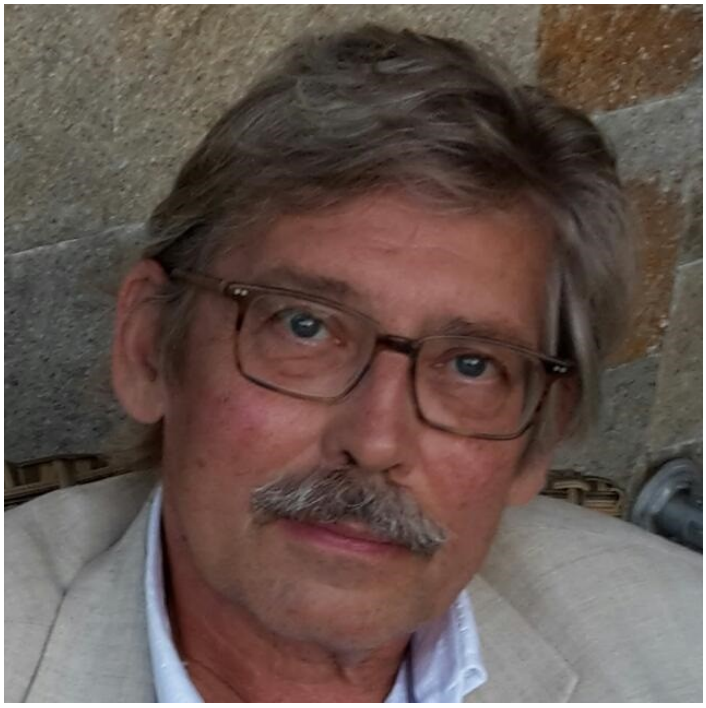
New approach for treating depression

According to the "Deutsche Depressionshilfe" foundation, one in five Germans suffers from depression once in their lifetime. Depression is the most common mental health condition; it must be taken seriously and requires treatment. Several therapies are available, each of which acts in a different way. Exactly how and where therapies work is still unclear. Prof. Dr. Dietrich van Calker and Prof. Dr. Knut Biber from the Department of Psychiatry and Psychotherapy at the Freiburg University Medical Center have been looking into mechanisms of action and have discovered a molecule that appears to be implicated in numerous neuropsychiatric disorders and the effect of various anti-depression therapies. This protein, known as Homer1a, could potentially be used for developing new approaches for treating depression.



Prof. Dr. Dietrich van Calker analyses the molecular causes of depression.

When sadness, inner emptiness, lack of motivation or suicidal thoughts take over and the simplest things like personal care become almost impossible, this could be a sign of depression. A person who is unhappy or sad is often described as "depressed". However, depression is actually a prolonged depressed mood lasting more than just a couple of weeks that cannot be lifted by willpower or encouragement. It is a life-threatening disease that must be treated, and it must be treated effectively. A depressive episode may occur more than once. "Around 50% of all cases of depression are once-in-a-lifetime events that never recur," says Prof. Dr. Dietrich van Calker from the Section of Psychopharmacotherapy at the Freiburg University Medical Center's Department of Psychiatry. "Unfortunately, the remaining 50% are recurrent depressive episodes. One episode of depression generates an elevated risk of another."

The mechanisms of action of drugs used for treating depressive moods are poorly understood. One problem associated with pharmacotherapies is that it usually takes several weeks for the effect of a drug to become apparent.

The ability to experience pleasure is pivotal

Depression often begins with nonspecific somatic symptoms such as pressure in the head or stomach pain. Depression is therefore not immediately recognised as such. This means that people usually see their GP rather than a specialist. "Good GPs will think to ask the patient whether he or she is happy and able to experience pleasure," says van Calker. A very simple question, but one which goes to the core of what depression essentially is. Common triggers for unipolar disorders are partnership problems, pathological grief and loneliness. The causes of depression are only partially understood because they interact in a complex way. Many different factors, including genetic predisposition, personality and environmental factors are thought to determine whether a person develops depression or not.

It is assumed that depression is due to the defective release and reuptake of either serotonin or noradrenalin, or both. But why does the behaviour of neurotransmitters differ between healthy and depressive brains, and how do antidepressant therapies work? Van Calker and Biber studied the effect of different therapies in mouse animal models in an attempt to better understand the neurobiological effects of antidepressant therapies. The animals developed depression-like symptoms when exposed to stress.

The mice were placed in a container of water which required them to swim. Although they are excellent swimmers, they do not like it, so they become stressed, which induces a depression-like state. "Eventually, they stop trying to swim, and just float on the surface of the water on their backs," says van Calker. "They save energy by displaying adaptive behaviour." Besides running out of energy, the stressed mice also lost the capacity to experience pleasure and happiness. When they were offered sugar solution, which they normally love, they did not choose the sugar solution in preference to water to any significant extent. The administration of antidepressants resulted in an unexpected finding: "Mice that were given antidepressants swam for longer and gave up less quickly than mice that were not given drugs," said the psychiatrist.

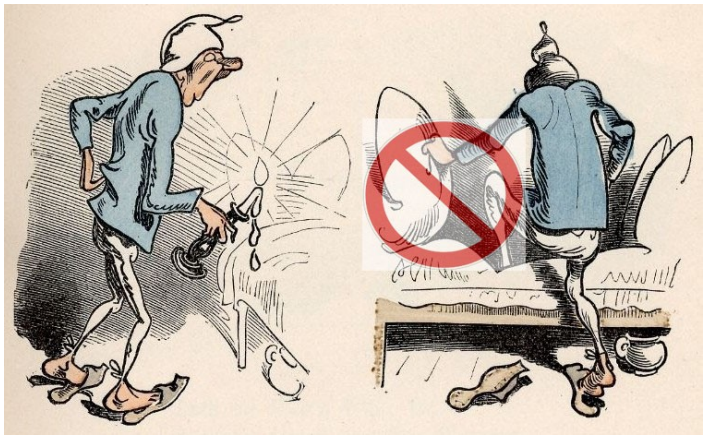
ECT, sleep deprivation and ketamine

Most antidepressants work by enhancing serotonergic or noradrenergic neurotransmission in the nerve cells. Serotonin-specific reuptake inhibitors (SSRI) do so indirectly by inhibiting the reuptake of serotonin into the presynaptic neuron, which normally limits the effect of the neurotransmitter. This leads to an increase in the level of neurotransmitter in the synaptic cleft available to bind to the serotonin receptors of the postsynaptic neuron, thus compensating for the lower levels of serotonin in depressed people. In general, antidepressants are well tolerated by patients, but it usually takes several weeks before any effect is felt. Treatment can also lead to adverse drug effects such as severe anxiety, fatigue and sexual dysfunction. Depression can also be treated with electroconvulsive therapy (ECT),

sleep deprivation and ketamine, a drug used to anaesthetise humans or sedate large animals. ECT requires a hospital stay and is done under general anaesthesia. Small electric currents are passed through the brain via electrodes, triggering brief brain seizures. ECT is very effective and usually applied when other treatments have proved unsuccessful.

A night without sleep also has an antidepressant effect. Sleep deprivation works around 60% of the time, but only until the next time the patient falls asleep again. "Depression returns when the patient sleeps again," says van Calker. Sleep deprivation is impractical as an ongoing therapy because it is incompatible with a functional social life.

The anaesthetic drug ketamine is currently being discussed as an effective means of treating depression. Research shows that it provides relief within a few hours. Despite this huge advantage over traditional depression medication, the drug is associated with severe adverse effects such as amnesia and pseudohallucinations as a result of overstimulation of the brain.



Sleep deprivation has a positive effect in around 60% of all patients suffering from depression - but only until the next time they fall asleep.
© Heyl, modified from Wilhelm Busch (1832-1908)

Homer1a plays a key role in generating an antidepressant effect

ECT and sleep deprivation have a common biochemical effect; they increase the number of adenosine binding sites in the brain. Adenosine is a neurotransmitter in the brain, mainly known for its ability to cause tiredness. However, the activation of some adenosine receptors can also have an antidepressant effect as has been shown by van Calker and Biber in genetically modified mice that had a large number of these receptors. The scientists also demonstrated that the antidepressant effect resulting from the activation of adenosine receptors was mediated by the protein Homer1a. Homer1a controls the signal transmission between nerve cells and is activated in response to neuronal stimulation. It inhibits the effect of certain receptors in neurons. "We assume that Homer1a modulates existing nerve cell connections in order to enable the creation of new ones," explains van Calker. This flexibility enables the brain to adapt better to changes.

The researchers found that Homer1a expression was downregulated in mice with depression-like behaviour and upregulated when antidepressant measures were initiated. They also found that the effect was independent of the type of therapy used. Antidepressant effects can be achieved with ECT, sleep deprivation, antidepressants and ketamine. Using Homer1a knockout mice, van Calker and Biber were able to show that Homer1a is, in fact, necessary for the antidepressant effect to occur. Without Homer1a, none of the therapies had any effect. The increased expression of Homer1a is part of a common signalling pathway that mediates antidepressant effects. The next questions that need to be solved are: "Can this effect also be achieved with something else? Which compounds or specific activations can increase Homer1a expression in the forebrain and pave the way to depression therapies with fewer adverse effects that are also quicker and more compatible with a patient's social life? Van Calker, who officially retired around two months ago, continues to practise as a psychiatrist and advise his former colleagues.