Circulation

ON MY MIND

Can an Old Ally Defeat a New Enemy?

Paul A. Gurbel, MD
Kevin P. Bliden, MBA
Karsten Schrör, MD

Infection with the beta coronavirus severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019 [COVID-19]) is a worldwide public health nightmare with nearly 5 million confirmed cases and >300 000 deaths. The fact that it has no proven therapy has created an urgency to find safe and effective early treatments. We must open our eyes to all reasonable candidates. Acetylsalicylic acid (ASA), the wonder drug of the last century, may be a magic bullet to repulse our new enemy. In the war against cardiovascular disease, the efficacy of ASA for secondary prevention is established and results largely from the acetylation-induced inhibition of platelet cyclooxygenase-1, a key mediator of thrombosis.[1] In the war against viral disease, another important effect of ASA, mediated by the salicylate component, should be exploited. ASA inhibits a key nuclear transcription factor, nuclear factor-κB (NF-κB).[1] Viral replication and the ensuing inflammatory response (cytokine storm) mandate activation of NF-κB in the host cell. The invading viruses conduct their "hostile takeover" of the cell by inactivating IκB, the endogenous inhibitor of NF-κB.[2] Viruses do this by activating a kinase, IκB kinase, which phosphorylates IκB (Figure). ASA and salicylate are known inhibitors of IκB kinase at millimolar concentrations. This effect is not seen with indomethacin or other nonsteroidal anti-inflammatory drugs, is concentration-dependent, and is reportedly mediated by blocking ATP binding to IκB kinase.[1]

In in vitro studies, D, L-lysine acetylsalicylate+glycine (LASAG) inhibited low (HCoV-229E) and highly (Middle East respiratory syndrome coronavirus) pathogenic beta coronavirus strain replication.[2] Cytotoxic concentrations were >20 mmol/L, whereas the EC_{50} values for vital titers were 1.31 mmol/L for HCoV-229E and 3.91 mmol/L for Middle East respiratory syndrome coronavirus, suggesting a potential therapeutic window. LASAG also inhibited virus-induced NF-κB activity and decreased viral protein formation, RNA synthesis, and the formation of replication transcription complexes.[2] In human lung epithelial cells infected with influenza A, 5 mmol/L LASAG inhibited IκB kinase–mediated NF-κB activation and virus production. In the same report, inhaled LASAG was associated with a survival benefit in mice infected with a severe influenza strain. Finally, in 24 patients afflicted with severe influenza, nebulized LASAG 3 times a day to achieve an estimated total daily alveolar dose of 133.5 mg was associated with faster alleviation of symptoms compared with control subjects.[3]

Systemic concentrations of ASA and salicylate obtained by oral conventional ASA may not reach the airway and alveolus at a level for meaningful antiviral effects. Moreover, high oral ASA doses can be limited by salicylate toxicity caused by (reversible) uncoupling of oxidative phosphorylation at anti-inflammatory doses and effects of cyclooxygenase inhibition.[1] However, treatment of patients by inhalation would likely achieve locally effective concentrations without major toxicity. Repeated administration of aspirin is followed by accumulation of salicylate resulting from prolongation

Key Words: aspirin ■ COVID-19 ■ cyclooxygenase 1 ■ virus

https://www.ahajournals.org/journal/circ

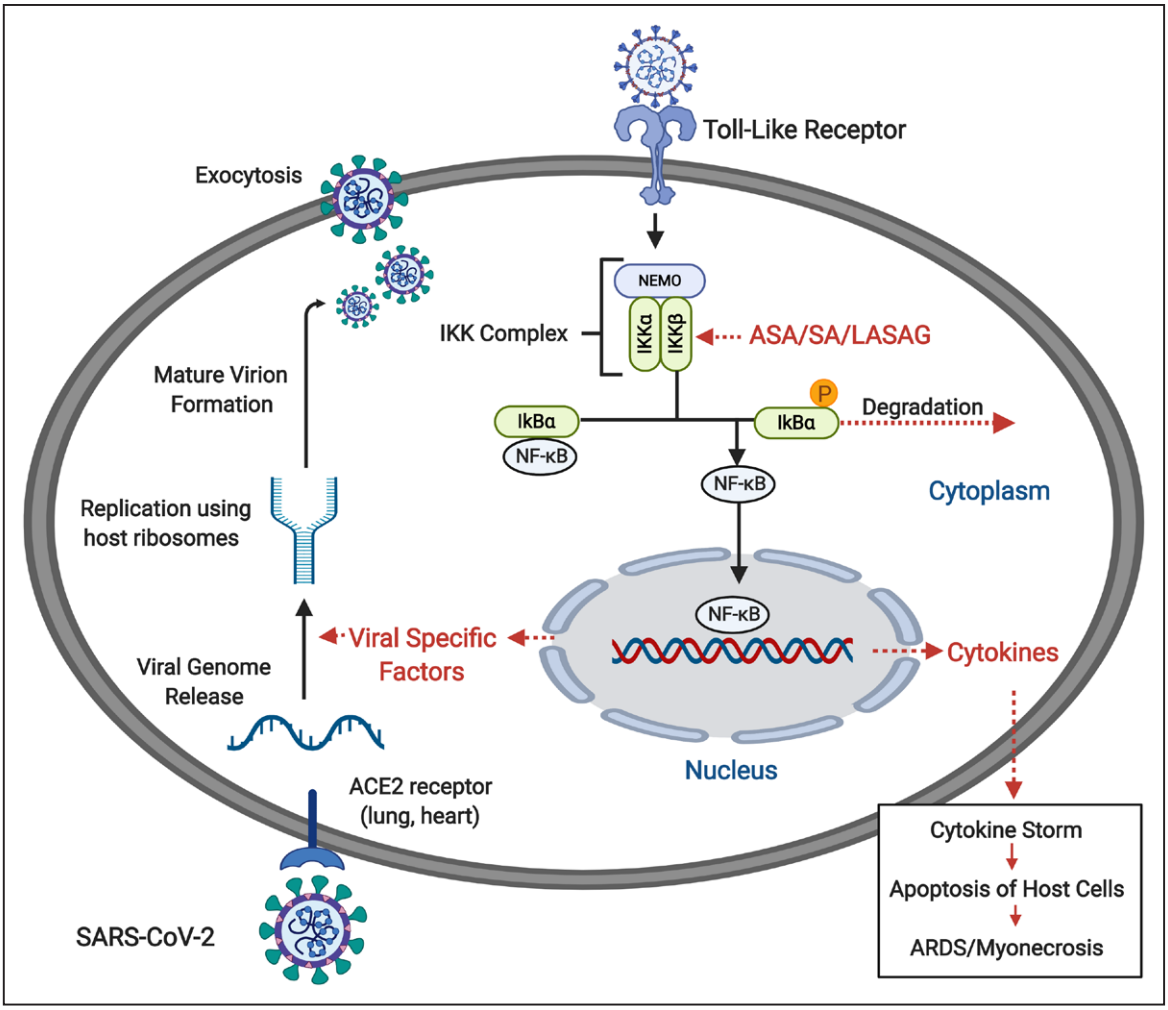

Figure. Schematic representation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, activation of the nuclear factor-κB (NF-κB) pathway leading to acute respiratory distress syndrome (ARDS) and myonecrosis.
ACE2 indicates angiotensin-converting enzyme receptor 2; ASA, acetylsalicylic acid; IκBα, inhibitor of NF-κB, IKK, IκB kinase; LASAG, D, L-lysine acetylsalicylate+glycine, NEMO, NF-κB essential modifier; P, phosphorylation; and SA, salicylate.

of half-life and high (>90%) protein binding. Repetitive local dosing might result in higher and longer-lasting tissue levels of salicylate than seen from plasmatic levels.[1] The unique pharmacokinetic property of salicylate to accumulate in cell membranes may further promote tissue concentrations that inhibit viral replication.

We have recently studied inhaled nanoparticle ASA and demonstrated that it enters the circulation much faster and at greater levels than chewed and swallowed ASA.[4] We have estimated that the inhaled dose of LASAG required for adequate alveolar deposition (EC_{50}, 3.9 mmol/L for Middle East respiratory syndrome coronavirus), assuming even distribution in the 36-mL lung lining fluid, is 51 mg. This dose is well below the cytotoxic dose. Therefore, on the basis of the tolerability of 10-fold higher doses, we would propose a dose of 500 mg LASAG to effectively reduce the virus load in patients with severe acute respiratory syndrome coronavirus 2–infected lungs. Because this treatment targets a host cellular pathway, the chance that resistant virus variants would emerge is limited. As an adjunct to its direct antiviral property, patients may also benefit from proven analgesic and anti-inflammatory effects. Finally, a hypercoagulable state has been associated with adverse outcomes during COVID-19 infection. The antiplatelet effects of aspirin mediated by cyclooxygenase-1 inhibition may be expected, in part, to address this serious pathophysiology. Moreover, inhibition of thrombin formation will additionally support these anticoagulatory actions.[1] Finally, a new micronized aspirin tablet that is rapidly dissolving achieves peak plasma levels of unmetabolized ASA that are 3 times higher than standard formulations. With repeated administration, one might have greater accumulation of salicylate because of its prolonged half-life.[5] The latter therapy could be used in concert with the inhaled route or as stand-alone therapy in patient groups with low risk of systemic toxicity. Because of interindividual variability in metabolism, determination of plasma salicylate levels during repeated use would be important to avoid toxic blood levels.[1]

Circulation. 2020;142:315–317. DOI: 10.1161/CIRCULATIONAHA.120.047830

In summary, we acknowledge that our hypothesis would be strengthened if there were greater demonstration in animal models and humans that aspirin modulated the response to severe acute respiratory syndrome coronavirus 2. However, we believe that the evidence we present provides a rationale for further investigations of aspirin that are on our minds in this urgent time. The totality of evidence supports a potent viral inhibitory effect of ASA that is estimated at local millimolar concentrations. These concentrations should be achievable without major toxicity by inhalation. ASA has been our ally in the war of cardiovascular disease. The time is now to investigate the strength of our old friend in a new infectious disease war.

ARTICLE INFORMATION

Correspondence

Paul A. Gurbel, MD, Sinai Center for Thrombosis Research and Drug Development, Sinai Hospital of Baltimore, Baltimore, MD 21215. Email pgurbel@lifebridgehealth.org

Affiliations

Sinai Center for Thrombosis Research and Drug Development, Baltimore, MD (P.A.G., K.P.B.). Department of Pharmacology and Clinical Pharmacology, Heinrich-Heine-University, Düsseldorf, Germany (K.S.).

Disclosures

Dr Gurbel reports grants and personal fees from Bayer HealthCare LLC, Janssen, and US WorldMeds LLC; personal fees from Otitopic Inc, Amgen, and UpToDate; and grants from Instrumentation Laboratory, Haemonetics, Medicure Inc, Idorsia Pharmaceuticals, and Hikari Dx. He is a consultant for Otitopic Inc, the company producing nanoparticle aspirin. In addition, Dr Gurbel has a patent, Detection of Restenosis Risk in Patients, issued and a patent, Assessment of Cardiac Health and Thrombotic Risk in a Patient. Dr Schrör received personal fees from Bayer. K.P. Bliden reports no conflicts.

REFERENCES

1. Schrör K. *Acetylsalicylic Acid*. 2nd ed. Schrör KK, ed. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co; 2016.
2. Muller C, Karl N, Ziebuhr J, Pleschka S. D, L-lysine acetylsalicylate + glycine impairs coronavirus replication. *J Antivir Antiretrovir*. 2016;8:142–150.
3. Scheuch G, Canisius S, Nocker K, Hofmann T, Naumann R, Pleschka S, Ludwig S, Welte T, Planz O. Targeting intracellular signaling as an antiviral strategy: aerosolized LASAG for the treatment of influenza in hospitalized patients. *Emerg Microbes Infect.* 2018;7:21. doi: 10.1038/s41426-018-0023-3
4. Gurbel P, Tantry US, Tehrani B, Tran H, Bliden K. First study of inhaled versus chewed aspirin: pharmacokinetic and pharmacodynamic effects. Paper presented at: ACC.20/WCC Congress of Cardiology; March 29, 2020; Atlanta, GA. Presentation 1314-151.
5. Voelker M, Hammer M. Dissolution and pharmacokinetics of a novel micronized aspirin formulation. *Inflammopharmacology.* 2012;20:225–231. doi: 10.1007/s10787-011-0099-z