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ALTERNATIVE PHARMACEUTICAL APPROACH TO OPIOID EPIDEMIC THROUGH ANALYSIS OF SENSORY NEURONS THAT SIGNAL PAIN AND FATIGUE

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Opioid addiction holds a global handicap, making it an unavoidable public health crisis. The opioid epidemic, a currently debated topic in politics, healthcare, and policy legislation, presents an interesting and necessary challenge to the research field to develop a method of treatment for abnormal pain and fatigue symptoms without the crippling effects of opiates. The goal of the Light Lab at the University of Utah, in collaboration with five other labs and the United States Department of Defense, aims to identify an alternative pharmaceutical by:

1. Focusing on the mechanisms of the sensations of pain and fatigue

2. Studying the plasticity these mechanisms undergo following various acute and chronic conditions

In order to understand the fundamental mechanisms that signal muscle pain and fatigue through sensory neurons and their relationships to chronic pain conditions, studies revolving the potential analgesic properties of venom were conducted. Isolated from a *Pleurobranchus* species, a shell-less marine gastropod mollusk, known to the Solomon Islands, venom from this species gave insight and hope into a new way of addressing pain management in lieu of opioids.

Among thousands of species of marine life, the *Pleurobranchus* species were found to be effective predators, having evolved a multitude of venoms to numb and control prey. This information was important in the development and testing of Compound N0P, synthesized with extracts from the venom.

Specific sensory receptors utilizing unique molecular receptors for ache, intense mechanical and chemical muscle pain, burning pain and several different types of fatigue

sensations were studied. It was found that different combinations of metabolites, such as ATP, activate a combination of receptors in the neuron. With this knowledge, the study design for Compound N0P included:

1. Calcium Imaging: Lumbar dorsal root ganglia (DRG) of C57/Bl6 mice were dissected and cultured for calcium imaging under microscope to analyze neurons' response to metabolite and Compound N0P.

2. Treatment with Compound N0P in formalin-induced pain in the mouse. Formalin (2%, 10 µl) was microinjected into the dorsal surface of the mouse hind paw. Compound N0P Treatment was given daily for 5 consecutive days. The animals were monitored over a span of 14 days per cycle.

3. Behavioral Analysis, including reflexive (von Frey, hot and cold plate tests) and voluntary activities (guarding, place preference, and running wheel tests), were conducted to analyze the presentation of pain for 14 days.

The testing of this compound serves as a significant precedent to synthesis and analysis of alternative pharmaceuticals to replace opioids. Results in behavioral and sensory neuron tests for Compound N0P showed less presentation of pain phenotypes in animals, which was in line with the reduced ATP response in cultured DRG neurons with the presence of the compound. Although results are preliminary and incomplete, there is good reason to continue with more complete study on the compound N0P, and the development and analysis of alternative pharmaceutical compounds synthesized from cone snail venom.

As newer drugs navigate social and neurological implications, it becomes important to conduct studies that are efficient in design and process. Public health issues such as the opioid epidemic call for the research field to be innovative and effective in promoting solutions. This research study suggests pain and fatigue relief is possible and quite possibly may lead to clinical application in the future.