February 4, 2020; updated March 9, 2020

[Int J Oral Sci.](https://www.ncbi.nlm.nih.gov/pubmed/32094336) 2020 Feb 24;12(1):8. doi: 10.1038/s41368-020-0074-x.

# High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa.

[Xu H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Xu%20H%5BAuthor%5D&cauthor=true&cauthor_uid=32094336)1, [Zhong L](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhong%20L%5BAuthor%5D&cauthor=true&cauthor_uid=32094336)1, [Deng J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Deng%20J%5BAuthor%5D&cauthor=true&cauthor_uid=32094336)1, [Peng J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Peng%20J%5BAuthor%5D&cauthor=true&cauthor_uid=32094336)1, [Dan H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Dan%20H%5BAuthor%5D&cauthor=true&cauthor_uid=32094336)1, [Zeng X](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zeng%20X%5BAuthor%5D&cauthor=true&cauthor_uid=32094336)1, [Li T](https://www.ncbi.nlm.nih.gov/pubmed/?term=Li%20T%5BAuthor%5D&cauthor=true&cauthor_uid=32094336)2, [Chen Q](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chen%20Q%5BAuthor%5D&cauthor=true&cauthor_uid=32094336)1.

### [Author information](https://www.ncbi.nlm.nih.gov/pubmed/32094336)

### Abstract

It has been reported that ACE2 is the main host cell receptor of 2019-nCoV and plays a crucial role in the entry of virus into the cell to cause the final infection. To investigate the potential route of 2019-nCov infection on the mucosa of oral cavity, bulk RNA-seq profiles from two public databases including The Cancer Genome Atlas (TCGA) and Functional Annotation of The Mammalian Genome Cap Analysis of Gene Expression (FANTOM5 CAGE) dataset were collected. RNA-seq profiling data of 13 organ types with para-carcinoma normal tissues from TCGA and 14 organ types with normal tissues from FANTOM5 CAGE were analyzed in order to explore and validate the expression of ACE2 on the mucosa of oral cavity. Further, single-cell transcriptomes from an independent data generated in-house were used to identify and confirm the ACE2-expressing cell composition and proportion in oral cavity. The results demonstrated that the ACE2 expressed on the mucosa of oral cavity. Interestingly, this receptor was highly enriched in epithelial cells of tongue. Preliminarily, those findings have explained the basic mechanism that the oral cavity is a potentially high risk for 2019-nCoV infectious susceptibility and provided a piece of evidence for the future prevention strategy in dental clinical practice as well as daily life.

[Nature.](https://www.ncbi.nlm.nih.gov/pubmed/14647384) 2003 Nov 27;426(6965):450-4.

# Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus.

[Li W](https://www.ncbi.nlm.nih.gov/pubmed/?term=Li%20W%5BAuthor%5D&cauthor=true&cauthor_uid=14647384)1, [Moore MJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Moore%20MJ%5BAuthor%5D&cauthor=true&cauthor_uid=14647384), [Vasilieva N](https://www.ncbi.nlm.nih.gov/pubmed/?term=Vasilieva%20N%5BAuthor%5D&cauthor=true&cauthor_uid=14647384), [Sui J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sui%20J%5BAuthor%5D&cauthor=true&cauthor_uid=14647384), [Wong SK](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wong%20SK%5BAuthor%5D&cauthor=true&cauthor_uid=14647384), [Berne MA](https://www.ncbi.nlm.nih.gov/pubmed/?term=Berne%20MA%5BAuthor%5D&cauthor=true&cauthor_uid=14647384), [Somasundaran M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Somasundaran%20M%5BAuthor%5D&cauthor=true&cauthor_uid=14647384), [Sullivan JL](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sullivan%20JL%5BAuthor%5D&cauthor=true&cauthor_uid=14647384), [Luzuriaga K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Luzuriaga%20K%5BAuthor%5D&cauthor=true&cauthor_uid=14647384), [Greenough TC](https://www.ncbi.nlm.nih.gov/pubmed/?term=Greenough%20TC%5BAuthor%5D&cauthor=true&cauthor_uid=14647384), [Choe H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Choe%20H%5BAuthor%5D&cauthor=true&cauthor_uid=14647384), [Farzan M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Farzan%20M%5BAuthor%5D&cauthor=true&cauthor_uid=14647384).

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### Abstract

Spike (S) proteins of coronaviruses, including the coronavirus that causes severe acute respiratory syndrome (SARS), associate with cellular receptors to mediate infection of their target cells. Here we identify a metallopeptidase, angiotensin-converting enzyme 2 (ACE2), isolated from SARS coronavirus (SARS-CoV)-permissive Vero E6 cells, that efficiently binds the S1 domain of the SARS-CoV S protein. We found that a soluble form of ACE2, but not of the related enzyme ACE1, blocked association of the S1 domain with Vero E6 cells. 293T cells transfected with ACE2, but not those transfected with human immunodeficiency virus-1 receptors, formed multinucleated syncytia with cells expressing S protein. Furthermore, SARS-CoV replicated efficiently on ACE2-transfected but not mock-transfected 293T cells. Finally, anti-ACE2 but not anti-ACE1 antibody blocked viral replication on Vero E6 cells. Together our data indicate that ACE2 is a functional receptor for SARS-CoV. {Li, 2003}.

[Redox Biol.](https://www.ncbi.nlm.nih.gov/pubmed/31421410) 2019 Sep;26:101295. doi: 10.1016/j.redox.2019.101295. Epub 2019 Aug 8.

**Vitamin D receptor activation regulates microglia polarization and oxidative stress in spontaneously hypertensive rats and angiotensin II-exposed microglial cells: Role of renin-angiotensin system.**

[Cui C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Cui%20C%5BAuthor%5D&cauthor=true&cauthor_uid=31421410)1, [Xu P](https://www.ncbi.nlm.nih.gov/pubmed/?term=Xu%20P%5BAuthor%5D&cauthor=true&cauthor_uid=31421410)2, [Li G](https://www.ncbi.nlm.nih.gov/pubmed/?term=Li%20G%5BAuthor%5D&cauthor=true&cauthor_uid=31421410)3, [Qiao Y](https://www.ncbi.nlm.nih.gov/pubmed/?term=Qiao%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=31421410)4, [Han W](https://www.ncbi.nlm.nih.gov/pubmed/?term=Han%20W%5BAuthor%5D&cauthor=true&cauthor_uid=31421410)2, [Geng C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Geng%20C%5BAuthor%5D&cauthor=true&cauthor_uid=31421410)2, [Liao D](https://www.ncbi.nlm.nih.gov/pubmed/?term=Liao%20D%5BAuthor%5D&cauthor=true&cauthor_uid=31421410)5, [Yang M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Yang%20M%5BAuthor%5D&cauthor=true&cauthor_uid=31421410)2, [Chen D](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chen%20D%5BAuthor%5D&cauthor=true&cauthor_uid=31421410)2, [Jiang P](https://www.ncbi.nlm.nih.gov/pubmed/?term=Jiang%20P%5BAuthor%5D&cauthor=true&cauthor_uid=31421410)6.

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**Abstract**

Hypertension is one of the major predisposing factors for neurodegenerative disease characterized with activated renin-angiotensin system (RAS) in both periphery and brain. Vitamin D (VitD) is recently recognized as a pleiotropic hormone with strong neuroprotective properties. While multiple lines of evidence suggest that VitD can act on RAS, the evidence concerning the crosstalk between VitD and RAS in the brain is limited. Therefore, this study aims to evaluate whether VitD can modulate brain RAS to trigger neuroprotective actions in the brain of spontaneously hypertensive rats (SHR). Our data showed that calcitriol treatment induced VDR expression and inhibited neural death in the prefrontal cortex of SHR. Sustained calcitriol administration also inhibited microglia M1 polarization, but enhanced M2 polarization, accompanied with decreased expression of proinflammatory cytokines. We then further explored the potential mechanisms and showed that SHR exhibited overactivated classical RAS with increased expression of angiotensin II (Ang II) receptor type 1 (AT1), angiotensin converting enzyme (ACE) and Ang II production, whereas the counteracting arm of traditional RAS, ACE2/Ang(1-7)/MasR, was impaired in the SHR brain. Calcitriol nonsignificantly suppressed AT1 and ACE but markedly reduced Ang II formation. Intriguingly, calcitriol exerted pronouncedly impact on ACE2/Ang(1-7)/MasR axis with enhanced expression of ACE2, MasR and Ang(1-7) generation. Meanwhile, calcitriol ameliorated the overactivation of NADPH-oxidase (Nox), the downstream of RAS, in SHR, and also mitigated oxidative stress. In microglial (BV2) cells, we further found that calcitriol induced ACE2 and MasR with no significant impact on ACE and AT1. In accordance, calcitriol also attenuated Ang II-induced Nox activation and ROS production, and shifted the microglia polarization from M1 to M2 phenotype. However, co-treatment with A779, a specific MasR antagonist, abrogated the antioxidant and neuroimmune modulating actions of VitD. These findings strongly indicate the involvement of ACE2/Ang(1-7)/MasR pathway in the neuroprotective mechanisms of VitD in the hypertensive brain.

[Eur J Pharmacol.](https://www.ncbi.nlm.nih.gov/pubmed/29715453) 2018 Jul 15;831:68-76. doi: 10.1016/j.ejphar.2018.04.032. Epub 2018 Apr 30.

**Role of Wnt4/β-catenin, Ang II/TGFβ, ACE2, NF-κB, and IL-18 in attenuating renal ischemia/reperfusion-induced injury in rats treated with Vit D and pioglitazone.**

[Ali RM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ali%20RM%5BAuthor%5D&cauthor=true&cauthor_uid=29715453)1, [Al-Shorbagy MY](https://www.ncbi.nlm.nih.gov/pubmed/?term=Al-Shorbagy%20MY%5BAuthor%5D&cauthor=true&cauthor_uid=29715453)2, [Helmy MW](https://www.ncbi.nlm.nih.gov/pubmed/?term=Helmy%20MW%5BAuthor%5D&cauthor=true&cauthor_uid=29715453)3, [El-Abhar HS](https://www.ncbi.nlm.nih.gov/pubmed/?term=El-Abhar%20HS%5BAuthor%5D&cauthor=true&cauthor_uid=29715453)1.

[**Author information**](https://www.ncbi.nlm.nih.gov/pubmed/29715453)

**Abstract**

Renal ischemia-reperfusion injury (I/RI) remains a critical clinical situation. Several evidence revealed the potential reno-protective effects of Vitamin D and/or pioglitazone, on renal I/RI. This study addresses the possible involvement of the Wnt4/β-catenin signaling, p-S536NF-κBp65, PPARγ, Ang II/TGF-β, and ACE2 as potential effectors to vitamin D and pioglitazone-mediated renoprotective effects. Two sets of Sprague-Dawley rats (n = 30 rat each), were randomized into sham, I/R, Vit D "alfacalcidol" (5 ng/kg/day), pioglitazone (5 mg/kg/day), and Vit D + pioglitazone groups. In all groups renal biochemical parameters, as well as inflammatory and structural profiles were assessed, besides the expression/contents of Wnt4/β-catenin and pS536-NF-κBp65. All treatments started 7 days before I/RI and animals were killed 24 h after I/RI in the first set, while those in the 2nd set continued their treatments for 14 days. After 24 h, all pre-treatments impeded theI/R effect on neutrophils recruitment, p-S536NF-κBp65, IL-18, NGAL, caspase-3, AngII, ACE-2, PPARγ and TGF-β, besides the expression of Wnt4 and ACE-2 with notable reflection on histological changes. Two weeks after I/RI, except a marked up regulation in Wnt4 expression and a striking elevation in the β-catenin content, the magnitude of the injurious events was relatively less pronounced, an effect that was mostly augmented by the different treatments. The current study pledges a promising and novel reno-protective role of the administration of Vit D and pioglitazone entailing a potential involvement of ICAM-1, MPO, NF-κB, Ang II, ACE2, TGFβ, and a modulation of Wnt4/β-catenin pathway.

[Mol Med Rep.](https://www.ncbi.nlm.nih.gov/pubmed/28944831) 2017 Nov;16(5):7432-7438. doi: 10.3892/mmr.2017.7546. Epub 2017 Sep 20.

**Vitamin D alleviates lipopolysaccharide‑induced acute lung injury via regulation of the renin‑angiotensin system.**

[Xu J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Xu%20J%5BAuthor%5D&cauthor=true&cauthor_uid=28944831)1, [Yang J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Yang%20J%5BAuthor%5D&cauthor=true&cauthor_uid=28944831)2, [Chen J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chen%20J%5BAuthor%5D&cauthor=true&cauthor_uid=28944831)3, [Luo Q](https://www.ncbi.nlm.nih.gov/pubmed/?term=Luo%20Q%5BAuthor%5D&cauthor=true&cauthor_uid=28944831)4, [Zhang Q](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhang%20Q%5BAuthor%5D&cauthor=true&cauthor_uid=28944831)1, [Zhang H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhang%20H%5BAuthor%5D&cauthor=true&cauthor_uid=28944831)2.

[**Author information**](https://www.ncbi.nlm.nih.gov/pubmed/28944831)

**Abstract**

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are the clinical manifestations of severe lung damage and respiratory failure. ALI and ARDS result are associated with high mortality in patients. At present, no effective treatments for ALI and ARDS exist. It is established that vitamin D exhibits anti‑inflammatory effects, however, the specific effect of vitamin D on ALI remains largely unknown. The aim of the present study was to investigate whether, and by which mechanism, vitamin D alleviates lipopolysaccharide (LPS)‑induced ALI. The results demonstrated that a vitamin D agonist, calcitriol, exhibited a beneficial effect on LPS‑induced ALI in rats; calcitriol pretreatment significantly improved LPS‑induced lung permeability, as determined using Evans blue dye. Results from reverse transcription‑quantitative polymerase chain reaction, western blotting and ELISA analysis demonstrated that calcitriol also modulated the expression of members of the renin‑angiotensin system (RAS), including angiotensin (Ang) I‑converting enzymes (ACE and ACE2), renin and Ang II, which indicates that calcitriol may exert protective effects on LPS‑induced lung injury, at least partially, by regulating the balance between the expression of members of the RAS. The results of the present study may provide novel targets for the future treatment of ALI.

[Nephrol Dial Transplant.](https://www.ncbi.nlm.nih.gov/pubmed/25813276) 2015 Jul;30(7):1176-85. doi: 10.1093/ndt/gfv025. Epub 2015 Mar 26.

# Circulating angiotensin-converting enzyme 2 activity in patients with chronic kidney disease without previous history of cardiovascular disease.

[Anguiano L](https://www.ncbi.nlm.nih.gov/pubmed/?term=Anguiano%20L%5BAuthor%5D&cauthor=true&cauthor_uid=25813276)1, [Riera M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Riera%20M%5BAuthor%5D&cauthor=true&cauthor_uid=25813276)1, [Pascual J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Pascual%20J%5BAuthor%5D&cauthor=true&cauthor_uid=25813276)1, [Valdivielso JM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Valdivielso%20JM%5BAuthor%5D&cauthor=true&cauthor_uid=25813276)2, [Barrios C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Barrios%20C%5BAuthor%5D&cauthor=true&cauthor_uid=25813276)1, [Betriu A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Betriu%20A%5BAuthor%5D&cauthor=true&cauthor_uid=25813276)3, [Mojal S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Mojal%20S%5BAuthor%5D&cauthor=true&cauthor_uid=25813276)4, [Fernández E](https://www.ncbi.nlm.nih.gov/pubmed/?term=Fern%C3%A1ndez%20E%5BAuthor%5D&cauthor=true&cauthor_uid=25813276)3, [Soler MJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Soler%20MJ%5BAuthor%5D&cauthor=true&cauthor_uid=25813276)1; [NEFRONA study](https://www.ncbi.nlm.nih.gov/pubmed/?term=NEFRONA%20study%5BCorporate%20Author%5D).

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### Abstract

#### BACKGROUND:

Patients with cardiovascular (CV) disease have an increased circulating angiotensin-converting enzyme 2 (ACE2) activity, but there is little information about changes in ACE2 in chronic kidney disease (CKD) patients without history of CV disease. We examined circulating ACE2 activity in CKD patients at stages 3-5 (CKD3-5) and in dialysis (CKD5D) without any history of CV disease.

#### METHODS:

Circulating ACE2 activity was measured in human ethylenediamine-tetraacetic acid (EDTA)-plasma samples from the NEFRONA study (n = 2572): control group (CONT) (n = 568), CKD3-5 (n = 1458) and CKD5D (n = 546). Different clinical and analytical variables such as gender; age; history of diabetes mellitus (DM), dyslipidemia and hypertension; glycaemic, renal, lipid and anaemia profiles; vitamin D analogues treatment and antihypertensive treatments (angiotensin-converting enzyme inhibitor and angiotensin receptor blockade) were analysed. Circulating ACE2 and ACE activities were measured using modified fluorimetric assay for EDTA-plasma samples, where zinc chloride was added to recover enzymatic activity.

#### RESULTS:

In CKD3-5 and CKD5D, significant decrease in circulating ACE2 activity was observed when compared with CONT, but no differences were found between CKD3-5 and CKD5 when performing paired case-control studies. By multivariate linear regression analysis, male gender and advanced age were identified as independent predictors of ACE2 activity in all groups. Diabetes was identified as independent predictor of ACE2 activity in CKD3-5. Significant increase in the activity of circulating ACE was found in CKD3-5 and CKD5D when compared with CONT and in CKD5D when compared with CKD3-5. By multiple regression analysis, female gender and younger age were identified as independent predictors of ACE activity in CONT and CKD3-5. Diabetes was also identified as an independent predictor of ACE activity in CKD3-5 patients.

#### CONCLUSIONS:

Circulating ACE2 and ACE activities can be measured in human EDTA-plasma samples with zinc added to recover enzymatic activity. In a CKD population without previous history of CV disease, ACE2 activity from human EDTA-plasma samples directly correlated with the classical CV risk factors namely older age, diabetes and male gender. Our data suggest that circulating ACE2 is altered in CKD patients at risk for CV event.

[Peptides.](https://www.ncbi.nlm.nih.gov/pubmed/23291307) 2013 Apr;42:25-34. doi: 10.1016/j.peptides.2012.12.023. Epub 2013 Jan 3.

**Angiotensin-(1-7) inhibits vascular calcification in rats.**

[Sui YB](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sui%20YB%5BAuthor%5D&cauthor=true&cauthor_uid=23291307)1, [Chang JR](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chang%20JR%5BAuthor%5D&cauthor=true&cauthor_uid=23291307), [Chen WJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chen%20WJ%5BAuthor%5D&cauthor=true&cauthor_uid=23291307), [Zhao L](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhao%20L%5BAuthor%5D&cauthor=true&cauthor_uid=23291307), [Zhang BH](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhang%20BH%5BAuthor%5D&cauthor=true&cauthor_uid=23291307), [Yu YR](https://www.ncbi.nlm.nih.gov/pubmed/?term=Yu%20YR%5BAuthor%5D&cauthor=true&cauthor_uid=23291307), [Tang CS](https://www.ncbi.nlm.nih.gov/pubmed/?term=Tang%20CS%5BAuthor%5D&cauthor=true&cauthor_uid=23291307), [Yin XH](https://www.ncbi.nlm.nih.gov/pubmed/?term=Yin%20XH%5BAuthor%5D&cauthor=true&cauthor_uid=23291307), [Qi YF](https://www.ncbi.nlm.nih.gov/pubmed/?term=Qi%20YF%5BAuthor%5D&cauthor=true&cauthor_uid=23291307).

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**Abstract**

Angiotensin-(1-7) [Ang-(1-7)] is a new bioactive heptapeptide in the renin-angiotensin-aldosterone system (RAAS) with potent protective effects in cardiovascular diseases, opposing many actions of angiotensin II (Ang II) mediated by Ang II type 1 (AT1) receptor. It is produced mainly by the activity of angiotensin-converting enzyme 2 (ACE2) and acts through the Mas receptor. However, the role of Ang-(1-7) in vascular calcification (VC) is still unclear. In this study, we investigated the protective effects of Ang-(1-7) on VC in an in vivo rat VC model induced by vitamin D3 plus nicotine. The levels of ACE2 and the Mas receptor, as well as ACE, AT1 receptor, Ang II type 2 receptor and angiotensinogen, were significantly increased in calcified aortas, and Ang-(1-7) reversed the increased levels. Ang-(1-7) restored the reduced expression of lineage markers, including smooth muscle (SM) α-actin, SM22α, calponin and smoothelin, in vascular smooth muscle cells (VSMCs) and retarded the osteogenic transition of VSMCs by decreasing the expression of bone-associated proteins. It reduced alkaline phosphatase activity and calcium deposition in VC and alleviated the hemodynamic disorders of rats with VC. We provide the first in vivo evidence that Ang-(1-7) can inhibit the development of VC by inhibiting the osteogenic transition of VSMCs, at least in part by decreasing levels of the ACE/Ang II/AT1 axis. The increased expression of ACE2 and the Mas receptor in calcified aortas suggests the involvement of the ACE2/Ang-(1-7)/Mas axis during VC. Ang-(1-7) might be an efficient endogenous vasoprotective factor for VC.

[Am J Physiol Renal Physiol.](https://www.ncbi.nlm.nih.gov/pubmed/26697977) 2016 Mar 15;310(6):F534-46. doi: 10.1152/ajprenal.00082.2015. Epub 2015 Dec 23.

**Paricalcitol modulates ACE2 shedding and renal ADAM17 in NOD mice beyond proteinuria.**

[Riera M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Riera%20M%5BAuthor%5D&cauthor=true&cauthor_uid=26697977)1, [Anguiano L](https://www.ncbi.nlm.nih.gov/pubmed/?term=Anguiano%20L%5BAuthor%5D&cauthor=true&cauthor_uid=26697977)2, [Clotet S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Clotet%20S%5BAuthor%5D&cauthor=true&cauthor_uid=26697977)2, [Roca-Ho H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Roca-Ho%20H%5BAuthor%5D&cauthor=true&cauthor_uid=26697977)2, [Rebull M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Rebull%20M%5BAuthor%5D&cauthor=true&cauthor_uid=26697977)2, [Pascual J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Pascual%20J%5BAuthor%5D&cauthor=true&cauthor_uid=26697977)1, [Soler MJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Soler%20MJ%5BAuthor%5D&cauthor=true&cauthor_uid=26697977)3.

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**Abstract**

Circulating and renal activity of angiotensin-converting enzyme 2 (ACE2) is increased in non-obese diabetic (NOD) mice. Because paricalcitol has been reported to protect against diabetic nephropathy, we investigated the role of paricalcitol in modulating ACE2 in these mice. In addition, renal ADAM17, a metalloprotease implied in ACE2 shedding, was assessed. NOD female and non-diabetic control mice were studied for 21 days after diabetes onset and divided into various treatment groups. Diabetic animals received either vehicle; 0.4 or 0.8 μg/kg paricalcitol, aliskiren, or a combination of paricalcitol and aliskiren. We then studied the effect of paricalcitol on ACE2 expression in proximal tubular epithelial cells. Paricalcitol alone or in combination with aliskiren resulted in significantly reduced circulating ACE2 activity in NOD mice but there were no changes in urinary albumin excretion. Serum renin activity was significantly decreased in mice that received aliskiren but no effect was found when paricalcitol was used alone. Renal content of ADAM17 was significantly decreased in animals that received a high dose of paricalcitol. Renal and circulating oxidative stress (quantified by plasma H2O2 levels and immunolocalization of nitrotyrosine) were reduced in high-dose paricalcitol-treated mice compared with non-treated diabetic mice. In culture, paricalcitol incubation resulted in a significant increase in ACE2 expression compared with nontreated cells. In NOD mice with type 1 diabetes, paricalcitol modulates ACE2 activity, ADAM17, and oxidative stress renal content independently from the glycemic profile and urinary albumin excretion. In tubular cells, paricalcitol may modulate ACE2 by blocking its shedding. In the early stage of diabetic nephropathy, paricalcitol treatment counterbalances the effect of diabetes on circulating ACE2 activity. Our results suggest that additional use of paricalcitol may be beneficial in treating patients with diabetes under standard therapeutic strategies.

[Mol Biol Rep.](https://www.ncbi.nlm.nih.gov/pubmed/26968558) 2016 May;43(5):397-406. doi: 10.1007/s11033-016-3971-5. Epub 2016 Mar 12.

**Calcitriol regulates angiotensin-converting enzyme and angiotensin converting-enzyme 2 in diabetic kidney disease.**

[Lin M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lin%20M%5BAuthor%5D&cauthor=true&cauthor_uid=26968558)1, [Gao P](https://www.ncbi.nlm.nih.gov/pubmed/?term=Gao%20P%5BAuthor%5D&cauthor=true&cauthor_uid=26968558)2, [Zhao T](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhao%20T%5BAuthor%5D&cauthor=true&cauthor_uid=26968558)1, [He L](https://www.ncbi.nlm.nih.gov/pubmed/?term=He%20L%5BAuthor%5D&cauthor=true&cauthor_uid=26968558)1, [Li M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Li%20M%5BAuthor%5D&cauthor=true&cauthor_uid=26968558)1, [Li Y](https://www.ncbi.nlm.nih.gov/pubmed/?term=Li%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=26968558)1, [Shui H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Shui%20H%5BAuthor%5D&cauthor=true&cauthor_uid=26968558)1, [Wu X](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wu%20X%5BAuthor%5D&cauthor=true&cauthor_uid=26968558)1.

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**Abstract**

To investigate the effects of calcitriol on angiotensin-converting enzyme (ACE) and ACE2 in diabetic nephropathy. Streptozotocin (STZ) induced diabetic rats were treated with calcitriol for 16 weeks. ACE/ACE2 and mitogen activated protein kinase (MAPK) enzymes were measured in the kidneys of diabetic rats and rat renal tubular epithelial cells exposed to high glucose. Calcitriol reduced proteinuria in diabetic rats without affecting calcium-phosphorus metabolism. ACE and ACE2 levels were significantly elevated in diabetic rats compared to those in control rats. The increase in ACE levels was greater than that of ACE2, leading to an elevated ACE/ACE2 ratio. Calcitriol reduced ACE levels and ACE/ACE2 ratio and increased ACE2 levels in diabetic rats. Similarly, high glucose up-regulated ACE expression in NRK-52E cells, which was blocked by the p38 MAPK inhibitor SB203580, but not the extracellular signal-regulated kinase (ERK) inhibitor FR180204 or the c-Jun N-terminal kinase (JNK) inhibitor SP600125. High glucose down-regulated ACE2 expression, which was blocked by FR180204, but not SB203580 or SP600125. Incubation of cells with calcitriol significantly inhibited p38 MAPK and ERK phosphorylation, but not JNK phosphorylation, and effectively attenuated ACE up-regulation and ACE2 down-regulation in high glucose conditions. The renoprotective effects of calcitriol in diabetic nephropathy were related to the regulation of tubular levels of ACE and ACE2, possibly by p38 MAPK or ERK, but not JNK pathways.

**Effect of vitamin D on ACE2 and vitamin D receptor expression in rats with LPS-induced acute lung injury**

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* VernacularTitle:维生素D对脂多糖致急性肺损伤大鼠肺组织血管紧张素转化酶2和维生素D受体表达水平的影响
* Author: Jialai YANG1; Jun XU; Hong ZHANG
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* Abstract: Objective To observe the effect of vitamin D on angiotensin converting enzyme 2 (ACE2) and vitamin D receptor (VDR) expression in Wister rat models of acute lung injury (ALI) induced by using lipopolysaccharide (LPS).Methods The rat models of ALI induced by LPS were established by intravenous injection of LPS via tail vein.Thirty Wistar rats were randomly (random number) divided into 6 groups:normal control group,LPS group,calcitriol (25 μg/kg) group,LPS + calcitriol 1 μg/kg group,LPS + calcitriol 5 μg/kg group and LPS + calcitriol 25 μg/kg group.The changes of general condition,lung pathology,lung wet/dry weight ratio and changes of VDR mRNA and ACE2 mRNA expressions and protein levels of VDR and ACE2 in rats were observed.Results The clinical manifestations (rapid shallow breathing;listlessness;the oral and nose hemorrhage) in LPS group were obvious,and the clinical manifestations and pathological changes of lung tissues in the LPS + calcitriol groups were significantly milder than those in LPS group.The expressions of VDR mRNA and ACE2 mRNA in LPS group was significantly lower than those in normal control group and calcitriol group (P ＜ 0.05).The expressions of VDR mRNA and ACE2 mRNA in LPS + calcitriol groups were significantly higher than those in LPS group (P ＜ 0.05),and lower than those in normal control group significantly (P ＜ 0.05).Meanwhile,among LPS + calcitriol groups,there was no significant difference in expression of VDR mRNA (P ＞ 0.05) and there was significant difference in ACE2 mRNA expression (P ＜ 0.05).Conclusions Calcitriol can increase the expressions of VDR mRNA and ACE2 mRNA and protein levels of VDR and ACE2 in rat models of LPS-induced ALI,thus suggesting the increased expressions of ACE2 mRNA and VDR mRNA playing a role in protection against the development of ALI.

[Mol Med Rep.](https://www.ncbi.nlm.nih.gov/pubmed/?term=Vitamin+D+alleviates+lipopolysaccharide%E2%80%91induced+acute+lung+injury+via+regulation+of+the+renin%E2%80%91angiotensin+system) 2017 Nov;16(5):7432-7438. doi: 10.3892/mmr.2017.7546. Epub 2017 Sep 20.

**Vitamin D alleviates lipopolysaccharide‑induced acute lung injury via regulation of the renin‑angiotensin system.**

[Xu J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Xu%20J%5BAuthor%5D&cauthor=true&cauthor_uid=28944831)1, [Yang J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Yang%20J%5BAuthor%5D&cauthor=true&cauthor_uid=28944831)2, [Chen J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chen%20J%5BAuthor%5D&cauthor=true&cauthor_uid=28944831)3, [Luo Q](https://www.ncbi.nlm.nih.gov/pubmed/?term=Luo%20Q%5BAuthor%5D&cauthor=true&cauthor_uid=28944831)4, [Zhang Q](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhang%20Q%5BAuthor%5D&cauthor=true&cauthor_uid=28944831)1, [Zhang H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhang%20H%5BAuthor%5D&cauthor=true&cauthor_uid=28944831)2.

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**Abstract**

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are the clinical manifestations of severe lung damage and respiratory failure. ALI and ARDS result are associated with high mortality in patients. At present, no effective treatments for ALI and ARDS exist. It is established that vitamin D exhibits anti‑inflammatory effects, however, the specific effect of vitamin D on ALI remains largely unknown. The aim of the present study was to investigate whether, and by which mechanism, vitamin D alleviates lipopolysaccharide (LPS)‑induced ALI. The results demonstrated that a vitamin D agonist, calcitriol, exhibited a beneficial effect on LPS‑induced ALI in rats; calcitriol pretreatment significantly improved LPS‑induced lung permeability, as determined using Evans blue dye. Results from reverse transcription‑quantitative polymerase chain reaction, western blotting and ELISA analysis demonstrated that calcitriol also modulated the expression of members of the renin‑angiotensin system (RAS), including angiotensin (Ang) I‑converting enzymes (ACE and ACE2), renin and Ang II, which indicates that calcitriol may exert protective effects on LPS‑induced lung injury, at least partially, by regulating the balance between the expression of members of the RAS. The results of the present study may provide novel targets for the future treatment of ALI.

[Am J Physiol Lung Cell Mol Physiol.](https://www.ncbi.nlm.nih.gov/pubmed/?term=Attenuation+of+pulmonary+ACE2+activity+impairs+inactivation+of+des-Arg9+bradykinin%2FBKB1R+axis+and+facilitates+LPS-induced+neutrophil+infiltration) 2018 Jan 1;314(1):L17-L31. doi: 10.1152/ajplung.00498.2016. Epub 2017 Sep 21.

# Attenuation of pulmonary ACE2 activity impairs inactivation of des-Arg9 bradykinin/BKB1R axis and facilitates LPS-induced neutrophil infiltration.

[Sodhi CP](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sodhi%20CP%5BAuthor%5D&cauthor=true&cauthor_uid=28935640)1, [Wohlford-Lenane C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wohlford-Lenane%20C%5BAuthor%5D&cauthor=true&cauthor_uid=28935640)2, [Yamaguchi Y](https://www.ncbi.nlm.nih.gov/pubmed/?term=Yamaguchi%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=28935640)1, [Prindle T](https://www.ncbi.nlm.nih.gov/pubmed/?term=Prindle%20T%5BAuthor%5D&cauthor=true&cauthor_uid=28935640)1, [Fulton WB](https://www.ncbi.nlm.nih.gov/pubmed/?term=Fulton%20WB%5BAuthor%5D&cauthor=true&cauthor_uid=28935640)1, [Wang S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wang%20S%5BAuthor%5D&cauthor=true&cauthor_uid=28935640)1, [McCray PB Jr](https://www.ncbi.nlm.nih.gov/pubmed/?term=McCray%20PB%20Jr%5BAuthor%5D&cauthor=true&cauthor_uid=28935640)2, [Chappell M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chappell%20M%5BAuthor%5D&cauthor=true&cauthor_uid=28935640)3, [Hackam DJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hackam%20DJ%5BAuthor%5D&cauthor=true&cauthor_uid=28935640)1, [Jia H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Jia%20H%5BAuthor%5D&cauthor=true&cauthor_uid=28935640)1.

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### Abstract

Angiotensin-converting enzyme 2 (ACE2) is a terminal carboxypeptidase with important functions in the renin-angiotensin system and plays a critical role in inflammatory lung diseases. ACE2 cleaves single-terminal residues from several bioactive peptides such as angiotensin II. However, few of its substrates in the respiratory tract have been identified, and the mechanism underlying the role of ACE2 in inflammatory lung disease has not been fully characterized. In an effort to identify biological targets of ACE2 in the lung, we tested its effects on des-Arg9 bradykinin (DABK) in airway epithelial cells on the basis of the hypothesis that DABK is a biological substrate of ACE2 in the lung and ACE2 plays an important role in the pathogenesis of acute lung inflammation partly through modulating DABK/bradykinin receptor B1 (BKB1R) axis signaling. We found that loss of ACE2 function in mouse lung in the setting of endotoxin inhalation led to activation of the DABK/BKB1R axis, release of proinflammatory chemokines such as C-X-C motif chemokine 5 (CXCL5), macrophage inflammatory protein-2 (MIP2), C-X-C motif chemokine 1 (KC), and TNF-α from airway epithelia, increased neutrophil infiltration, and exaggerated lung inflammation and injury. These results indicate that a reduction in pulmonary ACE2 activity contributes to the pathogenesis of lung inflammation, in part because of an impaired ability to inhibit DABK/BKB1R axis-mediated signaling, resulting in more prompt onset of neutrophil infiltration and more severe inflammation in the lung. Our study identifies a biological substrate of ACE2 within the airways, as well as a potential new therapeutic target for inflammatory diseases.

The results demonstrated that a vitamin D agonist, calcitriol, exhibited a beneficial effect on LPS‑induced ALI in rats; calcitriol pretreatment significantly improved LPS‑induced lung permeability, as determined using Evans blue dye. Results from reverse transcription‑quantitative polymerase chain reaction, western blotting and ELISA analysis demonstrated that calcitriol also modulated the expression of members of the renin‑angiotensin system (RAS), including angiotensin (Ang) I‑converting enzymes (ACE and ACE2), renin and Ang II, which indicates that calcitriol may exert protective effects on LPS‑induced lung injury, at least partially, by regulating the balance between the expression of members of the RAS. The results of the present study may provide novel targets for the future treatment of ALI. {Xu, 2017}

These results indicate that a reduction in pulmonary ACE2 activity contributes to the pathogenesis of lung inflammation, in part because of an impaired ability to inhibit DABK/BKB1R axis-mediated signaling, resulting in more prompt onset of neutrophil infiltration and more severe inflammation in the lung. Our study identifies a biological substrate of ACE2 within the airways, as well as a potential new therapeutic target for inflammatory diseases. {Sodhi, 2017}.