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Preface

Anxiety disorders as delineated in DSM-IV belong to the most prevalent psychiatric diseases, and, although anxiolytic drugs are available for several decades, pharmacological treatment of the various anxiety disorders is far from optimal. Since the sixties of the last century, one class of compounds, the benzodiazepines, is the first choice of treatment. Benzodiazepines, acting via the $GABA_A$-benzodiazepine receptor complex, are powerful anxiolytic drugs, but also may lead upon long-term use to dependence problems, which reduces their therapeutic potential. Hence, the continuous search for new anxiolytic agents as powerful as the benzodiazepines not leading to dependence and thus preferably acting through a different kind of mechanism of action. During the nineties of last century, 5-HT_{1A} receptor agonists promised to fulfil such a new role. In various animal models of anxiety, 5-HT_{1A} receptor agonists appeared potent and selective anxiolytic drugs without dependence potential. However, clinical development of such agents has, up to now, been rather disappointing. Apart from buspirone, initially not developed as an anxiolytic, no 5-HT_{1A} receptor agonist has reached the anxiety market.

The brain mechanisms involved in anxiety and fear are complex, possibly in addition to the GABA-benzodiazepine and serotonergic systems, consisting of many neuronal mechanisms. Disturbances in parts of such a complex neuronal substrate may lead to pathological anxiety. Understanding all the mechanisms involved and their mutual relationship enables also research opportunities for new therapeutic approaches. The genomic revolution and our increasing knowledge of gene function facilitates the finding of new targets involved in anxiety. However, to study a function of a gene or the gene product related to complex behaviours as anxiety is, to say at the least, not an easy job and needs animal models because such studies cannot be performed in humans.

Therefore, animal procedures and tests, modelling various aspects of fear and anxiety, are still and increasingly needed. Although human brain mechanisms involved in fear and anxiety are undoubtedly more complex than those in lower mammals, the basic mechanisms are more or less similar. This facilitates the use of animal models of anxiety and fear for human disease.

In the present issue, several research groups give up-to-date overviews of developments in the pharmacology of anxiety, anxiety models and procedures. Although new tests and procedures are continuously developed, 'classical' tests are still of prime importance. Several excellent reviews by the leaders in the field are presented in this issue, including the open field (Prut and Belzung), social interaction (File and Peth), light–dark box (Bourin and Hascoët) and Vogel conflict procedure (Millan and Brocco). Reviews of more recently developed tests and procedures include the mouse defence test battery (Blanchard et al.), stress-induced hyperthermia (Olivier), stress-induced vocalisations (Sanchez) and defensive burying (De Boer and Koolhaas). In addition, Korte and De Boer describe an interesting new procedure for measuring state anxiety: fear potentiation in the elevated plus maze. New animal models of anxiety are potentially generated in genetically modified mice. Toth describes the 5-HT_{1A} receptor knockout mouse as a genetic model of anxiety, whereas Groenink et al., in addition to the 5-HT_{1A} receptor knockout mouse as a model of anxiety, present evidence that a CRH-overexpressing mouse may represent a model of anxiety and depression.

The last four contributions are particularly dealing with brain and endocrine mechanisms involved in anxiety and stress. Several brain areas are intensively investigated in this realm, including the amygdala and bed nucleus of the stria terminalis (Walker et al.; Toufexis and Davis), the hippocampus (Sander et al.) and the midbrain tectum (Brandao et al.). Carraxo and Van de Kar give an extensive overview of the neuroendocrine aspects of the pharmacology of stress.

All contributions clearly show the developments in several areas of preclinical research on anxiety and fear and their underlying neuronal substrates. Potential new targets and mechanisms and the emerging pharmacology are described in most investigations. It is clear that 'classical' anxiety tests are still and will be very valuable for both screening new drugs and investigating of underlying neural mechanisms. Most of these tests are also extremely helpful to test mutant mice on their 'anxiety' phenotypes.

The present issue gives a good example of a field in movement. Animal (anxiety) research is needed to finally find and develop new and better drugs for severe brain disorders caused by pathology in various brain mechanisms of anxiety and fear.

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