Morphine response models

By Steve Edelson, Executive Editor

Most companies in the pain space are focused on new formulations of morphine and other opioid agonists.¹ The reason is clear: opioids provide excellent analgesia. However, many of those drugs come with a host of drawbacks, including tolerance and dependence. Although the new formulations seek to improve on the side effects, a challenge in developing the compounds is a lack of animal models that measure the actual causes of tolerance and dependence.

In a paper published in *Current Biology*, researchers at the **University of California, San Francisco (UCSF)**, the **Ernest Gallo Clinic & Research Center** and the **University of California, Berkeley** describe both the adaptive changes underlying chronic morphine treatment and a mouse model that would provide a way to test compounds in order to avoid tolerance and dependence.²

Morphine, like many of the body's endogenous opioids, binds to μ -opioid receptors. Unlike endogenous opioids, however, morphine keeps the receptors from undergoing endocytosis, a process in which the receptors and other surface proteins are internalized upon activation and are subsequently resensitized and sent back to the cell surface.

It is hypothesized that morphine tolerance and dependence are closely related to the failure of the bound μ -opioid receptor to be properly processed by the endocytic pathway. To test this hypothesis, Jennifer Whistler and colleagues generated a knock-in mouse that expresses a mutant μ -opioid receptor that does undergo endocytosis when it binds morphine. Whistler is an associate professor of neurology at UCSF and a principal investigator at the Ernest Gallo Clinic & Research Center.

According to the authors, the mice had "substantially reduced" morphine tolerance and dependence compared with wild-type controls. Equally important, morphine's analgesic effects were unaltered in the knock-in mice compared with wild-type mice.

A primary implication of the research is that the model could be useful to companies looking to test whether—and how—their morphine formulations or analogs have improved tolerance and dependence profiles compared with the parent molecule.

Indeed, the new model could help quantify whether a compound

triggers tolerance through endocytosis impairment or some other downstream mechanism. This could help researchers make decisions on how to proceed with developing the compound, if at all.

"If you put a compound in our model, you'll be able to differentiate between tolerance caused by failure to undergo endocytosis or tolerance caused by some other mechanism," said Whistler.

Despite the ability to delineate how a compound causes tolerance and dependence, the model likely will not solve a key problem for pain companies in the clinic—a dearth of clear definitions of those terms.

"The difficulty of going after tolerance and dependence is that there are no objective definitions," said Remi Barbier, chairman, president and CEO of **Pain Therapeutics Inc.** "Everyone knows tolerance and dependence exist, but people don't agree on what that means in practice. There's no universal agreement for a very good reason—the effects of opioids are different depending on the individual."

Pain Therapeutics has a pair of opioid agonists in Phase III testing for pain: Remoxy, a twice-daily abuse-deterrent formulation of oxycodone, and Oxytrex, a combination of immediate-release oxycodone and low-dose naltrexone. Naltrexone is expected to counteract the effects of chronic opioid use, such as dependence.

Barbier noted that the company has "made the decision to not go after antitolerance, anti-addiction claims" with both of its late-stage compounds.

"Without a formal protocol at FDA to define those terms, it's hopeless," he said. "On the other hand, what's entirely practical and doable is to go after the proxies of these things. You can test your drug in a group of opioid-dependent patients and rate the likeability of the drug."

He noted that Subutex buprenorphine from **Reckitt Benckiser Group plc** was approved on the basis of "less likeability by opioid-dependent patients." The drug is approved to treat opioid dependence.

A second, and broader, implication of the *Current Biology* paper is that companies should consider developing opioids that promote endocytosis.

Indeed, Whistler believes companies need to take another look at molecules that are on the shelf.

Opioids that drive endocytosis are "counterintuitive to drug developers," she said, because μ -opioid receptors undergo endocytosis when desensitized. Companies thus are likely to weed out compounds that promote endocytosis because they do not want compounds that desensitize receptors.

"The belief was that if you desensitize the receptor, it's bad for you," Whistler said. "A lot of companies screen for desensitization but probably don't follow up," or they potentially discard those compounds.

Whistler told *SciBX* that pain companies with libraries of opioid

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agonists may have endocytosis-promoting compounds on the shelf that could be good therapeutic candidates. “I’m hoping that our mice will stimulate drug companies working on pain to think about new opioid therapies,” she said. “Ideally what you want is to convince somebody with access to libraries that the finding is real, relevant and important.”

One problem is that “it’s not clear how you can use the model to identify new molecules,” said Diana Pliura at **YM BioSciences Inc.** “From a molecular basis, I don’t know what I need to look for, including what structures I need to put on a morphine molecule” to induce endocytosis.

Pliura is EVP for AeroLEF, a formulation of free and liposome-encapsulated nebulized fentanyl. In January, FDA placed a Phase II trial on hold and asked for additional safety information from a small group of patients who experienced oxygen desaturation in previous clinical trials. YM said oxygen desaturation is a class effect of opioids.

Whistler said it is unclear which structural features of morphine prevent the μ -opioid receptor from undergoing endocytosis.

“That’s the problem of not having the crystal structure” of the receptor, she said. “The receptor is not as simple as a kinase with a pocket. It’s a seven-transmembrane protein with a three-dimensional structure that changes with the lipid membrane.”

Indeed, a key problem is the difficulty in crystalizing G protein-coupled receptors. Only two have ever been crystalized: rhodopsin and adrenergic receptor $\beta 2$.

REFERENCES

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