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STOP-null Mouse Model of Schizophrenia *The Genetic Basis of Sleep and Sleep Disorders*

Sleep is a highly conserved behavioral state whose regulation is still unclear. In this thesis I initially briefly introduce the known sleep circuitry and regulation in vertebrates, and why zebrafish is seen as a good model to study sleep-regulation. I describe the existing two-process model of sleep regulation, which posits that the two processes C (circadian) and S (homeostatic) control timing of sleep-wake behavior. I then study the role melatonin plays in the circadian regulation of sleep using zebrafish. Firstly, we find that the absence of melatonin results in a reduction of sleep at night, establishing that endogenous melatonin is required for sleep at night. Secondly, melatonin mutants show a reduction in sleep in animals with no functional behavioral rhythms suggesting that melatonin does not require intact circadian rhythms for its effect on sleep. Thirdly, melatonin mutants do not exhibit any changes in circadian rhythms, suggesting that the circadian clock does not require melatonin for its function. Fourthly, we find that in the absence of melatonin, there is no rhythmic expression of sleep, suggesting that melatonin is the output molecule of process C. Lastly, we describe a connection between adenosine signaling (output molecules of process S), and melatonin. Following this we proceed to study the role adenosine signaling plays in sleep-wake behavior. We find that firstly, adenosine receptor A1 and A2 are involved in sleep-wake behavior in zebrafish, based on agonist/antagonist behavioral results. Secondly, we find that several brain regions such as PACAP cells in the rostral midbrain, GABAergic cells in the forebrain and hindbrain, Dopamine and serotonin

cells in the caudal hypothalamus and sox2 cells lining the hindbrain ventricle are activated in response to the A1 antagonist and VMAT positive cells are activated in response to the A2A agonist, suggesting these areas are involved in adenosine signaling in zebrafish. Thirdly, we find that knocking out the zebrafish adenosine receptors has no effect on sleep architecture. Lastly, we find that while the A1 agonist phenotype requires the zfAdora1a receptor, the antagonist and the A2A agonist behavioral phenotypes are not mediated by the zfAdora1a, zfAdora1b and zfAdora2Aa, zfAdora2Ab receptors respectively. Scientific Essay from the year 2017 in the subject Medicine - Pathology, grade: 1, Egerton University, language: English, abstract: Sleep plays significant health and physical roles in the body because it is linked to the humoral responses. As such, the quality of sleep acts as an indicator of one's optimal health and physical well-being. However, the quality of sleep is usually interfered with by sleep disorders. Sleep disorders interrupt sleep by causing sleep disturbances. The most common sleep disorders are insomnia, sleep apnea, narcolepsy, restless leg syndrome and circadian rhythm problems. Due to the biological mechanisms involved in sleep disorders, this paper will discuss sleep disorders and explain the role of hormones in sleep deprivation. The first comprehensive and up-to-date book to cover genetics and genetic techniques in the study of sleep and sleep disorders. Handbook of Sleep Research, Volume 30, provides a comprehensive review of the current status of the neuroscience of sleep research. It begins with an overview of the neural, hormonal and genetic mechanisms of sleep and wake regulation before outlining the various proposed functions of sleep and the role it plays in plasticity, and in learning and memory. Finally, the book discusses disorders of sleep and waking, covering both lifestyle factors that cause disrupted sleep and psychiatric and neurological conditions that contribute to disorders. Emphasizes a comparative and multidisciplinary approach to the topic of sleep Covers the neurobiology and physiology of sleep stages, mechanisms of waking, and dreaming Discusses in detail the proposed functions of sleep, from health and rest, to memory consolidation and synaptic plasticity Examines the current state of research in mammalian

and non-mammalian species, ranging from primates to invertebrates Thèse. Biologie. Médecine. 2016 There is no doubt that a major problem of present day research workers, especially in the life sciences, is the plethora of publications of all kinds, abstracts, short communications, full papers in journals of varying quality, reviews and proceedings of symposia with, in addition, an unprecedented duplication of publications. Even for experts working in the field, it is almost impossible to keep an up-to-date view of all current research articles. The Western grant and career system encourages scientists to publish as much as possible. The editors and publishers of our new series are convinced that the format of Current Topics in Neuroendocrinology leads a way out of this confusion. Each volume is conceived as a concise up-to-date textbook on one well-defined and currently exciting subject. Different from classic textbooks, however, the speed of publication compares favorably with that of many journals; this ensures an immediacy which is impossible in textbooks. On the other hand, topics to be included in this series are also sufficiently reliable, with enough work being done to treat them from several aspects. Each volume will supply four to six chapters treating such a broad topic as neuroendocrinology from several points of view, for example, anatomic, electrophysiologic, endocrine and behavioral views. Where clinical data are immediately available, they will be included. No other 36iles treating the nervous or endocrine systems provides such a coordinated set of chapters on an interesting topic in each volume. This volume provides the first major overview, by eminent authorities on the subject, of recent developments in the field of endogenous substances and their regulation of sleep processes. The first two sections discuss general aspects of sleep regulation; including an historical overview, the restorative and adaptive functions of sleep, and evolutionary features. The third section contains contributions focussing on circadian rhythms in relation to humoral factors, hormones, neurotransmitters and metabolism. The sleep substances currently receiving most attention --- delta-sleep-inducing-peptide (DSIP), muramyl peptides, interleukin-1, sleep-promoting substance (SPS) and prostaglandin D2 --- are extensively discussed. Substances that may selectively modulate REM sleep are dealt

with in the final section. All aspects of sleep sciences are included in this excellent resource text, with special reference to sleep substances and sleep modulators. The historical development of the theories of sleep are reviewed in conjunction with the technical problems. All candidate substances are overviewed as to their sites of presence, chemical nature, bioassay techniques, physiological and pharmacological effects. On the basis of a standardized methodology developed by the author, sleep-modulatory characteristics of some substances are compared and evaluated in quantitative terms. The sleep regulatory mechanisms, which are composed of complex neurohumoral subsystems, are analyzed from the results of recent neurophysiological and neuroendocrinological experiments. Furthermore, an evolutionary aspect of sleep substances is taken into consideration. Chapters Highlight: Techniques for isolation and evaluation Prostaglandins Paradoxical sleep factors Sleep-promoting substances and nucleosides A review of the current state of the clinical and basic science of the pharmacology of sleep. The information provided ranges from a historical perspective to current concepts of sleep mechanisms, including the interaction between pharmacology and sleep-wake regulation and between chronopharmacology and sleep-wake rhythms. For the first time in one single volume, both the basic mechanisms of sleep, and the basic and clinical aspects of the pharmacology of sleep are dealt with in a thorough, comprehensive and authoritative manner. The chapters, written by the foremost scientific authorities in this field, integrate the latest information on the basic mechanisms of drugs as they relate to their effects on sleep. Spanning over half a century of investigation into Rapid Eye Movement (REM) sleep, this volume provides comprehensive coverage of a broad range of topics in REM sleep biology. World renowned researchers and experts are brought together to discuss past and current research and to set the foundation for future developments. Key topics are covered in six sections from fundamental topics (historical context and general biology) to cutting-edge research on neuronal regulation, neuroanatomy and neurochemistry, functional significance and disturbance in the REM sleep generating mechanism. A reference source for all aspects of REM

sleep research, it also incorporates chapters on neural modelling, findings from non-human species and interactions between brain regions. This is an invaluable resource, essential reading for all involved in sleep research and clinical practice. Clinical practice related to sleep problems and sleep disorders has been expanding rapidly in the last few years, but scientific research is not keeping pace. Sleep apnea, insomnia, and restless legs syndrome are three examples of very common disorders for which we have little biological information. This new book cuts across a variety of medical disciplines such as neurology, pulmonology, pediatrics, internal medicine, psychiatry, psychology, otolaryngology, and nursing, as well as other medical practices with an interest in the management of sleep pathology. This area of research is not limited to very young and old patients—sleep disorders reach across all ages and ethnicities. Sleep Disorders and Sleep Deprivation presents a structured analysis that explores the following: Improving awareness among the general public and health care professionals. Increasing investment in interdisciplinary somnology and sleep medicine research training and mentoring activities. Validating and developing new and existing technologies for diagnosis and treatment. This book will be of interest to those looking to learn more about the enormous public health burden of sleep disorders and sleep deprivation and the strikingly limited capacity of the health care enterprise to identify and treat the majority of individuals suffering from sleep problems. Alterations in sleep are common manifestations of aging that can lead to significant health problems and contribute to behavioural problems associated with age-related neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. Recent advances have revealed key cellular and molecular mechanisms involved in sleep regulation, and this knowledge is helping to advance an understanding of both the normal functions of sleep and the mechanisms responsible for abnormalities in sleep in various neurological conditions and during normal aging. This volume of Advances in Cell Aging and Gerontology brings together chapters by leaders in the fields of sleep research and the neurobiology of aging. The book starts with chapters describing fundamental aspects of the

neurocircuitry involved in sleep, patterns of brain activity during the different stages of sleep and disturbances of sleep during aging. The links between depression, anxiety and insomnia are reviewed in regards to the underlying neurochemical alterations that appear to involve abnormalities in neurotransmitter and neurotrophic factor signalling. The evolutionary basis of sleep is reviewed and the emerging evidence supporting a major role for sleep in learning and memory is described. The bulk of the book focuses on specific sleep disorders associated with aging and age-related neurodegenerative disorders. A comprehensive consideration of this topic is woven through a number of chapters that address both basic research and clinical aspects of sleep abnormalities during aging and in disease. The impact of sleep on the immune system is described. The articles are written in a high level of detail and are comprehensive, thus providing valuable information for a range of scientists and other well-educated people. In particular, the book will be a valuable resource for graduate students, postdoctoral and senior scientists in the fields of sleep, aging, neurodegenerative disorders and learning and memory. In addition, clinicians will find this book valuable as it provides a bridge between basic research and the treatment of the patients with sleep disorders. * Covers the fields of sleep in aging and age-related disease from neurochemistry to the clinic * Includes detailed summary diagrams that depict key concepts * Provides views of the future of research on sleep and aging, and the potential for prevention and treatment of various sleep disorders This issue of Sleep Medicine Clinics, Guest Edited by Teofilo Lee-Chiong MD, will focus on Biology of Sleep, with article topics including: Neurology of Sleep; Normal Sleep and Circadian Rhythms: Neurobiologic Mechanisms Underlying Sleep and Wakefulness; Physiology of Sleep Disordered Breathing; Evaluation of the Patient Who Has Sleep Complaints: A Case-Based Method Using the Sleep Process Matrix; Sleep States, Memory Processing, and Dreams; Neurobiologic Mechanisms in Chronic Insomnia; Sleep Behavior and Sleep Regulation from Infancy through Adolescence: Normative Aspects; Biological Timekeeping; Neurologic Basis of Sleep Breathing Disorders; Genetics of Sleep Timing, Duration, and Homeostasis in Humans; Sleep

in Normal Aging; Modulation of Endocrine Function by Sleep-Wake Homeostasis and Circadian Rhythmicity; Cardiac Activity and Sympathovagal Balance During Sleep; Sleep and Cytokines; Neuropharmacology of Sleep and Wakefulness; Staging Sleep; Respiratory Physiology During Sleep; and Cyclic Alternating Pattern (CAP), Sleep Disordered Breathing, and Automatic Analysis. Analyzing ground-breaking research, this reference highlights the impact of sleep deprivation on the well-being of the individual and society-presenting current theories on the function of sleep, the effects of sleep deprivation on patients with medical and psychiatric conditions, as well as providing interpretative and methodological results in comparative studies of sleep deprivation. As the title suggests, and unlike other existing books on sleep medicine, Neuroendocrine Correlates of Sleep/Wakefulness will be devoted primarily to endocrine regulation of the behavioral state control. It will address a wide spectrum of sleep./wakefulness phenomena (both animals and humans), including pathogenesis, diagnosis, and management. From molecular biology to applied clinical therapy, sleep research has been transformed in the last few years from a research backwater to an important interdisciplinary field. Anyone who regularly reads the literature on sleep, biological rhythms, or neuroendocrinology is aware that one of the subspecialties within sleep medicine, the neuroendocrine correlates of sleep/wakefulness, has in particular experienced a growth rate that is even faster than that of the field as a whole. To a significant extent this has been due to the introduction of new research technologies. The widespread adoption of a range of new methods in sleep research has opened a window into activities at the cellular and molecular level, which previously had been tightly closed. Consequently these activities are being characterized with a degree of precision and sensitivity that is without precedent. This volume invites the reader to explore the new vistas that have been opened onto the neuroendocrine frontier of sleep medicine. The editors have selectively identified a number of key articles having a citation frequency, which is considerably above the norm or which otherwise have contributed importantly to defining the neuroendocrine perspective. This new volume

on Neuroendocrine Correlates of Sleep/Wakefulness is an up-to-date resource of research summaries and reviews written by major contributors to the fields of sleep, biological rhythms and neuroendocrinology. Its coverage is broad and its basic and clinical science reviews are detailed. In this volume, an international team of experts discuss their latest ideas, concepts, methods, and interpretations with supporting examples. This volume is intended for advanced students and specialists in psychobiology, neuroscience, neuroendocrinology, and psychiatry but might also be interest to anyone concerned with understanding the Neuroendocrine correlates of sleep/wakefulness. The contributions are directed more towards providing an integrated view of the field from the perspective of the authors, rather than being a compendium of recent results. The intent is to provide a reference book for recent and future workers in this and related areas of medicine and biology. Each topic in this volume has received the attention of a panel of authors who have responded to our request to review and place into perspective the major issues, which will undoubtedly confront newcomers to the field. The topics dealt with in Neuroendocrine correlates of Sleep/wakefulness are both diverse and complex. The editors hope that this volume will provide an authoritative summary of important issues in the neuroendocrine correlates of sleep/wakefulness. We also hope that it will motivate new researchers to join the quest for solutions to the problems that have been identified by our contributing authors. This book is published at a time when more and more advances are being made to bridge the gap between basic and clinical neuroscience. It is primarily intended for scientists and clinicians intent on linking the neurobiology of sleep with its associated disorders. Topics were selected that illustrate how contemporary research is being translated into clinical insights and therapies. The contributed chapters were written by scientists actively working at the interface between basic and applied sleep science, with subjects ranging from the mechanisms of intracellular signal transduction to the effects of ambient geophysical cycles. Essays include the physiologic regulation of sleep and its homeostatic collapse, the underlying neural and chemical

circuitry, and the biological basis for new therapies using melatonin and environmental light. ABSTRACT: Sleep disturbances are common in patients with schizophrenia. Mice lacking the cytoskeletal-associated protein Stable Tubule Only Polypeptide (STOP) display cognitive, behavioural and neurobiological deficits that mimic those seen in schizophrenia, but there is little evidence of sleep changes in these mice. To investigate their sleep patterns, electroencephalogram (EEG) and electromyogram were recorded under a 12:12 light:dark cycle in adult male STOP-null (KO; n=7) and wild-type (WT; n=8) mice, during a 24 h baseline period, followed by 6 h of sleep deprivation, and a 24 h recovery period. In the baseline period, KO mice spent more time awake and less time in non-rapid eye movement (NREM) and REM sleep compared to WT mice. Particularly in the dark phase, KO mice had more wake and NREM sleep episodes, and shorter NREM and REM sleep episodes relative to WT mice. Following sleep deprivation, during the first 12 h of recovery (i.e. dark phase), both groups showed similar increases in NREM and REM sleep amounts and NREM EEG delta power relative to corresponding baseline periods. These findings indicate that the STOP-null mice sleep less and their sleep is more fragmented compared to WT mice. These features are consistent with the sleep abnormalities found in individuals with schizophrenia. One of the world's leading sleep researchers provides the latest word on sleep, dreams, and sleep disorders. This volume contains the contributions to a course entitled "Sleep and its Pathology", which was organized by the Advanced School of the Italian Neuro science Society at the "Alessandro Volta" Center of Scientific Culture (Villa Olmo, Como, Italy, May 9-10,1996). The course was aimed at informing the medical audience about recent developments in the field with particular regard to the work of the sleep laboratories of the University of Bologna. The first part of this book presents experimental results dealing with the bio chemical specificity of hypothalamic sleep mechanisms, cerebral metabolism during sleep and the sleep-dependent systemic cardiovascular adjustments in relation to blood perfusion and thermal homeostasis of the brain. The second part covers pathophysiological aspects of human sleep, namely the circadian

rhythm of body core temperature in neurodegenerative diseases, the descriptive epidemiology of excessive daytime sleepiness, the disorders of breathing and motor control in sleep and the syndrome of nocturnal frontal lobe epilepsy. The Editors hope that the book may be useful not only to specifically interested readers, but also to general practitioners. The Editors wish to express special thanks to Professor Eugenio E. Muller for his suggestion to collect the lectures in book-form. The Editors thank the authors for their contributions to the course and to this publication and express their appreciation to Springer-Verlag for helping make this monography possible.

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