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The interplay of genotype and environment in the development of fear and anxiety

Introduction

Fear, the emotion elicited by a realistic threatening event or situation, for example by a competitor, and anxiety, a diffuse feeling of unease, a state of apprehension are phylogenetically old traits that are present in all mammals, if not already in vertebrates. From our human point of view, we usually see fear and anxiety as negative. However, it is easily understood why these traits evolved and why they have been positively selected for during evolution: individuals that were fearful and anxious in a dangerous environment had a higher chance of survival and thus could pass on their genes more efficiently to the next generation than conspecifics that lacked these emotions.

In humans and animals, members of every population differ significantly in terms of their basal levels of anxiety, which modulate the intensity of fear reactions and anxiety. There are individuals with low, moderate or high levels of anxiety. In extreme cases, particularly in humans, these emotions can be highly pronounced even in the absence of an objective threat, such that psychological strain becomes high and an anxiety disorder can be diagnosed. Individual levels of anxiety develop during the life history of an individual and are influenced by both genetic and environmental factors [21].

With regard to the role of the environment, it seems that an organism is especially susceptible to external influences during early phases of life, i.e., during the prenatal and early postnatal phase when the neuronal circuits of the brain are still largely plastic [12]. Studies in humans and animals show significantly increased levels of anxiety in offspring of mothers who experienced stress during pregnancy [18, 37, 46, 57]. In addition, negative experiences, such as isolation, neglect or abuse during early childhood also correlate significantly with increased fear and anxiety, as well as with anxiety disorders during adulthood [23, 24]. It is for this reason that most studies have hitherto concentrated on early phases of development. It seems, however, that anxiety circuits in the central nervous system (CNS), including the prefrontal cortex and parts of the limbic system, e.g., the hippocampus and the amygdala (see Wotjak and Pape, this edition), retain their plasticity during adulthood. Accordingly, the levels of anxiety in humans and animals can still be modified in later phases of life, as is also shown by the efficiency of psychotropic drugs and psychotherapies [21].

Over the last few years, a set of so-called candidate genes has been described regarding the genetic basis of anxiety and the development of anxiety disorders (see Domschke, this edition). For example, different variants of the serotonin transporter gene, the tryptophan hydroxylase-2 gene, the monoamine oxidase A gene, and the catechol-O-methyltransferase gene exist. These code for proteins with important functions in the regulation of neurotransmitter levels in the brain. Human carriers of certain variants of these genes suffer from an increased risk of developing anxiety disorders [10, 15]. Similarly, targeted modifications of these genes in rodents lead to predictable changes in anxiety-like behavior [34, 38].

Especially for the serotonin transporter gene, the complex interplay of genetic predisposition and environmental influences during different phases of life in the modulation of the anxious phenotype is well understood (see Domschke, this edition). In the following, the serotonin transporter genotype will serve as an example to show how anxiety and fear are shaped by gene-by-environment interactions during the life history of an individual. In addition, we will discuss how, in principle, adaptive levels of anxiety can develop into anxiety disorders. Finally, we will highlight open research questions concerning the interrelation of life history and anxious phenotype. For a more detailed review on the interaction of genotype and environment in the development of fear and anxiety see, for example, reviews [7, 21, 27, 52]. An introduction to the neuropsychological aspects (Glotzbach-Schoon et al.) and genetic bases of anxiety (Domschke), as well as an overview of the neuronal circuits of fear memory (Wotjak and Pape) can be found in this edition.

Serotonin transporter genotype and anxious phenotype

Serotonin acts as a neurotransmitter in the CNS and is critically involved in the control of behavior and emotions. A key element in the serotonergic neurotransmis-

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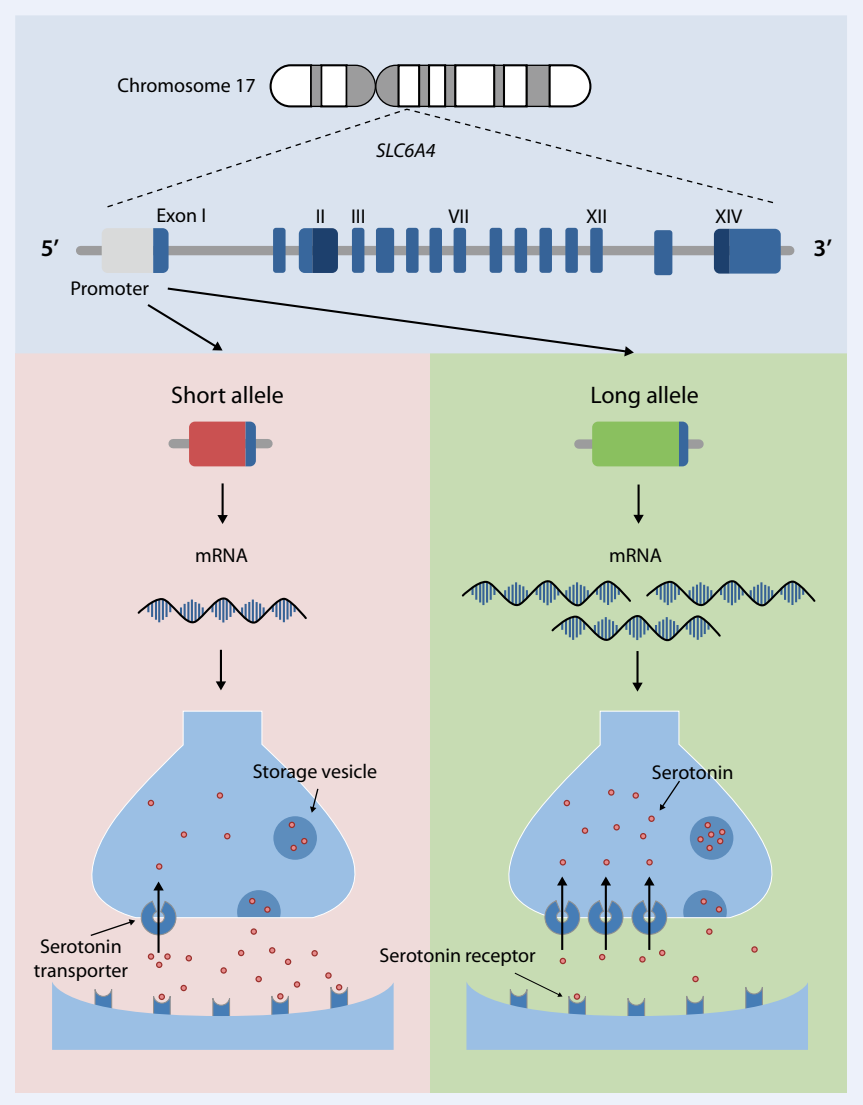

Fig. 1 ▲ Serotonin transporter (SERT) polymorphism. In humans, the SERT gene (SLC6A4) is located on chromosome 17. The short variant (*red*) of the repeat polymorphism at the promotor region is associated with reduced synthesis of SERT mRNA and protein, compared to the long allele (*green*). This in turn results in an increased concentration of serotonin in the synaptic cleft. Carriers of one or two short alleles show increased basal levels of anxiety and are more likely to develop an emotional disorder such as depression after adverse life experiences

sion is the serotonin transporter (SERT, often also abbreviated as 5-HTT). This protein stops serotonergic neurotransmission by transporting serotonin that was released into the synaptic cleft back into the presynapse. Hereafter, serotonin is recycled and becomes available for repeated release ([7]; see ◘ **Fig. 1**).

In 1996, Klaus-Peter Lesch and colleagues described a repeat-length polymorphism in the human SERT gene (SLC6A4) promotor region [39]: A person can be a carrier of either two short alleles, two long alleles or both a short and a long allele. The short allele results in reduced expression of SERT. Compared to carriers of two long alleles, carriers of one or two short alleles show higher basal levels of anxiety. Interestingly, a corresponding gene polymorphism was also found in populations of rhesus macaques and, similarly, carriers of the short allele displayed higher levels of anxiety-related behavior than animals with long alleles [5, 14].

In 1998, a so-called SERT knockout mouse was developed by genetic engineering. In this mouse model, both alleles of the SERT gene are inactivated [4], resulting in the absence of the SERT protein in these animals. When these homozygous knockout mice are bred with conspecifics with two intact alleles of the SERT gene (so-called wild-type mice), heterozygous SERT knockout mice that carry one intact and one inactive allele result. Biochemical analysis showed that SERT biosynthesis was reduced by 50% in heterozygous SERT knockout mice and completely absent in homozygous SERT knockout mice. The extensive behavioral characterization of mice of all three genotypes provided distinct differences, especially regarding anxiety-like behavior [29, 31, 33, 35]: Whereas homozygous SERT knockout mice showed the highest and wild-type mice the lowest levels of anxiety-like behavior, heterozygous animals exhibited predominantly intermediate levels. Thus, an excellent mouse model was provided to study the effects of reduced or absent expression of SERT on behavior and to analyze the underlying neural and molecular mechanisms.

The interplay of SERT genotype and environment during early phases of life in the development of the anxious phenotype

In 2003, Avshalom Caspi and colleagues presented evidence for an interplay of SERT genotype and stressful life events in the emergence of depressive disorders [10]. In their later life, carriers of at least one short SERT allele showed more depressive symptoms and were diagnosed as depressive or suicidal more often that control subjects with two long alleles. This effect was most pronounced in subjects that experienced serious stressful situations in earlier years, for example at their workplace, in their relationships or concerning their financial situation (see also [15]). This epidemiological study contributed considerably to a highly relevant hypothesis: The manner in which individuals react to a stressor in their environment depends significantly on their genotype. This means that emotional states and psychiatric disorders can result from gene-by-environment interactions.

To date, a whole range of comparative studies, especially in humans, rhesus macaques and SERT knockout mice, provide convincing evidence that the interplay of

SERT genotype and negative experiences during early phases of life significantly affect anxiety-like behavior in adulthood [1, 8, 9, 10, 25, 54]. For example, in a study by Heiming and colleagues, SERT knockout mice either experienced a dangerous or a safe environment during pregnancy and lactation [25]. Since behavioral-ecological studies showed that infanticide by an unfamiliar male poses a major risk factor for newborn mice, the dangerous environment was simulated by regularly introducing unfamiliar male bedding into the home cage of the mother. A safe environment was created by adding neutral bedding. The offspring of dams that lived in a dangerous environment during pregnancy and lactation showed more pronounced anxiety-like behavior in adulthood than offspring reared in a safe environment. Interestingly, this effect was modulated significantly by the SERT genotype of the offspring: Mice lacking the SERT showed considerably higher levels of anxiety-like behavior compared to mice with one or two intact SERT gene alleles. However, when the mothers lived in a safe environment, the offspring with different genotypes did not differ much from each other [25].

How can the adverse environment that the mother experiences during pregnancy and lactation influence the behavior of her offspring? During pregnancy, environmental stressors act on the maternal organism and can lead to a change in the release of hormones, especially of glucocorticoids (e.g., cortisol), catecholamines (e.g., adrenaline), and sex steroids (e.g., testosterone). These hormones pass—at least partially—the placenta, enter the blood circulation of the fetus and influence the developing CNS ([52]; see **Fig. 2**). For example, the introduction of unfamiliar male bedding into the home cage of a pregnant mouse leads to an increase in stress hormones (glucocorticoids) [26]. Other studies show that the exposure of the fetus to high levels of stress hormones permanently influences the expression of glucocorticoid receptors in the amygdala, which induces a distinct anxious phenotype in rodents [58].

While maternal hormones appear to mediate the influence of adverse conditions on offspring with an anxious phenotype during pregnancy, the presence and behavior of social companions are of major importance during lactation. This applies mainly to the mother but, depending on the species studied, also to the father, siblings, or the entire social group [28]. Numerous studies have indicated an interaction between the amount and intensity of maternal care on the one hand and the behavioral profile, anxiety-like behavior, and stress reactivity of the offspring on the other [8, 13, 45]. Maternal care itself in turn depends on the environment in which the individuals live [51]. When female mice raise their offspring in a dangerous environment they show a drastic reduction in maternal care in comparison to mothers that live in a safe environment with their offspring [26].

In summary, a causal relationship exists between the environment in which mothers live during pregnancy and lactation and the anxious profile of their offspring in adulthood. When stressors act upon the maternal organism, increased levels of anxiety-like behavior can be found in the offspring. Such an increase should, however, not be seen as a behavioral impairment, or even a disorder. Alternatively, and in line with recent evolutionary theory, it could represent a so-called adaptive maternal effect. This means: Via hormonal mechanisms and behavior, mothers can shape the phenotype of their offspring in such a way that they are adapted to the current (or predicted) environmental conditions (see **Fig. 2**). In a dangerous environment it could, for example, be beneficial for survival to be less bold and a bit more anxious [51, 52].

If the increased anxiety-like behavior of the offspring that is caused by an adverse environment during early phases of development indeed represents a phylogenetically old adaptation, then the question arises: Under which conditions can this in principle adaptive process develop into a behavioral disorder in certain individuals? One answer based on numerous studies in humans, rhesus macaques and SERT knockout mice and rats is: When adverse conditions during early phases of life act upon individuals with a genotype that is related to a decreased expression of SERT ([40]; see **Fig. 2**).

The interplay of SERT genotype and social experience during adulthood in the development of the anxious phenotype

The majority of studies to date on the influence of environment on the anxious phenotype have concentrated on early phases of development. However, for quite some time, studies in rodents show that experiences during adulthood can also have an impact on levels of anxiety-like behavior. On the one hand, living in a spatially enriched environment with a lot of hiding, climbing and exploration oppor-

Abstract

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The interplay of genotype and environment in the development of fear and anxiety

Abstract

Individual differences in fear, anxiety, and the etiology of anxiety disorders develop during ontogeny. They are due to both genetic and environmental factors. With regard to the role of the environment, the organism is most susceptible to external influences during early development. Accordingly, stressors that impinge on the maternal organism during pregnancy evoke high levels of anxiety in the offspring later in life, as does an adverse early postnatal environment. However, anxiety-related circuits in the central nervous system retain their plasticity in adulthood, i.e., levels of anxiety can also be modified by experience across the entire successive lifespan. Notably, the effects of external stressors on the individual's level of anxiety are modulated by genotype. Such genotype-by-environment interactions are particularly well studied in relation to genetic variants that modulate the function of the serotonin transporter. Thus, this review focuses on this candidate gene to elucidate the interplay of genotype and environment in the development of fear and anxiety.

Keywords

Fear · Anxiety · Anxiety disorder · Serotonin transporter genotype · Gene-by-environment interaction

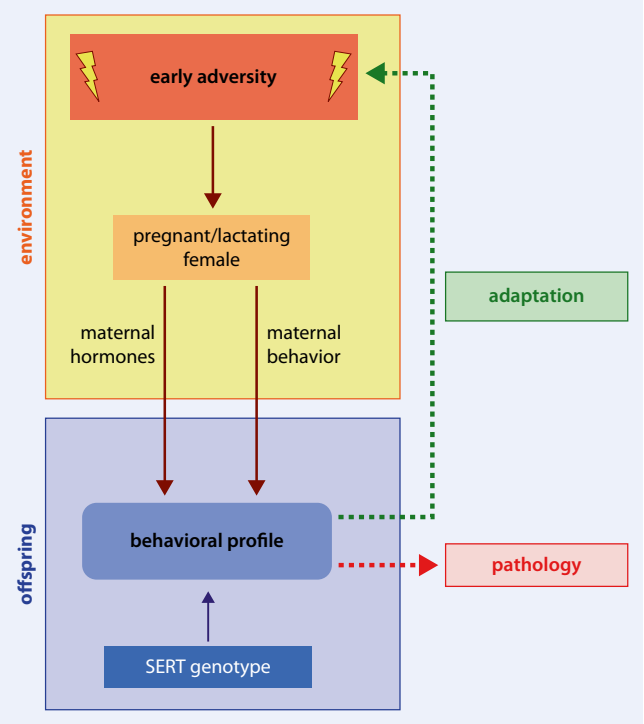

Fig. 2 ▲ The effects of SERT genotype and an adverse environment during early phases of life on the behavioral profile of the offspring. An adverse environment during pregnancy and lactation leads to alterations of maternal hormones and behavior. Thereby, brain development and thus also the later behavior of the offspring is modulated. In principle, this is a way to adapt the progeny to the adverse conditions the mother lives in. However, this process is also modulated by the SERT genotype of the offspring. In cases where the SERT genotype is associated with reduced production of the SERT protein, the interplay of genotype and adverse conditions can markedly increase the probability for the development of anxiety disorders. (Modified from [52] with permission)

tunities leads to a reduction of this behavioral trait [50]. On the other hand, the experience of a defeat in an agonistic interaction is associated with an increase in anxiety-like characteristics [6].

Based on these findings, it was recently tested in SERT knockout mice whether the effects of social experiences on anxiety-like behavior can be modulated by the SERT genotype also in adulthood [33]. In this study, adult male mice of all three SERT genotypes—with two intact alleles, with one or with no intact allele—made the experience of either being the winner or the loser in short-term interactions with conspecifics. Surprisingly, both experiences—being a winner and being a loser—led to an increase in anxiety-like behavior. However, while winners of all three genotypes did not differ concerning this trait, the losers showed a clear differentiation. Losers with two inactive alleles were significantly more anxious than losers of the other two genotypes. Thus, similar to the early phases of development, the way individuals react to stressors in adulthood is significantly influenced by their SERT genotype.

This finding could be confirmed in Pavlovian fear conditioning experiments ([47, 57]; Wotjak und Pape, this edition). Even before the mice encountered a 'loser' experience, the three genotypes already differed significantly in aspects of their fear extinction (more precisely, in the 'retrieval' of the extinction memory; see Wotjak and Pape, this edition); that is to say, in contrast to mice with one or two intact alleles, individuals with two inactive SERT alleles showed a considerable impairment to learning that a place in which they experienced a stressor earlier is now safe. The previous loser experience led to a deterioration of extinction learning in all three genotypes. But again, the magnitude of this effect was dependent on the SERT genotype: Individuals with two intact alleles learned faster and more sustainably that a previously dangerous place was now safe than conspecifics with two inactive SERT alleles. Mice with one intact and one inactive SERT allele showed intermediate levels of extinction learning [47].

Underlying mechanisms

The question arises as to why individuals that were exposed to stressful environmental influences during early phases of development and/or in adulthood show a higher risk of developing anxiety disorders when they have, depending on their genotype, less SERT proteins. At present, three factors are primarily discussed [27]:

Firstly, a reduced amount of SERT protein in humans and animals is related to higher sensitivity towards environmental stressors [36, 43, 55]. This is reflected, for example, in stronger hormonal stress reactions towards the same stimulus [20] or in stronger neuronal activity of the amygdala in response to fear-eliciting stimuli [22].

Secondly, a reduced amount of SERT proteins has a significant effect on fear memory. The impaired extinction of negative events could easily lead to the development of long-lasting fear associations. Accordingly, life-long reduced SERT expression is related to altered neuronal morphology (e.g., density of dendrites and dendritic spines) in key regions of the cortico-limbic circuitry mediating emotion processing (e.g., prefrontal cortex, specific nuclei of the amygdala) ([48, 59]; Wotjak and Pape, this edition). Furthermore, the extinction learning of an individual, which developed on the basis of the SERT genotype and the negative experiences made during development is directly reflected in the synchronization of oscillating brain waves between the amygdala and the prefrontal cortex [47]. (Strictly speaking, these brain waves are theta waves, which represent a neuronal communication element between different brain structures. A higher degree of synchronization correlates with impaired extinction learning.)

Lastly, there is increasing evidence that reduced SERT expression leads to an impaired ability to actively cope with stressors [30, 41, 42]. This deficit can cause an individual to passively endure a stressful situation instead of escaping, ultimately

leading to longer exposure to adversity. In summary, the combined effect of the three factors could explain why individuals with reduced or absent SERT expression suffer a higher risk of developing anxiety disorders under adverse conditions [27].

Life history and anxious phenotype: current research questions

It was traditionally assumed that negative experiences in particular during early phases of development increase the risk of developing anxiety disorders in adulthood. Over the years, this perspective has been expanded and environmental influences in later phases of life were also taken into consideration. The 'double-hit hypothesis' postulates that the combined effect of early ('*first hit*') and a later negative life event ('*second hit*'), for example during adolescence, increases the susceptibility for psychiatric disorders [3, 56]. The 'allostatic-load hypothesis' goes a step further and considers the accumulation of negative events across the whole life history as the substantial risk factor for the development of pathologies [44]. The common underlying assumption of all these hypotheses is that the risk of developing a psychopathology increases the more negative life events occur.

Recently, however, an alternative view has been proposed: The susceptibility for pathologies should be highest when a discrepancy exists between the early environment an individual was 'imprinted' to or 'programmed' for and the one it encounters later in life [2, 19]. According to this 'match-mismatch hypothesis', the risk of developing a psychiatric disorder depends on the degree of consistency ('match') or discrepancy ('mismatch') between the early and late environment [11, 49, 53]. A particularly high level of anxiety or an increased probability for anxiety disorders could for example result when individuals experience very positive circumstances during early phases of development, but find themselves under extreme adverse conditions in adulthood, i.e., when they experience a strong 'mismatch'. Thus, there are different hypotheses concerning the relationship between life history and the development of the anxious phenotype. Conclusive experiments are needed to decide between these alternative ideas.

In addition, an increasing number of scientists support the view that neither the accumulation of negative experiences over the life history, nor the discrepancy between the early and late environment are the critical factors, but instead an individual's resilience [16, 17, 32]. Resilience denotes the ability to maintain mental balance or regain it after adverse life events. Accordingly, a pronounced resilience is associated with a decreased probability to develop anxiety disorders. On the other hand, weak resilience is associated with an increased probability. However, to what extent an individual's resilience is determined by genotype, experiences made during life history or by an interaction between both factors is not yet known.

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N. Sachser Dr. Norbert Sachser is professor of zoology and head of the Department for Behavioral Biology at the University of Münster. He studied biology, chemistry, and sociology at the University of Bielefeld and earned his doctorate at the Department of Behavioral Biology. Subsequently, he worked as a post-doc and assistant professor at the Department of Animal Physiology at the University of Bayreuth, where he habilitated in 1992. In 1993, he accepted a call for a professorship in zoology/behavioral biology at the University of Münster. From 1999–2002 Norbert Sachser was president of the Ethological Society. Since 2008 he is a member of the research council of the University of Münster and in 2012 he became an honorary member of the Ethological Society. His research concentrates on the evolution and development of social behavior in mammals, on the interaction of genes and environment in the regulation of emotion, cognition and social behavior, as well as on the topic stress and welfare.

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K.-P. Lesch Since 2001, Dr. Klaus-Peter Lesch has been professor for psychiatry and psychotherapy and head of the clinical research group 'Attention Deficit/Hyperactivity Disorder', as well as of the Laboratory of Translational Neuroscience in Würzburg. He studied medicine in Würzburg, Cape Town and Bern and finished his PhD thesis on opioid peptides in neurological disorders in 1985. During his clinical training at the University of Würzburg as a psychiatrist he earned a research fellowship at the National Institute of Mental Health, NIH, Bethesda, USA (1990–1992). After his habilitation, he received a professorship for clinical neurosciences of the Hermann and Lilly Schilling Foundation in 1995. He has held the chair for Molecular Psychiatry at the Department of Psychiatry, Phychosomatics and Psychotherapy, University of Würzburg since 2010. His research concentrates on the molecular neurobiology of cognitive control and self-regulation, epigenetics of brain development and neuronal plasticity, genetic imaging, as well as on animal models for emotion, cognition, learning and memory.

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Compliance with ethical guidelines

Conflict of interest. N. Sachser and K.-P. Lesch state that there are no conflicts of interest.

All national guidelines on the care and use of laboratory animals have been followed and the necessary approval was obtained from the relevant authorities.

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