Why ACE-inhibitors and AT1R antagonists could work against Corona infection

Groessen, The Netherlands, 26-02-2020

(10)(2e)

Introduction

More than other fields of science, medical science is often directed by a sense of urgency. Because science is a profession in which patience, reflection and repetitive testing lead to accurate conclusions, being in a hurry is not a contributing factor. Eager conclusions, based on insufficiently explored assumptions, may lead to misjudging compensation mechanisms for causative factors and to insufficient knowledge on the entire disease mechanism.

During this Covid19 pandemic, time is certainly a factor in the wish to find a cure. During this episode of swift science, we fall back to what we know and we try to draw conclusions from the limited knowledge we have. During each outbreak we build on knowledge from former outbreaks.

What we know about Covid19, is that it invades the cell by binding to the ACE2 receptor. From here on, it is easy to draw the conclusion that we should block the ACE2 receptor in order to prevent Covid19 from entering the cell.

However, from what we know about ACE2, we should fear the effects of a deficiency of this receptor.

In this article, I will explain my hypothesis on the way Covid19 infects cells, and on how our immune system unwillingly facilitates that strategy.

This mechanism leads us to possible treatments.

A conclusion similar to my line of thought has independently been reported by Sun ML et al on February 16th.

Corona viruses

Although infections with Corona viruses are common and seldomly lethal (human coronaviruses cause approximately 30% of upper respiratory tract infections), too often a lethal Coronavirus evolves to cause a pandemic, like with SARS and MERS, and at this moment Covid19.

History taught us that when we start looking for a vaccine, the virus has an enormous head start and a vaccine is seldom available when the virus extinguishes, and the pandemic ends by itself.

Since there is no way to develop a vaccine prior to the evolvement of a new deathly virus, I think we should aim at finding the disease mechanism of Corona to find ways to support infected patient's health and weaken Corona mechanisms.

We know where Corona enters the cell. HCoV-229E uses CD13 as a receptor (Jia, 2005). CD13 is also called aminopeptidase N (APN) (Danziger, 2007), SARS-CoV and NL63 use ACE2 (Jia,2005). The cellular receptors for HCoV-OC43 and HKU1 are still unknown. The new Covid19 also uses the ACE2 receptor.

ACE2 and APN are both part of the renin angiotensin system (RAS). ACE2 converts angiotensin II to angiotensin 1-9. It also converts angiotensin I to angiotensin 1-7. APN converts angiotensin III to angiotensin IV.

Jia et al found that infection of human airway epithelia by SARS coronavirus correlates with ACE2 expression.

In case of stress and hypertension, ACE2 plays a protective role, in contrast to angiotensin II (ATII), which is associated with cardiovascular disease (Patel, 2015).

ACE2 and Angiotensin II

AngII, as part of the RAS system, has a role in body fluid homeostasis and inflammatory response. AngII has pro-inflammatory, proliferative and pro-fibrotic functions which are essential in the response to infection and hypoxia, but are deleterious if activated in a healthy person or in case of prolonged

activation during disease (Benigny, 2010). During pulmonary infection, AngII induces pulmonary vasoconstriction to reduce hypoxia and vascular permeability to facilitate extravasation of cytokines to the site of inflammation. Eventually, this inflammatory response causes edema and respiratory distress.

ACE2, located on the plasma membrane, converts AngII to Ang(1-7), thereby ending the AngII induced pro-inflammatory response. AngII in its turn induces internalization of ACE2 into the cell by endocytosis and its degradation in lysosomes (Deshotels, 2014). This means that it is the task of ACE2 to regulate and antagonize AngII actions, while AngII decreases the expression of ACE2 at the cell membrane. Resulting in a homeostatic-type interaction, steering towards a healthy equilibrium, rather than exacerbation of inflamation.

How does Covid19 enter the cell?

It may seem logical to assume that we should reduce ACE2 to limit the sites at which Covid19 enters the cell. However, plasma membrane-localized ACE2 is an important regulator of AngII induced inflammation. Indeed, increased ATII is a poor prognostic factor for severe pneumonia. Decreased ACE2 is associated with hypertension, fibrosis, heart failure and neurodegeneration.

Covid19 binds to ACE2, after which the entire complex is endocytosed. This means that Covid19 interferes with the normal ratio of AngII:ACE2. This causes an unregulated inflammatory response which is not adjusted to the threat which the primary infection poses. A more sensible thing to do therefore, appears to be inhibition of AngII. Inhibition of AngII prevents endocytosis of Covid19-bound ACE2 (Deshotels, 2014) and it would contribute to a decrease in the intensity of the inflammatory sequence. This can be done by medicines which are widely available and safe, AT1 receptor inhibitors and ACE-inhibitors.

The question remains what molecular signals cause the ongoing induction of AngII during an infection with Covid19?

Activation of AngII during Covid19 infection

AngII is endogenously produced in T cells, which is important for T cell activation and migration to the site of action (Silva-Filho, 2011). In SARS-CoV

and MERS-CoV infections, priming of virus-specific T cells was found to be reduced, restricting the amount of T cells that recognize the Corona viruses. This causes a delayed virus-specific immune response. In this case, AngII activation keeps the non specific immune reaction going. Binding of Covid19 to ACE2 in order to endocytose the virus and direct the complex to lysosomes for destruction, may be considered an alternative way of phagocytosis of the virus in an attempt to limit virus load. However, at the right pH, the virus has the ability to fuse its envelope with the endosome and release its particles into the cytoplasm before reaching the lysosome. Once in the cytoplasm, the virus has the capacity to replicate.

Conclusion

Because of the delayed virus-specific T cell immune response to Covid19, AngII is persistently activated to keep the non-specific immune response going, consisting of cytokine-induced inflammation. This non-specific immune response tries to keep the viral load low, in anticipation of the specific immune response. Prolonged activation of AngII induces an excessive and prolonged inflammatory reaction which in itself increases morbidity. AngII induces endocytosis of Covid19-bound ACE2, which should direct the virus to lysosomes for degradation. However, the virus escapes from the endosome by fusion of its envelope with the endosomal membrane, releasing viral particles into the cytoplasm where they can replicate. In the meantime, AngII is no longer downregulated by ACE2 by lack of expression of this receptor at the plasma membrane. Unrestrained AngII eventually causes death by respiratory distress induced by excessive inflammation.

I hypothesize that Covid19-induced mortality is caused by AngII intoxication caused by delayed specific immune response, inducing respiratory distress by excessive inflammation and facilitating virus replication by AngII induced endocytosis of ACE2-bound Covid19.

Parallel to the delayed specific immune response to Corona, developing a vaccine takes too long to prevent epidemics or pandemics. This means we should aim for another treatment in a first, non-specific, attempt to limit virus load and AngII intoxication. Since AngII both induces excessive inflammation

and the endocytosis of ACE2 bound Corona virus, inhibiting AngII with ACE inhibitors or AT1R antagonists appears to be a promising tactic, which may reduce morbid inflammatory distress and buy time to form an endogenous virus-specific T cell immune response. Developing the punctual treatment tactic proposed should mitigate the short term effects of the ongoing pandemic. In the longer term, the need to also prioritising the development a vaccine cannot be overemphasized.

References

Jia HP, Look DC, Shi L, et al. ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. J Virol. 2005;79(23):14614–14621. doi:10.1128/JVI.79.23.14614-14621.2005

Danziger RS. Aminopeptidase N in arterial hypertension. Heart Fail Rev. 2008 Sep;13(3):293-8. Epub 2007 Nov 16.

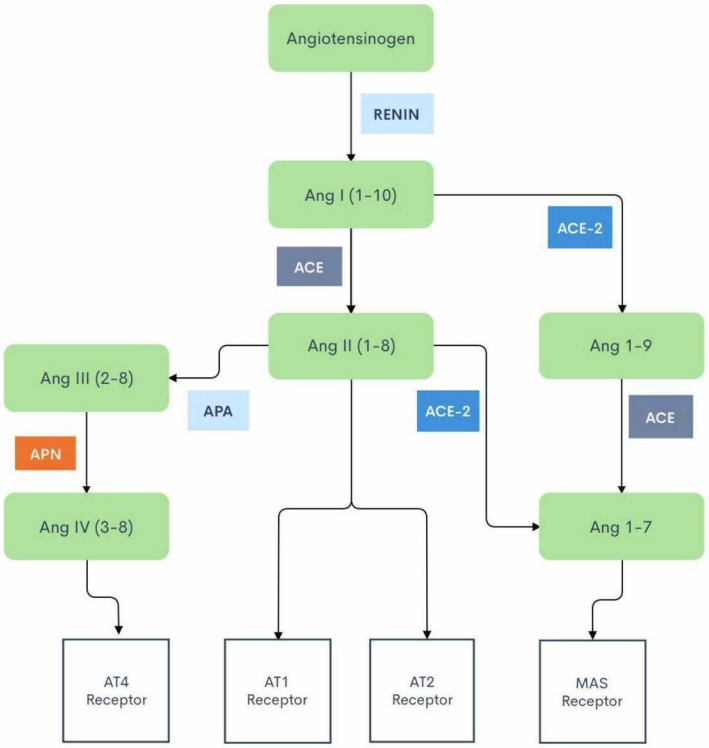
Patel VB et al. Antagonism of angiotensin 1-7 prevents the therapeutic effects of recombinant human ACE2. J Mol Med (Berl). Sep 2015.

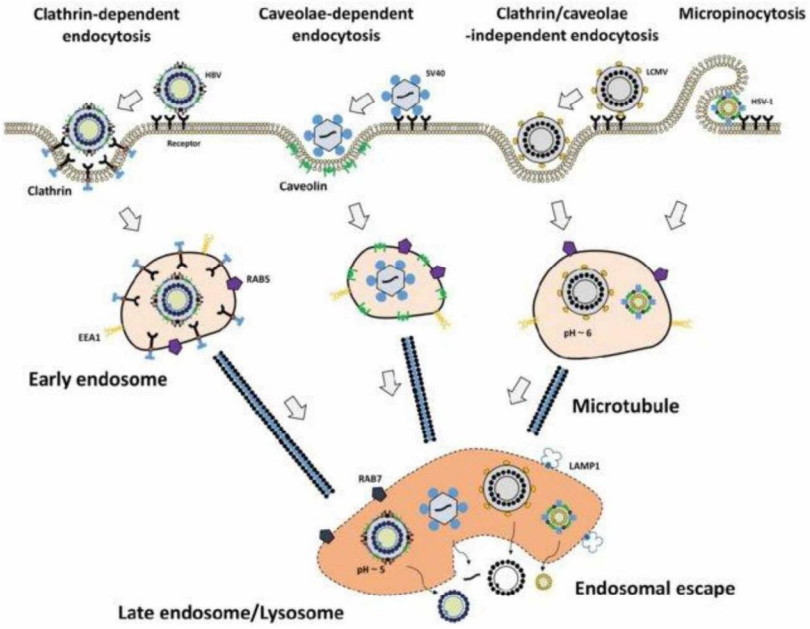
Benigny. Angiotensin II revisited: new roles in inflammation, immunology and aging. Mol Med 2010.

Deshotels. Angiotensin-II mediates ACE2 internalization and degradation through an angiotensin-II type I receptor-dependent mechanism. Hypertension, 2014.

Silva-Filho. AT1 receptor-mediated angiotensin II activation and chemotaxis of T lymphocytes. Mol Immunol, 2011.

Sun ML, Yang JM et al, Inhibitors of RAS might be a good choice for the therapy of COVID-19 Pneumonia, 2020 Feb 16, Epub ahead of print





Endosomal escape of virus.

From: Current Progress of Virus-mimicking Nanocarriers for Drug Delivery. Masaharu Somiya, Qiushi Liu, and Shun'ichi Kuroda. Nanotheranostics, 2017.