



# SARS-CoV-2 Infectivity and Neurological Targets in the Brain

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## Abstract

The gateway for invasion by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into human host cells is via the angiotensin-converting enzyme 2 (ACE2) transmembrane receptor expressed in multiple immune and nonimmune cell types. SARS-CoV-2, that causes coronavirus disease 2019 (COVID-19; CoV-19) has the unusual capacity to attack many different types of human host cells simultaneously via novel clathrin- and caveolae-independent endocytic pathways, becoming injurious to diverse cells, tissues and organ systems and exploiting any immune weakness in the host. The elicitation of this multipronged attack explains in part the severity and extensive variety of signs and symptoms observed in CoV-19 patients. To further our understanding of the mechanism and pathways of SARS-CoV-2 infection and susceptibility of specific cell- and tissue-types and organ systems to SARS-CoV-2 attack in this communication we analyzed ACE2 expression in 85 human tissues including 21 different brain regions, 7 fetal tissues and 8 controls. Besides strong ACE2 expression in respiratory, digestive, renal-excretory and reproductive cells, high ACE2 expression was also found in the amygdala, cerebral cortex and brainstem. The highest ACE2 expression level was found in the pons and medulla oblongata in the human brainstem, containing the medullary respiratory centers of the brain, and may in part explain the susceptibility of many CoV-19 patients to severe respiratory distress.

**Keywords** Alzheimer's disease · Angiotensin-converting enzyme 2 (ACE2) receptor · Coronavirus · COVID-19 · CoV-19 · Hartnup's disease · microRNA · miRNA-5197 · SARS-CoV-2 · single stranded RNA (ssRNA)

For interested readers and ACE2-CoV-19 researchers key updated website links, excellently presented, regarding multiple aspects of ACE2 expression, SARS-CoV-2 invasion and CoV-19 disease can be found at: <https://genome.ucsc.edu/covid19.html> (COVID-19 Pandemic Resources at UCSC); <https://www.rndsystems.com/resources/articles/ace-2-sars-receptor-identified> (ACE2: The Receptor for SARS-CoV-2); <https://academic.oup.com/eurheartj/article/26/4/322/439241> (ACE and ACE2: a tale of two enzymes, from the European Heart Journal 2005); and <https://medicalxpress.com/news/2020-05-ace2-receptor-coronavirus.html> (What is the ACE2 receptor, and how is it connected to coronavirus? From the Medical Express, 2020).

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## Introduction

Coronavirus disease 2019 (COVID-19; CoV-19) first emerged about ~mid-December 2019 in an open seafood, poultry and wild game wet market in the city of Wuhan in east-central China. Circumstantial evidence suggested the possibility of an initial zoonotic emergence of SARS-CoV-2 and the role of intermediate hosts such as the fruit

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bat (*Pteropus scapulatus*), pangolin (*Manis javanica*), feral chicken (*Gallus gallus*) and other wild animals, via ‘zoonotic spillover’, in SARS-CoV-2 interspecies transmission (Rodriguez-Morales et al. 2020; Tiwari et al. 2020; Ye et al. 2020). Not previously observed in humans, SARS-CoV-2 is now known to be caused by a single-stranded ribonucleic acid (ssRNA) beta-coronavirus known as ‘severe acute respiratory syndrome coronavirus 2’ (SARS-CoV-2; Bourgonje et al. 2020; Guan et al. 2020; Wackett 2020). Highly transmissible, widespread infection by SARS-CoV-2 was declared a global pandemic by the World Health Organization (WHO) by mid-March 2020 (<https://genome.ucsc.edu/covid19.html>). This novel human viral pathogen primarily induces a dangerous and acute pulmonary disruption with fever, cough, shortness of breath and severe respiratory dysfunction and distress often requiring assisted ventilation. The clinical symptoms of CoV-19 are similar to those reported for ‘severe acute respiratory syndrome coronavirus’ (SARS-CoV) and Middle Eastern respiratory syndrome coronavirus (MERS-CoV; Du et al. 2017; Evans et al. 2020; Ivashchenko et al. 2020). When established and severe, fulminant SARS-CoV-2 infection can rapidly evolve into a systemic illness characterized by hyper-inflammation, cytokine storm and rapid increase in systemic inflammatory biomarkers, elevations in cardiovascular malfunction and severe respiratory failure that is lethal in about 3% of all cases. Multiple neurological symptoms include loss of smell (anosmia), altered taste (ageusia), loss of the coordination of movement (ataxia), headache and nausea, dizziness, intermittent loss or impairment of consciousness, acceleration or aggravation of pre-existing cognitive deficits, direct negative effects of the heightened immune reaction, unusual hyper-inflammatory responses, increased vascular inflammation, inflammation of the brain and spinal cord and atherogenesis, exacerbation or de novo induction of inflammatory neurodegeneration, loss of respiratory control and progressive disturbances in cognition (Baig and Sanders 2020; Zhang et al. 2020) including encephalitis (Efe et al. 2020), stroke, seizures, encephalopathy (Zubair et al. 2019) and acute disseminated encephalomyelitis (ADEM; Panupattanapong and Brooks 2020; Parsons et al. 2020). One worrisome auxiliary sequela of CoV-19 infection called ‘multisystem inflammatory syndrome in children’ (MIS-C) has been observed in which children who have recovered from CoV-19 infection subsequently develop a severe inflammatory syndrome with Kawasaki disease-like features including persistent fever, conjunctivitis, hyper-inflammatory responses, elevated inflammatory markers and immunodeficiency, and a constellation of symptoms including hypotension, cardiac, gastrointestinal (GI), renal, hematologic, dermatologic and neurological involvement (Panupattanapong and Brooks 2020; Ronconi et al. 2020). The WHO reports that globally there are currently about ~ 17 million cases CoV-19 along with

about ~ 700,000 total deaths as of late July 2020 (<https://www.worldometers.info/coronavirus/>; last accessed 29 July 2020).

SARS-CoV-2 possesses an enveloped, positive-stranded ssRNA genome of 29,811 nucleotides (nt) and shares highly homologous RNA sequence with SARS-CoV and MERS-CoV (and like SARS-CoV and MERS-CoV causes severe and acute respiratory distress and a highly lethal pneumonia). SARS-CoV-2 encodes at least six membrane proteins: envelope (E), membrane (M), spike (S1) and nucleocapsid (N) proteins N3-to-N5 (Fehr and Perlman 2015; Sah et al. 2020; Shang et al. 2020). With regard to pathogenicity, spike (S) proteins are essential for viral entry into host cells (Du et al. 2017; Guan et al. 2020; Li et al. 2020a, b; Zubair et al. 2019). SARS-CoV-2 appears to bind exclusively to the angiotensin-converting enzyme (ACE2) protein, a single-pass type 1 transmembrane receptor with its enzymatically active domain exposed on the surface of multiple cell types, such as type II alveolar cells of the respiratory system, enterocytes and intestinal epithelial cells, endothelial cells, epithelial cells of the conjunctival epithelium, kidney cells (renal tubules) and certain immune cells, such as alveolar monocytes/macrophages and certain cells of the CNS including those of the cerebral cortex and brainstem (Guan et al. 2020; Kabbani et al. 2020; Li et al. 2020a, b; Zhou et al. 2020; Zubair et al. 2019). More specifically, the binding of the spike S1 protein of both SARS-CoV and SARS-CoV-2 to the enzymatic domain of ACE2 on the surface of cells results in the endocytosis and translocation of both SARS-CoV-2 and the ACE2 enzyme into endosomes of infected cells (Wang et al. 2008; Millet and Whittaker 2018; Lewis 2020). The cell surface associated transmembrane serine protease 2 TMPRSS2 (epitheliasin; EC 3.4.21.109) also facilitates CoV-19 entry into cells following binding of the viral spike protein S1 to ACE2 (<https://www.genecards.org/cgi-bin/carddisp.pl?gene=TMPRSS2>; Zhou et al. 2020). The inhibition of SARS-CoV-2 and ACE2 recognition, TMPRSS2 signaling and SARS-CoV-2 translocation into host cells is currently under extremely intense research investigation as a cornerstone to the implementation of prospective and efficacious anti-SARS-CoV-2 therapeutic strategies (Akhmerov and Marbán 2020; Bourgonje et al. 2020; Datta et al. 2020; Saavedra 2020; Shang et al. 2020).

Because of the singular importance of ACE2 metalloprotein in the recognition, attachment and entry of SARS-CoV-2 into cells, in the current communication we investigated the expression of ACE2 in 85 human tissues and controls including 21 different anatomical regions of the human brain using multiple tissue expression (MTE) arrays. Interestingly, ACE2 expression was easily detected in multiple brain regions. The highest levels of ACE2 expression in the brain were found in the pons and medulla oblongata, the breathing centers of the brain, which may in part explain

SARS-CoV-2 unusually strong ability to disrupt normal respiration and pulmonary manifestations including shortness of breath, impaired breathing and severe respiratory distress.

## Methods

Human MTE arrays (Invitrogen-Clontech, Palo Alto, CA; cat no. 7775-1) were used at minimum in triplicate to analyze tissue- or brain-specific expression of ACE2 mRNA; this MTE array contains polyA + mRNA samples (each sector containing ~2.0 µg polyA<sup>+</sup> RNA) enriched from 77 human tissues with 8 independent DNA and RNA controls (Fig. 1). A unique human-specific 26 nt ACE2-specific DNA probe 5'-CTTGCAGCTACACCAGTCCCAGGCA-3' (US NIH/NLM Sequence ID: AY217547.1; <https://blast.ncbi.nlm.nih.gov/Blast.cgi#27978647>; see also accession AB046569.1 <https://www.ncbi.nlm.nih.gov/nucore/AB046569.1>) and a human-specific 35 nt ACE2 DNA probe (5'-GGGCTCGAGTTTTCTAAAAGGAGGTCTGAACATC-3'; derived from exon 18 of the ~3.4

knt ACE2 mRNA; Genbank Accession AF291820; NM\_021804.2; <https://www.genscript.com/gene/homo-sapiens/59272/ace2.html>; <https://www.ncbi.nlm.nih.gov/gene/59272>; last accessed 29 July 2020) and exhibiting no homology to ACE1; (Tipnis et al. 2005; Hofmann et al. 2004) were generous gifts from Dr. PN Alexandrov; both the 26 nt and 35 nt ACE2 DNA probes gave similar hybridization signals; data for the 26 nt ACE2 DNA probe is presented here; both of these DNA probes were specifically designed so that they crossed two exons, thereby detecting only ACE2 mRNA and not ACE2 genomic DNA; several other ACE2-specific radiolabeled cDNA probes were used that gave similar hybridization signals; DNA probes were used because RNA–DNA hybrids elicit a more accurate and stable hybridization with a higher energy of association ( $E_A$ ) between the ACE2 DNA probe and the membrane-bound polyA + mRNA target (see Lukiw et al. 1992; Goulter et al. 2004; <https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=DetailsSearch&Term=59,272>); ACE2 DNA probes were radiolabeled (i) using Random Primer Labeling and the direct incorporation of [ $\alpha$ -<sup>32</sup>P]

	1	2	3	4	5	6	7	8	9	10	11	12
<b>A</b>	whole brain	cerebellum, left	substantia nigra	heart	esophagus	colon, transverse	kidney	lung	liver	leukemia, HL-60	fetal brain	yeast total RNA
<b>B</b>	cerebral cortex	cerebellum, right	nucleus accumbens	aorta	stomach	colon, descending	skeletal muscle	placenta	pancreas	HeLa S3	fetal heart	yeast tRNA
<b>C</b>	frontal lobe	corpus callosum	thalamus	atrium, left	duodenum	rectum	spleen	bladder	adrenal gland	leukemia, K-562	fetal kidney	<i>E. coli</i> rRNA
<b>D</b>	parietal lobe	amygdala	pituitary gland	atrium, right	jejunum		thymus	uterus	thyroid gland	leukemia, MOLT-4	fetal liver	<i>E. coli</i> DNA
<b>E</b>	occipital lobe	caudate nucleus	spinal cord	ventricle, left	ileum		peripheral blood leukocyte	prostate	salivary gland	Burkitt's lymphoma, Raji	fetal spleen	poly r(A)
<b>F</b>	temporal lobe	hippocampus		ventricle, right	ileocecum		lymph node	testis	mammary gland	Burkitt's lymphoma, Daudi	fetal thymus	human Cyt-1 DNA
<b>G</b>	p.g.* of cerebral cortex	medulla oblongata		inter-ventricular septum	appendix		bone marrow	ovary		colorectal adenocarcinoma, SW480	fetal lung	human DNA 100 ng
<b>H</b>	pons	putamen		apex of the heart	colon, ascending		trachea			lung carcinoma, A549		human DNA 500 ng

\* paracentral gyrus

**Fig. 1** Organization of human MTE blot for Northern blot analysis; ACE2 signals were compared to G3PDH signals in the same sample and expressed as 'relative signal intensity'; these are shown bar graph

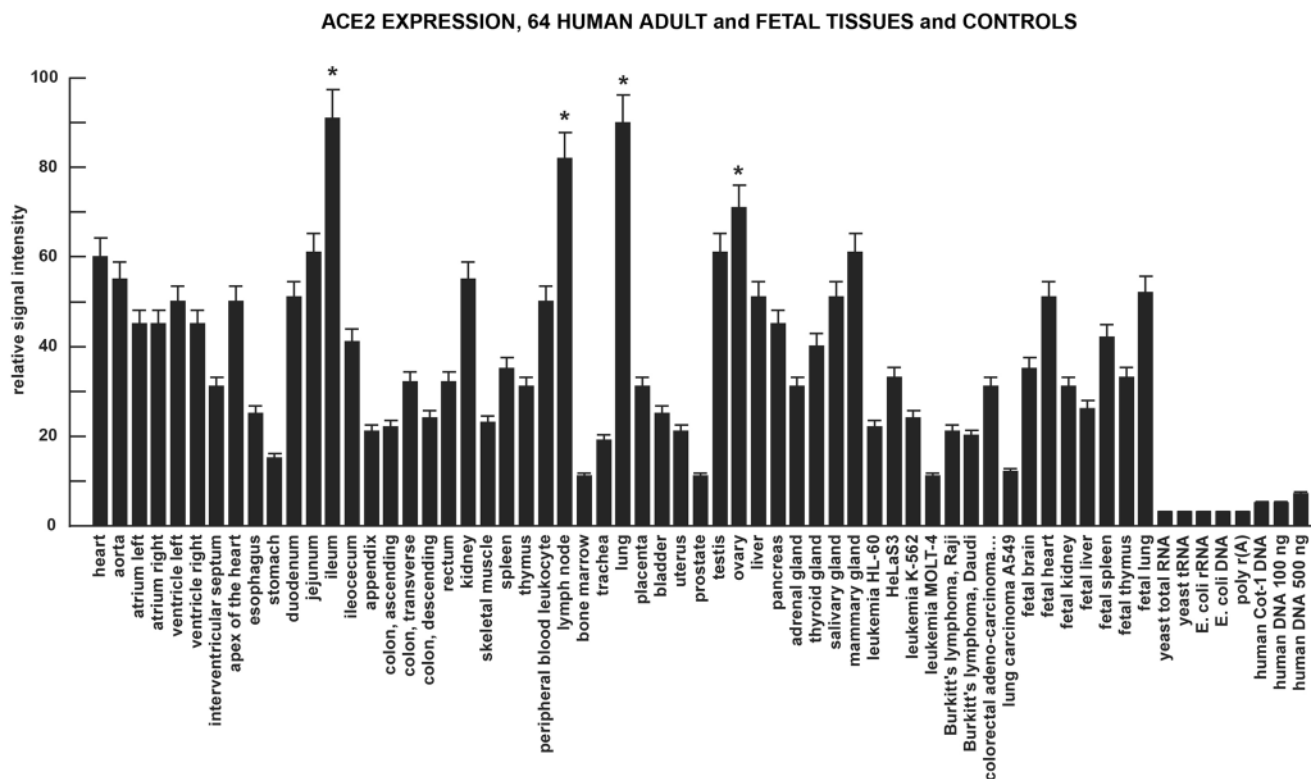
format in Figs. 2 and 3; a minimum of  $N=6$  MTE arrays (3 for ACE2 and 3 for G3PDH) were used in each type-of-tissue determination

dCTP (3000 Ci/mmol, Amersham, Chicago, IL) or (ii) were end-labeled using [ $\gamma$ - $^{32}$ P]dATP (3000 Ci/mmol, Amersham redivue); glyceraldehyde 3-phosphate dehydrogenase (G3PDH) was used for control normalization (see <https://www.takara.co.kr/file/manual/pdf/PT3307-1.pdf>; Lukiw et al. 1990,1992; Goulter et al 2004); to obtain maximal signal quantitation accuracy hybridized and washed membranes were overlaid on the MTE template (Fig. 1) excised and each sector counted separately in 10 ml liquid scintillation fluid (Ultima Gold, PerkinElmer, Waltham, MA) in a Liquid Scintillation Counter (LS600016 LSC, Beckman, Fullerton, CA); relative signal intensities (Figs. 2, 3) were expressed by comparing the ACE2 hybridization signal to the G3PDH signal for each polyA + mRNA on the MTE array (see Lukiw et al. 1990, 1992; Zhao et al. 2001; Jaber et al. 2017; Piras et al. 2020). Statistical significance was analyzed using a two-way factorial analysis of variance ( $p$ , ANOVA; SAS

Institute, Cary, NC). A  $p < 0.01$  (ANOVA) was deemed as high statistical significance; experimental values are expressed as the means  $\pm$  SD.

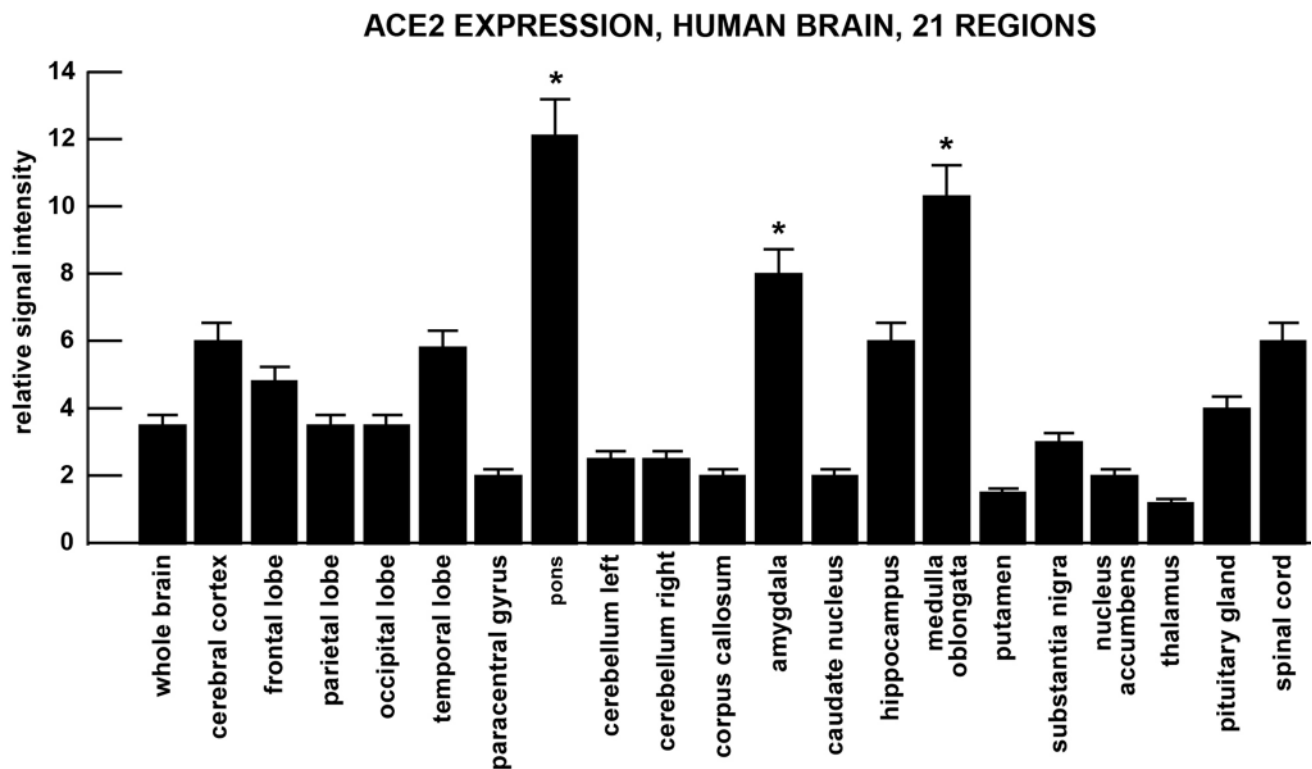
## Results

At the mRNA level ACE2 is very widely expressed in multiple human cell- and tissue-types and organ systems. The most consistent expression was found in all regions of the heart sampled and was highest in the adult lung, ileum, lymph node, testis and ovaries. This pattern of high ACE2 expression is reciprocated in both adult and fetal heart and lung (Fig. 2). In the brain there was a consistent ACE2 expression across the cerebral cortex and the highest ACE2 expression was found in the pons and medulla oblongata (Fig. 3). Patterns of cell-, tissue- and organ-specific expression of ACE2 suggests that this common dipeptidyl



**Fig. 2** Tissue-specific patterns of ACE2 expression are a strong indicator of gene function and susceptibility to SARS-CoV-2 invasion and the development of CoV-19. High ACE2 expression in vascular, gastrointestinal (GI) tract, respiratory, excretory and reproductive tissues and some relevant cancers and controls; the highest values of expression were found in the heart (both adult and fetal), ileum, kidney, lung (both adult and fetal), testes, ovary and mammary gland; ACE2 is a member of the angiotensin-converting enzyme family of dipeptidyl carboxydipeptidases and has considerable homology to human angiotensin 1 converting enzyme (ACE1), however the ACE2 DNA probe here was unique showing no homology with ACE1;

ACE2, expressed as both a secreted protein and trans-membrane form catalyzes the cleavage of angiotensin I (ANG) into ANG<sub>1-9</sub>, and ANG II into the vasodilator ANG<sub>1-7</sub>; ACE-2 is also a receptor to the spike (S1) glycoprotein of the human coronavirus HCoV-NL63 and the human SARS-CoV and SARS-CoV-2 virus that causes CoV-19 (see: <https://www.youtube.com/watch?v=W1k1sUoLPIA>; <https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=DetailsSearch&Term=59,272>; last accessed 29 July 2020); at least  $N=6$  MTE arrays (at minimum 3 for ACE2 and 3 for G3PDH) were used in each tissue determination; \* $p < 0.01$  (ANOVA); error bars represent one standard deviation of the mean



**Fig. 3** ACE2 expression in 21 anatomical regions of the human brain. The highest expression of the SARS-CoV-2 receptor ACE-2 was found in the amygdala, pons and medulla oblongata; the later two regions contain the respiratory control centers of the brain; considerable expression of ACE2 in the brain, temporal lobe and hippocampus may in part explain neurological disruption and cognitive dysfunction associated with SARS-CoV-2 infection; note difference of scale in the Y-axis (ordinate) compared to Fig. 2; to obtain maximal signal quantitation hybridized and washed membranes were overlaid

on the MTE template (Fig. 1) excised and counted in liquid scintillation fluid as previously described; relative signal intensities (Figs. 2, 3) were expressed by comparing the ACE2 hybridization signal to the G3PDH signal for each polyA+mRNA on the same MTE array sector (see Lukiw et al. 1990, 1992; Zhao et al. 2001; Jaber et al. 2017); at least  $N=6$  MTE arrays (3 for ACE2 and 3 for G3PDH) were used in each brain tissue determination;  $*p < 0.01$  (ANOVA); error bars represent one standard deviation of the mean

carboxydipeptidase (E.C.3.4.17.23) plays an important role in the regulation of respiratory, cardiovascular, GI-tract and renal-excretory system functions, as well as in a wide range of brain and CNS anatomical regions with multiple neurological functions (see Figs. 2, 3 and legends). In general, the data indicate that ACE2 represents a very common and widespread receptor type and that the SARS-CoV-2 virus has taken advantage of this wide range of potential cellular entry points and a remarkably efficient viral invasion strategy to ensure its survival and proliferation in multiple human cell types (see below).

## Discussion

The major established biological function for the 805 amino acid, 92.5 kDa, zinc-containing ACE2 membrane-integral metalloprotein (E.C.3.4.17.23) is catalyzing the hydrolysis of the vasoconstrictor peptide angiotensin II (ANG II) into the vasodilator ANG<sub>1-7</sub>. Reducing the amount of

ANG II while increasing ANG<sub>1-7</sub> results in a relaxation of vascular smooth muscle, a lowering of both local and systemic vascular resistance to blood flow and hence elicits a decrease in blood pressure (Wang et al. 2016; Datta et al. 2020; Li et al. 2020a, b). ACE2 therefore plays a key regulatory role in the classical axis of the renin-angiotensin system (RAS), a hormonal system that regulates not only systemic vascular resistance to blood flow and blood pressure but also fluid and electrolyte balance (Kehoe et al. 2016; Wang et al. 2016; Datta et al. 2020). ACE2 has also been reported to have ancillary physiological roles: (i) in the regulation of membrane trafficking of the sodium-dependent neutral amino acid transporter SLC6A19 that has been implicated in Hartnup's disease (a disorder of amino acid homeostasis and translocation; Gheblawi et al. 2020); (ii) in the interaction with other vasoactive peptides such as Apelin that regulate blood pressure and myocardial contractility (Kuba et al. 2013); and (iii) in GI-tract inflammation and the regulation of the complexity and speciation of the GI-tract microbiome (Kuba et al. 2013; Gheblawi et al. 2020; Lukiw 2020;

Zuo et al. 2020; unpublished observation). Other important contributory factors associated with variable ACE2 receptor expression (and hence potential for SARS-CoV-2 infection and CoV-19 severity) include age, sex, ethnicity, medication and several co-morbidities, such as cardiovascular disease, metabolic syndrome and obesity, and dementia and cognitive decline (Baig and Sanders 2020; Gheblawi et al. 2020). As might be expected the blockage or downregulation of ACE2 leads to ‘unopposed’ ANG II accumulation resulting in pleiotropic effects including vasoconstriction, aldosterone secretion, endothelial dysfunction and altered inflammatory signaling which may impact the progress of CoV-19 infection all via increased activity of the RAS (Du et al. 2017; Datta et al. 2020; Saavedra 2020). Indeed molecular-based rational design of angiotensin receptor blockers (ARBs) with enhanced affinities for ACE2 or the spike (S1) protein of the coronaviruses may further advance the development of neutralizing antibodies, decoy ligands and perhaps advance more effective pharmacological strategies for the suppression of SARS-CoV-2 infection, but these therapeutic approaches are currently in the very earliest stages of CoV-19 research investigation and their clinical efficacies, if any, remains to be established (Du et al. 2017; de Vries 2020; Evans et al. 2020; Lewis 2020).

Besides considerable ACE2 expression in cells and tissues of the respiratory, cardiovascular, GI-tract, renal-excretory and reproductive systems (Harmer et al. 2002; Datta et al. 2020) there is in addition significant ACE2 expression in different anatomical regions of the brain and CNS (Fig. 3). This is in concordance with the multiple neurological anomalies associated with CoV-19 infection including headache, anosmia, ageusia, lethargy, confusion, cognitive impairment and loss of autonomic respiratory control (Baig and Sanders 2020; Bourgonje et al. 2020; Datta et al. 2020; Efe et al. 2020; Heneka et al. 2020; Kabbani and Olds 2020). Significant neuro-invasion involving SARS-CoV has been reported from both patients and experimental animals where the brainstem was heavily infected from apparent spreading via a synapse-connected route to the medullary cardiorespiratory centers (Zubair et al. 2019; Chigr et al. 2020). Indeed SARS-CoV-2-mediated neuro-invasion may be achieved by several routes, including blood-borne transport to highly vascularized brain tissues, by trans-synaptic transfer across infected neurons, via entry through the olfactory nerve, infection via the ocular epithelium or vascular endothelium, or leukocyte migration across the blood–brain barrier (Kabbani and Olds 2020; Zhou et al. 2020). Interestingly ACE2 receptor expression was also easily detected in retinal cells of the eye and visual system (manuscript in preparation), suggesting that the eye and/or visual system may provide additional entry points for SARS-CoV-2 invasion (and suggesting that eyeglasses or face shields may be as important as face masks in reducing SARS-CoV-2

transmission). Co-localization studies have suggested that SARS-CoV-2 viral entry may be mediated by a clathrin- and caveolae-independent mechanism and that cholesterol- and sphingolipid-rich lipid raft micro-domains assist in SARS-CoV-2-ACE2-interaction and subsequent SARS-CoV-2 entry into susceptible cells via the ubiquitous ACE2 receptor (Simmons et al. 2004; Wang et al. 2008; Gheblawi et al. 2020).

Interestingly (i) ACE2 expression is significantly decreased in Alzheimer’s disease (AD) affected brain tissues and in amyloid over-expressing transgenic murine models of AD (Kehoe et al. 2016; Rocha et al. 2018; Royea and Hamel 2020), (ii) this deficit is associated with increased amyloid-beta (A $\beta$ ) peptide load and tau pathology, the two pathophysiological hallmarks of AD (Kehoe et al. 2016; Rocha et al. 2018; Evans et al. 2020), and (iii) hyperactivity of the classical axis of the renin-angiotensin system (RAS), mediated by ANG II activation of the ANG II type 1 receptor (AT1R), is further implicated in biofluid imbalance in the neurovascular and neuro-immune pathology associated with AD (Kehoe et al. 2016; Evans et al. 2020).

Lastly, the ssRNA SARS-CoV-2 virus (at about ~30,000 nt), considerably larger than the size of the average cellular messenger RNA (mRNA), may be intrinsically susceptible to complementary base-pair interaction with other ssRNAs including microRNAs (miRNAs) and the RNA binding proteins associated with pre-miRNA processing into mature miRNA and translocation. For example the 23 nt human miRNA hsa-miRNA-5197 is well over 90% homologous to a 3’ down-stream region of the SARS-CoV-2 RNA sequence (Ivashchenko et al. 2020; unpublished observations). Targeting and inactivation of SARS-CoV-2 by pre-existing or artificially synthesized and stabilized miRNAs (such as hsa-miRNA-5197): (i) may provide a natural protection mechanism against SARS-CoV-2 invasion; (ii) may help explain individual natural immunity to SARS-CoV-2 infection of some persons who naturally express hsa-miRNA-5197 or other miRNAs or ssRNAs that target pathological viruses such as SARS-CoV, SARS-CoV-2 or MERS-CoV; and (iii) may be of therapeutic value in the accelerated depolymerization and destruction of the invading SARS-CoV-2 viral sequence itself, resulting in SARS-CoV-2 degradation and the rapid cessation and termination of SARS-CoV-2’s lethal effects.

## Conclusions

The omnipresence of ACE2 expression in multiple human cell- and tissue-types is noteworthy. SARS-CoV-2 has evolved a remarkable evolutionary strategy to ensure its replication, survival and spread by exploiting the presence of a very common, abundant and susceptible transmembrane

ACE2 receptor making many different neural and extra-neural human cell- and tissue-types at high risk and susceptibility to SARS-CoV-2 invasion. Many research gaps remain, and additional basic investigative research is urgently required to more fully understand the etiology, epidemiology, pathological mechanisms and neurobiology of CoV-19 disease. A real danger of SARS-CoV-2 infection is not only its highly transmissible and contagious nature and lethality but also: (i) SARS-CoV-2's simultaneous and multipronged attack on many human cell- and tissue-types involving vital and critical respiratory, immunological, vascular, renal-excretory and neural systems; and (ii) an unprecedented coordinated disruption of the complex neurophysiology, neurochemistry and neurology of the cells of the brain that normally regulate these multiple neurobiological systems.

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**Author Contributions** JMH and WJL conceived and wrote the paper; AP participated in literature search and data collection and analysis; all authors read and approved the manuscript.

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