Safer opioids may be on the horizon, but mitigating addiction is a long shot

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Opioids are well-known to be lethally addictive, spurring a nationwide crisis. Less well-known are the drugs' other complications: dangerous breathing difficulties, nausea, gastrointestinal distress, and paradoxically, a hypersensitization that worsens feelings of pain. Inevitably, frequent users grow tolerant of the drugs' pain-relieving effects, leading them to use increasingly higher doses of opioids, which can spiral into lethal respiratory depression.

Clearly, there are good reasons to seek alternatives. But a challenge looms: although some newer drugs for chronic pain do target alternate cellular pathways, nothing else is quite as effective as opioids at treating acute trauma. "As much as we wish there were something that worked better than or at least as well as the endorphin pathway mediated by the μ-opioid receptor, we haven't found it yet," says Jonathan Violin, senior vice-president of scientific affairs at Pennsylvania-based biopharma startup Trevena and an adjunct professor at Duke University Medical Center.

These hurdles are well-known. In June, the NIH announced a new initiative, dubbed Helping to End Addiction Long-term (HEAL), that aims to address the issues of opioid addiction in a many-pronged effort (1). One arm of the initiative aims to find safer drugs and new drug targets, developing new therapies for opioid-induced respiratory depression, and improving existing medications.

In fact, efforts to find these safer alternatives to opioids are already well underway. Academic researchers and startups seeded in academic laboratories, as well as large pharmaceutical companies, are testing a range of molecules that target opioid receptors yet lack the slew of side effects.

Some of these alternatives work by binding the opioid receptor in unique ways, whereas others act only in peripheral tissues that need pain relief. Still others aim to bypass the morphine-binding μ-opioid receptor (MOR) and target different receptors, such as the κ- and δ-opioid receptors, to achieve analgesia with fewer side effects. Whether any of them will successfully help patients avoid the risk of addiction, however, remains to be seen. Even so, reducing distressing side effects could improve patients' recovery.

Multiple research efforts are trying to find opioid alternatives that target the opioid receptor without the usual slew of dangerous side effects. Image courtesy of Shutterstock/Tomas Nevesely.

"It may be that for certain types of trauma, you could try taking one of these better opioids so you get the benefits but not the side effects," says Nora Volkow, director of the National Institute on Drug Abuse in Bethesda, who co-authored a recent *JAMA* article describing the NIH initiative. "There's definitely space in the market for better opioids."

Historic Power

Opioids extracted from opium, laudanum, and poppies have been used since ancient times. Their potency has long been recognized. "If the entire materia medica at our disposal were limited to the choice and use of only one drug," David Macht, a clinical medicine instructor at Johns Hopkins University, wrote in 1915, "I am sure that a great many, if not the majority, of us would choose opium…" (2).

Pharmaceutical giant Merck first sold a commercial form of the opium derivative morphine in 1827. Although its addictive potential became quickly apparent, it didn't halt the boom in newer forms of opioids—or prescriptions for the drugs. In fact, the overwhelming

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evidence for their analgesic power led to a rare turnabout in the pharmaceutical industry: opiate drugs were developed and put to work in the early 20th century, long before preclinical studies uncovered the drugs' mechanisms of action.

More recently, changes in medical practice and pain management guidelines, along with aggressive marketing practices by some pharmaceutical companies, have made opioid-based drugs such as oxycontin popular choices for physicians. Dispensed in large quantities, the drugs were easily acquired for illegal use and drug manufacture. Exacerbating the problem, different forms of opioids have different pharmacokinetics—delayed-release, long-acting pills, for example, might be crushed and taken as a powder. This not only speeds up their delivery but also accelerates addiction.

Painful Revelations

The problem of opioid use is compounded by another mystery: pain itself. "We don't know enough about pain as a condition," Volkow says. "It's very heterogeneous."

"There's a sensory component, it's emotional, cognitive…you have memories of times you've been in pain before," says neuroscientist and pain researcher Gregory Scherrer of Stanford University. "There are many different brain regions that contribute to the complexity of experiencing pain."

Already, opioids are no longer a recommended treatment for most types of long-term, chronic pain because such use heightens the chances of side effects and addiction. Instead, researchers have begun to identify analgesics that bypass the need to activate opioid receptors. In May, one such drug, a calcitonin gene-related peptide inhibitor manufactured by Amgen and Novartis, became the first to be approved by the US Food and Drug Administration (FDA), as a migraine treatment.

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To identify more such mechanisms—and learn precisely how and why opioids offer such potent pain relief—researchers are homing in on how we perceive pain. Scherrer's laboratory is trying to dissect how different opioid receptors, located in distinct brain regions and cell types, may play unique roles in processing pain signals. For example, the δ-opioid receptor is present in the brain's dorsal horn interneurons and seems to regulate responses to mechanical pain but not heat (3). In rodent studies, the researchers report that removing the MOR from a subset of pain-sensing neurons known as nociceptors blocks morphine tolerance—the main reason for overdoses—and some side effects such as hypersensitivity but doesn't reduce analgesia (4).

Uncovering these nuances is crucial in the quest for safer analgesics, Scherrer says. "I don't think you can go chasing a molecule until you understand what brain regions and what cells in these regions are most important for pain." Such data, coupled with a better understanding of how opioid receptors act within individual cells, are already helping advance drug development.

Chasing G-proteins

Many new strategies aim to better understand how opioid receptors work at the cellular level. These receptors belong to a class of proteins called G-protein–coupled receptors (GPCRs). Also called seven-transmembrane domain receptors, they thread seven times across a cell's membrane, with loops that project outside and within the cell. When an opioid binds to its receptor, it alters the shapes of intracellular loops so they activate intracellular targets. Classical opioids trigger a G-protein–related pathway and another mediated by β-arrestin.

For many years, GPCRs were viewed as simple receptors that operated on–off signals. Violin recalls thinking of them "kind of like light switches" while he was in graduate school. "You could turn them on with an agonist and off with an antagonist, and then there were things like partial agonists that turned them partly on."

But then he came across the work of biochemist Robert Lefkowitz at Duke University, whose Nobel Prize-winning work revealed these receptors were far more sophisticated. Lefkowitz's studies led to the discovery that GPCRs coupled to multiple pathways inside cells, and—with the right molecules—it was possible to selectively activate certain signaling pathways and not others. For example, molecules that selectively activate the G-protein pathway and bypass β-arrestin could potentially avoid gastrointestinal and respiratory side effects.

Violin joined Lefkowitz's laboratory as a postdoctoral scholar to study these selective activators, better known as biased ligands. Violin and his colleagues eventually developed a library of molecules that triggered the MOR to turn on just G-protein signaling. The group moved on to cofound Trevena with the goal of developing these molecules into opioid drugs with fewer side effects.

In clinical trials focused on treatment of postsurgery pain, lower percentages of patients experienced nausea or respiratory side effects when treated with Trevena's oliceridine versus morphine (5). Ten years after the company's founding, this novel compound is pending FDA approval as a new drug application.

A different approach, from Massachusetts-based Blue Therapeutics, aims to achieve fewer side effects via a different molecular mechanism. Instead of creating biased ligands, the researchers cross-linked the MOR with other cell-surface receptors. Ligands that bind to each are connected with scaffolds of different lengths. When a molecule bearing both ligands latches on to the receptors, the cross-linking alters their downstream activity. In 2011, Ajay Yekkirala, chief scientific officer at Blue Therapeutics, and his colleagues reported that one such molecule, named NNTA, created a heteromer of MOR and κ-opioid receptors. NNTA had potent analgesic effects in mice (6).

The results of their NNTA studies, originally conducted in Philip Portoghese's laboratory at the University of Minnesota, spurred the team to cofound Blue Therapeutics. Now the team is working to develop clinically useful ligands that target heteromers. The molecules "work well for neuropathic pain, and we're probing safety and toxicity for IND [Investigational New Drug] studies," Yekkirala says, although he declined to offer further details.

Academic laboratories have reported several other ways to target the MOR receptor's cellular function (see table 1 in ref. 7), but few have advanced along the drug development pipeline.

Site-Specific Solutions

Rather than focusing on the receptor's intracellular functions, another set of molecules aims to restrict opioids' activities to specific sites where they are needed, thus avoiding off-target effects.

Opioid receptors are widespread in the central nervous system, heart, immune system, joints, gastrointestinal tract, and other tissues. This abundance makes it easy to use the same drug no matter where a person's pain originates. But it is also the reason for side effects: When opioids cross the blood–brain barrier and bind to cells in different brain areas, the opioids can cause nausea and breathing difficulty and activate the brain's reward pathways, increasing risk of addiction.

Molecules that act only in peripheral tissues without entering the brain can avoid these effects. For example, Christoph Stein of the Free University of Berlin and his colleagues designed a fentanyl derivative that had a fluorine residue added to create a strong negative charge. As a result, it worked only in highly acidic environments typically seen in injured or inflamed tissues and not, according to work published last year, in the healthy brain (8).

Connecticut-based Cara Therapeutics is also developing a peripherally restricted molecule to treat the chronic condition pruritus. Another strategy, being pursued by Cara and others, relies on activating other kinds of opioid receptors. Cara's CR845 molecule, for example, targets only peripheral κ-receptors.

In preclinical studies, molecules such as NNTA from Blue Therapeutics and a biased ligand named PZM21—which works by the same mechanism as Trevena's oliceridine—reduce rodents' propensity to seek out more of a substance after they've been exposed to it. That finding suggests these compounds may have a lower potential for addiction—but they've yet to be tested in clinical trials.

Many researchers doubt whether any molecule that activates the MOR can ever be nonaddictive. But even so, having new drugs that provide the potent pain relief mediated via opioids—without the problematic side effects—could prove a powerful tool in helping combat the opioid crisis. Indeed, offering more targeted ways to manage acute pain is part and parcel of the NIH's HEAL initiative, which aspires to do nothing less, say NIH leaders, than foster a nation with "far less disabling pain and opioid addiction" (1).

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