Epithelial Cell TRPV1-Mediated Airway Sensitivity as a Mechanism for Respiratory Symptoms Associated with Gulf War Illness

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PUBLIC ABSTRACT

Veterans deployed to the Persian Gulf during the 1991 Gulf War have an unexplained high prevalence of multisymptom health problems compared to non-veterans or veterans not deployed to the Persian Gulf. Despite 17 years passing since the end of the war, veterans with Gulf War Illness continue to suffer from these symptoms. Frustratingly, neither the cause of Gulf War Illness nor the mechanisms responsible for continuing symptoms have been determined. The failure to understand the underlying mechanisms of this illness strongly contribute to the failure to develop effective therapy.

Respiratory symptoms are among the more common complaints of Veterans with Gulf War Illness. While these symptoms resemble those experienced by patients with asthma or chronic bronchitis, previous investigators have shown that the respiratory symptoms of Veterans with Gulf War Illness is not accounted for by asthma, chronic bronchitis, or any known inflammatory lung disease. The failure to link Gulf War Illness symptoms with classic inflammation is not unique to respiratory symptoms, but has also been found for many of the other Gulf War Illness symptoms.

We propose the alternative possibility that the respiratory symptoms in Gulf War Illness occur as a consequence of enhanced airway sensitivity. This is a diagnosis that does not involve classic inflammation and may not be detected by standard classification or lung testing. Enhanced airway sensitivity is defined as an abnormal sensitivity of the airway to nonspecific stimuli, causing: increased symptoms in response to a given exposure, symptoms at a lower dose of a noxious agent, or symptoms even in response to a normally innocuous stimuli. Importantly, preliminary data from our laboratory suggest that enhanced airway sensitivity can be self-perpetuating and potentially account for the sustained ongoing nature of the illness. We propose, therefore, a two-pronged research approach to, first, prove that subjects with Gulf War Illness do indeed have increased airway sensitivity, and then to elucidate the mechanisms that allow this state to become self-sustaining.

If our hypothesis is correct, we anticipate that this research will be directly applicable to Gulf War Illness patients with respiratory disease. It will have at least two immediate and substantial benefits for these patients. First, it will provide a simple and clear way to establish a definitive diagnosis. Without clear understanding of the nature of the illness, establishing a diagnosis has been highly subjective and many patients who likely have the illness have been wrongly given psychiatric or other incorrect diagnoses. Second, it will provide a measurable quantitative endpoint to use for evaluating potential therapy. Therapeutic studies that lack a clear endpoint require many more subjects and are much harder to perform. We believe that having a means to assess severity will enhance the likelihood of finding effective treatments. Over the longer term, we believe that our research could readily result in the development of entirely new therapeutic strategies for Gulf War Illness. The mechanisms and molecules that cause enhanced airway sensitivity have other roles in a variety of other diseases. Many of these mechanisms and molecules are the subject of active clinical programs by pharmaceutical companies, and several of these drugs are in clinical trials. If we can show that these mechanisms and molecules pertain to Gulf War Illness, it will be relatively simple to test them for this illness. We also speculate that

the mechanisms and molecules being studied in this proposal will apply to problems in Gulf War Illness beyond the respiratory symptoms. If true, this would suggest that these approaches could be rapidly investigated for other symptoms, although other symptoms will not be part of this project.

As described above, we believe that the benefit of this research would be translated into improved patient care very quickly if we show that our hypothesis is correct. Even the longer term benefit from new therapeutic approaches is likely to occur within several years of reporting positive results because these novel drugs are on the threshold of clinical approval. The risk to the Veterans with Gulf War Illness from the approaches described is exceedingly small.

It is possible that our hypothesis is not correct or that the mechanisms we will find could only apply to the respiratory symptoms; however, we expect the opposite to be true. It is also important to note that this study will not address the initial cause of Gulf War Illness. While our studies could shed light on possible initiating causes, we will entirely focus on studies that address how to deal with the existing problem. Once this is defined, it should be easier to develop approaches to learn why the illness developed initially.

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