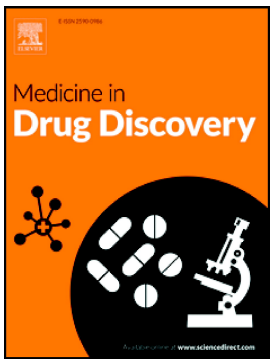
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



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Editorial

Potential TRPV1 blockade to treat severe lung dysfunction in COVID-19 infection

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The world is in a crisis mode due to the COVID-19 pandemic. Many medical research institutions and biopharmaceutical companies around the world are seeking solutions, which include devoting massive assets towards these goals. Before spelling out any concerns, suffice it to say that resources spent in areas of high visibility may not necessarily translate to clinical success, while experimental visions outside the traditional medical mindset for treating critical symptoms of COVID-19 can go unnoticed.

For example, considerable energies have been allocated to the building of ventilators. The alarm has been sounded on the shortage and the need to mobilize for increased manufacture of these breathing apparatus. For the moment we need only point out that ventilators can be life saving devices and critical elements in healthcare delivery. However, building hundreds of thousands of these devices may only yield marginal benefit. Despite critical care application, less than half of the patients put on ventilation support survive. Depending on circumstances, as many as 80% of ICU patients on ventilator support may perish, and many of those will succumb with sequalae related to extended anesthesia and hospitalization.

A major triumph in this global crisis will come when we can properly control edema and inflammation in the lung, which is responsible for the acute respiratory distress at advanced stages of the disease. Accordingly, with such intervention patients could be managed without overburdening the healthcare infrastructure, their disease progression blunted, and their chances of survival significantly improved.

This most recently published review (ARTICLE LINK) looks at the tantalizing possibility of TRPV1 (The transient receptor potential cation channel subfamily V member 1, also known as the capsaicin receptor or the vanilloid receptor 1) playing a substantial role in the prognosis of viral infections and in particular with COVID-19. Preclinical data suggest, and the authors posit, that COVID-19 pulmonary changes are linked to a strong immune response and an inability to ablate or dampen the immune response. Available data also indicate that inhibition of afferent activity in particular removal of TRPV1+ afferent fibers from the lung and airways can have a beneficial action on the compromised lung function and clearance of infection. Moreover, inactivation of the TRPV1+ innervation could also be "beneficial for the prevention or treatment of ventilator-associated lung injury".

Identifying a drug that could reduce the immune response in a highly specific manner is challenging and would seem forbidding. Yet, reports have shown that that down regulation or inactivation of TRPV1 nerve fibers can provide a protective pulmonary environment associated with neutrophil infiltration, enhanced T cell responses and bacterial clearance. This enabled logic would lead one to look for therapeutic agents to down regulate the inflammatory response due to TRPV1 activation.

While maintaining a critical mindset, and being properly skeptical of predictive power of rodent models, a good case can be made that blocking of TRPV1 may greatly alter the outcome of COVID-19 infection. The idea of using resiniferatoxin, a known potent agonist of TRPV1, has the potential to be a highly specific intervention for long-term inactivation of TRPV1 fibers. Resiniferatoxin has already been successfully used in clinical trials, albeit for different indications and with the routes of administration used has not been problematic. A challenge for use in the lung will be mastery of the injection procedure for optimal localization of the therapeutic effect. This challenge is elemental to all interventional procedures.

The central idea proposed, *i.e.*, local application of the potent TRPV1 agonist (resiniferatoxin) to nerves innervating the lung is a unique therapeutic strategy that fits squarely into the preclinical data indicating the involvement of this population of fibers and the beneficial effect of blocking their actions; resiniferatoxin is capable of removing these fibers or terminals. Moreover, an abundance of preclinical and clinical data strongly supports this conclusion. Another particularly attractive feature of this approach is that a single treatment will likely last throughout the recovery period.

However, use of this agent is not without risk, yet, the risk-benefit equation favors evaluation in a clinical trial once the basic safety and parameters for injection have been worked out. Suffice it to say that without effective intervention patients progressing to acute respiratory distress have a high probability of succumbing to death.