DRUG DISCOVERY

Designing the ideal opioid

The development of a drug that mimics the pain-relieving activity of opioid compounds, but has fewer side effects, points to an effective strategy for the discovery of many types of drug. SEE ARTICLE P.185

BRIGITTE L. KIEFFER

Opium has been used medicinally and recreationally for more than 4,000 years because of its remarkable pain-relieving and euphoria-inducing properties[1]. Today, abuse of prescription opioids — morphine and its derivatives — has escalated[2], and heroin addiction represents a worldwide health and societal burden. An ideal opioid would kill pain potently without producing morphine's harmful respiratory effects, would show sustained efficacy in chronic treatments and would not be addictive. On page 185, Manglik *et al.*[3] describe a step towards this perfect drug.

It has been a long road. It was naively thought that identifying receptor proteins for morphine would rapidly deliver the ideal opioid. In the early 1990s, three opioid-receptor (OR) genes were isolated that encode the G-protein-coupled receptors (GPCRs) mu (μOR), delta and kappa[4]. Genetic disruption of μOR in mice revealed that this protein mediates morphine-induced pain relief, reward and dependence all at once[5]. This discovery, coupled with the fact that thousands of morphine-related drugs had no better pharmacology than conventional opioids, dampened enthusiasm for developing μOR-targeting drugs.

The realization that distinct drugs acting at a given receptor can trigger diverse signalling responses[6] has since opened up the possibility of designing 'biased' opioids that activate signalling pathways relevant to therapy, but not those that produce unwanted effects. However, another breakthrough was required to move the field effectively to the next level — the development of a method to crystallize these rare, unstable membrane proteins. This technique has transformed GPCR research, leading to resolution of the structure of many proteins[7], including μOR (ref. 8). Today, the availability of these crystal structures allows researchers to probe both the active and inactive conformations of GPCRs and the ways in which they bind their ligands, facilitating structure-based drug discovery[9].

As part of this effort, Manglik *et al.* undertook a search for a molecule that would bind to μOR. Their goal was to use the power of computational docking to find new opioid structures (chemotypes), in the hope that some might stabilize μOR in as-yet-unexplored conformations, show unique, biased signalling profiles, and perhaps generate previously unseen biological effects.

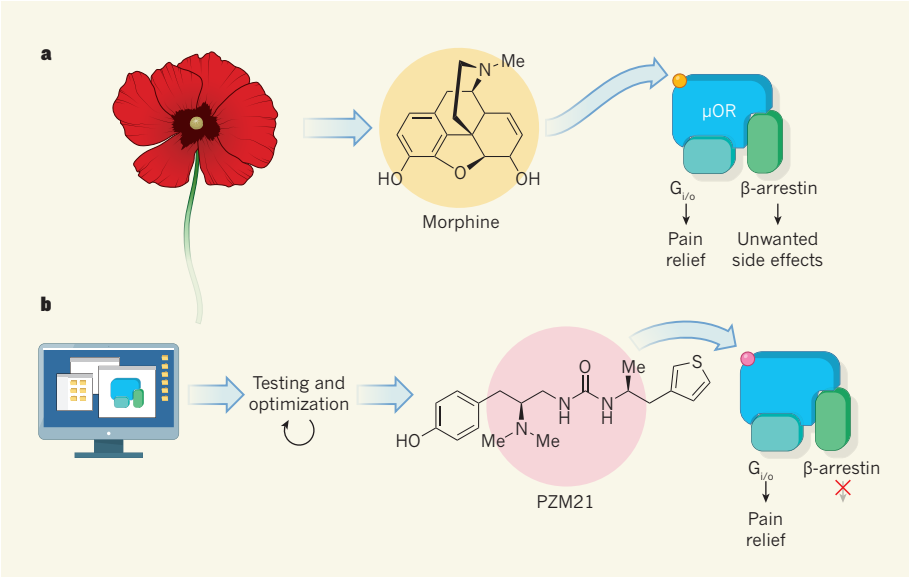

Figure 1 | New biology for an old receptor. a, The opioid molecule morphine is derived from poppies. Morphine binds to the μ opioid receptor (μOR) protein in the mammalian brain to form an active complex with signalling proteins, including $G_{i/o}$ and β-arrestin. The $G_{i/o}$ signalling pathway is thought to mediate morphine's pain-relieving properties, whereas β-arrestin signalling results in unwanted side effects — euphoria, which can lead to addiction, as well as respiratory depression and gastrointestinal effects. **b**, Manglik *et al.*[3] used the crystal structure of μOR to develop a computational screening programme. The authors docked 3 million molecules to the μOR binding site, selected the most promising candidates and then tested and optimized these to produce the drug PZM21. This compound produces highly $G_{i/o}$-biased signalling, and effectively reduces pain in mice without other detectable effects. (Me; methyl.)

The authors computationally docked 3 million commercially available molecules to the μOR binding pocket. For each compound, more than 1 million configurations were tested for complementarity to the binding site, and the 2,500 best-fitting molecules were examined by eye to identify those with chemotypes unrelated to known opioids. The authors selected 23 compounds for experimental testing, and further docking–testing rounds produced a set of molecules that had novel chemotypes, unusual docking poses in the receptor-binding site, and reasonable binding affinities and selectivity for μOR.

Activation of μOR triggers two major signalling cascades — those involving $G_{i/o}$ and β-arrestin proteins. Manglik and colleagues found that, of their 23 molecules, compound 12 had strongly biased activity for $G_{i/o}$ signalling. This is interesting because μOR agonists (activators) that poorly engage β-arrestin signalling are thought[10] to confer more-efficient pain relief and cause fewer side effects than those that strongly activate this pathway. Indeed, a drug named TRV130 that is unrelated to either morphine-related drugs or compound 12 has been developed on this basis using conventional drug-screening methods and is currently in phase III clinical trials[11]. In their final optimization step, the authors used docking information from compound 12 to create a drug dubbed PZM21 (Fig. 1). They then compared PZM21 with morphine and TRV130.

In mice, the pain-relieving efficacy of PZM21 was comparable to that of morphine and lasted longer. PZM21 reduced pain responses mediated by the central nervous

system, but not those mediated at spine level. This activity has not previously been reported for a μOR agonist, and potentially has therapeutic value for targeting components of pain mediated by the central nervous system. The compound induced less constipation than morphine and did not modify respiratory activity. Strikingly, mice did not show a preference for the testing chamber in which they received PZM21 over the one in which they received saline, and the compound did not induce hyperactivity — signs of addiction-like behaviour in mice.

TRV130 produced effective pain relief in all modalities, induced only subtle respiratory depression and caused no significant place preference. Thus, despite slightly differing effects *in vivo*, the pain-relieving properties of both PZM21 and TRV130 supersede the adverse effects classically observed for morphine. Manglik and co-workers' study therefore definitively establishes the promise of $G_{i/o}$-biased μOR agonists for pain control.

There is little doubt that structure-based computational screening will accelerate the pace of drug discovery[12]. The current work provides a compelling example of how this technology can efficiently generate chemotypes, enable rapid optimization of candidate molecules with minimal experimental testing, and lead to the discovery of molecules that have innovative biological activities. The open-access docking tools now available (such as http://blaster.docking.org) should expand the practice of this approach.

Many challenges lie ahead in ligand-docking research. In particular, predicting biased activity remains beyond reach, and was not a goal of the present study. However, Manglik *et al.* did find that PZM21 and TRV130 adopt distinct docking poses in the μOR binding pocket. Hence, molecular interactions common to the PZM21–μOR and TRV130–μOR complexes deserve further attention, because they may contribute to selective $G_{i/o}$ activation.

Whether the *in vivo* effects of PZM21 reflect only $G_{i/o}$-biased activity remains uncertain. Similarities in the pharmacology of PZM21 and TRV130 argue in favour of common modes of action for the two compounds, probably stemming from $G_{i/o}$ signalling. On the other hand, the authors' docking analyses suggest that the compounds engage μOR amino-acid residues in different ways. The drugs also show opposing activities when binding kappa opioid receptors in cells, and have different pharmacokinetics *in vivo*. The authors did not investigate whether animals develop tolerance to PZM21, and other *in vivo* activities of the drug may yet be discovered. The common and distinct actions of PZM21 and TRV130 should be investigated in the brains of living organisms, which might reveal activities at the level of brain networks.

In summary, Manglik and colleagues study is an impressive demonstration that new chemotypes can offer unusual biological opportunities, particularly for the study of opioids. Are we getting closer to the ideal pain-reliever? PZM21 is a leading member of a nascent club of pain-effective μOR agonists that seem to have reduced risk for abuse. These are not exactly opioids, and structure-based discovery approaches should increase their number and enhance the chances of a successful drug reaching the market at last. ■

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NANOSCIENCE

Slippery when narrow

An experimental technique has been developed to measure water flow through carbon nanotubes. Measurements reveal that flow can be almost frictionless, posing challenges for computer simulations of nanofluidics. SEE LETTER P.210

ANGELOS MICHAELIDES

Carbon nanotubes are hollow cylinders formed from carbon atoms arranged in a hexagonal, graphite-like lattice and have nanometre-scale diameters. It has been suggested that water transport through carbon nanotubes is almost frictionless, and that the flow rate exceeds predictions made using classical theories by many orders of magnitude (see refs 1–3, for example). However, because of challenges in performing reliable measurements and computer simulations, and given the huge differences in the reported results, claims of rapid water transport have at times been met with scepticism (see, for example, ref. 4). On page 210, Secchi *et al.*[5] help to resolve this issue by reporting unambiguous measurements of water flow through individual carbon nanotubes. The unprecedented sensitivity of the authors' measurements reveals a strong dependence of water friction on the radius of the carbon nanotube: the

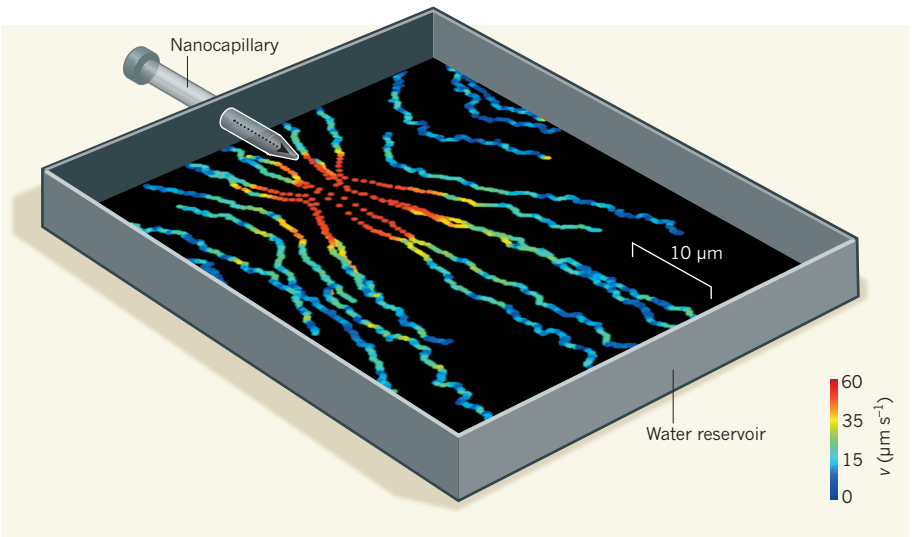

Figure 1 | Tracking minuscule water flow. Secchi *et al.*[5] measured the flow of water passing through a carbon nanotube (not visible) at the tip of a nanocapillary into a water reservoir by observing the motion of polystyrene nanoparticles suspended in the reservoir. The trajectories of different nanoparticles are indicated; colours correspond to the particle velocity, *v* (measured in micrometres per second).