Preface: Focus on the serotonin transporter

The serotonin transporter (SERT) has gained research popularity due to its prominent role in normal and aberrant brain processes. This key brain protein reuptakes serotonin from the synaptic cleft into presynaptic neurons, thereby modulating serotonergic neurotransmission. An entire class of psychotropic drugs, the serotonin reuptake inhibitors (SRIs), is dedicated to the action of this single protein. The fact that selective SRIs are becoming the world's most prescribed psychotropic medication emphasizes the utmost importance of SERT research for clinical psychiatry. The growing body of knowledge on SERT's role in the brain also emphasizes the need for experimental models of SERT function. Collectively, this has stimulated the compilation of this book, the aim of which is to provide a comprehensive update spanning the breadth of SERT research from animal models to their clinical parallels.

Although the exact functional mechanisms of SERT are not yet fully elucidated, it is thought to contain 12 hydrophobic transmembrane domains and to bind Na^+, Cl^-, and serotonin simultaneously. This results in a conformational change in the molecule, forming a barrier against the exterior of the cell, and opens the protein inwardly to the cytoplasmic membrane. The serotonin then disassociates from SERT, and the transporter returns to its original conformation receptive to extracellular serotonin once again. This process is the main mechanism of serotonin modulation in the brain, and the dysregulation of this system can affect brain and behavior markedly.

Genetic studies have also implicated SERT in many psychiatric disorders, including anxiety, major depression, cognitive dysfunctions, bipolar disorder, autism, and obsessive compulsive disorder. As will be discussed further in the book, genetic heterogeneity, phenotypic diversity, and gene $\times$ environment interactions contribute to the

complexity of clinical and animal phenotypes. For example, a strong correlation between the SERT genetic variants and stressful life events indicates that SERT plays a key role in stress responses, which makes modeling these clinically relevant scenarios an important goal in neurobehavioral research.

Since human geneticists have identified the SERT gene, neurogeneticists have identified different polymorphisms, and their behavioral and neurobiological effects. Human SERT gene is 37.8 kb, and is located on chromosome 17q11.2. There are several known polymorphisms of the gene, some of which are exclusive to humans and non-human primates. Two major variants of the SERT promoter region, a "long" (L) allele and a "short" (S) allele, differentially modulate the activity of the SERT promoter region, and therefore the activity of the protein. Numerous studies have consistently confirmed that the S allelic variant results in lower expression and diminished function of SERT, which leads to altered responses to SRI treatment. In contrast, the individuals with the LL genotype were more sensitive to SRI antidepressants in different groups of patients with depression. Thus, the implementation of different genetic methods has begun to shed light on SERT's role in developing treatments for psychiatric disorders.

The chapters collected in this book aim to reflect all these developments. Since altered serotonergic functioning is the neurochemical basis for many psychotropic drugs, the first two chapters summarize molecular synaptic adaptive responses to chronic antidepressant treatment. They will focus on alterations in SERT expression, extracellular and intracellular serotonin levels, and serotonergic innervation. The chapters will next contrast these data with studies on constitutive loss of SERT gene expression, and discuss whether presynaptic neuroadaptive responses are sufficient to explain the paradoxical increases in trait anxiety that accompany constitutive reductions in SERT expression in animals.

Since serotonin plays a critical role in brain development, the next chapter will review the current knowledge of SERT's influence during the developmental stages. This chapter will concentrate on the trophic effects of serotonin cell development in mammals, and cover the role of SERT in brain development, neural plasticity, synaptogenesis, and cell proliferation. The available rodent experimental models will be discussed, as well as the clinical and translational implications for human neurodevelopment.

Continuing with the rodent models, there is also a chapter on behavioral and genomic correlates of targeted genetic manipulations in

the mouse, with a focus on SERT and its role in emotional disorders. The chapter will also address the limitations and advantages of knock-down, knock-out and over-expressing SERT for modeling aspects of anxiety-like and depression-related behaviors in rodents with regards to gender, genetic risk factors, and environmental modifiers.

Along this line, another chapter will more specifically focus on depression-like behaviors in mice in relation to SERT. The chapter will detail many rodent models of depression, and will discuss how they are created through genetic and epigenetic manipulations involving SERT. Special attention will be given to the biological and behavioral manifestations of SERT alterations, particularly examining the role of early-life serotonin in depression. The authors put forth an interesting developmental hypothesis of SERT dysfunction and examined its utility for translational research.

The book's next chapter will review a unique SERT knock-out rat model, covering experimental approaches in a slew of different paradigms, ranging from pharmacological phenotypes to social behaviors. Important comparisons will be made in a separate, but related, contribution on rats with high and low activity of platelet SERT phenotypes. Selective breeding for extreme values of platelet serotonin levels produced two sublines of rats with constitutional hyper and hypo-serotonemia. The chapter will discuss the changes in serotonin homeostasis in relation to the neurochemical, pharmacological, and behavioral phenotypes in these rats.

Addressing a more specific behavioral domain, another chapter will discuss how psychiatric disorders affect the reward system and related phenotypes. This chapter will specifically focus on the role of serotonin and SERT in mouse drug reward paradigms, also discussing the interaction between the serotonergic and dopaminergic systems in this domain. The chapter will also explain how SERT genetic variation may contribute to individual differences in response to drugs of abuse, as part of the polygenic and heterogeneous genetic basis of addiction.

While the previous chapters have focused on the genetic manipulations with SERT in animals, this can also be combined with other mutations: for example, with brain-derived neurotrophic factor (BDNF) gene. Several clinical reports have shown that SERT and BDNF genes may interact and co-determine psychiatric phenotypes. The chapter will cover the relationship of SERT and BDNF, paralleling clinical data and experimental models such as SERT and SERT $\times$ BDNF knock-out mice. Emphasis will be put on SERT and BDNF genetic polymorphisms and their biomolecular effect on protein expression and neuronal survival,

as well as the role of these interactions in the development of neuropsychiatric disorders.

Usefully complementing the rodent models, a chapter on SERT in non-human primates will make another step towards creating cross-species bridges between animal and human data. As clinical data link polymorphisms in the SERT gene with environmental risk factors of depression, anxiety, antisocial and borderline personality disorders, as well as substance abuse, investigations with the rhesus monkey reveal similar gene–environment interactions. This chapter will review the history of primate models in SERT research, and highlight the interaction between early experience and the resulting changes in behavior that are found in conjunction with alterations in serotonergic functioning.

The book's final chapter provides a logical recap that focuses on the application of basic research to the clinical field. The author addresses the topic of innate SERT variability from numerous experimental perspectives, emphasizing how the formerly distinct realms of social and biological sciences are now emerging into a discipline of biosocial science. The chapter will address these new developments in relation to SERT research, and how they utilize techniques such as neuroimaging to ascertain the neurobiological substrates of the genetic variations, thereby providing new perspectives and hypotheses for clarifying the epigenetic mechanisms of brain disorders.

Overall, the collected chapters provide an excellent scholarly summary of neuroscientific investigations of SERT. The book caters to an international audience of basic and clinical neuroscientists who would like to gain knowledge in this rapidly developing field. Similarly, while providing an important update to professional researchers in the disciplines of psychology, biology, and neuroscience, the text will also remain accessible to students studying different topics of biological psychiatry.

Finally, the valuable contribution of the National Alliance for Research on Schizophrenia and Depression (NARSAD) – the world's leading charity dedicated to mental health research – must be acknowledged. NARSAD has an established history of promoting education and research on neuropsychiatric disorders, and the YI Award from this organization has been pivotal to the creation of this book. We take this opportunity to thank NARSAD for their important work, and hope that this multidisciplinary book on SERT will become yet another contribution to advancing translational neuroscience and biological psychiatry.

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