Neurobiology of Anxiety

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Abstract

An organism is more likely to survive dangerous situations when it experiences anxiety and fear, which are feelings that have been conserved throughout evolution. Multiple brain regions are involved in the neural networks that control anxiety and alertness states. This complex regulatory mechanism is compromised in anxiety disorders, causing excessive or protracted anxiety or terror. There are environmental and genetic risk factors for anxiety disorders. Genetic research offers the capacity to pinpoint particular genetic variants that are causally linked to particular behaviours. Recent decades have seen the discovery of polymorphisms predisposing to neuropsychiatric diseases by Genome-Wide Association Studies (GWASs), which have suggested new neuronal pathways in the pathogenesis of these disorders. Here, we discuss current genetic investigations in rodent models of anxiety-like behaviour and human GWASs of anxiety disorders. These investigations are opening the door to a greater comprehension.

Keywords: Anxiety disorder • Genome-wide association study • Gene expression • Brain • Mouse model • Stress

Objective

Fear and anxiety are common reactions to prospective or actual threats. They might increase in frequency, intensity, and duration, disrupting daily activities and resulting in pathological anxiety. The most prevalent mental disorders, with a prevalence of about 14%, are anxiety disorders, which include panic disorder, social anxiety disorder, particular phobias, and generalized anxiety disorder. They are treated with medication and/or cognitive behavioural therapy and affect women more frequently than males. There are many pharmacotherapeutic choices, including benzodiazepines, anxiolytic drugs, and Selective Serotonin Reuptake Inhibitors (SSRIs), antidepressants. However, because the molecular mechanisms underlying excessive anxiety are largely unknown, the efficacy of currently available drugs is very varied and poorly targeted. They also have negative side effects, and in the case of benzodiazepines, these side effects include. As a result, there is a clear need to comprehend the molecular underpinnings of anxiety disorders and to create improved preclinical models, which are necessary for the creation of novel, individualized treatments.

In this review, we discuss genetic research on anxiety disorders in people and anxiety-like behaviour in rodents, and we look at the conclusions drawn about the neurological underpinnings of anxiety disorders from these studies. We conclude by discussing the significance of genetic background for improved translational validity in rodent studies and advocating for the creation of more etiologically pertinent rodent models of anxiety. Epigenetics and genetics both play significant roles in anxiety disorders, although the current review does not include these or other elements that contribute to the etiology of anxiety disorders.

Anxiety and fear are adaptive reactions that have been preserved throughout evolution due to their importance for survival. Stress, especially psychosocial stress, is a risk factor for developing anxiety disorders in the environment. As a result, stress exposures serve as the foundation for the most popular animal models of anxiety disorders. Humans and rats exhibit considerable similarities in their stress response and the brain circuits underlying danger detection and anxiety responses, despite physiological and anatomical differences. Therefore, using rats as models for anxiety disorders is particularly appropriate. While animal models of anxiety disorders try to address key characteristics of the condition, the whole clinical symptomatology cannot be modelled in laboratory animals since cognitive capacities are vital in the human stress response, especially in coping with stress.

The ability to precisely manipulate the experimental settings, such as environmental exposures, and to have access to tissue samples at certain time points in animal models is one of their main advantages over human investigations. Importantly, recent developments in transgenic, optogenetic, and chemogenetic approaches provide exquisite spatiotemporal control of cell type- and circuit-specific alterations.

Studies on peripheral biomarkers, neuroimaging, and genetics are the main research areas for anxiety disorders in humans. In addition to heredity, environmental factors are significant contributors to inter-individual variability and play a significant role in the etiology of anxiety disorders. Rodent studies allow for the precise control of environmental conditions and the accessibility of brain tissue at various times. Rodent models provide resources for future research into the functional effects of genetic variants discovered by the Genome-Wide Association Study (GWAS), which in theory could result in the discovery of new therapy targets and the creation of improved treatment strategies for anxiety disorders.

Stress early in life, notably in the perinatal and childhood years, is linked to an increased risk of psychiatric problems in humans. Maternal separation and/or a lack of nesting material during the first few weeks of birth are frequently used to simulate postnatal stress in mice, which results in anxiety-like behaviour and increased vulnerability to stressors later in life. Social exclusion and a lack of social support are increasingly being recognized as risk factors for anxiety disorders in humans, and social deprivation models are becoming more and more common in animal studies. Since the first few weeks after weaning are so important for the social, cognitive, and emotional development of mice, social isolation is frequently used during this time.

When an animal is experiencing chronic mild stress, they are repeatedly exposed to mild stressors like loud noises, bright lights, and little bedding or nesting material for days or weeks at a time. Rodents exhibit anxious and depressive-like behaviours as a result of repeated restraint stress, another physical stressor. Physical encounters between an intruder and an aggressive resident animal that lead to the defeat of the intruder and the emergence of anxiety- and depressive-like behaviour are a model of chronic social defeat in psychosocial stress. Mice exhibit an early rise in social avoidance of an unknown target following social defeat stress. Not all mice exhibit avoidance behaviour; instead, they behave more like non-stressed controls, simulating individual variances in the susceptibility to stress in people. These models can be used to investigate the neurological factors underlying resilience and susceptibility to stress.

Better animal models are needed for the creation of new anti-anxiety medications. Developing etiologically sound animal models to comprehend underlying neurobiological mechanisms and measure therapy efficacy can be accomplished by identifying hereditary risk factors. Once a genetic risk mutation is identified, it is possible to research the genes it affects, the proteins it encodes, and the molecular, cellular, and circuit activities of the proteins. Alternatively, it is feasible to identify the gene regulatory networks

implicated if the variation affects a noncoding RNA molecule. Schizophrenia contains examples of mouse models created using a similar methodology.

A GWAS in 2014 discovered 108 distinct genetic loci that contribute to schizophrenia risk. The C4 gene area on chromosome 6 contains the strongest link, and it has been demonstrated that individuals with schizophrenia exhibit higher levels of C4A expression than do controls. In comparison to wild-type mice, transgenic mice overexpressing human C4A exhibit impaired social behaviour, working memory, and anxiety-like behaviour as well as reduced cortical synapse density and an increase in microglial-mediated synaptic pruning. These findings point to an overactive complement system as a pathogenetic mechanism of schizophrenia and present opportunities for the creation of novel therapeutic approaches.

Recently, using exome sequencing of a significant number of patients and controls, ultra-rare protein-truncating mutations in schizophrenia were discovered. The carriers of the found rare variants had a significant chance of developing schizophrenia, despite the fact that the odds ratios of the individual common variants discovered through a GWAS are quite modest. The risk's severity was comparable to rare Copy Number Variants (CNVs) that have been found in schizophrenic patients. There aren't any exome-sequencing studies on anxiety disorders that we are aware of. One case of anxiety disorder and none of the controls in a research looking at individuals with diverse psychiatric diseases had a CNV within SLC6A3. Other research still need to confirm this result. The construction of etiologically relevant animal models will benefit greatly by knowing whether the genetic landscape of anxiety disorders includes high risk-conferring uncommon variants and CNVs. Larger investigations in anxiety disorders are required to answer this question.

Conclusion

Despite the significant incidence and burden of anxiety disorders, we still know very little about their origin. Although small sample sizes and consequently low statistical power to identify significant associations have historically hampered progress in anxiety disorders, recent larger-scale biobank or register-based studies have led to the identification of genetic variants predisposing to anxiety disorders. Genetic research has also revealed significant pathogenetic mechanisms in other psychiatric disorders. The significant genetic association between anxiety disorders and other mental and physical problems reflects the substantial comorbidity of anxiety disorders with these illnesses as well as with one another. There is a possibility to identify subgroups of people based on disease trajectories, comorbidities, and genomic information in large register-based studies having information on all medical diagnoses. Opportunities are presented by the identification of common and group-specific genetic variables related with anxiety.

The neurological underpinnings behind anxiety disorders must be understood through investigations in both model organisms and people. Although there is still only a small amount of overlap between mouse model gene expression studies and human GWASs, both methods have been successful in identifying the gene encoding estrogen receptor 1. 'omics experiments involving rodents and people are still uncommon, as are translational studies in which the advantages of mouse models are exploited for unbiased 'omics screens to formulate hypotheses for testing in human anxiety disorders. The translational validity of the current rat models needs to be improved by creating etiologically sound models based, for instance, on genetic data in order to achieve better concordance between rodent and human investigations.

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