Researchers link orphan receptor to opioid-induced itching

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Opioids have long been an important tool in the world of pain management, but the side effects of these drugs - from addiction and respiratory failure to severe itching and dizziness, can be overwhelming. Scientists have been trying to understand how these side effects happen so they can create better, less problematic pain relievers.

New findings published in the journal *Nature Chemical Biology* by UNC School of Medicine scientists show that MRGRPX2, a receptor protein on the surface of mast cells, can trigger the immune system response that leads to itching associated with some opioids.

Kate Lansu, the paper's first co-author and a graduate student in the lab of Bryan Roth, MD, PhD, explains how this process works.

"Receptors in mast cells - part of the immune system - respond to an activation signal and release inflammatory factors like histamine, in a process called degranulation," she said. "When that happens, other cells are recruited to the site of inflammation to clear the infection. This response is also important for things like allergies. And this is what presents itself as itching."

"Opioid drugs have been link to degranulation also, but it was through an unknown mechanism. We think that our data could potentially explain why degranulation occurs as a side effect of opioid ligands (morphine and other drugs), something that is well-known but not well-understood."

The findings are significant not only because they offer a potential explanation for opioid-induced itching, but also because the data suggest a way to characterize the function of the orphan receptor MRGRPX2.

Currently there are about 120 orphan receptors in humans. They are "orphan" because, though we know they exist, we don't yet know what they do. The Roth lab screens these receptors against thousands of small molecules to find out what might activate them. This process involves a combination of physical screening and computational modeling.

"We start with the physical screening data to give us a sense of what types of molecules interact with the receptor," Lansu said. "Working on MRGRPX2, I screened around 7,000 molecules, and that data gave us a sense of what the binding site might look like. Once that tentative picture was in place, we were able to use computational tools to create a more precise model of the site."

The computer modeling, performed by co-first author Joel Karpiak, a graduate student at the University California at San Francisco, tested 3.7 million models for potential interaction with the receptor.

"And that's so many more different types of chemicals than I could do by hand in an assay," said Lansu.

The physical data combined with the computational models allowed the researchers to create a chemical probe designed to interact specifically with MRGRPX2. This new tool made it possible to gain a more precise understanding of this receptor's effects without the noise of other receptors. An opioid might activate the orphan receptor, but it might also activate other receptors that it interacts with.

Imagine trying to recreate a musical score by listening to an orchestra perform a piece of music. "You hear the whole ensemble play and you

might think 'this is very moving' but it may not explain much about how that effect is achieved," Lansu said. "But if you had a tool that allowed you to isolate just the trumpets, for example, it could teach you something about how that part contributes to the whole - something you may not be able to hear otherwise."

Understanding what triggers the itching response could help pharmacologists develop an antagonist for this receptor to reduce the itching side effect. In other cases, clinicians may want to induce histamine release, thereby boosting the immune response, as in the case of vaccine adjuvants, where an increased immune response may improve immunity. These findings suggest there may be a way to do that selectively.

The researchers will now move onto other orphans. There are four receptors in the same family as MRGRPX2, and Lansu hopes to find chemical probes that can interact with each one.

She also emphasized that work like this would not be possible without the cooperation of a wide variety specialists.

"This kind of work speaks to the importance of collaborative sciences because you have modeling, you have pharmacologists doing in vitro experiments and you have chemists making stepwise changes on the molecule. And all of these specialists working together makes findings like these possible."

More information: Katherine Lansu et al, In silico design of novel probes for the atypical opioid receptor MRGPRX2, *Nature Chemical Biology* (2017). DOI: 10.1038/nchembio.2334