2024 Research Grantees/Projects: Archived

Putative Roles of NTS Neurons in Maintenance of Breathing and Survival in a Mouse Model of CCHS

Drs. Sobrinho and Mulkey are investigating nucleus tractus solitarius (NTS) neurons role in breathing.

Congenital central hypoventilation syndrome (CCHS) is characterized by severe hypoventilation during sleep and an inability to increase breathing in response to CO_2 (central chemoreflex). Most cases of CCHS are caused by mutations in the PHOX2B gene, which encodes a protein important for development and maintenance of various neural populations. Although mouse models that express a CCHS-associated Phox2b mutation recapitulate features of the disease including hypoventilation and premature death, it remains unclear which component(s) of the respiratory neural network contribute to features of CCHS. We consider Phox2b-expressing neurons in a brainstem region called the nucleus tractus solitarius (NTS). These neurons might play an important role in breathing because they are thought to function as respiratory chemoreceptors (the loss of which is a hallmark feature of CCHS). Additionally, these neurons serve as a primary pathway for controlling breathing based on oxygen levels, which can help maintain breathing when the main carbon dioxide control system is not working properly.

The goal of this research is to determine the significance of these particular NTS neurons in relation to breathing and survival in mice with CCHS. This investigation aims to enhance our understanding of the condition and may lead to the identification of potential treatment approaches.

$75,000/1 year

Towards a Deeper Understanding of PHOX2B Loss of Function in CCHS to Provide Sequential Hot Spots for Therapeutic Action

Dr. Javier Oroz Garde and his team are studying the structure of the PHOX2B protein.

In many cases of CCHS, there are issues with a repeating pattern of amino acids (polyalanine tract) in a protein called PHOX2B. These abnormal amino acid patterns can harm the protein's structure, often causing it to stop working properly and clump together (aggregation). This can lead to cell damage and disease symptoms. Until recently, very little was known about the structure of these troublesome repeating amino acids, making it difficult to grasp why the protein doesn't work properly. But we've just achieved a breakthrough in my lab, revealing the detailed structures of mutated PHOX2B. This opens the door to the precise molecular characterization of mutated PHOX2B deleterious assembly in CCHS and how the problematic changes in the PHOX2B protein happen. With this new knowledge, we are focused on figuring out the exact reasons behind the quick transition of the protein from a liquid to a solid-state clump (aggregate) due to these changes in PHOX2B. After we've looked closely at how the PHOX2B polyalanine tract behaves, our next step is to study how the other parts of PHOX2B interact with the expanded polyalanine tract. This interaction might be a key factor in understanding what goes wrong with PHOX2B. If we can figure out the step-by-step process that causes PHOX2B to become toxic, it could help us develop treatments for CCHS patients. We believe our approach will be useful in understanding CCHS and other diseases caused by similar protein issues.

$75,000/1 year