

New research reveals why low oxygen damages the brain

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Paul Tesar, a professor in the Department of Genetics and Genome Sciences at the Case Western Reserve School of Medicine and the Dr. Donald and Ruth Weber Goodman Professor of Innovative Therapeutics. Credit: Case Western Reserve University

Brain cell dysfunction in low oxygen is, surprisingly, caused by the very same responder system that is intended to be protective, according to a new published study by a team of researchers at the Case Western Reserve University School of Medicine.

"These powerful protein responders initially protect [brain cells](#) from low oxygen as expected, but we find that their prolonged activity leads to unintended collateral damage that ultimately impairs brain cell function," said the study's principal investigator Paul Tesar, a professor in the Department of Genetics and Genome Sciences at the Case Western Reserve School of Medicine and the Dr. Donald and Ruth Weber Goodman Professor of Innovative Therapeutics.

Defining the mechanism of brain-cell damage in low oxygen conditions provides an opportunity to develop effective therapies, including a class of drugs studied in their research that could inform future clinical approaches for many [neurological diseases](#) caused by low oxygen. The work also clarifies how the [response](#) to low oxygen causes disease in other tissues outside the brain.

Their research was published online Oct. 21 in the journal *Cell Stem Cell*.

The body's response to low oxygen

With the dawn of an oxygenated atmosphere, a burst of multicellular life was possible, as oxygen could be used to produce the energy needed to support complex life functions. Given the requirement of oxygen for life, nearly all organisms evolved a mechanism to rapidly respond to low oxygen—a condition called [hypoxia](#). The Noble Prize in Physiology or Medicine was awarded in 2019 for discoveries of how [cells](#) in our body sense low oxygen levels and respond to stay alive.

At the core of this ancient response are proteins called hypoxia-inducible factors (HIFs), which instruct the cell to minimize oxygen consumption and maximize their access to oxygen. In this way, HIFs can be thought of as valiant heroes attempting to protect and resuscitate cells in the immediate response to low oxygen.

Prolonged hypoxia causes dysfunction in many tissues. In particular, stem cells in the brain are impaired by hypoxia in many diseases, including stroke, cerebral palsy related to premature birth, respiratory distress syndromes, multiple sclerosis and vascular dementia. Even the significant neurological damage caused by COVID-19 is attributed to hypoxia.

Until now, the precise causes of cell malfunction due to low oxygen were unknown.

The dark side of the hypoxia response

In this study, researchers developed a new approach to closely study how the hypoxia responder proteins function. By comparing how they work in brain-[stem cells](#) with other tissues, such as heart and skin, the scientists confirmed that the hypoxia responder proteins perform a beneficial function to promote cell survival in low oxygen in all tissues. However, these same hypoxia responder proteins had a previously unappreciated dark side, as they also switched on other cellular processes outside of the core beneficial response.

The team then demonstrated that this additional—and previously unknown—response is what impaired brain-stem cell function. This suggests that, while hypoxia responder proteins evolved to promote cell survival in all tissues of the body in low-[oxygen](#) conditions, their powerful effects can also have unintended consequences to disrupt cell function.

New opportunities for treating hypoxia damage

The authors tested thousands of drugs to try to restore brain-stem cell function to overcome the damaging effects of the hypoxia responder proteins. They discovered a group of drugs that specifically overcome the damage-inducing response, while leaving the beneficial response intact.

"One of the exciting avenues that stems from this work is identifying drugs that specifically target the damaging side of the hypoxia response while sparing the beneficial side," said first author Kevin Allan, a graduate student in Case Western's

Medical Scientist Training Program. "This offers a new perspective on combating tissue damage due to hypoxia."

"Whether the damaging side of the hypoxia response is solely an unintended pathological effect or potentially a previously undiscovered normal process that goes awry in disease remains unknown," Tesar said. "Our work opens the door to a new way of thinking about how cells respond to [low oxygen](#) in health and disease."

Provided by Case Western Reserve University

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