



## From Model to Patient – New Avenues in Depression Research

The World Health Organization (WHO) assumes that by the year 2020 depressive illnesses – along with cardiovascular diseases – will represent the largest group of diseases in industrialized countries. In the Clinical Cooperation Group (KKG) “Molecular Neurogenetics” scientists from the GSF and the Max-Planck-Institute of Psychiatry join forces to elucidate the molecular mechanisms and causes of depression and anxiety-related disorders, and to find new approaches for suitable therapies. In a clinical study the scientists showed that there is a clear disturbance of the hormonal balance in patients with these psychiatric disorders, indicating that pharmaceuticals acting on a hormonal level may be applied as an alternative to classical antidepressants in the near future.



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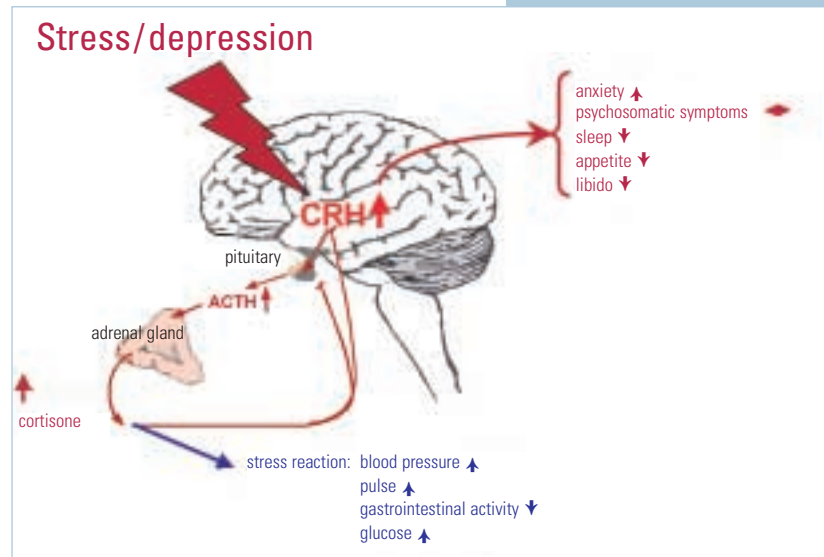
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**T**here are many prejudices about depressed persons, which equate depression with a weak character or personal failure, resulting in the idea of having attracted an untreatable destiny. But what are depressions from a medical point of view? The clinical term depression includes

all affective disorders that can be characterized by a pronounced, continuously irritated, and depressed mood or the loss of interest and pleasure in usual activities. It is assumed that depression is a multifactorial disorder caused by a genetic predisposition as well as lifestyle and the environment.

At this point the work of the Clinical Cooperation Group “Molecular Neurogenetics” sets in, which was established by the GSF Institute of Developmental Genetics headed by Prof. Wolfgang Wurst, and the Max-Planck-Institute of Psychiatry headed by Prof. Florian Holsboer. “Our aim is to elucidate the molecular mechanisms and causes of depression and anxiety-related disorders and thus to find novel therapeutic strategies for the treatment of depressive illnesses”, says Wolfgang Wurst. For this purpose, the scientists from the GSF and their colleagues from the Max Planck Institute of Psychiatry have developed special mouse models, which emulate the clinical symptoms of human depression. Only recently a major breakthrough was achieved in clinical research. The observation that patients with psychiatric diseases have elevated levels of CRH in the cerebrospinal fluid, a reduced density of CRH receptors in the frontal cortex, and elevated stress hormone (cortisol) levels in the blood indicates that CRH plays a central role in the development and course of depression and anxiety-related disorders. The scientists found changes in the complex interactions between corticotropin-releasing hormone (CRH) and its receptors. CRH plays a key role in the physiological response of the organism to stress by regulating the hypothalamic-pituitary-adrenal (HPA) axis. In addition, CRH is released in the brain and may thus directly influence central behavioral patterns, which is an important factor when dealing with stress-related situations.

Wolfgang Wurst and his colleagues have created a mouse model that allows the dissection of these two functions. By genetically ablating the CRH receptor type 1 (CRH-R1) in the mouse brain, they could show that CRH regulates anxiety-related behavior in a particular area of the brain, the limbic system – irrespective of its role in the HPA axis. Apart from this, the KKG could also show that the function of CRH-R1 plays an important role in stress-induced alcohol consumption. These results corroborate the significance of CRH-R1 in the development of psychiatric disorders. “We now take this knowledge back to the clinic”, says Dr. Jan Deussing from the



Max-Planck-Institute of Psychiatry. “In some first clinical trials we could confirm that specific CRH-R1 antagonists have an antidepressive effect.” This paves the way for an establishment of CRH-R1 antagonists as a possible alternative to classical antidepressants in the near future.

Elevated levels of corticotropin-releasing hormone (CRH) are found in the brain of depressed patients, similar to stressful situations in which the endogenous hypothalamic-pituitary-adrenal axis is activated. In animal models, it was shown that the increase in CRH levels in the brain causes changes in behavior, which can also be observed in depression.

	<i>Crhr1<sup>loxP/loxP</sup> CaMK</i>		<i>Crhr1<sup>loxP/loxP</sup> CaMK</i>	
CRHR1				
CRHR1				

Mice (*Crhr1<sup>loxP/loxP</sup>CaMKCre*), which do not express CRH receptor 1 in the forebrain – in particular in the limbic system – (c, d, f compared to a, b, e), are less timid than their genetically unmodified siblings (*Crhr1<sup>loxP/loxP</sup>CaMK*).