Sarthak edit

With so many aspects of Covid-19 yet to be unravelled by research, every hypothesis, even if emerging out of limited evidence, is perhaps worth examining. One such, termed ‘the bradykinin hypothesis’, has been discussed in recent research, but nowhere has it been as strongly argued for as in a study authored by researchers at the Oak Ridge National Lab, Tennessee, the US, published in the journal eLife. The researchers, an article in Medium says, base their hypothesis on the analysis of the results of data-crunching by the supercomputer, Summit. The study proposes that SARS-CoV-2 interferes in the regulation of bradykinin—a peptide that is responsible for vasodilation in the human body—in a manner that can possibly explain many traits and symptoms of Covid-19, including the less common ones.

As per the Oak Ridge researchers, SARS-CoV-2 hijacks the body’s ACE2 regulatory mechanism—ACE2 receptor proteins are key to SARS-CoV-2’s pathology in the body—and forces the body to produce more of these receptors. Now ACE2 counters the effect of ACE in the renin-angiotensin-aldosterone system (RAAS) that regulates blood pressure in the body. With decreased ACE activity, bradykinin levels are not controlled, and this leads to a bradykinin storm. Given bradykinin increases blood vessels permeability, fluid and immune cells leak out of the vessels into the lungs. While the latter cause local inflammation, SARS-CoV-2 complicates the problem of fluid accumulation in the lungs further by causing increased production of hyaluronic acid, a superabsorbent, in the lungs. This precipitates the formation of a hydrogel in the alveoli that makes it difficult for patients to breathe, sometimes even with ventilator support. Bradykinin storms may also explain the cardiovascular conditions reported in some cases, even when the patient had no history of this. Apart from the virus’s direct action through ACE2 receptors in the heart, the RAAS malfunction too could explain the cardiac arrhythmia often seen in Covid-19 cases. Bradykinin’s role in weakening the blood-brain barrier—that protects the brain against damaging chemicals and cells (unregulated immune cells, etc)—could be behind Covid-19-linked neuropathologies. The researchers contend that the virus has an effect similar to ACE-inhibitors that are prescribed for controlling high blood pressure—ACE2 inhibitors are known to cause dry cough and fatigue, two common Covid-19 symptoms.

The bradykinin hypothesis could also explain some of the demographic features of the disease—for instance, the lower mortality amongst women. While in India, men account for 69% of the Covid-deaths, in the US, they account for 54%. The researchers note that given the gene coding for a protein that plays a significant role in the regulation of blood-clots—another reported Covid-19 symptom—and in RAAS regulation is linked to the X-chromosome, women are likely to have twice the levels of this protein than men. Given bradykinin suppresses this protein, women have a comparative advantage. Even as researchers hold that cytokine storms

are strongly linked to Covid-19 fatality, the Oak Ridge researchers say that bradykinin storms could explain Covid-19 pathology better, even though there could be an “intricate link” between cytokine storms and bradykinin storms. This calls for testing of the hypothesis with due scientific rigour. Meanwhile, as AIIMS director Randeep Guleria has pointed out, there is a need to ready post-Covid healthcare infrastructure, given the infection’s lingering physiological effects. The Oak Ridge researchers call for testing of commonly-available RAS-regulating drugs, such as danazol, stanozolol, etc, apart from timbetasin (the non-proprietary name of the protein encoded by the X-chromosome gene) and some hyaluronic acid regulating drugs. Given how these are already approved by developed-country drug regulators, commencing safety and efficacy trials is a good idea indeed.