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Finding the off-switch for side effects

Opioids are powerful painkillers that act on the brain, but they have a range of harmful side effects including addiction. Researchers have developed a tool that gives deeper insights into the brain's response to opioids. Using mass spectrometry, they determined changes of proteins' phosphorylation patterns – the molecular switches of the proteins – in five different regions of the brain and assigned them to the desired and the undesired effects of opioid treatment. Their results, which are published in the journal *Science*, will lead the way for the identification of novel drug targets and the design of a new class of painkillers with fewer side effects. The study was performed by researchers at the Max Planck Institute of Biochemistry (MPIB) in collaboration with researchers from the Medical University of Innsbruck, Austria, University of Innsbruck, and Temple University, USA.

The signaling cascades that are used by cells to respond to external stimuli resemble the chain of command of a company. Activation of a receptor, which acts as the head of the company, gives instruction to other proteins inside the cells, which act as groups of subordinates. This information is then passed down to lower levels of the organizational structure via signaling cascades of other interacting proteins. Like the employees who perform different tasks to keep a company running, proteins are the molecular machines in the cells that conduct the majority of functions. In cells, instructions are passed along to other proteins by changing the function of these 'cellular employees'. One way to change the function is by "phosphorylations" – the attachment of a phosphate molecule to the proteins. By analyzing all the molecular switches at the same time, the activity of signaling pathways in cells or an organ can be determined. Studying this chain of command gives a more precise insight into the currently occurring processes within cells than studying the DNA, the genetic "blueprint", which is almost identical in all cells.

Snapshot of protein activities

Researchers in the laboratory of MPIB director Matthias Mann use mass spectrometry – a method that determines the identity and quantity of proteins in a sample – to describe phosphorylation patterns of thousands of proteins in many organ specimens, an approach coined as phosphoproteomics. In the recent study, they analyzed the activation of signaling pathways in the different regions of the brain, responding to opioid-like drugs. To achieve this goal, the researchers used a recently developed method named *EasyPhos*.

To understand how drugs like opioids work, researchers must know their influence on the brain. “With phosphoproteomics, we can analyze more than 50,000 phosphorylation sites at once and get a snapshot of all pathways that are active in the brain samples during that time. We found more than 1,000 changes after exposure to an opioid-like drug, showing a global effect of these drugs on signaling in the brain.”, says Jeffrey Liu, the lead author of the study. Previous methods could not capture the protein phosphorylations at a comparable scale and missed many important signaling pathways that were switched on or off.

Phosphoproteomics – a versatile tool

“In our study, we looked at the activation of pathways in the brain that are responsible for desired effects of opioids like painkilling. In contrast, the parallel activation of other pathways causes undesired side effects”, says Liu. The researchers used phosphoproteomics to measure how active these beneficial and side effects-causing pathways were. Christoph Schwarzer from the Medical University in Innsbruck, who collaborated with Liu and Mann for this study, focuses his research on these opioid-activated signaling cascades in the brain. During the development of new drugs, the phosphoproteomics data can be used to identify potential substances that give strong therapeutic benefits and have few side effects. In addition, this study also shows the promise of reducing side effects by interfering with the signal cascades responsible for these effects. Current drugs of the opioid family are potent painkillers but quickly lead to addiction. Thus, there is an urgent need for novel non-addictive opioids.

Imagining the proteins in the brain as a company, phosphoproteomics allows the researchers to follow the activity of all employees at once instead of focusing on a selected few. Mass spectrometry can be a powerful tool to study drug targets in the brain or other organs. The mass spectrometry expert Matthias Mann says, “The current epidemic of opioid-related deaths in the US is a shocking example for the potential consequences of prescription drugs with strong side effects like addiction. With mass spectrometry, we can get a global view of the effects of drugs and streamline the development of new drugs with fewer side effects.” Mann explains that the

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design of new drugs is just one of many potential applications of phosphoproteomics and predicts that the method can also be used to generate knowledge on how cells use their chains of command to process information and the effects on drugs in other organs. [CW]

Caption:
Tens of thousands protein phosphorylation events occur in the brain with different brightness, much like the cosmo in the sky. Many of the phosphorylation events are organized into signaling pathways, like the constellations. These signaling pathways that are activated by opioid-like drugs can be therapeutic (painkilling), but can also cause side effects. Mass spectrometry reveals the patterns of these signaling pathways and provides an approach to alleviate side effects of the opioid-like drugs.

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About Matthias Mann
Matthias Mann studied physics at the Georg August University in Göttingen and obtained his PhD from Yale University, New Haven, USA. He held group leader positions at the European Molecular Biology Laboratory (EMBL) and the University of Southern Denmark in Odense before becoming a director at the MPIB in 2005. His department "Proteomics and Signal Transduction" uses mass spectrometry to study the proteome, the entirety of all proteins of an organism. Additionally, Mann was appointed director of the Department of Proteomics at the University of Copenhagen in 2007. Mann has received numerous awards for his research including the Louis-Jeantet Prize for Medicine, the Körber European Science Prize and the Gottfried Wilhelm Leibniz Prize.

About Christoph Schwarzer
Christoph Schwarzer studied microbiology and biochemistry at the University of Innsbruck and obtained his *venia docendi* in Neurobiochemistry at Medical University of Innsbruck. Since 2002 he is head of the Neurobiochemistry group of the Department of Pharmacology, Medical University of Innsbruck. His group focuses on the functional implications of endogenous opioids in health and disease. Since several years the pharmacological separation of beneficial and adverse effects of opioids is one of the main research interests.

About the Max Planck Institute of Biochemistry
The Max Planck Institute of Biochemistry (MPIB) belongs to the Max Planck Society, an independent, non-profit research organization dedicated to top-level basic research. As one of the largest Institutes of the Max Planck Society, about 800 employees from 45 nations work here in the field of life sciences. In currently about 35 departments and research groups, the scientists contribute to the newest findings in the areas of biochemistry, cell biology, structural biology, biophysics and molecular science. The MPIB in Munich-Martinsried is part of the local life-science-campus in close proximity to the Max Planck Institute of Neurobiology, a Helmholtz Center, the Gene-Center, several bio-medical faculties of the Ludwig-Maximilians-Universität München and the Innovation and Founding Center Biotechnology (IZB). (http://biochem.mpg.de)

About the Medical University of Innsbruck
Medical University of Innsbruck has approximately 2,000 employees and around 3,150 students and, together with the University of Innsbruck, is the largest educational and research institution

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in western Austria and the regional university for Tyrol, Vorarlberg, South Tyrol and Liechtenstein. The following courses are offered at Innsbruck Medical University: Medicine and Dentistry as the basis of an academic medical degree and a PhD degree (PhD) as the postgraduate aspect of scientific work. The bachelor's degree in Molecular Medicine is new in the curriculum since autumn 2011. There is the possibility to continue with a master degree in Molecular Medicine.
Medical University of Innsbruck is involved in numerous international educational and research programmes and networks. The research focuses on the areas Oncology, Neuroscience, Genetics, Epigenetics and Genomics as well as Infectious Diseases, Immunology & Organ and Tissue Repair. In addition to scientific research, Medical University of Innsbruck is also nationally and internationally very successful in the highly competitive field of research funding. (https://www.i-med.ac.at/mypoint/)

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