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First photoactive drug for pain treatment

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A team of the Institute of Neurosciences of the University of Barcelona has participated in the design of the first light-activated drug, JF-NP-26, for the treatment of pain, according to a study with animal models published in the journal *eLife*. The new study is conducted by the teams led by Professor Francisco Ciruela, from the University of Barcelona, and Amadeu Llebaria, from the MCS group of the Institute of Advanced Chemistry of Catalonia (IQAC-CSIC).

Optopharmacology: light-operated drugs

In general, common pharmacology has important limitations—slow and inexact distribution of the drug, lack of spatiotemporal traits in the organism, difficulties in dose adjustments, etc. These can limit the therapeutic action of any drug. In this context, optopharmacology is an emerging discipline in pharmacology, based on the use of light to control drug activity. Thus, using light on a photosensitive drug, the pharmacological process can be controlled with spatial and temporal precision.

The new study published on the journal *eLife* has come up with the design of a "photo-drug," JF-NP-26, with powerful therapeutic applications to treat pain.

"In the clinical field, there is no precedent for the use of optopharmacology to improve pain treatment or any disease associated with the nervous system. This is the first light-activated drug designed for the treatment of pain in vivo with animal models," says Professor

Francisco Ciruela.

Designing a nontoxic photosensitive compound

In this new optopharmacology proposal, a drug with a known action mechanism (in this case, an analgesic) is chemically modified to make it photosensitive and inactive. This drug is activated when receiving light of a suitable wavelength via optical fiber, with exact precision on the target tissue (brain, skin, joints, etc.).

The drug JF-NP-26 is photocaged with a chemically inactive molecule that is activated with light. Compared to other photosensitive compounds, JF-NP-26 has no pharmacological effect until the target tissue receives light from the visible spectrum (405 nm wave length). Moreover, JF-NP-26 does not have toxic or unwanted effects, even if the dose is high, in short-duration studies on animals.

The drug releases the active molecule (raseglurant) that blocks the metabotropic glutamate type 5 (mGlu5) receptor, found in lots of neuronal functions such as the spread of neuronal pain. Blocking this receptor allows preventing the pain from spreading into the brain.

An analgesic effect which was not quite described so far

"The molecule created by the action of the light, the raseglurant, does not belong to any group of drugs from the classic anti-pain drugs: non-steroidal anti-inflammatory drugs (paracetamol, ibuprofen, etc.) and opioids (morphine, phentanyl). Consequently, this study describes an analgesic mechanism which has not been well explored thus far," says Ciruela. "Actually, the raseglurant was examined in clinical trials as an analgesic to treat migraine, but it was ruled out due its hepatoxicity. This

new optopharmacology of the raseglurant can stop adverse effects in the liver and opens a new path to start using it as an analgesic."

Searching for new drugs using optopharmacology

Optopharmacology is a new field for delivery of drugs and administration and control methods for pharmacological action. This discipline can help widen the therapeutic range to treat pain and notably reduce the unwanted effects of lots of drugs (for example the high risk of addiction in morphine, the low analgesic efficacy of NSAIDs in severe and chronic pain, etc.).

"If we compare natural biological molecules that act in living beings with drugs, we can see that the former can work with great precision, acting in centralized areas and with regulated doses, with defined lengths. However, the drugs we have act in all areas of the body, and without strict control. The use of light-controlled molecules offers more precise drugs that can act like biological molecules," says Llebaria. The team of the Group MCS (Medicinal Chemistry & Synthesis) of IQAC is now participating in several projects on optopharmacology, working on the design and synthesis of several light-activated molecules. "This approach is more complex than conventional drug development, since, apart from the therapeutic features, the molecule's photochemical and photophysical responses have to be prioritized," says Llebaria.

The research team of the UB and IDIBELL is working on research lines in optopharmacology to respond to lots problems related to conventional pharmacology. "At this moment we are examining other molecules with different action mechanisms, but also based on G protein-coupled membrane receptors, the biggest therapeutic target at the moment. Therefore, we have drugs under study for the treatment of Parkinson's disease or psoriasis. We are also exploring the optopharmacological use of light with different wavelengths (green, yellow and red). Regarding

the future, we cannot rule out some symptomatology to be lowered with optical fibers in the brain, just like electrodes are used for deep brain stimulation for Parkinson's disease," concludes Ciruela.

More information: Joan Font et al, Optical control of painwith a photoactive mGlureceptor negative allosteric modulator, *eLife* (2017). DOI: 10.7554/eLife.23545

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