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SARS-CoV-2 E HIPERTENSÃO: EVIDÊNCIAS SUPORTAM A INVASÃO DO CÉREBRO POR MEIO DA CIRCUITARIA DO BARORREFLEXO E O PAPEL DO DESBALANÇO DO SISTEMA RENINA-ANGIOTENSINA-ALDOSTERONA

MACEIÓ – AL
2023

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Dissertação submetida ao corpo docente do Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Alagoas, em cumprimento às exigências para a obtenção do título de mestre.

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"A ciência é uma disposição em aceitar fatos,
mesmo quando esles são opostos aos desejos".
B. F. SKINNER, 1957

AGRADECIMENTOS

Estudos apontam que os agradecimentos são, sem sombra de dúvida, a sessão mais lida em um trabalho científico como esse. Eles despertam a curiosidade de um jeito único! Por essa razão, acredito que eles devem ser escritos com um imenso cuidado e muito carinho. Mas eu decidi fazer isso de um jeito diferente, escrevendo uma carta destinada a quem, por ventura, venha ler esse trabalho.

Maceió, 19 de agosto de 2023.

Caro leitor,

Newton ficou conhecido como o homem que pesou e mediu os céus... Um título muito bonito para um cara que ajudou a estabelecer a mecânica clássica a partir da observação de corpos celestes. E foi numa carta, que Newton, ao falar desse feito, escreveu uma expressão que, embora não seja de sua autoria, o eternizaria, uma frase que eu nunca esqueci: "**Se eu pude ver mais longe, foi porque estava de pé, sobre os ombros de gigantes**". Para mim, essa frase remonta a um senso de coletividade e humildade fundamentais para ciência, especialmente quando se tenta construir conhecimento científico num país de terceiro mundo, fora de um grande centro. Essa expressão me fez pensar também em quem são os meus gigantes. Falar deles é muito importante porque, sem esses gigantes, essa pesquisa nunca poderia ter sido feita.

Devido à pandemia, os últimos anos representaram um desafio imenso para todos, sobretudo psicologicamente. Cada um precisou “se virar nos 30”, enfrentar seus medos, e fazer o que precisava ser feito. Por isso, eu preciso, logo de início, agradecer a todo o meu laboratório pela total compreensão e acolhimento que recebi quando precisei me afastar. Isso significou e significa (porque ainda penso nisso hoje) muito pra mim. Eu espero poder recompensar todo o grupo por isso um dia.

E se você não sabe quem é meu grupo, não se preocupe, eu lhe apresento! Eu pertenço ao LNFI (**Laboratório de Neurofarmacologia e Fisiologia Integrativa**), o lab mais legal da UFAL inteira, porque é composto por uma galera que faz o adjetivo excepcional parecer ter sido cunhado especificamente para descrevê-los.

O meu orientador, o professor **Olagide**, se destaca pela enorme educação e generosidade com que trata a todos com quem interage. Eu nuca o vi, uma vez sequer, ser rude com ninguém, mesmo em situações de conflito. E essas características vindas

dele fazem com que o LNFI seja um lab diferente de todos os outros que já vi. As oportunidades que ele me deu encaro como verdadeiros desafios, que busco completar sempre tentando fazer o melhor que posso para justificar a confiança depositada em mim. Muito obrigado por acreditar em mim, professor!

Além do professor, a gente tem a sorte de ter por perto a **Nanda** (e **Flor,** tão pequena e já metida no meio da ciência!). Nanda é a personalização do carinho, da assertividade, da amizade, e, como se isso tudo fosse pouco, é uma cientista de mão cheia. Pessoas talentosas sempre existiram no LNFI, cada uma a seu modo! No LNFI antigo, aquele que conheci antes da pandemia, **Yngrid, Maisa, Igor, Cibelle**, **Amanda** e a **Juci** sempre ensinaram coisas de valor, algumas vezes com palavras, outras com ações. Dessa galera das antigas, sempre senti uma conexão mais forte com a **Amanda** e a **Juci.** Nunca disse isso a ninguém, mas toda vez que paro e olho para a Amanda, não consigo não pensar o quanto ela amadureceu rápido, e eu fico orgulhoso de ter visto essa menina desabrochar! Quanto a **Juci**, particularmente eu sinto uma falta imensa da presença dela no lab. Foi um grande prazer ter sido IC dela, e ter podido aprender mais sobre ciência com uma pessoa que tem o jeito tão leve, engraçado, respeitoso e carinhoso. Torço para que a gente ainda trabalhe junto novamente! Juci é maravilhosa e fez uma diferença enorme na minha trajetória.

Do lab antigo ainda falta falar de duas pessoas, que não são quaisquer pessoas para mim. Se você que está lendo não conhece **Keylla** e **Bianca**, tais perdendo de conhecer a dupla com a maior sinergia que já existiu na face da terra. Essa sinergia é tanta que, para o lab, elas são quase um ser só. Não canso de observar como elas, mesmo sendo tão diferentes entre si, se complementam em tudo. É curioso também ver como elas se construíram esse tempo todo não só como amigas, mas como uma sendo a força da outra. E ouso dizer que elas são a força por trás de todo o LNFI. A gente entrou juntos como ICs, e de cara a gente se reconheceu como iguais. É uma alegria imensa poder dizer que mais que colegas que trabalham bem, a gente se tornou amigo, e que essa amizade é a coisa mais valiosa que achei naquele lab. Vocês duas são a parte principal de eu sempre ter visto o lab como minha casa também. Eu tenho vocês como meus modelos, e, para mim, o LNFI só faz sentido de verdade por causa de vocês. Eu devo muito a Keylla e a Bianca, tanto que eu nem sei como que faz para pagar um negócio desses.

Mas o LNFI mudou muito na minha ausência, e um lab novo me recebeu e acolheu depois da pandemia, todos sempre sendo muito pacientes comigo. Quando eu

voltei, achei que seria um grande desafio me adaptar novamente. Para minha felicidade, tudo aconteceu tão naturalmente, tudo foi tão leve. E hoje, eu sinto que voltei a me sentir em casa, graças a essa galera nova, que me faz dar gargalhadas estrondosas capazes de serem ouvidas há distância. Sofro da síndrome da gargalhada mundiça! E faço muito gosto em citar cada um: **Edite** (sabe aquelas pessoas que, por alguma razão que você não sabe muito bem o porquê, você gosta de graça e faz tudo para ver ela sorrir?! É assim que eu a percebo. Edite parece guardar uma sabedoria secreta e ancestral de como se deve viver a vida (deve ter aprendido isso na botânica!). É como se perto dela não tivesse tempo ruim, e qualquer problema fosse terminar numa gargalhada gostosa.)**; Paulinho** (é o doutorando mais gente boa de todo o ICBS. Pense na simpatia dessa figura! Não tem que não goste dele!); **Fernanda** (a major do lab! A moral de me mandar trabalhar em inglês é toda dela! A dona do sotaque mais marcante do LNFI. E, só porque eu tenho um coração grande, quero dizer que eu lhe concedo o meu perdão! Kkkkkkk)**; Bruna** (a melhor parceira de decapitação que alguém pode desejar. Zero frescura, super disposta a ajudar, humilde, esperta, gente boa, e capaz de descobrir umas paradas minhas que eu vou te contar, viu?! Toda vez que eu penso nela, vem a imagem de uma praia (isso é a cara dela), e de uma conversa que a gente teve em que ela disse era forte, tentando me convencer que poderia ir para uma reunião mesmo estando com febre. Você é mesmo muito forte! Nunca duvidei disso. Por isso que lhe admiro tanto!)**; Vanessa** (ela é um daqueles casos raros de pessoas com que você se identifica de cara, dona de uma simpatia cativante, e da maior cara lisa de Pernambuco. De todas as pessoas do lab, ela é a que eu sei que mais me entende, porque sempre achei a gente muito parecido, arteiros do mesmo jeito.)**; Iasmim** (o que ela tem de pequena, tem de esperta! E isso a coloca numa posição diferente, e muito legal. Dona de uma moral impressionante, e de um senso de responsabilidade e organização invejável, traduzido nas placas e avisos mais diversos que ela ama fazer)**; Letícia** (ela foi a maior surpresa para mim, suas gentilezas e pequenos gestos de carinho não esperados não passam desapercebidos, guardo tudo na memória, assim como todas as suas ajudas a minha pessoa. Boa sorte na tua nova jornada!)**; Eloísa** (é a menina prodígio do laboratório. Algo me diz que essa galeguinha vai muito longe, pode escrever o que eu estou dizendo!). O laboratório, hoje, está gigante e ainda existem pessoas que estou começando a conhecer, mas que sei que a gente vai ter muitas oportunidades para interagir e aprender juntos, como a **Mércia** e a **Coutinho** e as novas ICs: **Luma**, **Suellen**, **Luana**, **Rikelly**, **Auana**, **Giselle, Vitória** e **Mariana**.

Mas, nem só de lab vive um homem, e algumas outras pessoas, fora desse ambiente, precisam ser citadas por serem enormemente importantes. **Matutinha**, ela esteve esses anos todos do meu lado, e mesmo distante fisicamente sempre a senti perto, sempre me apoiando em tudo. Seu carinho e cuidado comigo foram as coisas mais valiosas que experimentei em muito tempo. Por isso, desejo "que a vida lhe seja leve!" (sei que você vai entender isso). **Ataídes** e **Mailson**, que mesmo sem entender muito bem o que eu faço, torcem para que eu me torne o que eu sempre quis ser, um cientista!

A única coisa maior que minha vontade de ser um cientista é o amor que tenho pela minha família: minha Mãe, D. **Rute** (a mulher mais sabida que eu já conheci! Também pudera, filha de D. **Lúcia**, não podia ser diferente não! E que falta ela faz, né, mãe?!). Muito obrigado, mãe, por sempre que eu fiquei confuso, a senhora ter sentado e me ajudado a ver as coisas de modo mais claro, sempre com tanto carinho. A gente tem uma conexão diferente, e pode assumir que sou seu filho favorito! kkkkkkkkkk Meu pai, seu **Ivan** (dono do coração mais bonito, e da gargalha mais gostosa. O senhor é meu orgulho e me deixa impressionado até hoje, do mesmo jeito de quando eu era só um menininho). E meu irmão, **Zé** (não costumo fazer isso, mas vou lhe dar uma colher de chá, e dizer que tenho muito orgulho de tu. Você é um Homem de verdade! É muito bom ser teu irmão!). Nossa convivência nos últimos anos se intensificou na mesma proporção que meu amor por eles. Conviver com eles é um privilégio que a vida me dá. E por essa razão, eu nunca poderei reclamar dela! Nasci com sorte, porque nasci na família certa, a mais resenha e amorosa do mundo!

Os elementos institucionais também são fundamentais em nosso mundo! A **UFAL** é o meu lar hoje. E participar dessa grande instituição tem sido uma experiência incrível, especialmente por estar vinculado ao **PPGCS**, um programa que vêm crescendo graça aos esforços de professores muito dedicados e de alunos muito batalhadores. Ter sido financiado pela **FAPEAL**, além de uma grande felicidade, foi fundamental na busca por alcançar o meu sonho de ser cientista dentro do meu próprio estado.

Muito obrigado a todos por toda a ajuda!

Por fim, desejo que você, que está lendo essa carta, tenha a mesma sorte que tive. E que na sua vida, você tenha gigantes como esses que tenho a honra de ter na minha, que me fazem não só ver mais longe, mas são o ambiente para que eu possa me construir sempre querendo ser melhor do que fui ontem!

Kellysson Bruno Oliveira

RESUMO

Um entendimento mais preciso sobre a COVID-19 e seu prognóstico requer um olhar amplo e integrativo sobre a relação do SARS-CoV-2 com diferentes estruturas e tecidos. O endotélio e o SNC têm se mostrado como peças-chave nesse processo. A infeção endotelial pelo SARS-CoV-2 pode resultar na fragilização vascular, o que tem sido associado à entrada do vírus em múltiplos órgãos e estruturas, com destaque para o os vasos de grande calibre e para o cérebro. O presente estudo é uma revisão de literatura que objetivou: 1) descrever uma nova possível via de neuroinvasão do SARS-CoV-2, a partir dos barorreceptores; e 2) investigar a possível relação entre a ANG-II e ADAM17, associado à infecção por do SARS-CoV-2, com a hipertensão neurogênica. A infecção do SARS-CoV-2 em células humanas favorece um desequilíbrio do RAAS, caracterizado pelo aumento da atividade do seu eixo pró-inflamatório e pró-hipertensivo (ANG II/ AT1R), e da ADAM17/TACE. Evidências indicam que o acesso do vírus aos barorreceptores, presentes em vasos de grande calibre, pode permitir a entrada vírus no cérebro. A partir disso, efeitos diretos e indiretos do vírus no SNC podem impactar significativamente o controle da pressão. A redução da integração de aferências que chegam ao NTS vindas dos barorreceptores, além da ativação do PVN, são mecanismos relacionados com o aumento da atividade simpática, que podem ser desencadeados pela invasão do SARS-CoV-2. De maneira pioneira, propusemos um mecanismo possível central capaz de explicar o surgimento ou o agravamento de um quadro de hipertensão sistêmica, e e o desenvolvimento de um pior prognóstico da COVID-19. A relação entre COVID-19 e o desenvolvimento ou piora do quadro de hipertensão tem sido demostrada em publicações recentes. Entretanto, mais estudos são necessários a fim de verificar experimentalmente as hipósteses aqui defendidas.

Palavras-Chave: SARS-CoV-2; COVID-19; RAAS; neuroinvasão, hipertensão.

ABSTRACT

A precise understanding of COVID-19 and its prognosis requires a broad and integrative look at the relationship of SARS-CoV-2 with different structures and tissues. The endothelium and the CNS have been shown to be key players in this process. Endothelial infection by SARS-CoV-2 can result in vascular weakening, which has been associated with the entry of the virus into multiple organs and structures, especially large vessels and the brain. The present study is a literature review that aimed to: 1) describe a new possible neuroinvasion route of SARS-CoV-2, from baroreceptors; and 2) investigate the possible relationship between ANG-II and ADAM17, associated with SARS-CoV-2 infection, and neurogenic hypertension. SARS-CoV-2 infection in human cells favors an imbalance of the RAAS, characterized by increased activity of its pro-inflammatory and pro-hypertensive axis (ANG II/AT1R), and ADAM17/TACE. Evidence indicates that the virus's access to baroreceptors, present in large vessels, may allow the virus to enter the brain. Therefore, direct and indirect effects of the virus on the CNS can significantly impact blood pressure control. The reduction in the integration of inputs that reach the NTS from the baroreceptors, in addition to the activation of the PVN, are mechanisms related to the increase in sympathetic activity, which can be triggered by the invasion of SARS-CoV-2. In a pioneering way, we proposed a possible central mechanism capable of explaining the emergence or worsening of systemic hypertension, and the development of a worse prognosis of COVID-19. The relationship between COVID-19 and the development or worsening of hypertension has been demonstrated in recent publications. However, more studies are needed in order to experimentally verify the hypotheses defended here.

Key Words: SARS-CoV-2; COVID-19; RAAS; neuroinvasion, hypertension.

LISTA DE FIGURAS

ARTIGO – SARS-CoV-2 and Hypertension: Evidence Supporting Invasion into the Brain Via Baroreflex Circuitry and the Role of Imbalanced Renin-AngiotensinAldosterone-System

LISTA DE ABREVIATURAS

ACE	Angiotensin converting enzyme
ACE2	Angiotensin II-converting enzyme
ADAM17	Disintegrin, and metalloproteinase 17 domain
ANG-II	Angiotensin II
ANG-(1-9)	Angiotensin-(1-9)
ANG-(1-7)	Angiotensin-(1-7)
APC	Antigen-presenting cells (APCs)
AT1R	Angiotensin type I receptor
AT2R	Angiotensin type II receptor
BBB	Blood-Brain Barrier
BP	Blood pressure
BDNF	Brain-derived neurotrophic factor ()
CNS	Central nervous system ()
CVD	Cardiovascular diseases
CVLM	Caudal ventrolateral medulla
CSF	Cerebrospinal fluid
CVO	Circumventricular organ
COVID-19	Coronavirus disease-2019
DMV	Dorsal motor nucleus of the vagus
EGFR	Epidermal growth factor receptor
GABA	Gamma-aminobutyric acid
GLT1	Glutamate transporter 1 (GLT1)
ICU	Intensive care unity
IL-1β	Interleukin-1β
IL-6	Interleukin-6
INFγ	Interferon-gamma
IL-10	Interleukin-10
NET	Neutrophil extracellular trap
NF-κβ	Nuclear factor kappa β
NO	Nitric oxide
NTS	Nucleus of the solitary tract

NA	Nucleus ambiguous
[NAD (P) H]	Enzyme dinucleotide phosphate oxidase nicotinamide adenine
NMDA	N- methyl- d -aspartate
MCP-1	Monocyte Chemoattractant Protein-1
PVN	Paraventricular nucleus of the hypothalamus
RAAS	Renin-angiotensin-aldosterone system
RVLM	Rostral ventrolateral medulla
ROS	Reactive oxygen species
SFO	Subfornical organ
SON	Supraoptic nucleus
TACE	Tumor necrosis factor-α converting enzym**e**
TIMP-3	Tissue inhibitor of metalloproteinase 3
TMPRSS2	Transmembrane serine protease
TNF-α	Tumor necrosis factor-α converting
USA	United states of America
WHO	World Health Organization (WHO)

SUMÁRIO

INTRODUÇÃO

Em março de 2020, a Organização Mundial de Saúde (OMS) decretou o status de pandemia, em decorrência do rápido alastramento de uma nova doença, denominada COVID-19. A causa desta foi identificada como um novo vírus da família *coronaviridiae*, o SARS-CoV-2 – um β-coronavírus, caracterizado por possuir um RNA envelopado, não segmentado, de fita simples. Esse novo vírus é capaz de gerar um quadro de síndrome respiratória aguda severa tão transmissível, que ele tem a capacidade de gerar o colapso dos sistemas de saúdes dos países ao redor do planeta (Long *et al.*, 2020; Syed *et al.*, 2020). Os efeitos da COVID-19 ainda se fazem sentir, não só pelos impactos severos em termos de mortes e hospitalizações em todo o mundo, mas também pelos impactos sociais e econômicos relacionados a essa infeção, os quais se arrastam pelo tempo (Nicola et al.,2020).

Os sintomas mais comuns da COVID-19, são: febre, tosse, dificuldades respiratórias, dores musculares, anorexia, indisposição, congestão nasal, alteração de olfato e paladar, dispneia, dor de garganta e de cabeça e até diarreia e vômito (Freni *et al.*, 2020; Lukiw; Pogue; Hill, 2020; Mansueto; Niola; Napoli, 2020; Melo *et al.*, 2021; GUAN *et al.*, 2020; SYED *et al.*, 2020; YANG *et al.*, 2020). Por essa razão a COVID-19 é amplamente descrita como uma infecção respiratória. Entretanto, além desses, sintomas neurológicos também tem sido descritos em cerca de 35 a 40% dos pacientes, especialmente nos que apresentaram formas moderadas e severas da COVID-19 (Frohmana *et al.*, 2020; Kabbani; olds, 2020; Mao *et al.*, 2020; Egbert, Cankurtaran, Karpiak, 2020). Esse fato tem ampliado a compreensão da manifestação do SARS-CoV-2 pelo corpo, demonstrando que essa infecção pode afetar outros tecidos. Além do SARS-CoV-2, outros vírus da família *coronaviridiae* também já foram descritos como sendo capazes de gerar efeitos neurológicos, como o MERS-CoV e o SARS-CoV (Freni *et al.*, 2020; Khan *et al.*, 2020; Wang *et al.*, 2020).

Dentre os principais sintomas ou complicações centrais decorrentes da COVID-19, estão: anosmia, ageusia, perda da coordenação de movimentos (ataxia); parestesia, mutismo acinético; dores de cabeça; náusea; tontura; perda de consciência ou prejuízos nessa função; delírio; alucinação; confusão; perda de audição; agravamento de déficits cognitivos; neuroinflamação; inflamação neurovascular e aterogênese; neurodegeneração; perda de controle progressivo da função respiratória; encefalite e

encefalomielite; acidente vascular cerebral; crise convulsiva; encefalopatia, além do desenvolvimento de sequelas na forma de transtornos psiquiátricos/psicológicos (como ansiedade e depressão) (Asadi-Pooya; Simanic, 2020; Dey *et al.*, 2021; Dos Santos *et al.*, 2020; Freni *et al.*, 2020; Hao *et al.*, 2020; Lukiw; Pogue; Hill, 2020; Mao *et al.*, 2020; Melo *et al.*, 2021; Wu *et al.*, 2020; Xydakis *et al.*, 2020; Acharya et al., 2020).

Diante disso, existiu um grande esforço da comunidade científica em identificar e descrever os meios e mecanismos capazes de explicar esses sintomas neurológicos, como também a neuroinvasão (a entrada do vírus no sistema nervoso, em especial o central). Nesse esforço, muitos estudos propuseram diferentes vias de neuroinvasão possíveis, como: a transsináptica ou transneuronal, a entérica, a pulmonar, a olfatória, a ocular, a bucal, e a placental) (Acharya *et al.*, 2020; Alexopoulos *et al.*, 2020; Dey *et al.*, 2021; Dos Santos *et al.*, 2020; Esposito *et al.*, 2020; Freni *et al.*, 2020; Frohmana *et al.*, 2020; Kabbani; Olds, 2020; Lehtinen *et al.*, 2013; Melo *et al.*, 2021; Pellegrini *et al.*, 2020; Porzionato *et al.*, 2020; Song *et al.*, 2020; Syed *et al.*, 2020; Xu; Lazartigues, 2020; Wang *et al.*, 2020a; Zhou *et al.*, 2017; Melo *et al.*, 2021). Também foi proposta a via hematológica, através de efeitos diretos ou indiretos do vírus na vasculatura, em especial sobre a barreira hematoencefálica (BHE). Em caso de infecção, a BHE pode se tornar mais permeável, facilitando a entrada do vírus, de células imunes ou de moléculas (como citocinas) capazes de impactar o SNC (Lupu; Palmer; Huber-Lang, 2020; Boyle; Haverich, 2020; Gambardella; Santulli, 2020; Kaur; Tripathi; Yadav, 2020; Carnevale; Beretta; Morbin, 2021; Fukuhara; Rosati; El-Dalati, 2020; Gomez-Arbelaez *et al.*, 2020; Ran *et al.*, 2020; Porzionato et al., 2020).

A relação do SARS-CoV-2 com as estruturas vasculares também foi amplamente estudada (Lupu; Palmer; Huber-Lang, 2020; Morassi *et al.*, 2020; Varga *et al*., 2020), o que permitiu uma maior compreensão sobre seus efeitos sistêmicos, e a infecção em múltiplos órgãos e tecidos, e especialmente sua relação com o desenvolvimento de doenças cardiovasculares. Evidências suportam que tanto as doenças cardiovasculares (DCV) e ou cerebrovasculares preexistentes podem influenciar o curso da COVID-19, como, reciprocamente, a própria COVID-19 pode auxiliar no surgimento ou agravamento das DCVs (Mai; Pinto; Ferri, 2020; Mansueto; Niola; Napoli, 2020; Pranata *et al.*, 2020). Esses achados estão em consonância com outros dados que demonstram que outras doenças virais podem causar quadros semelhantes, existindo registros associando o SARS-CoV, o MERS-CoV e até o influenza com o desenvolvimento de doenças cardiovasculares graves (Cappuccio; Siani, 2020; Long *et*

al., 2020; Mansueto; Niola; Napoli, 2020; Pranata *et al.*, 2020; Rizzo *et al.*, 2020). Outras evidências sugerem que a infecção por SARS-CoV-2 pode afetar de maneira significativa o sistema cardiovascular ao promover o enfraquecimento da parede de grandes vasos, seja diretamente, seja via vasa-vasorum (Lupu; Palmer; Huber-Lang, 2020; Gambardella; Santulli, 2020; Kaur; Tripathi; Yadav, 2020; Boyle; Haverich, 2020; Varga *et al.*, 2020; Carnevale; Beretta; Morbin, 2021; Fukuhara; Rosati; El-Dalati, 2020; Gomez-Arbelaez *et al.*, 2020; Ran *et al.*, 2020).

A partir do exposto, e baseados em dados da literatura propomos a hipótese de uma nova via de neuroinvasão do SARS-CoV-2, a partir da infecção de barorreceptores carotídeos e aórticos (Accorsi-Mendonça *et al.*, 2005; Thrasher, 2002; Yates; Chen, 1980; Légat; Smolders; Dupont, 2019; Tsai *et al.*, 2013; Pyner, 2014). A partir dela, o vírus pode acessar o cérebro levando à infecção para núcleos e estruturas importantes para o controle neurovegetativo, como o núcleo do trato solitário (NTS), e, desse, podendo se alastrar até o núcleo hipotalâmico paraventricular (PVN) (Accorsi-Mendonça *et al.*, 2005; Stern *et al.*, 2016). Propusemos também que, por uma ação indireta do vírus, via SFO, este poderia chegar ao PVN e desse núcleo, inversamente, chegar ao NTS, NA, RVLM e CVLM, comprometendo o controle adequado da respiração e da pressão arterial (Accorsi-Mendonça *et al.*, 2005; Stern *et al.*, 2016).

Exploramos adicionalmente a hipótese de que o SARS-CoV-2 favorece a internalização dos receptores ACE2 de membrana gerando um desequilíbrio do sistema renina-angiotensina-aldosterona (RAAS), aumentando a atividade da angiotensina II (ANG-II), e da desintegrina e metaloproteinase 17 domínio (ADAM17/TACE) (Sharma et al., 2021; Assersen; Sumners; Steckelings, 2020; Chakravarty *et al.*, 2021; Zipeto *et al.*, 2020; Xavier *et al.*, 2021; Queiroz; Lakkappa; Lazartigues, 2020; Xu *et al.*, 2020; Palau; Riera; Soler, 2020; Lartey *et al.*, 2021). Esse desbalanço pode acabar por modular a integração de aferências que chegam ao NTS a partir de barorreceptores, promovendo aumento da pressão arterial. Esses mecanismos estão relacionados ao aumento da atividade simpática, que leva à hipertensão transitória ou permanente associada à invasão do SARS-CoV-2 (Légat; Smolders; Dupont, 2019). Esses efeitos centrais podem ajudar a explicar os casos de hipertensão associados a infecção por SARS-CoV-2 documentados recentemente (Akpek, 2022; Clark *et al.*, 2021; Angeli *et al.*, 2022; Athyros, Doumas, 2022; Simonini, 2022; Khani; Entezari-Maleki, 2022; Bouhanick *et al.*, 2021).

Grande parte dos muitos efeitos neurológicos relacionados a infecção por SARS-

CoV-2 permanecem com suas fisiopatologias pouco conhecidas. Essa dissertação buscou, portanto, lançar luz sobre a relação entre a hipertensão e a COVID-19, trazendo hipóteses explicativas para esse fenômeno baseadas na literatura científica. O propósito final desse estudo foi contribuir com o esforço científico mundial na luta contra o SARS-CoV-2 a partir da construção de mais conhecimento sobre esse agente patológico, possibilitando o desenvolvimento futuro de novas propostas terapêuticas.

2. PROBLEMA

O SARS-CoV-2 pode provocar hipertensão arterial sistêmica em função de sua possível capacidade de neuroinvasão e ou alteração do funcionamento do sistema RAAS cerebral?

3. HIPÓTESE

O SARS-CoV-2 é capaz de alterar o funcionamento do sistema RAAS sistemicamente, e também dentro do cérebro, e promover hipertensão.

4. OBJETIVOS

OBJETIVO 1:

Descrever uma nova possível via de neuroinvasão do SARS-CoV-2.

OBJETIVO 2:

Investigar a possível relação entre a ANG-II e ADAM17, decorrentes do desequilíbrio do RAAS associado à infecção por do SARS-CoV-2, com a hipertensão neurogênica.

5. METODOLOGIA

Este estudo se caracteriza como uma revisão de literatura não sistemática. A busca de manuscritos na literatura foi realizada em três bases de dados: PUBMED, EMBASE Google Scholar. A escolha dessas visou a busca não só em bases com conteúdos indexados, como também na área cinza. Foram utilizadas em diferentes combinações as seguintes palavras-chaves: COVID-19, SARS-CoV-2, hipertensão, hipertensão neurogênica, barorreceptores, vasos de grande calibre, neuroinvasão, endotélio, ADAM-17, TACE, angiotensina ou ANG-II, sistema renina-angiotensina-Aldosterona ou RAAS. Não foram usados filtros na pesquisa. A busca foi feita em língua inglesa, e foram aceitos artigos majoritariamente nesse idioma.

5.1 Seleção dos manuscritos

A seleção dos manuscritos foi feita prioritariamente por apenas um revisor. A seleção foi feita em três etapas:

1) a primeira foi realizada a partir da leitura dos títulos (onde foram pré-selecionados artigos com pelos mesmos três das palavras-chaves escolhidas nas estratégias de busca possíveis a partir das combinações dos termos descritos anteriormente);

2) em caso de contemplação do item 1, partiu-se para a segunda etapa de seleção, a análise do resumo. Foram aceitos artigos experimentais *in vivo* ou *in vitro*, e revisões de literatura sistemáticas e não sistemáticas;

3) na terceira etapa da revisão, foi realizada a leitura na íntegra dos artigos pré-selecionados nas etapas anteriores. Foram aceitos aqueles que atenderam aos seguintes critérios de inclusão: a pertinência do tema, e o rigor da metodologia que aparou os resultados apresentados.

ARTIGO

SARS-CoV-2 and Hypertension: Evidence Supporting Invasion into the Brain Via Baroreflex Circuitry and the Role of Imbalanced Renin-Angiotensin- Aldosterone-System

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ABSTRACT: Hypertension is considered one of the most critical risk factors for COVID-19. Evidence suggests that SARS-CoV-2 infection produces intense effects on the cardiovascular system by weakening the wall of large vessels via vasa-vasorum. In this commentary, we propose that SARS-CoV-2 invades carotid and aortic baroreceptors, leading to infection of the *nucleus tractus solitari* (NTS) and paraventricular hypothalamic nucleus (PVN), and such dysregulation of NTS and PVN following infection causes blood pressure alteration at the central level. We additionally explored the hypothesis that SARS-CoV-2 favors the internalization of membrane ACE2 receptors generating an imbalance of the renin-angiotensin-aldosterone system (RAAS), increasing the activity of angiotensin II (ANG-II), disintegrin, and metalloproteinase 17 domain (ADAM17/TACE), eventually modulating the integration of afferents reaching the NTS from baroreceptors and promoting increased blood pressure. These mechanisms are related to the increased sympathetic activity, which leads to transient or permanent hypertension associated with SARS-CoV-2 invasion, contributing to the high number of deaths by cardiovascular implications.

KEYWORDS: SARS-CoV-2, hypertension, baroreflex, angiotensin II

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Introduction

In March 2020, the World Health Organization (WHO) declared pandemic status due to the rapid spread of a new disease, called the coronavirus disease-2019 (COVID-19), caused by the SARS-CoV-2 virus belonging to the coronaviridae family.[1,2] SARS-CoV-2 has reached more than 200 countries, with over 250 million confirmed cases and >5 million confirmed deaths (https://ourworldindata.org/coronavirus-data, worldometers.info, and World Health Organization).[3]

Many of the severe and fatal cases are related to elderly patients or those with some comorbidity, including cardiovascular diseases (CVDs), especially hypertension, which is considered one of the most critical risk factors for the severity of COVID-19.[1,4-12] However, other studies disagree about hypertension participation as a risk factor for more ICU hospitalization and higher mortality for COVID-19.[13] Elderly patients present higher hypertension levels, increasing the risk of death when infected by SARS-CoV-2.[4,6] In China, it is estimated that the prevalence of hypertension among COVID-19 hospitalized patients in 2020 was in the range of 16.9% to 31.2%, and in the USA (data referring to New York City), this prevalence reached an alarming 56.6%; in Italy, the prevalence of hypertensive patients among patients with COVID19 who required ICU admission in 2020 was 49%.[14]

Hypertension is one of the most common cardiovascular diseases worldwide, affecting about 1.38 billion people with blood pressure equal to or greater than 140 mmHg/90 mmHg.[15] In addition, lifestyle (diet, alcohol consumption, and physical activity), age,[16] and ethnicity[15,17] are risk factors. Interestingly, the elderly and African descendants are part of the groups most

affected by hypertension, being also the most compromised by COVID-19, which indicates a possible synergistic relationship between hypertension and COVID-19.[8]

Evidence supports that CVDs and cerebrovascular diseases can influence COVID-19, facilitating the occurrence of infections, and COVID-19 can assist in the onset or worsening of CVDs.[5,6,18] SARS-CoV-2 could generate diseases of the cardiovascular system or aggravate existing pathologies due to the virus's ability to damage the vessels and the heart directly, either by activating adaptive immune and autoimmune mechanisms or by the occurrence of hypoxia due to respiratory changes or failures caused by SARS-CoV-2 infection in the lungs.[5,6,18] Similarly, other studies with viral diseases like SARS-CoV, MERS-CoV, and even influenza have shown the occurrence of similar conditions, increasing the development of severe cardiovascular diseases, heart attacks, hypertension, and mortality from cardiovascular problems as a consequence of viral infection.[1,4,6,7,18]

The mechanisms underlying the association between hypertension and COVID-19, particularly the increased severity of the condition and lethality in hypertensive patients, and the possible development of transient or permanent hypertensive conditions as an after-effect of COVID-19 remain unknown.[7,14,18] The hypothesized mechanisms include an imbalance in the renin-angiotensin-aldosterone system (RAAS) activation due to the use of the angiotensin II-converting enzyme (ACE2) by SARS-CoV-2 to enter human cells,[14,19-21] and the ability of SARS-CoV-2 to deregulate the RAAS system via immunological interference.[6]

However, when considering all symptoms related to COVID-19, especially those linked to more severe cases with a greater chance of death, it is possible to assume that these symptoms may be related to the entry of the virus into the central nervous system (CNS). Due to the expression of ACE2 in the brain,[14,20-22] several findings relate the neurotropic profile of the CoVs family viruses to the CNS.[22-24] Based on the possibility of viral invasion in the CNS, this review aims to (i) propose a new pathway for neuroinvasion that compromises the baroreflex system; and (ii) to establish the possible relationship between angiotensin II (ANG-II), a disintegrin, and metalloproteinase 17 domain (ADAM17) with the imbalance of the RAAS system that leads to sympathetic activation. Together, all these factors support the association between COVID-19 and hypertension, which can be a determining factor in patient survival.

SARS-CoV-2 neuroinvasion and neurofunctional implications

The neurotropic and neuroinvasive characteristics of the CoV family viruses[23,25-27] and the occurrence of symptoms associated with CNS involvement seem to support the real possibility of SARS-CoV-2 invading the brain and spinal regions.[14,19-21,28]

Several neuroinvasion pathways for SARS-CoV-2 and other members of its family have already been proposed, such as hematological, enteric, pulmonary, olfactory, ocular, buccal (through salivary glands), and placental routes.[2,19,20,22,24,27,29-39] In addition, some authors have suggested that the element that seems to unite almost all these pathways is the apparent capacity of contamination from one neuron to another for neuroinvasion, the trans-synaptic or trans-neuronal pathway, whose viral agent is disseminated between different neurons that are connected by circuits.[20,27,30,31] The trans-synaptic pathway is used to describe the invasion of the virus in the brain through the peripheral nerves, using sensitive nerve endings located in the organs or tissues.[27,30,31] The virus can spread in the brain through these circuits and adversely affect different functions.[27,30,31]

Patients with COVID-19 have symptoms or complications related to central nervous system alterations: anosmia, ageusia, loss of movement coordination (ataxia), paresthesia, akinetic mutism, headaches, nausea, dizziness, loss or impairment of consciousness, delirium, hallucination, confusion, loss of hearing, worsening cognitive deficits, neuroinflammation of the brain and spinal cord, neurovascular inflammation and atherogenesis, neurodegeneration, loss of progressive control of respiratory function, encephalitis and encephalomyelitis, seizures, encephalopathy, neuropsychopharmacological disorders, stroke, and hypertension (especially pulmonary and intracranial).[20,22,28,30,31,40-47] A recent study analyzing several original research articles comprising neurological and neuroimaging data from patients with COVID-19 has suggested that at least one-third of the patients had brain injuries or abnormalities caused by SARS-CoV-2.[48]

The clinical symptoms that COVID-19 presents are widespread, depending on the severity of cases and tissues or organs affected by the virus.[49] It is estimated that about 35% to 40% of patients have neurological symptoms, especially in the elderly and in patients presenting severe infection[33,34,42] or those with a history of cerebrovascular, cardiovascular, renal, and liver diseases.[33,34]

When SARS-CoV-2 invades the CNS, its removal is difficult because of the lack of an antigen of the major histocompatibility complex in neurons, dense parenchyma, and characteristics of the nervous tissue that favor viral permanence for a long time.[44,50] Furthermore, an intense neuroinflammatory condition weakens the blood-brain barrier (BBB), culminating in the entry of T cells and microglial activation to "fight" the virus in the brain.[51] The combination of these factors leads to chronic neurological damage. It can also make the brain or nervous structures a reservoir of viruses that can compromise the patient's systemic condition due to the association of neural areas with the regulation of vital peripheral organs/functions.[34] Therefore, the neuroinvasion can also allow the worsening of the systemic condition of the COVID-19 patient, causing disturbances in the regulation of blood pressure with the occurrence of systemic or pulmonary

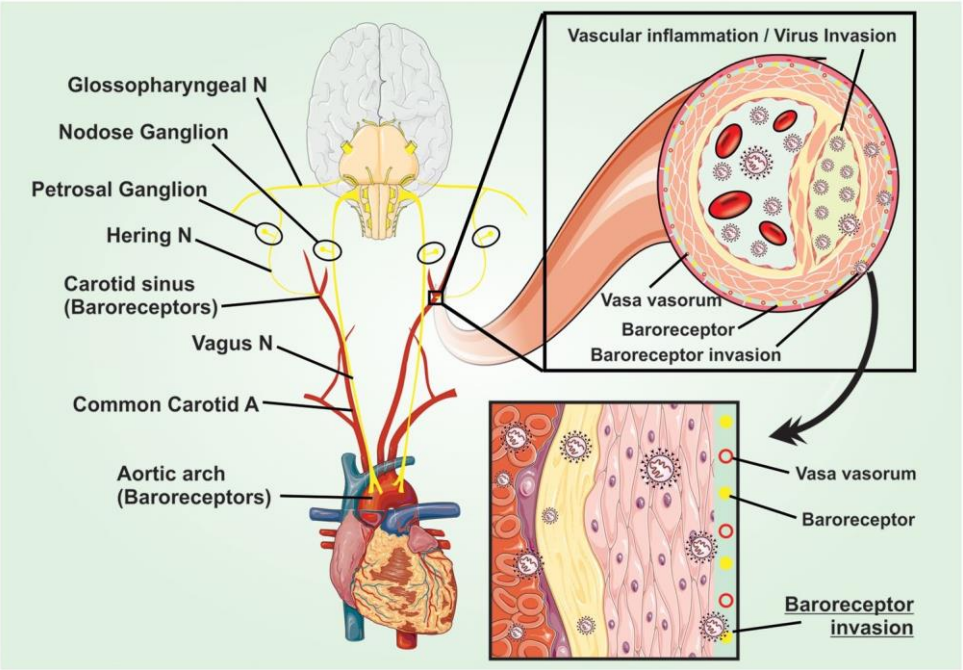

Figure 1. The cartoon depicts the vasculature invasion by SARS-CoV-2 by weakening vessel walls and baroreflex. In addition, the possible neuroinvasion through vagal and glossopharyngeal nerves is indicated.

hypertension that can lead to the evolution of the disease, culminating in the failure of several organs, especially when it occurs together with hyper inflammation, cytokine storm and increased systemic inflammation.[34]

Subsequently, we will discuss the hypothesis of how SARS-CoV-2 can reach the brain and lead to the worsening/generation of arterial hypertension. Many authors have argued based on animal experiments and clinical studies and hypotheses related to the capacity of neurotropism and neuroinvasion of other viruses in the same family.[6,21,32,42,55,73] Although additional studies are needed to fill the many gaps regarding the mechanism, it is crucial to understand the association between hypertension and COVID-19 for the advancement of treatment, prognosis, and especially the prevention of more severe forms of the disease.

SARS-CoV-2 and the baroreflex: A newneuroinvasion proposal

Recently, clinical studies have shown an important role for the endothelium during the development of COVID-19 because of its strong relationship with the immune system, which generally determines the course of the disease.[52] Endothelial cells have high ACE2 expression and are the primary targets for SARS-CoV-2 invasion, leading to contamination of vessels, especially those with a large caliber, which may justify neuroinvasion.[49,53]

Recent studies have shown that SARS-CoV-2 infection of the endothelium increases the activity of the immune system and the interaction of its components with the vessels, resulting in endothelial damage due to the activation of defense cells and the disordered release of pro-inflammatory cytokines that contribute to the degradation and weakening of the vessel wall and apoptosis and pyroptosis of endothelial cells.[52] This scenario favors the viral entry into the deepest histological layers of the vessels, such as the connective layer, the muscle, and the adventitia, either indirectly, through the contamination of the vasa-vasorum by SARS-CoV-2 (as seen in cases of Kawasaki disease associated with COVID-19)[54] or directly, by the action of pro-inflammatory cytokines that could damage the vessel wall.[55] Thus, profound vascular changes, including in large-caliber vessels, resulting from COVID-19 may be associated with the following factors: (i) endothelial inflammation[56]; (ii) endothelial damage, which changes the vascular balance and generates vasoconstriction, ischemia, thrombus formation, and inflammation associated with edema[57]; (iii) vasculitis[58]; (iv) formation of thrombus in large vessels (aorta) due to the formation of neutrophil extracellular traps (NETs) and changes in the functioning of platelets and pro-coagulating factors.[13,23-25,55,59,71] Because of the weakening of the vessel wall and possible viral penetration, the virus can access nerve structures within the vessels, such as the aorta and the common carotid artery, which have neural circuits that integrate these vessels into the nucleus of the solitary tract (NTS) (Figure 1).

Carotid chemoreceptors have been suggested as possible loci for SARS-CoV-2 entry into the brain via neuronal afferents (such as glossopharyngeal) to the NTS.[36] Recent studies have associated the carotid chemoreceptors affected by SARS-CoV-2 with silent hypoxia, suggesting the virus acts by decreasing baroreflex sensitivity.[60,61] Such alteration is linked to local inflammation caused by the virus, leading to baroreceptors' breakdown and their function.[36] We hypothesize that

SARS-CoV-2 neuroinvasion also occurs via aortic baroreceptors using the entire baroreflex structure.

Endothelial damage resulting from an over-stimulation of the immune system[52] and the invasion of SARS-CoV-2 via vasa-vasorum[54] can disrupt the vessel, allowing the penetration of the viruses and their contact with baroreceptors. Disruption of baroreceptors likely explains the relationship between hypertension and COVID-19 because baroreceptors are directly related to blood pressure control (BP). The baroreflex likely provides a trans-synaptic transmission pathway for SARS-CoV-2 to invade the CNS and compromise sensitive nuclei involved in cardiorespiratory control.

Baroreceptors, the nerve endings linked to elastic connective tissue fibers of collagenous origin, are in specialized portions of the tunica media and adventitia of large vessels. They are sensitive to stretching and are located mainly at the bifurcation of the common carotid artery and the aortic arch.[62,63] This system acts as an autonomic pacemaker and strictly regulates BP. Baroreceptors have cell bodies in the petrosal and nodose ganglia, projecting central endings to the NTS and distal endings to the walls of the great vessels.[62-64] The increase in blood pressure stretches the artery wall, which leads to depolarization of the distal terminations of the baroreceptors and stimulates the NTS via the vagus nerve (aortic baroreceptors) or glossopharyngeal nerve (carotid chemoreceptors). The efferents emerging from second-order neurons in NTS will orchestrate sympathetic and parasympathetic output to return BP to normal levels.[62-64]

Autonomic modulation occurs in 2 main ways. (i) The parasympathetic-excitatory pathway is formed by NTS projections to the nucleus ambiguous (NA) and the dorsal motor nucleus of the vagus (DMV). The excitatory stimulation of this pathway increases parasympathetic activity in the heart, promoting bradycardia and resulting in decreased cardiac output, which, in turn, lowers the blood pressure inside the vessels.[62,63] (ii) The sympathetic-inhibitory pathway is formed by the glutamatergic projections from NTS to the caudal ventrolateral medulla (CVLM), which, in turn, emit inhibitory projections to the rostral ventrolateral medulla (RVLM), where most of the presympathetic neurons are located. CVLM neurons release GABA in RVLM and hyperpolarizing spinally-projecting presympathetic neurons that control vasomotor function. As a result, the inhibition of sympathetic outflow to the vasculature decreases peripheral resistance, and consequently, BP. In addition, the baroreflex-mediated inhibition of RVLM neurons also suppresses the sympathetic outflow to the heart (decreasing contraction force and cardiac output) and the adrenal glands (decreasing the release of epinephrine into the circulation) both effects contributing to the lowering of BP.[64-66] Besides modulating RVLM presympathetic neurons, the baroreflex can regulate sympathetic activity through connections with the paraventricular nucleus of the hypothalamus (PVN). The PVN contains presympathetic neurons and controls sympathetic activity by sending direct projections to the

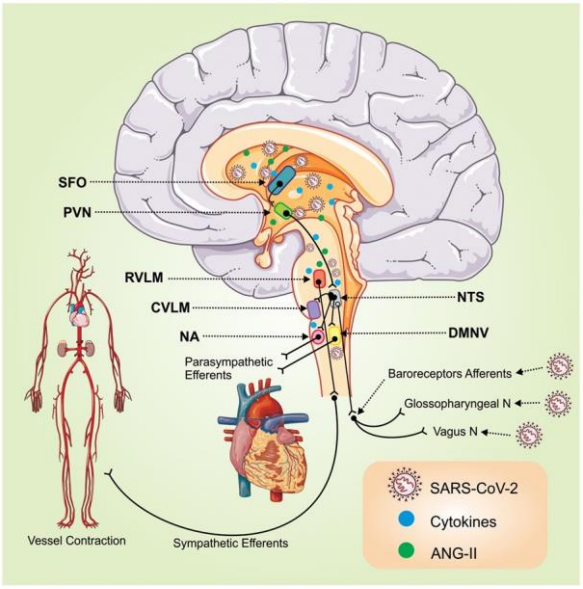

Figure 2. The cartoon illustrates the possible SARS-CoV-2 neuroinvasion through baroreceptor circuitry. Increased Ang-II and cytokine levels in the brain, as a consequence of viral infection, damage the endothelium and disrupt BBB, which adversely affects the function ofbrain nuclei controlling blood pressure (SFO, PVN, NTS, NA, RVLM, CVLM) and impairments in heart and the control of hypertension in bloodvessels.

intermediolateral cell column of the spinal cord (exciting preganglionic sympathetic neurons) or via excitatory projections to RVLM presympathetic neurons. The PVN also establish connections with the NTS, which stand out because their cardiovascular afferents bring information to the CNS capable of modulating the PVN response.[67] Thus, baroreflex activation can also inhibit sympathetic outflow through the modulation of PVN presympathetic neurons, affecting peripheral resistance, cardiac output, and the release of catecholamines from the adrenal glands and contributing to normalizing BP levels.[64,68] The dysfunction of baroreflex mechanisms has been reported to contribute to neurogenic hypertension since the inhibitory modulation of RVLM, and PVN presympathetic neurons are compromised, leading to sympathetic overactivity and elevated BP. Therefore, we hypothesized that SARS-CoV-2 invades neurons through vessels via the weakening of the wall of large vessels and with the possibility of contamination via vasa-vasorum in the adventitia layer, accesses the baroreceptors located in the carotid artery and aortic arch. The baroreflex circuitry can promote the access of the virus to the NTS via the vagus and glossopharyngeal nerves, deregulating blood pressure at the central level (Figure 2).

SARS-CoV and unbalance in RAAS: Alterationof the baroreflex and promotion of neurogenic hypertension

The control of BP is a complex and refined process performed by the nervous, endocrine, and renocardiovascular systems.[69] Traditionally, RAAS has been described as an endocrine system

that controls vascular function, hydroelectrolytic balance, blood pressure, and peripheral vascular resistance.[70-76] RAAS plays an important role peripherally in different organs such as vessels, kidneys, heart, adrenal gland, and intestine.[36,70,77] In addition, RAAS acts on the CNS through 2 components, ANG-II and ACE2. ANG-II is an activator molecule of RAAS, described as a peptide composed of 8 amino acids. As it does not cross the BBB, the ANG-II is only able to access central structures from the circumventricular organ (CVO), especially from the subfornical organ (SFO), due to the absence of BBB from these brain structures.[20,78,79] ACE2 is a molecule that inhibits RAAS activity and is described as a protein widely expressed in the brain, such as SFO, PVN, NTS, NA, NMDV, RVLM, and hippocampus. Many of these brain areas are related to central BP control.[19,20,41,70,80]

Lately, it was discovered that RAAS promotes and maintains the inflammatory response and plays a role in the manifestation of many diseases.[81-83] The RAAS imbalance has been critically associated with SARS-CoV-2 infection,[20,70,77] possibly due to the high affinity of this virus to ACE2, being 10 to 20 times higher than the affinity of SARS-CoV.[36] Interestingly, some of the conditions that compose the main comorbidities of COVID-19, which are associated with the development of more severe conditions and a greater chance of death, such as obesity, diabetes, cardiovascular diseases, hypertension, kidney, and lung diseases, are conditions that have, to a greater or lesser degree, their pathophysiology influenced by the unbalance of the RAAS.[77] Not by chance, these diseases or conditions are also characterized by the strong presence of chronic inflammatory processes.[77,84,85] Elevated levels of inflammation have also been recorded in patients with moderate and severe cases of SARS-CoV-2 infection. Such inflammation is related to CNS damage, and a worse prognosis is associated with a greater chance of death from COVID-19. Thus, some studies suggest that alleviating inflammation following SARS-CoV-2 infection improves the general condition of patients and decreases the risk of death.[51]

The influence of SARS-CoV-2 on RAAS unbalance likely occurs due to the internalization induction effect of membrane ACE2 receptors after virus entry into cells.[8] This effect promotes an increase in ANG-II/AT1R levels concerning ACE2/Ang(1-7)/MasR levels since the conversion of ANG-II to Ang (1-7) is made by the action of ACE2.[8] Thus, the lower availability of ACE2 reduces the conversion of ANG-II, making it more prevalent (Figure 3A and B). Therefore, the effects related to ANG-II mediated by AT1R activation are exacerbated. The AT1R receptor is expressed in brainstem areas, such as in RVLM, increasing sympathetic activity and blood pressure, which may indicate a possible relationship of AT1R with the development of neurogenic hypertension and changes in baroreflex sensitivity.[8,84-86]

Among the effects of ANG-II, its effect on the AT_1R receptor is in addition to the already-known vasoconstrictor effect.[86,87] There are several other effects with a direct influence

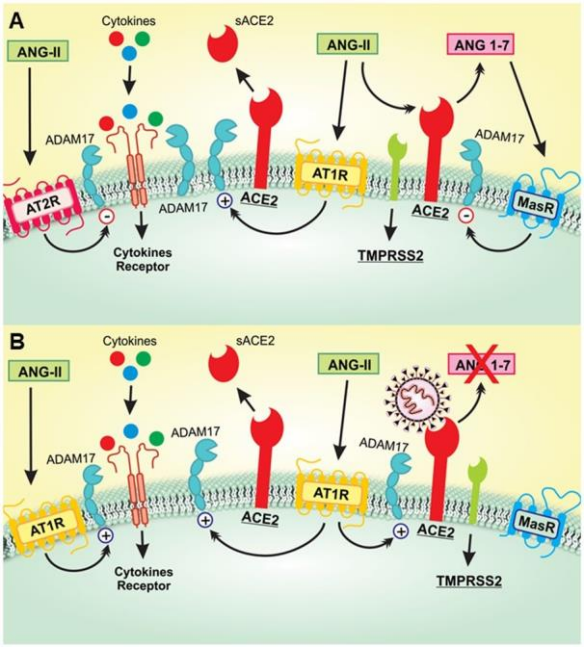

Figure 3. The cartoons depict the renin-angiotensin-aldosterone system (RAAS) homeostasis and imbalance. (A) RAAS homeostasis is characterized by a balance between molecules and receptors responsible for proinflammatory (ANG-II, AT1R, ADAM-17) and antiinflammatory (ANG 1-7, MasR, and AT2R) responses. (B) The RAAS imbalance caused by SARS-CoV-2-ACE2 results in increased AT1R and ADAM17 activity, exacerbating the proinflammatory response. In addition,this disorder releases sACE2, compromises ANG 1-7 formation, and reduces MasR and AT2R activity.
Abbreviations: ACE2, angiotensin converter enzyme 2; ANG-II, angiotensin II; ANG 1-7, angiotensin 1-7; AT1R, angiotensin receptors 1; AT2R, angiotensin receptors 2; MasR, macrophages receptor; sACE2, soluble angiotensin converterenzyme 2; TMPRSS2, transmembrane serine protease 2.

on pressure control. One of the most described is the elevation of ROS production because of their activating action on the enzyme dinucleotide phosphate oxidase nicotinamide adenine [NAD (P) H]. The increase in oxidative stress would lead to an increase in the action of chemokines, which would activate and attract T cells. These cells, in turn, would infiltrate key organs such as the heart, and help to generate hypertension.[86,87] In the CNS, the increase in ROS levels and oxidative stress in SFO, PVN, and RVLM are related to hypertensive conditions. In addition, it has been recorded that oxidative stress in areas such as CVO, hypothalamus, and brainstem can trigger cardiovascular problems.[86,88] Hypertension caused by ANG-II elevates the level of ROS, but hypertension induced by norepinephrine does not infer this parameter, indicating a characteristic effect of ANG-II.[86,88]

It has been described that the increased activity of enzymes involved in the production of ROS can disconnect NTS and NA, leading to loss of baroreflex sensitivity.[65] Consistent with this concept, studies have shown that antioxidant treatment administrated systemically or directly into RVLM and SFO can reduce hypertension.[86]

Additionally, ANG-II promotes the inflammatory response via the activation of defense cells. Previous studies have shown

that ANG-II plays a chemoattractant role in defense cells and induces endothelial and smooth muscle cells to release cytokines, P-selectins, and adhesion factors, resulting in the attraction and adhesion of monocytes and neutrophils to vessels.[70] Furthermore, ANG-II acts on helper and cytotoxic T lymphocytes (which can express not only the AT_1R receptor but also release the Ang II itself), acting with an autocrine profile in cell activation, proliferation, differentiation, migration, and adhesion. The activation of leukocytes, in turn, causes vascular inflammation and renal and vascular hypertension.[70,87,88] The stimulation of defense cells weakens the BBB, facilitating the entry of T cells and ANG-II circulating in the CNS and increasing neurological damage.[25,30,31,68,89]

Another factor that associates ANG-II with a comprehensive inflammatory response is the ANG-II-induced release of pro-inflammatory chemokines and cytokines (IL-1□, IL-6, TNF-□, TGF-□, MCP-1 INF□); and inhibition of anti-inflammatory cytokines, especially IL-10, in central autonomic regions that control BP, such as PVN and RVLM.[87,88] The increased inflammatory status induced by ANG-II within the PVN and the RVLM have been associated with a vasomotor sympathetic tone, which contributes to hypertension.[87,88] Effects of the production of these cytokines and the alterations in immune pathways affect kidneys and the heart, contributing to the fibrosis response of peripheral structures and the development of CVDs. The increase in peripheral cytokines can even exert effects in central areas, such as SFO, because it does not have BBB[20] and lead to the development of hypertension, suggesting that, even if neuroinvasion does not occur, peripheral effects of SARS-CoV-2 infection, as the increase in the arrival of ANG-II and cytokines, can trigger the hypertensive response via central mechanisms, which implies the possibility of direct or indirect action of this virus in the pressure control structures.[87] It is important to consider that the anti-inflammatory mediators of the RAAS pathway are reduced because there is a low conversion of ANG-II into Ang(1-7).[87]

ANG-II also appears to act on microglia. Rats with ANG-II-induced hypertension showed an increase in microglial activation, either due to microgliosis or the increase in pro-inflammatory cytokines generated by ANG-II. Increased microglial activation has been associated with increased neuroinflammation and expression of glutamatergic receptors in the PVN. This configuration can favor the activation of this nucleus and reduce the threshold for firing in these neurons, activating the entire sympathetic excitatory pathway, promoting, among other effects: the increase in plasma vasopressin levels and an increase in BP.[87,88] Along with the effects on the PVN caused by ANG II-induced microglia activation, there are the effects caused by the ANG II itself on this nucleus. In vitro studies demonstrated the action of ANG II on the 2 main classes of PVN neurons via AT1R: the parvocellular neurons (which control sympathetic activity) and the magnocellular ones (which synthesize oxytocin and vasopressin and secrete them at the neurohypophysis). However, while parvocellular neurons directly respond to ANG II, magnocellular neurons can also respond directly or indirectly, depending on excitatory (glutamatergic) stimulation coming from other neurons around the PVN.[90,91] Thus, it is possible that an imbalance in the RAAS promotes changes in the 2 main PVN neuronal populations, contributing to the pathological scenario described here. Changes in astrocytes due to the action of ANG-II have also been recorded. Astrocytes regulate neuronal and neurohumoral function in hypothalamic nuclei such as PVN and supraoptic nucleus (SON). The release of glutamate in the extracellular space in nuclei such as PVN may evoke a persistent activation of NMDA receptors. Astrocytes determine the magnitude of this activation through the glutamate transporter 1 (GLT1) expression. However, it was found that ANG-II can modulate this process since it can block GLT1 from astrocytes, preventing the uptake of glutamate by these cells.[68] Such an effect leads to elevated glutamate levels and an overexcitation of the PVN sympathetic excitatory pathway, especially in extrasynaptic neurons that project to the RVLM. The excitation of this bulbar nucleus is associated with increased BP and contributes to the installation of the condition of neurogenic hypertension.[68]

ANG-II also modulates the integration of afferents that reach the NTS from the baroreceptors, which can increase pressure. Such effect is due to the ability of ANG-II to promote an increase in GABAergic neurotransmission, skewing afferent transmissions from baroreceptors to second-order neurons in NTS, which stands out not only for expressing both AT_1R and ANG-II itself but also for being a nucleus sensitive to GABA modulation.[66] The high sensitivity of NTS to GABA may be associated with many GABAergic neurons, nerve endings, and type A and B receptors, which reduce the effects of ANG-II or increase the BP induced by intracerebral administration of ANG-II, respectively.[66]

Furthermore, recent studies show that GABA and ANG II can alter the sympathetic tone when interacting in the NTS, indicating the participation of GABA in the control of cardiovascular function. NTS is described as an indirect inhibitor of RVLM, acting via CVLM. Therefore, NTS can be inhibited by the release of GABA induced by ANG-II/AT1R, which can decrease the baroreflex sensitivity and lead to an increased BP due to the inhibition of baroreceptor signals and RVLM upregulation.[66]

Activation of ADAM17 is another factor in the pathophysiology of SARS-CoV-2. ADAM17, a disintegrin and metalloprotease of the ADAM family, is also known as tumor necrosis factor-□ converting enzyme (TACE).[8,87] ANG-II activates AT1R and promotes upregulation of ADAM-17, which leads to increased shedding of ACE2 due to cleavage and release of its ectodomain. Such an effect leads to reduced expression of ACE2 on the cell surface and increased release of its soluble free form (sACE2).[8,87] In addition, ADAM17 can

cleave more than 80 molecules, which is associated with the dysregulation of immunological cytokines.[87]

ADAM17 is widely expressed in vessels, the heart, kidneys, testes, lungs, spleen, muscles, and brain, contributing to hypertension at peripheral and central levels.[8,87] Peripherally, ADAM17 promotes the transactivation of the epidermal growth factor receptor (EGFR), induced via Ang II, and can generate hypertrophy in vascular musculature, contributing to hypertension and other cardiovascular diseases. At the central level, the activation of ADAM17 contributes to the development of a hypertensive condition from the invasion of defense cells in the CNS, activation of microglia, and production of cytokines in the CNS (such as TNF-□, making it challenging to produce the enzyme glutamic acid decarboxylase (Gad) and, therefore, GABA) and neuroinflammation.[8,87]

However, its action in controlling sympathetic activity, specifically in PVN, draws the most attention when analyzing the influence of ADAM17 in conditions such as neurogenic hypertension and changes in baroreflex sensitivity. These conditions seem to be directly influenced by the ACE2 shedding performed by ADAM17 since ACE2, when converting ANG-II to Ang (1-7), plays a fundamental role in the inhibitory control of PVN, given the necessary stimulation of Ang (1-7) for the formation of GABA. Thus, without ACE2, the inhibitory control of this nucleus is impaired, and the firing of glutamatergic neurons increases, thus promoting an increase in sympathetic activity. ADAM17 expression in glutamatergic neurons is related to decreased regulation and strength of GABA receptors, reducing inhibitory control over this group of GABAergic neurons.[92] Therefore, ANG-II is directly or indirectly related to the increase in glutamate levels, which intensifies the activation of the sympathetic pathway, and to the reduction of GABA levels in the PVN and RVLM, which contributes to the increase in BP.[93]

Because of its presence in the CNS, ANG-II/ADAM17 may be related to the pathophysiology of SARS-CoV-2. ADAM17 is considerably more expressed in the brain than TMPRSS2,[25] which provides greater importance to ADAM17 in developing SARS-CoV-2 infection, and in the relationship of COVID-19/brain. Therefore, increased ADAM17 in the CNS could contribute to neurotropism and neurovirulence in the viral neuroinvasion of SARS-CoV-2.[25]

Besides ACE2, the virus entry into the cell is conditioned by other molecules, like proteases, such as TMPRSS2.[25] ADAM17 acts as a viral cofactor and competes with TMPRSS2 in the "shedding" of ACE2. The cleavage of TMPRSS2 does not produce an active molecule, unlike ADAM17, whose shedding produces sACE2 capable of counterbalancing the action of ANG-II, which could potentially block or reduce viral circulation.[8,70,94] However, beyond this assumption, sACE2 is associated with increased blood pressure[95] and the activation of defense cells, which can contribute to worsening the immune system's imbalance,[70] especially in patients who already have conditions that directly or indirectly affect this system.

Some publications propose that the production of sACE2 would have a protective effect against SARS-CoV-2. However, in the SARS-CoV epidemic, the downregulation of ADAM17 decreased the viral infection. Therefore, sACE2 was not responsible for the decrease in the action of this viral agent.[25] It is believed that something like this could also happen with SARS-CoV-2.[25] This perspective agrees with recent findings demonstrating that SARS-CoV-2's entry into cells is facilitated after the ACE2 receptor's cleavage. Also, the shedding activity can help promote the expression of molecules involved in this process, such as ADAM17.[25]

Furthermore, it was observed that in pulmonary epithelial cells of patients infected with SARS-CoV-2, ADAM-17 activity could be reduced by an inhibitor of tissue metalloproteinases 3 (TIMP3). Such results imply that the action of SARS-CoV-2 on cells significantly affects the expression and action of TIMP3, resulting in increased activity of ADAM-17. In the lungs, the increasing activity of ADAM-17 is related to the development of fibrotic tissue and an increase in infection.[19] Although much remains to be understood, it is believed that ADAM17 inhibitors can play a protective role in the infection by reducing the shedding of ACE2, reducing the infectivity of the virus,[96] and the inflammatory condition.[70] Such inference is supported by a study in an animal model demonstrating that ADAM17 inhibitors (such as apratastat and TMI-1) can prevent the progression of COVID-19's severity by preventing lung injury caused by the invasion of neutrophils.[97] The action of ADAM17 favors the production of the active form of TNF-□, which is strongly linked to critical events, such as cytokine storms and neutrophil recruitment (both linked to the most severe cases of COVID-19). Thus, the inhibition of ADAM17 decreases the levels of pro-inflammatory cytokines and endothelial adhesion molecules (necessary for the migration of defense cells from vessels to tissues affected by the infection), as well as the infiltration of neutrophils, attenuating lung inflammation and improving the overall outcome.[97]

ADAM17 has broad implications for the brain. The phenomenon seen in pulmonary epithelial cells could also occur in neuronal and glial cells. Thus, the increased activity of ADAM17 in the brain could contribute to neuronal damage and alterations in the neuroinflammatory response, which can cause many neurological symptoms observed in COVID-19 patients. Recent evidence demonstrates that the inhibition of ADAM17 following cortical brain injury promotes new neuron production and repair. The action of ADAM17 is, therefore, directly involved in altering the differentiation of neural progenitor cells into neurons (neurogenesis). Indeed, ADAM17 has been shown to facilitate the differentiation of neural precursors into glial cells, actively contributing to the formation of a glial scar. In addition, ADAM17 impacts the migration of newly formed neurons from neurogenic zones to the damaged cortical areas and neuronal survival by releasing cytokines and other molecules that contribute to neurodegeneration.[98]

Hypertensive patients display elevated ADAM17 and reduced ACE2 expression, especially in the brain.[95] ADAM-17 inhibition could attenuate inflammation and hypertension.[87,99] Furthermore,from its involvement in the comorbidities and pathophysiology of COVID-19, ADAM17 inhibition can potentially block severe SARS-CoV-2 infection.[97] Thus, elevated ADAM17 is likely the cause of the severe COVID-19 associated with neurological symptoms in hypertensive people. Moreover, the worsening of hypertension and multiple neurological symptoms in COVID-19 patients is likely a result of intense activation of ANG-II and ADAM17.

The loss of blood pressure control can also lead to neurological sequelae, which could be caused by different events, including damage to specific neural circuits, especially the GABAergic neurotransmission in the PVN and NTS, in addition to effects directly linked to ANG-II activity, such as increased levels of ROS and oxidative stress, activation of defense cells, BBB damage, alterations in the GABA-ergic and glutamatergic neurotransmission in different nuclei of the medulla and the hypothalamus. Collectively, the factors described above support our hypothesis of the direct involvement of SARS-CoV-2 in the development or worsening of the hypertensive [100,101] response by influencing the baroreflex and/or the PVN-driven neurogenic hypertensive response. Additionally, other studies have associated hypertension after immunization against COVID-19 using different immunizers.[102-106] However, because of many controversies and obscure points on this topic, more studies targeting these issues are needed to understand the mechanisms involved.

Conclusion

This commentary proposes a new route of neuroinvasion by which the virus systematically acts to promote hypertensive conditions in many COVID-19 patients. While many issues regarding neuroinvasion, neurotropism, and neurovirulence, and the neurological effects of SARS-CoV-2 are still under investigation, the available evidence supports our hypothesis.

Author Contributions

Conceptualization: OWC and KBO; Formal analysis and Investigation: KBO, BRMS, OWC and KLSO; Project administration and Supervision: OWC and AKS; Roles/Writing—original draft: KBO, ISS, and OWC; Writing—review & editing: RSS, ISS, LA, PLK, VRS, AKS, and OWC.

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7. CONCLUSÃO

Uma compreensão mais precisa dos efeitos da infeção pelo SARS-CoV-2 requer um olhar amplo e integrativo sobre a relação desse vírus com diferentes estruturas e tecidos. Essa postura é fundamental para a identificação dos fatores que podem desencadear quadros de maior gravidade e sequelas pós-COVID-19. Um conjunto complexo de fatores parece ser determinante para o prognóstico da COVID-19. O endotélio e o SNC têm se mostrado como peças-chave nesse processo.

A infeção endotelial pelo SARS-CoV-2 pode resultar na fragilização vascular, o que tem sido associado à entrada do vírus, de moléculas indesejadas e de células de defesa em múltiplos órgãos, com destaque para o cérebro. Essa fragilização nos vasos, resultado da atividade viral, tem sido explicada em função do desbalanço do sistema RAAS, caracterizado pela promoção da atividade linfocitária, tempestade de citocinas e aumento do estresse oxidativo (Lupu; Palmer; Huber-Lang, 2020; Gambardella; Santulli, 2020; Kaur; Tripathi; Yadav, 2020; Boyle; Haverich, 2020; Varga *et al.*, 2020; Carnevale; Beretta; Morbin, 2021; Fukuhara; Rosati; El-Dalati, 2020; Gomez-Arbelaez *et al.*, 2020; Ran *et al.*, 2020). É sabido que o SARS-CoV-2, infecta células humanas principalmente a partir da ACE2, favorecendo, na sequência, a internalização dos receptores ACE2 de membrana. Dessa forma, o vírus desencadeia um conjunto de alterações que podem gerar um desequilíbrio do RAAS, caracterizado pelo aumento da atividade da angiotensina II via seu receptor AT1R, e da ADAM17/TACE (Sharma *et al.*, 2021; Assersen; Sumners; Steckelings, 2020; Chakravarty *et al.*, 2021; Zipeto *et al.*, 2020; Xavier *et al.*, 2021; Queiroz; Lakkappa; Lazartigues, 2020;).

Esse mecanismo fisiopatológico, além de efeitos vasculares, também tem sido associado a efeitos neurológicos relacionados ao controle da pressão, entre outras respostas (Queiroz; Lakkappa; Lazartigues, 2020; Queiroz; Monteiro; Braga, 2013; Carvalho-Galvão *et al.*, 2019; Xavier *et al.*, 2021). A atividade do vírus pode modular a integração de aferências que chegam ao NTS a partir de barorreceptores, promovendo aumento da pressão arterial, além de promover indiretamente a ativação do PVN. Esses mecanismos estão relacionados ao aumento da atividade simpática, que leva à hipertensão transitória ou permanente associada à invasão do SARS-CoV-2 (Légat; Smolders; Dupont, 2019).

Nosso estudo permite, de maneira pioneira, propor, baseado em evidências presente na literatura, que a ação direta ou indireta do vírus no cérebro pode promover

um quadro de hipertensão sistêmica. A relação entre COVID-19 e o desenvolvimento ou piora do quadro de hipertensão tem sido demostrada em publicações recentes (Akpek, 2022; Clark *et al.*, 2021; Angeli *et al.*, 2022; Athyros, doumas, 2022; Simonini, 2022; Khani; Entezari-Maleki, 2022; Bouhanick *et al.*, 2021). Além disso, os mecanismos propostos também permitem ampliar o conhecimento sobre a intricada relação entre hipertensão e o desenvolvimento de um pior prognóstico da COVID-19 (Ran *et al.*, 2020; Shibata *et al.*, 2020, Kamyshnyi *et al.*, 2020). Este estudo, a partir de suas limitações, fornece também uma direção para investigações futuras, como: 1) a identificação mais precisa do papel da aldosterona na COVID-19; 2) o estabelecimento da relação entre os sistema RAAS e outros sistemas fisiológicos importantes para o controle da homeostasia e da resposta inflamatória, em especial no cérebro, como: o sistema de endocanabinóides (ECS); sistema de calicreina-cinina (KKS); sistema de neuroesteróides; 3) e um aprofundamento sobre a relação entre as aquaporinas e a COVID-19. Entretanto, mais estudos são necessários a fim de verificar experimentalmente as hipósteses aqui levantadas e defendidas com base nas evidências disponíveis atualmente.

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