SARS-CoV-2 Receptor ACE2 Gene Expression in Small Intestine correlates with Age

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Abstract

SARS-CoV-2 binds via its spikes to its receptor angiotensin-converting enzyme 2 (ACE2). ACE2 is also expressed in small intestinal enterocytes, making the intestine a possible entry site.

We examined duodenal biopsies from 43 healthy human adults. ACE2 gene expression was directly correlated with age (Spearman's r= 0.317, p=0.039. With each year duodenal ACE2 expression increased by 0.083 RU.

The higher intestinal ACE2 mRNA expression in older patients might make them more susceptible to oral SARS-CoV-2 infection.

Introduction

In December 2019 a novel infectious disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected in Wuhan, China, causing the serious epidemic COVID-19 (Zhang et al. 2020). Similar to the SARS coronavirus (SARS-CoV) that had caused outbreaks from 2002-2004, SARS-CoV-2 binds via its spikes to its receptor angiotensin-converting enzyme 2 (ACE2) with high affinity on cell surfaces (Hoffmann et al. 2020; Walls et al. 2020). This may enable SARS-CoV-2 to spread easily from person to person and makes ACE2 a potential target for vaccines and therapies. ACE2 is abundantly present in humans on epithelial cells of the lung (alvelolar epithelial type II cells), kidney, heart, blood, and the small intestine (Hamming et al. 2004). In small intestinal enterocytes, ACE2 is necessary for the expression of luminal membrane amino acid transporters B\(^0\)AT1 (SLC6A19) and SIT1 (SLC6A20) (Camargo et al. 2009; Meier et al. 2018; Verrey et al. 2009; Vuille-dit-Bille et al. 2015). The intestine might therefore be an entry site for SARS-CoV-2, in particular when the protective role of gastric acid is reduced by drugs or surgically. Infection of human might even have started by eating food from the Wuhan market (Zhang et al. 2020). The carboxymonopeptidase ACE2 – similar to its structural homologue angiotensin converting enzyme ACE – also acts as an enzyme that belongs to the renin-angiotensin system (RAS) and whose expression is induced in many tissues by application of RAS-active medications including ACE-inhibitors (ACE-Is) and angiotensin II AT1 receptor blockers (ARBs). The increased ACE2 expression could facilitate infection with SARS-CoV-2. We previously showed in healthy human adults that ACE2 is expressed in the brush border membrane of small intestinal enterocytes, as well as in colonic crypts (Vuille-dit-Bille et al. 2015). ACE2 mRNA expression was almost twice as high in patients treated with ACE-Is, when compared to patients without treatment (Vuille-dit-Bille et al. 2015). More recently we could show that ACE2 protein is also expressed in the brush border membrane of small intestinal enterocytes in human neonates (aged 0-4 days) (Meier et al. 2018). Small intestinal ACE2 mRNA expression was almost 1.5 times higher in human adults versus neonates (Meier et al. 2018).

Methods
Duodenal biopsies were obtained from n= 43 healthy human adults undergoing routine upper endoscopies. Patients with gastrointestinal disorders and/or bleeding disorders, hepatic or kidney dysfunction and/or malignant disease were excluded. Tissue sampling, RNA extraction and real-time PCR analysis were performed as described elsewhere (Vuille-dit-Bille et al. 2015).

Duodenal ACE2 mRNA expression was calculated relative to the housekeeping gene Villin. The study was approved by the local ethics committee (EK-1744).

Correlation with different patient related factors (including age, BMI, weight, height, diabetes mellitus, use of arterial blood pressure medications (ACE-Is and ARBs) was assessed with Spearman's rank correlation and predictors of ACE2 mRNA expression were examined with univariable linear regression.

The effect of ACE inhibitors and Angiotensin II AT1 receptor blockers on intestinal ACE2 and amino acid transporter expression has been published elsewhere (Vuille-dit-Bille et al. 2015).

Results

The analysis of n= 43 specimen revealed that ACE2 gene expression was directly correlated with patient's age (Spearman's r= 0.317, p=0.039; Figure 1). In univariable linear regression each increment (of a year) in age was related to an increase of the duodenal ACE 2 mRNA expression of 0.083 RU. Patients <60 years had a 2.009 RU lower duodenal ACE 2 mRNA expression than patients 60 years and older. Age as scale variable, with an R² of 0.173, showed a strong effect.

Age ranged from 22 to 77 years and did not significantly correlate with the use of ACE inhibitors (Spearman's r= 0.268, p=0.083). ACE 2 mRNA expression according to age was dichotomized for patients with (stars) and without ACE-I treatment (circles).

Discussion

The higher intestinal ACE2 mRNA expression in small intestine of older patients suggests a higher receptor expression that might make them more susceptible to oral SARS-CoV-2 infection.

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Figures

**Figure 1**

Duodenal ACE 2 mRNA expression (relative to Villin) according to age of the n= 43 patients dichotomized for ACE inhibitor consumption.