

Peripheral nerve endings: messenger substances released in endometrial tissue can cause a direct sensation of pain.

NEW TREATMENT FOR ENDOMETRIOSIS

Two-fold effect

For many women, endometriosis means severe abdominal pain, and not only during menstruation. Researchers at Bayer HealthCare are now investigating new active substances for treatments that are aiming for a two-fold effect: rapidly easing the pain and simultaneously treating the original abdominal inflammation that causes it, all without intervening in the female hormone balance.

Sometimes there is a state of emergency inside the female body: once a month – or in some cases even more frequently – many women are plagued by extreme abdominal pain. Their daily life is hugely restricted by persistent menstrual bleeding, not to mention nausea and fainting. The cause is endometriosis, a hormonal and inflammatory disease in which menstrual blood and small bits of tissue shed from the endometrium flow backwards via the fallopian tubes into the abdominal cavity and begin growing there. The abdominal pain is often chronic and leads to problems during sexual intercourse, urination and defecation. Endometriosis also frequently turns out to be the cause of unwanted infertility.

Although 10 percent of all women of child-bearing age suffer from endometriosis, the disease is only identified after a number of years in many patients: up to ten years can pass between the onset of discomfort and diagnosis. "Unlike comparable diseases in which pain is likewise the primary symptom, endometriosis is still frequently not recognized in our society today, which can lead to a delay in reaching a diagnosis and therefore lengthens the suffering experienced by the patients," says Dr. Thomas M. Zollner, Head of the Gynecological Therapies Research Department at Bayer HealthCare. "A lot of times, the symptoms are not taken seriously and palmed off as 'completely normal' menstrual pain, and that causes additional emotional stress for these women." But the disease has other implications as well: on account of their limited ability to work, many women with endometriosis have to frequently call in sick, which leads to considerable financial losses every year. "The economic cost of endometriosis is substantial as well," says Zollner.

The significant pain associated with endometriosis is caused partly by inflamed tissue. "Because endometriosis can be located in many different places, for instance in the blad-



Investigating endometriosis together: physicians Dr. Matthias Schäfers (right) and Dr. Thomas Zollner (left) discuss new therapies with medicinal chemist and alliance manager Dr. Christoph Huwe (center) at Bayer HealthCare in Berlin using a model of a uterus for reference.

der, intestines or pelvic wall, the characteristic pain can be very complex," says PD Dr. Sylvia Mechsner from the Department of Gynecology at Charité University Hospital in Berlin. The existing treatments are based on hormonal drugs that suppress ovulation and keep estrogen at a low level. However, as many women are affected by the side effects of these drugs, they generally do not represent a long-term solution.

Sensitive nerve fibers and neuropeptides lead to pain

In recent years, physicians have made significant discoveries that explain why endometriosis is so painful. The lesions in the abdominal cavity are innervated by small nerve fibers which generally grow along with the vessels supplying blood. Mechsner and her working group found that the sensitive nerve fibers that are responsible for pain perception are particularly common here.

“We need new forms of treatment”

research spoke with PD Dr. med. Sylvia Mechsner from the Department of Gynecology at Charité University Hospital in Berlin.



Sylvia Mechsner

What treatment options are currently available for endometriosis?

The first step is to surgically remove the endometriosis lesions, while at the same time sparing the organs involved as far as possible. Then supportive hormone therapy should be initiated. Patients planning to have children should also take advantage of the possibilities offered by reproductive medicine.

What are the drawback to this treatment?

Most patients suffering extreme pain accept the need for surgery. What is a problem however is when surgical removal does not have the desired outcome, the pain remains unchanged or improves only for a short time. In this case, more surgery must be given very critical consideration. The second pillar of treatment is hormones, which

also support long-term therapy. However, these drugs frequently have side effects that restrict a woman's quality of life. All round, the situation is very unsatisfactory ...

Where do you see a need for research?

For me as a clinical researcher who has patients suffering from endometriosis, the most urgent goal is to find new, innovative approaches to therapy. In addition to hormonal and surgical treatment, we also need therapies that target the inflammatory component of the disease, in other words counteract inflammation. We urgently need new, non-hormonal forms of treatment that eliminate the underlying cause of the disease.

The corresponding nerve cells also produce neuropeptides that are released into the lesions and increase the symptoms of inflammation there. At the same time, the number of sympathetic nerve fibers that regulate pain in the abdominal cavity is reduced. Zollner and his colleagues in research at Bayer HealthCare therefore chose an entirely new approach to treatment, because they discovered that a process known as retrograde menstruation, which is under discussion as a main trigger of the disease, has a direct influence on the peripheral nervous system. "The cells in the endometrium contain a vast number of messenger substances which, when released, promptly lead to inflammation,"

Zollner explains. What's more, these messenger substances can activate structures known as peripheral nerve endings, which cause a direct sensation of pain in the female body.

Collaborating with partners to develop new active ingredients

In view of these findings, the Bayer researchers are working on active substances that intervene simultaneously in both processes. "In our approach, we want to treat the site of inflammation directly and at an early stage, but also minimize the resulting pain perception," Zollner explains. To drive research in the field of endometriosis forward in this direction, the gynecology specialists at Bayer HealthCare are steadily expanding their international research network. Bayer has been collaborating with Evotec AG in this area since October 2012. The objective of the five-year research partnership is to develop three innovative substances that support alternative forms of treatment in the field of endometriosis and have both an anti-inflammatory and pain-relieving effect. Roughly half of Bayer's endometriosis product portfolio is currently being worked on in collaboration with Evotec. In all activities, the two companies work together closely. "Our research cooperation is a real partnership. We work on every one of our projects in joint teams; both partners have a significant share in their success," comments Dr. Christoph Huwe, a medicinal chemist and the alliance manager for External

Up to **6** million women
in Germany suffer from
endometriosis.

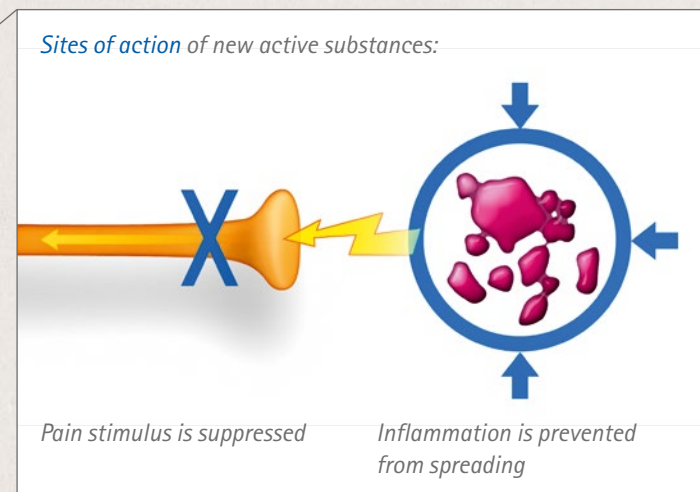
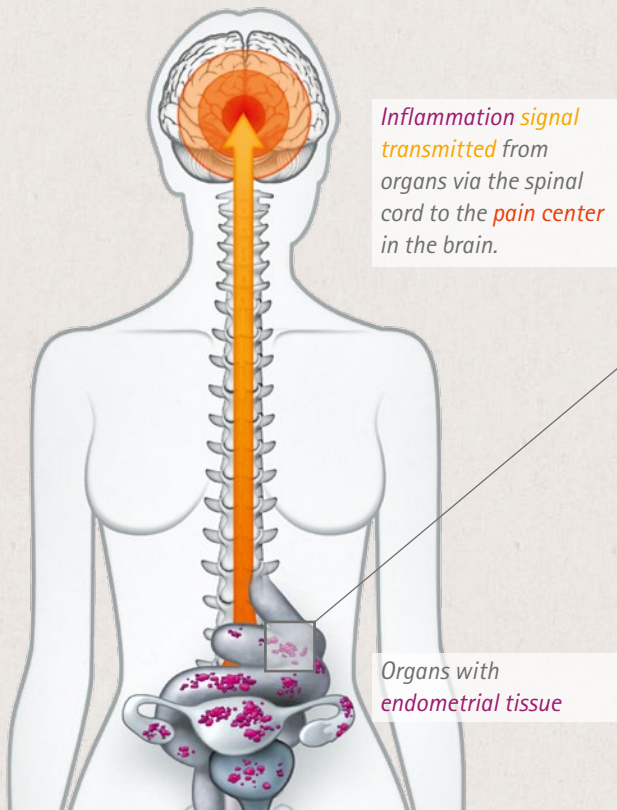
Source: Endometriosevereinigung Deutschland

Relieving pain

Endometrial tissues can migrate to various organs in the abdominal cavity and cause inflammation there. Women who are affected by this condition generally suffer extreme pain. Bayer scientists are now taking a two-fold approach to the disease: they are developing active substances that both inhibit inflammation and influence the onset of pain signals in the endometrial lesions and the peripheral nervous system.



A crisis in the abdomen: endometriosis causes extreme pain that can seriously restrict the sufferer's daily life.



Innovation Therapeutics at Bayer HealthCare responsible for the collaboration with Evotec.

The first active ingredient candidate is already in preclinical development

The partners have made major progress over the last two years in developing innovative active substances to treat the disease. "This year already, our first candidate went into preclinical development," Huwe adds. The active substances, however, must have as little influence as possible on the hormone balance – and thus on the female menstrual cycle and fertility. "We hope that these newly discovered drugs will work faster than previous, hormone-based endometriosis medications. We expect a significant reduction in pain just one month after a patient takes the first tablet," says Dr. Matthias Schäfers, Clinical Head of Gynecological Therapies at Bayer HealthCare. "What's more,

thanks to their targeted effect, the new products could potentially be better tolerated than the conventional pain medications." In addition to the partnership with Evotec, Bayer also launched a joint venture with the University of Oxford, U.K., an academic leader in the field of endometriosis and pain therapy, in July 2014. As all these activities show, Bayer HealthCare has set a course for long-term and successful treatment of endometriosis.



www.research.bayer.com/endometriosis

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