Anxiety and Anxiolytic Drugs

Contributors

Editors
Florian Holsboer and Andreas Ströhle

Springer
Research on anxiety and anxiety disorders is undergoing a paradigmatic transformation as disparate areas of psychiatric nosology, epidemiology, pharmacology and cognitive neuroscience converge towards an integrated understanding of the pathophysiology of these disorders.

In the last century, the basic treatment indicated for patients with anxiety disorders was to employ psychotherapy to facilitate changes in behaviour and develop ways of coping with stressful life events. A wide spectrum of somatic treatments from catharsis and emetics to opium and strengthening tonics, from atropine and digitalis to potassium bromide and chloral hydrate, from benzodiazepines to antidepressants came to be used as well. Systematic studies of antidepressants revealed that these drugs have antipanic properties independent of their antidepressive effects. This finding stirred a new classification of anxiety disorders, which is reflected in the current classification systems, such as the international classification of diseases (ICD) published by the World Health Organization (WHO). Anxiety has evolved as a defensive mechanism disposing the individual to recognize changes. As a warning signal, anxiety has life-saving qualities, and a species without appropriate anxiety would not survive. While normal anxiety is beneficial to co-ordinate response patterns in a threatening situation, pathological anxiety has many facets that can burden an individual substantially and warrants therapeutic intervention. The new classification of anxiety disorders encouraged basic and clinical research on the pathophysiology and treatment of pathological anxiety. Using newly developed methods and techniques, we are now beginning to understand the molecular mechanisms of anxiety, anxiety disorders and their treatment. In parallel, new drug targets have been generated and the first clinical studies with new compounds have been started.

In the first chapter, C.T. Wojcik describes the results of studies on the cellular basis of learning and memory together with a description of the methods that led to these discoveries. Aversively motivated learning and memory enable us to recognize and to appropriately respond to potentially dangerous situations. These abilities, which ensured the survival of humans and animals throughout evolution, bear the risk of pathological alteration that might be directly linked to distinct human anxiety disorders, such as phobias or post-traumatic stress disorder.
A detailed overview of animal models for anxiety-related behaviour is presented by F. Ohl. These models are indispensable tools to unravel the neurobiological mechanisms underlying normal anxiety as well as its pathological variations. The main concepts in generating animals models for anxiety, i.e. selective breeding, experience-related models, genetically engineered mice, and phenotype-driven approaches, are described and the potential opportunities and caveats of current models as well as the emerging possibilities offered by gene technology are discussed.

Although current views emphasize the joint influence of genes and environmental sources during early brain development, the physiological complexities of multiple gene and environment interactions as well as cross-talk between minor gene variants in the developmental neurobiology of fear and anxiety remain poorly understood. Focusing on the hypothalamic–pituitary–adrenocortical system, substance P and the serotonergic system, three chapters describe the impact of mutagenesis and knockout techniques on our current understanding of anxiety-related behaviour. K.P. Lesch reviews findings showing that variations in genes coding for proteins that control serotonin (5-HT) system development and plasticity establish 5-HT neuron identity and modulate 5-HT receptor-mediated signal transduction, and cellular pathways have been implicated in the genetics of anxiety and related disorders. In particular, pertinent approaches regarding phenotypic changes in mice bearing inactivating mutations of 5-HT receptors, 5-HT transporter, monoamine oxidase A and other genes related to 5-HT signalling are discussed. M.E. Keck and M.B. Müller describe how neuroendocrine and behavioural phenotypes of anxiety disorders are at least in part mediated via modulation of corticotropin-releasing-hormone (CRH) and vasopressin (AVP) neurocircuitry and that normalization of an altered neurotransmission after treatment may lead to restoration of disease-related alterations. A. Bilkei-Gorzo and A. Zimmer show that anxiety and depression-related phenotypes are profoundly affected by the tachykinin system.

The genetic epidemiology of anxiety disorders is reviewed by K.R. Merikangas and N.C.P. Low. They conclude that better comprehension of the phenomenology of the specific anxiety disorders and their overlap should guide the development of the next phase of diagnostic categories. In light of the rapidly accumulating information on genetic variations associated with anxiety disorders, we can expect that based on these genetic data new drugs will emerge not only for better treatment of the clinical conditions but also for preventing their onset.

The interactions between CRH and 5-HT and the implications for the aetiology and treatment of anxiety disorders are reviewed by A.C.E. Linthorst. A. Neumeister, R.J. Daher and D.S. Charney focus on the central role of noradrenergic neurotransmission for fear, anxiety and consequently the development and treatment of anxiety disorders. H. Möhler, K. Vogt, F. Crestani and U. Rudolph review the pathophysiology and pharmacology of the γ-
aminobutyric acid (GABA) receptors. The diversity of the GABA<sub>A</sub> receptors as described in the past decade is the basis for novel subtype selective benzodiazepine site ligands with hypnotic, anxiolytic, anticonvulsive or memory-enhancing activity.

The physiology and pathology of excitatory amino acid neurotransmission is described by C.G. Parsons, W. Danysz and W. Zieglgänsberger. At present, there seems to be a consensus that competitive AMPA and N-methyl-d-aspartate (NMDA) receptor antagonists have a low chance of finding therapeutic applications. Antagonists showing moderate affinity and satisfactory selectivity for certain NMDA receptor subtypes seem to have a more favourable profile.

C.H. and R.S. Duman focus on signal transduction and neural plasticity in the neurobiology and therapy of anxiety. The challenge of identifying intracellular signalling pathways and related molecular and structural changes that are critical to the aetiology and treatment of anxiety disorders will further confirm the importance of mechanisms of neuronal plasticity in functional outcome and improve treatment strategies.

Anxiety modulation by neuropeptides is described by R. Landgraf. Particularly due to their high number and diversity, the dynamics of their central release and the multiple and variable modes of interneuronal communication they are involved in, neuropeptides play a major role in the regulation of anxiety-related behaviour. Despite the immense progress in the field of neuropeptides and anxiety, we are far from mimicking these processes simply by administering synthetic agonists or selectively attenuating the pathology by administration of receptor antagonists. The only exception seems the development of antagonists blocking the effects of CRH. One of the CRH receptor antagonists has been probed in a clinical study with promising results. From the clinical perspective, R. Yehuda describes the neuroendocrine aspects of post-traumatic stress disorder (PTSD). The observations in PTSD are part of a growing body of neuroendocrine data providing evidence of insufficient glucocorticoid signalling in stress-related psychiatric disorders.

The clinical presentation of anxiety disorders according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders is summarized by R. Lieb. In addition, selected aspects (prevalence, correlates, risk factors and comorbidity) of epidemiological knowledge on anxiety disorders are presented.

Pharmacogenetics is a field of research increasing our knowledge on the use of psychotropic drugs in different ethnic patient populations. K.-M. and M.T. Lin's chapter on transcultural issues summarizes current knowledge on the metabolism of anxiolytic agents with emphasis on pharmacogenetics and ethnic variations in drug responses.

Challenge studies in anxiety disorders are highlighted by M.E. Keck and A. Ströhle. The heterogeneity of agents capable of producing panic attacks
in susceptible patients and the inconsistency of autonomic responses during a panic attack has led to the assumption that panic originates in an abnormally sensitive fear network, which includes the prefrontal cortex, insula, thalamus, amygdala and amygdalar projections to the brainstem and hypothalamus. The differences in sensitivity to certain panicogens, therefore, might be fruitful in serving as biological markers of subtypes of panic disorders and should be a major focus of research, as the identification of reliable endophenotypes is currently one of the major rate-limiting steps in psychiatric genetic studies.

The current state on the pharmacotherapy of anxiety disorders is summarized by J.R. Nash and D.J. Nutt. The recent shift in clinical practice towards the use of antidepressants, particularly SSRIs, for the first-line treatment of anxiety disorders is supported by research evidence from randomized controlled trials. It is only in recent years that drugs acting via GABA neurotransmission have been supplanted as first-line treatments, and new drugs in this class with improved tolerability compared to the benzodiazepines are likely to be marketed in the near future.

New developments in the pharmacological treatment of anxiety disorders are summarized by A. Ströhle. Further characterization of pathophysiological processes including evolving techniques of genomics and proteomics will generate new drug targets. Drug development design will generate new pharmacological substances with specific action at specific neurotransmitter and neuropeptide receptors or their reuptake and metabolism. New anxiolytic drugs may target receptor systems which only recently have been linked to anxiety-related behaviour. Combining psychopharmacological and psychotherapeutic interventions is a further field where benefits for the treatment of anxiety disorders could be achieved. Although the road of drug development is arduous, improvements in the pharmacological treatment of anxiety disorders are expected for the near future.

Pharmacogenetic strategies in anxiety disorders are described by E.B. Binder and F. Holsboer. This field holds great promise for the treatment of anxiety disorders, and in the future psychiatrists may be able to base the decision regarding the type and dose of a described drug on more objective parameters than only the diagnostic attributions used so far. This will limit adverse drug reactions and could reduce time to response, resulting in a more individualized pharmacotherapy.

Introducing proteomics, C.W. Turck shows that the comprehensive analysis of the protein complement of the genome of an organism is becoming an increasingly important discipline for the identification of disease targets. The effects of drug treatment and metabolism can now be studied on the protein level in a comprehensive manner.

We thank all the contributing authors for their excellent manuscripts. We thank K. Starke, who has initiated this volume and the Springer-Verlag team, especially S. Dathe, for the smooth co-operation. With this volume of the
Handbook of Experimental Pharmacology, we are happy to present an overview on the current state of basic and clinical research on “Anxiety and Anxiolytic Drugs”.

Munich and Berlin, March 2005

F. Holsboer, A. Ströhle
List of Contents

Learning and Memory ............................................. 1
  C. T. Wotjak

Animal Models of Anxiety ................................. 35
  F. Ohl

Genetic Alterations of the Murine Serotonergic Gene Pathway:
The Neurodevelopmental Basis of Anxiety .............. 71
  K. P. Lesch

Mutagenesis and Knockout Models:
Hypothalamic–Pituitary–Adrenocortical System .......... 113
  M. E. Keck, M. B. Müller

Mutagenesis and Knockout Models: NK1 and Substance P .... 143
  A. Bilkei-Gorzo, A. Zimmer

Genetic Epidemiology of Anxiety Disorders ............. 163
  K. R. Merikangas, N. C. P. Low

Interactions Between Corticotropin-Releasing Hormone and Serotonin:
Implications for the Aetiology and Treatment of Anxiety Disorders . . . 181
  A. C. E. Linthorst

Anxiety Disorders: Noradrenergic Neurotransmission ......... 205
  A. Neumeister, R. J. Daher, D. S. Charney

Pathophysiology and Pharmacology of GABA_A Receptors .......... 225

Excitatory Amino Acid Neurotransmission ..................... 249
  C. G. Parsons, W. Danysz, W. Ziegglänsberger
Neurobiology and Treatment of Anxiety: Signal Transduction and Neural Plasticity ........................................ 305
  C.H. Duman, R.S. Duman

Neuropeptides in Anxiety Modulation .......................... 335
  R. Landgraf

Neuroendocrine Aspects of PTSD ............................... 371
  R. Yehuda

Anxiety Disorders: Clinical Presentation and Epidemiology ......................................................... 405
  R. Lieb

Transcultural Issues ............................................. 433
  M.T. Lin, K.-M. Lin

Challenge Studies in Anxiety Disorders ....................... 449
  M.E. Keck, A. Ströhle

Pharmacotherapy of Anxiety ................................... 469
  J.R. Nash, D.J. Nutt

New Pharmacological Treatment Approaches for Anxiety Disorders ................................................. 503
  A. Ströhle

Pharmacogenomics ................................................. 527
  E.B. Binder, F. Holsboer

Pharmacoproteomics .............................................. 547
  C.W. Turck

Subject Index ...................................................... 561
List of Contributors
(Addresses stated at the beginning of respective chapters)

Bilkei-Gorzo, A. 143
Binder, E.B. 527
Charney, D.S. 205
Crestani, F. 225
Daher, R.J. 205
Danysz, W. 249
Duman, C.H. 305
Duman, R.S. 305
Fritschy, J.-M. 225
Holsboer, F. 527
Keck, M.E. 113, 449
Landgraf, R. 335
Lesch, K.P. 71
Lieb, R. 405
Lin, K.-M. 433
Lin, M.T. 433
Linthorst, A.C.E. 181
Low, N.C.P. 163
Merikangas, K.R. 163
Möller, H. 225
Müller, M.B. 113
Nash, J.R. 469
Neumeister, A. 205
Nutt, D.J. 469
Ohl, F. 35
Parsons, C.G. 249
Rudolph, U. 225
Ströhle, A. 449, 503
Turck, C.W. 547
Vogt, K. 225
Wotjak, C.T. 1
Yehuda, R. 371
Zieglgänsberger, W. 249
Zimmer, A. 143