Stress vulnerability and resilience
Insights from a novel mouse model

The prevalence of psychiatric disorders has increased in recent years. Psychiatric disorders ranging from depression and anxiety, post-traumatic stress disorder (PTSD), autism spectrum disorder, psychosis, and others may impact a person’s quality of life, social interactions, and careers.

Both environmental factors and genetic predisposition influence stress vulnerability and resilience in humans, making them more prone to develop psychiatric disorders. The brain is highly adaptable, but stress can induce both physical and psychological changes. All individuals will experience moments of stress or adverse events during their lifetime. However, the quantity or severity of stress (chronic or traumatic) and the timing of the stress (during pregnancy, childhood, and adolescence) can profoundly affect the stress response and impact later life.

Adverse events during childhood such as abuse, neglect, or trauma (known as early life adversity, or ELA) detrimentally affect the brain during this important developmental stage and can lead to abnormal coping strategies. In addition to external factors such as stress, genetics plays a role with several genes identified as predisposing an individual to an abnormal stress response.

By studying such gene x environment interactions it’s possible to elucidate the underlying mechanisms involved in abnormal stress responses, so that biomarkers for diagnosis and treatment can be identified. Animal models use either whole organisms or cultured cells to study physiology and pathology, but typically do not contain human genetic variants. Verena Nold and colleagues have developed a novel animal model that enables such investigations, providing valuable insights in this area.

THE STRESS-RESPONSE NETWORK
Our body initiates a stress response to cope with changing and challenging conditions in our environment. This ability to cope and adapt is vital for survival. The stress-response network involves several interconnected components. The psycho-immune-neuro-energy (PINE) network regulates physiology by interlinking neuronal activity of the brain, the hypothalamic-pituitary-adrenal (HPA) axis, the immune system, and metabolism.

Changes in the PINE network are implicated in diseases such as major depressive disorder. It’s also known that stress in early life can negatively affect immune function and increase the risk of developing other pathologies such as cardiovascular disease. With such interconnection, communication within the PINE network is essential to its function and any effects on this communication can lead to an abnormal stress response.

Two fundamental parts of the stress-response network are the sympathetic nervous system and the HPA axis. Initial response to stress activates the sympathetic nervous system to release adrenaline during the ‘fight-or-flight response’. Subsequently, the HPA axis becomes activated, causing release of glucocorticoids (steroid hormones) from the adrenal glands. Glucocorticoids are universal messengers in the stress response and coordinate many physiological processes. One fundamental role of glucocorticoids is to increase blood glucose levels to ensure sufficient energy is available to deal with stress. Under normal physiological conditions, once the stress trigger resolves, the HPA axis activity diminishes, and the body returns to a homeostatic (steady and stable) state. However, continuous stress triggers may change this cycle long term, resulting in a chronically activated HPA axis and an abnormal stress response system. In addition to the pivotal role glucocorticoids play in the stress response, they have important functions under normal physiological conditions. Glucocorticoid levels reflect an organism’s increased stress-stimulated expression of the FKBP5 gene. This is thought to result in a reduction in subsequent glucocorticoid signalling. Such reduced glucocorticoid signalling negatively affects the communication within the PINE network, leading to stress vulnerability.

GENETIC PREDISPOSITION TO STRESS VULNERABILITY AND RESILIENCE
Previous studies show that individuals who experienced childhood trauma and developed psychiatric disorders have differential expression of the FKBP5 gene (change in levels of this gene) after a stress trigger, compared to those without disease. A mutation, specifically a single nucleotide polymorphism (SNP) in the human FKBP5 gene increases the risk of developing psychiatric disorders. A SNP is where one change or variation in a DNA base pair exists. Although this is an alteration of only one DNA base pair, its presence results in two different forms of a gene (known as alleles). In the case of the FKBP5 gene, one of these is the A/T allele (associated with higher risk of detrimental effects of stress) and the other is the G/C allele (associated with better resilience to stress).

A recent study by the research team aimed to understand how FKBP5 gene mutations in mice who experienced ELA affected the stress response system and the animal’s behaviour in adulthood. Another study goal was to establish if there was a difference in response to stress for carriers of the A/T allele compared to carriers of the G/C allele and if so, what the underlying mechanisms were.

Mice carrying either the A/T or the G/C allele were studied to determine the adrenal glands. Glucocorticoids are universal messengers in the stress response and coordinate many physiological processes. One fundamental role of glucocorticoids is to increase blood glucose levels to ensure sufficient energy is available to deal with stress. Under normal physiological conditions, once the stress trigger resolves, the HPA axis activity diminishes, and the body returns to a homeostatic (steady and stable) state. However, continuous stress triggers may change this cycle long term, resulting in a chronically activated HPA axis and an abnormal stress response system. In addition to the pivotal role glucocorticoids play in the stress response, they have important functions under normal physiological conditions. Glucocorticoid levels reflect an organism’s increased stress-stimulated expression of the FKBP5 gene. This is thought to result in a reduction in subsequent glucocorticoid signalling. Such reduced glucocorticoid signalling negatively affects the communication within the PINE network, leading to stress vulnerability.

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Factors leading to abnormal stress responses and vulnerability to psychiatric disorders.

Animal models can help to untangle the complex interplay between genetics and the environmental factors leading to abnormal stress responses and vulnerability to psychiatric disorders. This genotype also had decreased expression of genes involved in both synaptic communication (passing on of information between neurons in the brain) and circadian entrainment (when the body's physiological events align with environmental factors such as time or light/dark). These findings suggest important physiological processes such as synaptic communication and circadian entrainment are interrupted in these mice. Conversely, A/T allele carriers had increased expression of genes involved in mitochondrial respiration (energy equivalents for body cells to use) suggesting more energy is needed for these individuals. Interestingly, the study findings revealed sexual dimorphism, that is the female at-risk A/T allele carriers were more affected than their male counterparts.

FROM BENCH TO BEDSIDE

This research begins to unravel the complex interplay between genetics and the environmental factors leading to abnormal stress responses and vulnerability to psychiatric disorders. These findings provide a clearer understanding of the effects of FKBP5 genetic predisposition and ELA on both the stress response system, neurophysiology, and behaviour in adulthood. By elucidating such mechanisms, biomarkers for potential therapies to counter the risk to develop (psychiatric) disorders due to genetic risk and a lifetime of environmental influences. With the understanding of these limitations, the hope would be that understanding the role of FKBP5 better leads to identification of new drug targets to counteract the modeled pathology. A further hope would be that changes in the animal model might as well be measurable in man, providing biomarkers for FKBP5-related pathology. As our goal is to move towards a ‘precision psychiatry’ approach, knowing the physiological impact of these manipulations could lead to better matching of patient to treatment.

What are important considerations for new models to study complex psychiatric phenotypes?

If a model is based on putative pathomechanisms and shows face validity by mimicking abnormal behaviour and physiology resembling the human condition, it is a good start. Nevertheless, understanding the limitations of any animal model is equally important. We cannot reproduce real psychiatric syndromes in animals, since they result from complex interactions between genetic risk and a lifetime of environmental influences. With the understanding of these limitations, the hope would be that understanding the role of FKBP5 better leads to identification of new drug targets to counteract the modeled pathology. A further hope would be that changes in the animal model might as well be measurable in man, providing biomarkers for FKBP5-related pathology.

References

- Nold, V, Portenhauser, M, Del Prete, D, et al (2022) Impact of Fkbp5 polymorphisms and their impact on psychiatry comes already from the clinic. First determined by Elisabeth Binder and then confirmed in numerous clinical studies, the interaction of FKBP5 and early life adversity compromises adult psychiatric health. By developing a mouse model where the ‘why’ and ‘how’ of this impact can be better studied, we can someday understand the precise pathological trajectory of FKBP5-related disorders. This understanding will lead to better and more precise treatments for affected individuals.

Behind the Research

Verena Nold

Dr Kelly A Allers

Research Objectives

Investigating the consequences of stress on the psycho-immune-neuro-energy network and further develop animal models of psychiatric disorders.

Personal Response

How can the novel mouse model developed in your research be used in future studies into the etiology and mechanisms of psychiatric disorders?

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What is Boehringer Ingelheim doing to address the needs of patients with psychiatric disorders by ‘Precision Psychiatry’?

Current psychiatric diagnoses do not map well onto the neurobiological processes that underlie the complex emotional and behavioural change that patients experience. Boehringer Ingelheim is therefore taking a ‘precision psychiatry’ approach to addressing unmet need. We believe that by understanding how brain circuit function relates to the symptoms that individuals experience we will be able to develop therapeutic approaches – be these pharmacological, psychological or digital - tailored to the needs of individual groups of patients, irrespective of their diagnosis.

How is Boehringer Ingelheim working to address the unmet needs of patients with psychiatric disorders by ‘precision psychiatry’?

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By elucidating such mechanisms, biomarkers for potential therapies to counter the negative effects of FKBP5 gene variants can be investigated.

Animal models can help to untangle the complex interplay between genetics and the environmental factors leading to abnormal stress responses and vulnerability to psychiatric disorders.