

Preface

This volume attempts to answer the question of how sex influences brain and behaviour. It brings together experts in this field, psychiatrists and other mental health care professionals with preclinical researchers to review the latest work in this area and give a thorough overview of how males and females are different in terms of brain function and behaviour. This is followed by a clinical perspective, applying brain biology to explain why some illnesses are gender specific and how gonadal steroids are involved in the aetiology and symptomatology of psychiatric diseases and may be modulated to provide new therapeutic approaches to mental illnesses. Appreciation and improved understanding of sex differences will certainly lead to improvements in the diagnosis, tailored treatment approaches and hence outcomes for people suffering with mental disorders. This volume will be essential reading for all health care professionals.

Animal behavioural models of efficacy studies in pharmacology generally use male rodents. However, the presentation of sex differences in behaviour underscores the need to include female animals in basic research studies. Similarly, gender differences in the presentation, treatment and outcomes of mental illnesses are often overlooked. The biological basis of sex differences and its application in clinical disorders are important issues that are highlighted by the research discussed in this volume.

The volume is divided into two sections, the first deals with the importance of recognising and studying sex differences in brain function and behaviour in animal models. The second section is dedicated to the consideration of biological sex differences in the presentation of aspects of mental illnesses such as schizophrenia, bipolar disorder, depression and anorexia nervosa. The two sections are inter-related and provide an integrated approach with animal research informing the human application in considering the biological basis of sex differences in psychopharmacology.

The volume starts with an overview by Professor Kay Marshall (a reproductive endocrinologist who has been persuaded to study the brain!) This chapter gives an important introduction into the mechanisms by which gonadal steroids produce their effects which explains how sex differences come about. The second chapter by Berend Olivier and colleagues explores how sex matters for rats. They provide an

overview of rodent sexual behaviour and how to measure this in the laboratory. The chapter has a particular emphasis on the role of serotonin (5-HT) on sexual activity and on sexual dimorphism in response to serotonergic agents. This is clearly of much relevance as drugs such as SSRIs cause sexual dysfunction in the clinic, and it is essential to model this appropriately in the laboratory. In a later clinical chapter on the impact of sex on antidepressants, John Sramek and colleagues detail clinical trial work on this important area. An investigation into sex differences and the effect of gonadal steroids on cognitive function in rodents is provided by Jane Sutcliffe, which is of particular importance as cognitive dysfunction occurs in many psychiatric illnesses such as depression, ADHD and PTSD. In schizophrenia most notably this remains an unmet clinical need, with emphasis on the development of new therapies for cognitive and other symptoms of this illness. Implications for the aetiology of schizophrenia are explored by Veena Kumari in her chapter dealing with human sensorimotor gating. Chapter 9 written by Anita Riecher-Rossler and Jayashri Kulkarni, and Chapter 10 by Angelika Wieck present the very important role that oestrogen plays as a key neuroprotective agent, and its impact on the timing and gender differences in illness presentation. The possibility of using hormone modulation as a new treatment approach is also discussed with respect to psychotic disorders.

Chapter 4 by Dai Mitsushima illustrates that in rodents neurotransmitters show sexual dimorphism, and that neurotransmitter release is affected by gonadectomy with a focus on acetylcholine, again of particular importance for cognition. A subsequent chapter by Justin Anker and Marilyn Carroll deals with the very important topic of drug dependence. They show that females are more sensitive than males to the reinforcing effects, and less sensitive to withdrawal effects, of certain drugs of abuse, making them more vulnerable to drug dependence which can be effectively modelled in animals. The translation from animals to humans here is impressive with female rats showing greater propensity for drug self-administration and relapse in animal models. The authors go on to demonstrate how these effects in females may be mediated by gonadal steroid hormones, in particular oestrogen and progesterone (which is important, as it is not all about oestrogen, as Kay Marshall explains in her opening chapter). They discuss possible mechanisms including oestrogen receptors and their interaction with the mesolimbic dopamine system with the emphasis on addiction to psychostimulants such as cocaine. Applying this framework, a novel proposal for the noted sex differences in anorexia nervosa is described in a chapter by Charlotte Keating, with applicability for new thinking about the aetiology of this severe and female dominant eating disorder.

Stress is of course an important feature of human lives, including our response to drugs of abuse and Christina Dalla and her colleagues cover this topic in some depth in their chapter. Men and women differ in their vulnerability to stress and stress-related psychiatric disorders such as depression. The authors explore sex differences in the response to acute and chronic stress in several animal models in some detail. Male and female rodents differ in their reactivity and adaptation to various stressors, and the authors demonstrate the link between this and differences in the

neuroendocrine system and its interaction with neurotransmitter systems, such as serotonin and dopamine. The final preclinical chapter provides an elegant review by Elizabeth Tunbridge and Paul Harrison into sex differences in the catechol-*O*-methyltransferase (COMT) gene. The gene encodes an enzyme that metabolises catechol compounds including dopamine, and the authors explain how sexual dimorphism in this gene and its interaction with oestrogen impacts on psychiatric disease states. Many of the preclinical studies suggest that sex-specific interventions may be a beneficial approach when treating patients, and understanding the sex differences in developmental disorders experienced early in life is an important area detailed by Bruce Tonge and colleagues in a clinical chapter that also proposes treatment strategies for early psychiatric presentations.

In summary, sex differences are observed in humans and animals in brain function and behaviour and in the response to illness. Men and women have different advantages in many aspects of behaviour particularly cognitive function which is a key component of many psychiatric disorders. Indeed, there is both clinical and preclinical evidence to support a role for the sex steroids in modulating performance in certain cognitive domains. At present, these interactions are complex and the underlying mechanisms have yet to be elucidated. Once these relationships are understood, there is potential for more effective therapeutic exploitation. This volume covers in some depth many illnesses in which sex differences and gonadal steroids are important in terms of aetiology, symptomatology, progression and treatment. It is the first volume to successfully achieve this and will be of considerable importance to workers in all aspects of mental illness.

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