, androgens are capable of inducing genomic anti-inflammatory and nongenomic hypotensive responses. The aim of this report is to associate the relationship between COVID-19 and aging men as well as the comorbidities presented in this group of patients linked with androgen deficiency. Remarkably, the nongenomic mechanisms of androgens as potential protectors are reviewed. On this basis, it is suggested that hypotestosteronemia may be a risk factor for COVID-19 severity.

Key words

Androgens • COVID-19 severity • Male sex steroids • Nongenomic actions • Coronavirus infection

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Introduction

The SARS-CoV-2 pandemic, which causes

coronavirus-induced disease (COVID-19), has spread all over the world. COVID-19 produces upper respiratory tract infections and can progress to severe disease by affecting the lower respiratory tract with dyspnea and severe chest symptoms corresponding to pneumonia. In addition, inflammatory markers, such as C-reactive protein and proinflammatory cytokines are elevated. All these characteristics do not help in oxygenation, contributing to respiratory failure in COVID-19 patients. SARS-CoV-2 acts through the angiotensin-converting enzyme 2 (ACE2) receptor where the novel coronavirus enters the respiratory mucosa. This is, in fact, a key component for the pathogenesis of COVID-19 (for review see Paces *et al.* 2020). Moreover, androgens that mediate viral entry in the cell (TMPRSS2; transmembrane protease, serin2) have been recognized (Goren *et al.* 2020, Wambier and Goren 2020). The first biologic step required for potential infectivity of SARS-CoV-2 is the priming of the spike proteins by TMPRSS2 (revised by McCoy *et al.* 2021), whose expression is associated with an increase in androgen receptor (AR) expression (Mikkonen *et al.* 2010). Therefore, the current evidence of blocking AR by antiandrogens (AR antagonists) during COVID-19 in hospitalized patients shows an important reduction in mortality (McCoy *et al.* 2021).

It has been reported that diabetes, hypertension, chronic respiratory diseases, and other cardiovascular and cerebrovascular diseases are major risk factors for patients with COVID-19 (Huang *et al.* 2020, Chen *et al.* 2020b, Liu *et al.* 2020). The most common comorbidities reported are; hypertension 56.6 %, obesity 41.7 % and

diabetes 33.8 % (Richardson *et al.* 2020). It is also important to highlight that the death rate is higher in people aged above 80 and those having comorbid conditions, with at least one comorbidity. In this respect, older age and comorbidities are associated with higher severity and mortality in regard to COVID-19 illness.

It has also been observed that men tend to develop more serious cases than women. It has been reported that men have a threefold higher odds of lethality than women (Porcheddu *et al.* 2020) with a worldwide average male/female sex ratio of 2 (mostly in the 70-89 age group). Indeed, these data establish a clear sexual dimorphism in the development of COVID-19 (Jin *et al.* 2020). Nevertheless, the endocrine status in women, such as pregnancy, could be a risk factor for COVID-19 severity because pregnant women are more susceptible to infectious disease due to immune suppression during pregnancy. Additionally, during pregnancy the reduction in total lung capacity and inability to clear secretions can make pregnant women more susceptible to severe respiratory infections. Despite numerous studies, it is difficult to draw absolute conclusions on whether pregnant women are at increased risk of severe consequences of COVID-19 (Mikkonen *et al.* 2010).

Moreover, the available information has described that the clinical symptoms of COVID-19 in pregnancy were not significantly different from those of nonpregnant women (Chen *et al.* 2020a); reviewed by Panahi *et al.* (2020). Admittedly, further studies are needed to verify this.

Notably, as previously mentioned, there is limited information describing sexual differences; thus, the aim of this report is to provide an additional point of view to explain these differences on the basis of one's own experimental findings and to review the published literature (including multiple search strategies in MEDLINE with the PubMed interface).

Biological actions of androgens

Male sex C19-steroids (androgens) are traditionally considered for the maintenance of male sex characteristics, with testosterone being the main androgen. Likewise, testosterone levels decrease with the age of men (for review see Dušková *et al.* 2020). Considerable evidence exists that the natural aging process estimates testosterone decreases by approximately 10 % every decade after men reach the age

of 30.

The male sex steroids (also called androgens or C19-steroids), traditionally considered for the maintenance of male sex characteristics, have also been documented to have relevant biological actions in bone, muscle, prostate, adipose tissue and the reproductive, cardiovascular, immune, neural and hematopoietic systems (Mooradian *et al.* 1987, Rana *et al.* 2014). The responses produced by these male sex steroids have been studied extensively in most of the known biological functions such as: the secondary male sexual characteristics, sexual behavior, spermatogenesis, increment of muscle mass, loss of adipose tissue, prostate growth, prevention of osteoporosis, and action in the haematopoietic, immune and nervous systems, and hair follicles in the skin, emotions and libido (Mooradian *et al.* 1987, Rana *et al.* 2014).

In addition to the masculinizing effects of androgens there are also their anabolic properties. It is accepted that TES produces muscle hypertrophy by increasing fractional muscle protein synthesis (Brodsky *et al.* 1996, Urban *et al.* 1995).

Androgens may modify cellular function by both (i) their well-known classical genomic action and (ii) their more recently identified nongenomic mechanisms of action. This last mechanism of action is very rapid, and the effects are not mediated by the classic intracellular AR. Notably, the physiological nongenomic mechanisms of androgens regulate the cardiovascular and respiratory systems, among others. This report focuses on the nongenomic mechanism of action of androgens and their relationship with COVID-19. In this context, any effort to understand the development and critical condition of COVID-19 is of considerable importance and merits continued investigation.

Androgen-induced nongenomic vasorelaxation

Acute vasorelaxing effects of androgens have been widely documented in a number of isolated vascular beds of various species of mammals including humans; likewise, this acute vasorelaxing effect of androgens has been characterized as nongenomic mechanism of action (revised in Perusquía 2003, Perusquía *et al.* 2007, Perusquía and Stallone 2010, Kelly and Jones 2013, Lorigo *et al.* 2020a, Lorigo *et al.* 2020b). This vasorelaxing effect is not privative of testosterone because testosterone's precursor dehydroepiandrosterone (DHEA) and the 5 β -reduced metabolite of testosterone

(5 β -dihydrotestosterone; 5 β -DHT) elicit a more potent vascular relaxation than testosterone itself, and they do not bind to AR and are totally devoid of androgenic properties. Notably, steroids that were previously considered to be insignificant byproducts of metabolism or degradation products have become to be seen as important in physiology and in pathological states (Dušková *et al.* 2020).

Consequently, vasorelaxation induced by androgens correlates with an increase in blood flow, as testosterone infusion increases coronary artery blood flow in experimental animals and in humans (Webb *et al.* 1999, English *et al.* 2000). The acute *in vitro* vasorelaxation of androgens may also exert regional or systemic hypotensive responses *in vivo*. Our *in vivo* experimental contributions in animals have also reported that BP regulation is expected as a consequence of androgen-induced vasorelaxation, and we reported reduced BP in normotensive and hypertensive rats, as well as observations where hypertension can be developed by orchidectomy in rats and prevented by treatment with testosterone (Perusquía *et al.* 2015, Perusquía *et al.* 2017, Perusquía *et al.* 2018, Perusquía *et al.* 2019). Androgens are also antihypertensive in females, which was demonstrated in an *in vivo* rat model of preeclampsia (Perusquía *et al.* 2018). All of this information confirms that androgen deficiency is linked to an increased prevalence of hypertension and cardiovascular diseases. In addition, a body of work has associated low circulating levels of testosterone with cardiovascular dysfunction, particularly hypertension (Webb *et al.* 1999, Khaw and Barrett-Connor 1988, Phillips *et al.* 1994, English *et al.* 1997, Pugh *et al.* 2000).

A body of information has also documented that other risk factors for cardiovascular diseases such as hyperinsulinemia, diabetes, functional hypogonadism, obesity, smoking and age are also associated with hypotestosteronemia (revised by English *et al.* 1997). Low circulating levels of testosterone have been associated with cardiovascular dysfunction, particularly hypertension (Webb *et al.* 1999, Khaw and Barrett-Connor 1988, Phillips *et al.* 1994, English *et al.* 1997, Pugh *et al.* 2000). Taken together, these lines of evidence indicate that the systemic hypotensive response of androgens involves a direct vasodilatory action of the peripheral vasculature which suggests a beneficial physiological role for androgens in cardiovascular regulation; therefore, androgen deficiency clearly

indicates a risk factor for hypertension, suggesting that hypertension in older men may be due to the lower androgen levels in patients with hypertension, a comorbidity highly susceptible to COVID-19. Vasodilation also plays an important role in inflammation which is a process that helps defend the body against harmful pathogens and repair damage caused by injury or disease. Notably, in COVID-19, the beneficial response of androgen-induced vasorelaxation may help during the inflammatory process to allow increased blood flow to the affected area.

Nongenomic relaxing effects of androgens in airway smooth muscle

Asthma severity decreases during adolescence only among males, when androgens start to be secreted; moreover, low testosterone levels in elderly men may exacerbate asthma. Based on this logic, androgens seemingly diminish the severity of asthma symptoms.

More recent findings have provided evidence that DHEA, testosterone and particularly 5 β -DHT, which is devoid of androgenic actions, induce bronchorelaxation and prevent bronchospasm induced by ovalbumin in an animal model of allergic asthma which is mediated by a nongenomic mechanism of action (Espinoza *et al.* 2013, Montañó *et al.* 2014), reviewed by Montañó *et al.* (2020). Importantly, the anti-inflammatory responses of androgens (Traish *et al.* 2011, Koziol-White *et al.* 2012) may contribute significantly to the prevention of asthma, reviewed by Montañó *et al.* (2020).

These studies indicated that androgens are capable of relaxing airway smooth muscle to increase airflow, suggesting the low levels of androgens may contribute drastically to the severity of COVID-19.

Currently, we do not know if COVID-19 is a trigger for asthma exacerbation but salbutamol medication (a β -adrenergic agonist) which is used to prevent bronchospasm, has been recently used to treat the critical respiratory condition of COVID-19 (Elbeddini *et al.* 2020). Indeed, the nongenomic bronchorelaxing and preventive bronchospasm effects of androgens plus their genomic anti-inflammatory action may be an alternative to treating the severe phase of the disease. Hence, it is important to note that dexamethasone, acting only as an anti-inflammatory agent, is not the only steroid that has shown promise in the battle against COVID-19.

Androgen responses characterized as nongenomic mechanisms of action

It is important to highlight that the steroid response latency has been used as an indicator of genomic versus nongenomic mechanisms of action. Therefore, the rapid (1-2 min) and reversible vasorelaxing and bronchorelaxing effects could be explained as a nongenomic (membrane) action (reviewer in Espinoza *et al.* 2013, Perusquía and Villalón 1999). In addition, the vasodilatory and bronchodilating nongenomic mechanisms of androgens are supported by a wide variety of evidence that shows that androgen-induced vasorelaxation persists a) when testosterone is covalently bound to albumin and cannot cross the cell membrane; b) in the presence of inhibitors of DNA transcription (actinomycin D) or mRNA translation (cycloheximide); c) in the presence of antagonists of androgen receptors (AR) such as flutamide; and d) in AR-deficient testicular-feminized rats (revised in Perusquía and Stallone 2010, Espinoza *et al.* 2013, Montañó *et al.* 2014, Perusquía *et al.* 2012, Bordallo *et al.* 2008, Kouloumenta *et al.* 2006). Similarly, androgen-reduced blood pressure and androgen-prevented bronchospasm are also characterized as a nongenomic mechanism of action, since the antihypertension and bronchospasm prevention caused by androgens is immediate to their i.v. bolus administration, as well as to their hypotensive response elicited in Tfm rats (male rats with androgen receptor deficiency) (Perusquía *et al.* 2019, Espinoza *et al.* 2013, Montañó *et al.* 2014, Bordallo *et al.* 2008, Kouloumenta *et al.* 2006, Hanson *et al.* 2020).

Relevant findings and what we need to know

Taking into account the knowledge gained on the nongenomic mechanisms of androgens that do not bind to AR in the systems involved in COVID-19 development i.e., both in the respiratory and cardiovascular systems, it is important to consider the relevance they have, and such data suggest a potential therapeutic use of C19-steroids as coadjuvant treatment in COVID-19. This information may suggest clues to treat severe COVID-19 in aging men.

Do to their potency and efficacy in inducing vasorelaxing and bronchorelaxing effects, male sex steroids have been named “vasoactive and bronchoactive androgens” (Perusquía and Stallone 2010, Espinoza *et al.*

2013, Montañó *et al.* 2014). It is important to note that this series of androgens, DHEA, testosterone and 5 β -DHT are, more potent relaxants than female steroids, estrogens and progestins to induce relaxation in smooth muscles.

The nongenomic mechanisms of androgens are directly exerted on both vascular and airway smooth muscles, an effect independent of vascular endothelium and airway epithelium, respectively. Accordingly, androgen-induced smooth muscle relaxation is mainly attributed to voltage-gated L-type Ca²⁺ channel blockade (a natural Ca²⁺ antagonist) (Perusquía and Stallone 2010, Perusquía *et al.* 2015, Espinoza *et al.* 2013, Montañó *et al.* 2008, Montañó *et al.* 2014, Flores-Soto *et al.* 2017, Scragg *et al.* 2007) acting as dihydropyridines used most frequently as antihypertensives. Likewise, it has been documented that TES-induced vasorelaxation may also activate different types of K⁺ channels in some vascular beds (Deenadayalu *et al.* 2001, Ding and Stallone 2001, Tep-areenan *et al.* 2002, Seyrek *et al.* 2007, Seyrek *et al.* 2011, Cairraö *et al.* 2008, Yildiz *et al.* 2009).

It has been noted that older adults accounted for a disproportionate number of severe cases and deaths due to COVID-19 (Wang *et al.* 2020, Nikolich-Zugich *et al.* 2020, Onder *et al.* 2020, Ruan *et al.* 2020, Shahid *et al.* 2020, Wu *et al.* 2020, Zhou *et al.* 2020). In this respect, it is a priority to consider the significant decline in male sex steroids and its clinical consequences, a conjunction that has been dubbed androgen deficiency in aging males (Morley 2001). Thus, an aging-associated decline in testosterone levels is accompanied by age-related diseases, such as cardiovascular risks, including hypertension, obesity, metabolic syndrome, dyslipidemia, osteoporosis, hypogonadism, urinary incontinence, loss of muscle strength and deterioration of mood with sexual dysfunction, including erectile dysfunction, premature ejaculation and diminished libido (for review see Kelly and Jones 2013, English *et al.* 2000, Wang *et al.* 2011, Traish *et al.* 2009). Taking together this huge body of information, androgens turn out to be a protective shield against COVID-19, which is in agreement with a study that reported that reduction in total testosterone and calculated free testosterone are correlated with high severity of COVID-19 and their low levels have been suggested as novel predictors of poor prognosis in SARS-CoV-2 men (Rastrelli *et al.* 2021). Unfortunately, this study did not associate testosterone levels with age. Later, it was reported that the serum total testosterone level of COVID-19 in the male patients group was significantly

lower than that of the control group (median, 140 ng/dl; range, 0.21-328, 322 ng/dl; range, median, 125-674, $p < 0.001$, respectively) (Cinislioglu *et al.* 2021).

Certainly, the genomic mechanism of action of androgens by binding to cytosolic ARs may also play an important role in the protective action of androgens against COVID-19, such as the anti-inflammatory responses of androgens (Traish *et al.* 2011, Koziol-White *et al.* 2012); thus, androgens may have a good effect on the so-called “cytokine storm” produced by patients with severe COVID -19. Likewise, several lines of evidence have documented the blockade of AR during COVID-19 as a successful treatment because ACE2 and TMPRSS2 levels in lung and cardiac cells are reduced by antiandrogens, as revised in McCoy *et al.* (2021).

Because men have a threefold higher odds of lethality than women, one important question is: *Why are women less susceptible to COVID-19 infection?*

The simple answer may be based on the well-established facts that estradiol can cause vasodilation by both estrogen receptor (ERs)-dependent and second messengers (Dubey *et al.* 2002). It is accepted that female steroids (estrogens and progestins) have a protective effect on the vascular system but are less effective than androgens in inducing nongenomic vasorelaxing (Perusquía *et al.* 1996, Perusquía *et al.* 2007) and bronchorelaxing (Perusquía *et al.* 1997) effects. Therefore, it is tempting to speculate two possible causes: (i) premenopausal women are relatively protected by female sex steroids several years until menopause (approximately 40-50 years old) and (ii) in some populations, the postmenopausal period of women might be protected by the use of hormone replacement therapy (HRT): in fact, androgens such as testosterone or tibolone have been added to HRT to treat sexual dysfunction in postmenopausal women.

Moreover, estrogens are protective against more severe disease than men by downregulating the expression of ACE2 receptors (Schurz *et al.* 2019). Maleki *et al.* (2020) reported that the ACE2 gene is located on the X-chromosome. In this respect, the X-chromosome contains a high density of immune-related genes; consequently, women generally mount stronger innate and adaptive immune responses than men.

On the other hand, theoretically children are not predisposed to COVID-19 infection but recently it has been seen that cases in young children began to rise. In this respect it may be tentatively assumed that the incidence in children might be associated with low

testosterone levels during childhood, especially in younger children, and consequently, children both boys and girls are not protected by steroid hormones against COVID-19. This is in line with a multicenter Chinese study where children aged less than 3 years old accounted for the majority of cases (approximately 40) (Zheng *et al.* 2020). This population of children demands more attention during home care and hospitalization. Similarly, as this is a risk factor during androgen deficiency in aging males, the time when the circulating levels of androgens start to decline. Therefore, it may be carefully concluded that hypotestosteronemia is, indeed, an important factor for the vulnerability of COVID-19 in aging men, and obviously in prostate cancer patients who are receiving androgen deprivation therapy (ADT) as well as in hypogonadal individuals.

The present contribution is, indeed, the first association of COVID-19 and the nongenomic mechanism of action of sex steroid hormones. In addition, very few works have attempted to explain why women are less susceptible to COVID-19.

Conclusions

The severity of COVID-19 has been explained by numerous arguments. In the present review, it is suggested that physiological androgen levels may represent a protective action against COVID-19 by a nongenomic mechanism of action, such as their i) vasorelaxing and bronchorelaxing effects and subsequently ii) antihypertensive responses and prevention of bronchospasm. In addition, it is relevant to consider the anti-inflammatory property of androgens mediated by genomic mechanisms. Consistent with this suggestion, low circulating levels of androgens are also linked with cardiovascular and respiratory dysfunctions; thus, androgen deficiency may have a detrimental influence on COVID-19 severity. However, further clinical studies are needed to clarify whether androgens could be used to assist COVID-19 patients.

In the same way, children may be predisposed to COVID-19 infection because both aging men and children are suffer hypotestosteronemia. The explanation accounting for the reduced case rate in women may be the protective action of female steroids as well as the use, if any, of HRT during the menopausal period.

In recent times, much information has stunned us about COVID-19. The present reflection gives a bird's eye view about COVID-19 and male sex C19-steroid

status. Currently, to understand this disease slightly more, it can only hypothesize that the beneficial effects of androgens may defend against COVID-19 severity.

Conflict of Interest

There is no conflict of interest.

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