Improving the healing of inflammatory illnesses

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Pharmacists at Jena University develop new drug candidates against inflammation. Credit: Jan-Peter Kasper

It is something like the police force of our body: the immune system. It disables intruding pathogens, it dismantles injured tissue and boosts wound healing. In this form of 'self-defense' inflammatory reactions play a decisive role. But sometimes the body's defense mechanism gets out of control and cells or tissues are affected: "Then excessive reactions can

occur and illnesses along with them," Prof. Dr. Oliver Werz of the Friedrich Schiller University Jena (Germany) says. He gives asthma, rheumatism, arteriosclerosis and cancer as examples: "For many of these diseases there are only few effective therapies without severe side effects."

But the team of researchers working together with the Jena pharmacist has now developed three active agents which may be able to improve the healing of inflammatory illnesses better in future. The scientists present the potential therapeutic agents in renowned scientific journals. The agents are able to suppress a key enzyme in the body's own cascade of inflammation.

"The enzyme called 5-LOX plays a pivotal role in the synthesis of so-called leukotrienes, which are part of numerous immunological and inflammatory processes," Prof. Werz explains. Hence, the effort to prevent the synthesis of leukotrienes has been the focus of international research for inflammatory therapy for a long time. "Thousands of publications on the subject have emerged in the last 30 years," says Werz. But apart from one exception none of these efforts have made it to the stage of an approved medication. Either the efficacy of the substances was poor or they were accompanied by unwanted side effects.

As a reason behind this, the Jena pharmacist sees the insufficient understanding of cellular regulation of the leukotriene biosynthesis and the lack of knowledge of the molecular mechanisms of agent and target molecule. "Instead of testing a number of substances to see if one of them might show any activity, we took a close look at 5-LOX and tried to find where exactly this enzyme is vulnerable and what the agents, which can interact with our target molecule, should look like," Werz describes the basis-orientated approach. In this way the scientists of the Jena University together with partners from Austria, Italy, Turkey and Greece, were able to identify three possible agents. So for instance, a so-

called benzoquinone proved to be an effective inhibitor of the 5-LOX. This is a substance which is derived from the natural product embelin from the "False Black Pepper"-plant (Embelia ribes). The pharmacists were able to show that this substance fits exactly into the active center of the enzyme and thus blocks its function. "This specifically only happens with 5-LOX," Werz says and stresses that benzoquinone may practically show no side effects.

A related substance of the red-violet natural dye indirubin, called 6-BIO, proved to be similarly promising. For this substance, the Jena researchers were able to clarify the mechanism of action as well: the 6-BIO inhibits the enzyme 5-LOX by blocking receptor sites for other molecules which are necessary for it to work properly. "In addition, 6-BIO also intervenes with the synthesis of additional inflammatory factors – the cytokines implying additional synergistic effects." This is why 6-BIO could for instance be of interest for the therapy of Alzheimer's disease, in which cytokines are also playing a role.

The third possible active agent from the Jena University's laboratory does not inhibit the 5-LOX itself, but it deactivates a helper-protein, which the enzyme needs for its effectiveness within the cell. The researchers identified this active agent, a benzimidazole with the short term BRP-7, by a virtual screening in a library consisting of nearly three million substances. "From our point of view all three of the drug candidates are very well suited to a further development as medications," Prof. Werz summarizes. However, for this, the support of the pharmceutical industry is needed.

More information: Schaible AM et al. "Elucidation of the molecular mechanism and the efficacy in vivo of a novel 1,4-benzoquinone that inhibits 5-lipoxygenase." *British Journal of Pharmacology* 2014 (DOI: 10.1111/bph.12592)

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Pergola C et al. "The novel benzimidazole derivative BRP-7 inhibits leukotriene biosynthesis in vitro and in vivo by targeting 5-lipoxygenase-activating protein (FLAP)." *British Journal of Pharmacology* 2014 (DOI: 10.1111/bph.12625)