

Pain relief without side effects and addiction

October 4 2022



Doctoral candidate and co-lead author Philipp Seemann was one of the FAU researchers who have discovered substances that provide very effective pain relief, but without the addictive and sedative effects of drugs currently available. Credit: FAU/Stefan Löber

New substances that activate adrenalin receptors instead of opioid receptors have a similar pain relieving effect to opiates, but without the negative aspects such as respiratory depression and addiction.

This is the result of research carried out by an international team of researchers led by the Chair of Pharmaceutical Chemistry at FAU. Their findings, which have now been published in the journal *Science*, are a milestone in the development of non-opioid pain relief.

Opiates cause addiction, new substances do not

They are a blessing for patients suffering from [severe pain](#), but they also have [serious side effects](#): Opioids, and above all morphine, can cause nausea, dizziness and constipation and can also often cause slowed breathing that can even result in respiratory failure. In addition, opiates are addictive—a high percentage of the drug problem in the U.S. is caused by pain medication, for example.

In order to tackle the unwanted medical and social effects of opioids, researchers all over the world are searching for alternative analgesics. Prof. Dr. Peter Gmeiner, Chair of Pharmaceutical Chemistry is one of these researchers. "We are focusing particularly on the molecular structures of the receptors that dock onto the pharmaceutical substances," says Gmeiner. "It is only when we understand these on the [atomic level](#) that we can develop effective and safe active substances."

Collaborating with an international team of researchers, Prof. Gmeiner discovered an active substance in 2016 that bonds to known opioid receptors and that offers the same level of pain relief as morphine, even though it has no chemical similarity to opiates.

New approach: Adrenaline receptors instead of opioid

receptors

Peter Gmeiner is currently following a lead that seems very promising. "Many non-[opioid receptors](#) are involved in pain processing, but only a small number of these alternatives have as yet been validated for use in therapies," he explains.

Gmeiner and a team of researchers from Erlangen, China, Canada and the U.S. have now turned their attention to a new receptor that is responsible for binding adrenaline—the alpha 2A adrenergic receptor. There are already some analgesics that target this receptor such as brimonidine, clonidine and dexmedetomidine. "Dexmedetomidine relieves pain, but has a strong sedative effect, which means its use is restricted to [intensive care](#) in hospital settings and is not suitable for broader patient groups," says Gmeiner.

The aim of the research consortium is to find a [chemical compound](#) that activates the receptor in the central nervous system without a sedative effect. In a virtual library of more than 300 million different and easily accessible molecules, the researchers looked for compounds that physically match the receptor but are not chemically related to known medication. After a series of complex virtual docking simulations, around 50 molecules were selected for synthesis and testing and two of these fulfilled the desired criteria. They had good bonding characteristics, activated only certain protein sub-types and thus a very selective set of cellular signal pathways, whereas dexmedetomidine responds to a significantly wider range of proteins.

Pain relief without sedation in animal models

By further optimizing the identified molecules, for which extremely high-resolution cryo-electron microscopic imaging was used, the researchers

were able to synthesize agonists that produced high concentrations in the brain and reduced the sensation of pain effectively in investigations with animal models.

"Various tests confirmed that docking on the receptor was responsible for the analgesic effect," explains Gmeiner. "We are particularly pleased about the fact that none of the new compounds caused sedation, even at considerably higher doses than those that would be required for [pain relief](#)."

The successful separation of analgesic properties and sedation is a milestone in the development of non-opioid [pain medication](#), especially as the newly-identified agonists are comparatively easy to manufacture and administer orally to patients.

However, Prof. Gmeiner has to dampen any hopes of rapid widespread use in [human medicine](#): "We are currently still talking about basic research. The development of medication is subject to strict controls and in addition to significant amounts of funding, it takes a long time. However, these results still make us very optimistic."

More information: Elissa A. Fink et al, Structure-based discovery of nonopioid analgesics acting through the α 2A -adrenergic receptor, *Science* (2022). [DOI: 10.1126/science.abn7065](https://doi.org/10.1126/science.abn7065)

Provided by Friedrich–Alexander University Erlangen–Nurnberg

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