様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

科学研究費助成事業　　研究成果報告書

令和　３ 年　 ５ 月 ２１ 日現在

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研究種目：基盤研究(B)（一般）
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研究課題名（和文）動機づけ行動による徐波睡眠制御における側坐核の役割

研究課題名（英文）The role of the nucleus accumbens in regulating slow-wave sleep by motivated behavior

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研究成果の概要（和文）：私たち人間は、注意を必要とするとき、しばしば眠気に逆らい起き続けますが、退屈な状況や楽しみのない状況で眠りたいという避けられない欲求も経験します。 認知的および感情的要因による睡眠調節を支配する脳のメカニズムは十分に理解されていません。 我々は以前、動機と快楽に関連する脳の一部である側坐核のアデノシンA2A受容体を部位特異的に除去したげっ歯類において、世界で最も消費されている向精神性化合物であるカフェインの覚醒効果が消失することを示しました。 本研究課題では、側坐核が睡眠を誘発する可能性を明らかにしました。 この研究結果は、退屈しているときに眠たくなる理由を説明してくれるかもしれません。

研究成果の学術的意義や社会的意義
The achievement has initiated a new area of sleep research on hedonic motivation as a major sleep-gating factor. The achievement also provides further evidence that sleep is the brain's default state that is established in the absence of arousing inputs.

研究成果の概要（英文）：As humans, we often defy sleepiness and stay awake when attention is necessary, but also experience an inescapable desire to sleep in boring or pleasureless situations. The brain mechanisms governing the regulation of sleep by cognitive and emotional factors are not well understood. We previously demonstrated that the arousing effect of caffeine, the most consumed psychoactive compound in the world, is abolished in rodents with site-specific deletion of adenosine A2A receptors in the nucleus accumbens, a part of the brain that is associated with motivation and pleasure. In this project, we revealed that the nucleus accumbens can produce sleep. The findings may explain why we have the tendency to fall asleep in the absence of motivating stimuli, i.e., when bored.

研究分野：sleep neurobiology

キーワード：sleep　motivation　nucleus accumbens

１．研究開始当初の背景

Virtually all living organisms with a nervous system, ranging from worms to humans, show sleep or sleep-like behavior as a neurological function (Siegel J.M. Trends Neurosci. 2008, 208; Trojanowski N.F.et al. Trends Neurosci. 2016, 54). Classic total sleep deprivation experiments in rats produced many abnormal symptoms that included death (Rechtschaffen A., et al. Sleep 1989, 68), suggesting that sleep is a fundamental vital function. The knowledge how to control sleep is highly important to clarify the biological function of sleep or improve sleep in our busy society, but the sleep-regulatory brain systems have not been well established. Neural systems that promote sleep were identified in the brainstem and basal forebrain (Anaclet C., et al. Nat. Neurosci. 2014, 1217; Xu M., et al. Nat. Neurosci. 2015, 1641). However, animals with lesions of these brain areas still have a significant amount of sleep (Anaclet C., et al. J. Neurosci. 2012, 17970; Lu J., et al. J. Neurosci. 2000, 3830; Vetrivelan R., et al. Sleep 2012, 1511), suggesting the possibility of other sleep-inducing circuitry.

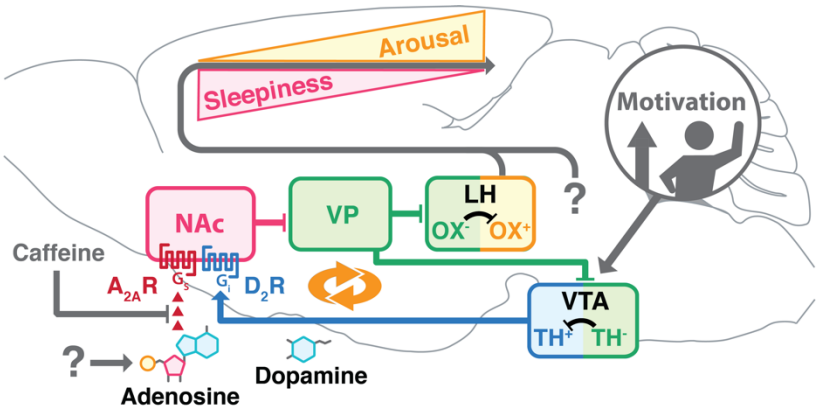

Fig. 1. The nucleus accumbens (NAc) links motivation and sleep. Motivation increases dopamine release from ventral tegmental area (VTA) neurons into the NAc, causing arousal. In the absence of dopamine release, adenosine stimulates NAc neurons to induce sleepiness via inhibition of the ventral pallidum (VP) and downstream disinhibition of neurons inhibiting orexin (OX) neurons in the lateral hypothalamus (LH) and dopaminergic VTA neurons.

The arousal effect of caffeine depends on adenosine A_{2A} receptors ($A_{2A}R$) on neurons in the nucleus accumbens (NAc; Fig. 1; Lazarus M., et al. J. Neurosci. 2011, 10067), which is a major component of the mesolimbic brain system. $A_{2A}R$-positive NAc inhibitory medium spiny neurons also express dopamine D_2 receptors (D_2R) and thus, are involved in the dopaminergic control of motor function and motivational behavior. However, their role in the regulation of sleep was not known.

２．研究の目的

Sleep is one of the most mysterious functions of the brain and therefore, one of the biggest black boxes of today's brain science. Sleep regulation was conceptualized in the popular "two-process" model that posits homeostatic and circadian drives controlling sleep (Borbely A. A. Hum. Neurobiol. 1982, 195). Sleep/wake behaviour, however, is also influenced by cognitive and emotional factors (Saper C. B., et al. J. Comp. Neurol. 2005, 92; Mullins H. M., et al. J. Appl. Psychol. 2014, 1096; Fernandez-Mendoza J., et al. J. Sleep Res. 2014, 489). However, the mechanisms by which motivational stimuli interact with sleep/wake behavior are not accounted for by the two-process model and consequently, the brain mechanisms governing the regulation of sleep by cognitive and emotional factors are largely unknown.

The NAc is a critical brain area for reinforcement and reward (Volkow N. D., et al. Cell 2015, 712; Russo S. J., et al. Nature Rev. Neurosci. 2013, 609) and thus the NAc-VP brain circuit may explain the tendency to fall asleep in the absence of motivating stimuli, i.e., when bored. A tonic sleep drive by neurons in the NAc may be inhibited by ongoing cognitive and emotional stimuli, but in the absence of such stimuli, i.e. under low dopamine conditions, may allow the brain to fall asleep by depressing firing of arousal circuits in the basal forebrain.

３．研究の方法

Sleep recording: The electroencephalogram (EEG), i.e., electrical activity produced by the brain, in conjunction with the electromyogram (EMG), i.e., electrical activity produced by skeletal muscles, is used for experimental assessment of sleep (Fig. 4). These EEG recordings are performed by using a cable-based system wherein acquired data is subjected off-line to pattern and spectrum analysis to determine the vigilance state of the mice being recorded (Oishi Y., et al. J. Vis. Exp. 2016, e53678).

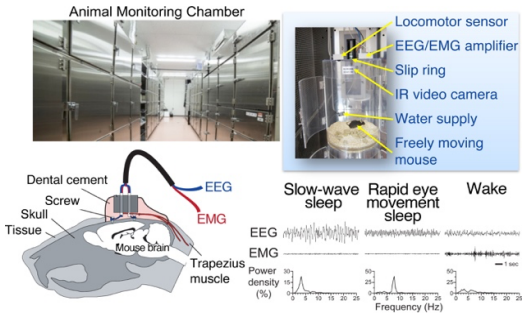

Fig. 2. Sleep measurement.

Optogenetic/chemogenetic modulation of neurons in mice: Significant research efforts have been directed during the past decade at developing genetic-molecular tools to achieve reversible and cell-type specific in vivo silencing of neurons in awake, freely behaving animals. The obvious goal in developing these tools is to help establish a causal relationship between the activity of specific neurons (or neuronal populations) and behavioral and physiological outcomes. One tool that has been developed and come close to achieving the goal of reversible, in vivo activation/silencing of neurons is optogenetics technologies. It would not be an exaggeration to say that optogenetics has ushered in a new era of neurobiology by providing a mechanism that directly links in vivo neuronal activity with behavioral and physiological outcomes in freely behaving animals. Another recently developed system permits the selective and "remote" manipulation (activation and silencing) of neuronal activity via all three major GPCR signaling pathways (Gi, Gs and Gq). Termed "designer receptors exclusively activated by a designer drug" (DREADD) these systems involve, broadly speaking, mutant GPCRs that do not respond to their endogenous ligands but are responsive to otherwise inert biological compounds.

４．研究成果

a. The gating of sleep homeostasis by motivation

We used chemo-genetic and optical techniques to remotely control the activities of NAc neurons that express adenosine A_{2A} receptors ($A_{2A}R$), also known as indirect pathway neurons. As a result, we discovered that NAc $A_{2A}R$ neurons have an extremely strong ability to induce sleep (Fig. 3) that is indistinguishable from the major component of natural sleep, known as slow-wave sleep, as it is characterized by slow and high-voltage brain waves (Oishi Y., et al. Nat Commun. 2017, 734). The findings may explain why we have the tendency to fall asleep in the absence of motivating stimuli, i.e., when bored. The achievement has initiated a new area of sleep research on hedonic motivation as a major sleep-gating factor (Lazarus M., et al. Trends Neurosci. 2012, 35:723). The teleological problem of sleep function arises from the presumption of sleep's evolution from a default state of waking. Humans are likely biased towards this presumption by the egocentricity of waking consciousness. Our research, however, provides further evidence that sleep is the brain's default state that is established in the absence of arousing inputs. Finally, the newly identified sleep circuit may open new therapeutic avenues for treating insomnia and other sleep or psychiatric disorders.

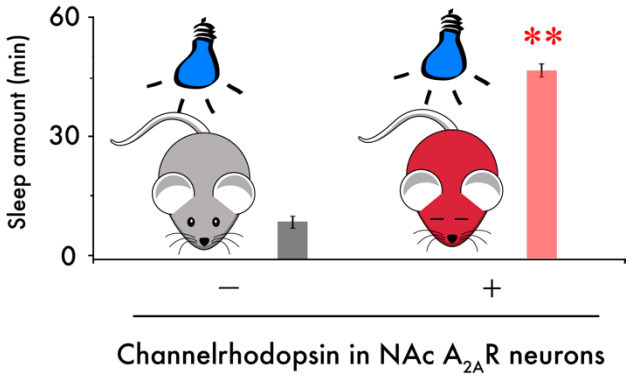

Fig. 3. Optogenetic excitation of NAc $A_{2A}R$ neurons drastically increases sleep amount.

b. Novel treatment of insomnia by enhancing adenosine A2A receptor signaling

Adenosine has long been known to represent a state of relative energy deficiency and to induce sleep via adenosine receptors. Caffeine, the most widely consumed psychostimulant in the world, produces its arousal effect also in the NAc by blocking $A_{2A}R$ (Lazarus et al., J. Neurosci. 2011, 31:10067). Compounds that promote $A_{2A}R$ signaling in the NAc may open therapeutic avenues for treating insomnia, which is a sleep disorder affecting millions of people around the world and it frequently co-occurs with a wide range of psychiatric disorders. Although $A_{2A}R$ agonists strongly induce sleep, classical $A_{2A}R$ agonists have adverse cardiovascular effects and cannot be used clinically to treat sleep disorders. Moreover, the development of adenosine analogs for treating disorders of the central nervous system, including insomnia, is hampered by the poor transport of these drugs across the blood-brain barrier (BBB). We hypothesized that selective physiologic $A_{2A}R$ responses may be evoked by a positive allosteric modulator, because its action, in contrast to an agonist, is limited to when and where adenosine is released.

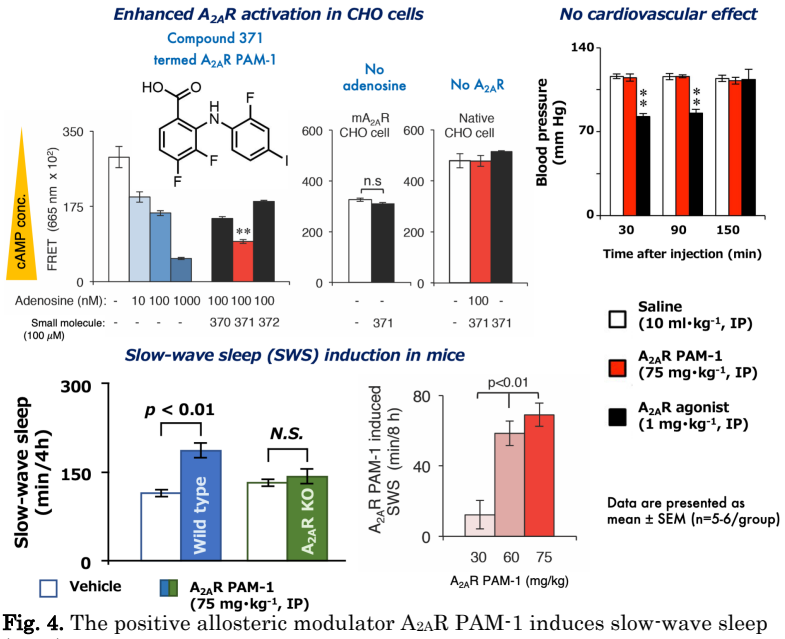

Fig. 4. The positive allosteric modulator $A_{2A}R$ PAM-1 induces slow-wave sleep (SWS) without affecting cardiovascular function.

We developed the first positive allosteric modulator of $A_{2A}R$, named $A_{2A}R$ PAM-1, that evokes $A_{2A}R$ responses in the brain (e.g., sleep induction) without affecting cardiovascular function, unlike classic $A_{2A}R$ agonists (Fig. 4). It should be noted that sleep disturbances are also common in schizophrenia patients and other psychotic conditions. Given that $A_{2A}R$ are also implicated in psychotic conditions, enhanced $A_{2A}R$ signaling may constitute an important molecular mechanism for sleep regulation and sound mental health. (Korkutata M., et al., Neuropharmacology 2019, 144:122). Furthermore, we collaborated with the Manabu Abe Lab (Hiroshima University, Graduate School of Advanced Science and Engineering) to develop a visible-light (420 nm) photoactivatable ('caged') $A_{2A}R$ PAM-1. Using the opto-version of the $A_{2A}R$ PAM, we, for the first time, optochemically induced sleep in freely behaving mice [Roy K et al., in preparation]. In the future, pharmacotherapy may offer the possibility to cure diseases and alleviate symptoms while preventing uncontrolled drug activity in time and space, i.e. the drug is only active at times and sites where it produces its therapeutic effect. Our approach should aid in the generation of visible-light photocactivatable compounds for virtually any druggable target.

c. Understanding the mechanism of sleepiness by exploring mesolimbic glia-neuron interactions

The cellular and molecular processes underlying the build-up of sleepiness and maintenance of sleep are unknown. Glia are far from being merely support cells of the brain. They may just be as dynamic as neurons and actively guide brain function and behavior. One of the intriguing possibility of this is sleep. The NAc, a new sleep-regulating area through the integration of motivational stimuli provides an excellent opportunity to study the regulation of sleep by glia–neuron interactions. We revealed that elevated adenosine levels caused by ablation of NAc astrocytes promote sleep via $A_{2A}R$ (Fig. 5; Zhou X, et al., Neurochem Int 2019, 124:256). These findings may indicate

that sleep control is an essential physiological function of astrocytes and provide the first evidence that adenosine is an endogenous candidate for activating NAc A2AR neurons that have the ability to induce slow-wave sleep. In a new project which is generously supported by the Japan Society for the Promotion of Science [Grants-in-Aid for Scientific Research B (grant number 21H02802)], we pursue an integrated research approach based on imaging of extracellular ATP/adenosine, in-vivo manipulation of glial cells, and single-cell gene expression profiling of NAc cells in response to different sleep/wake and motivated behaviors to study the regulation of sleep and motivation by glia-neuron interactions.

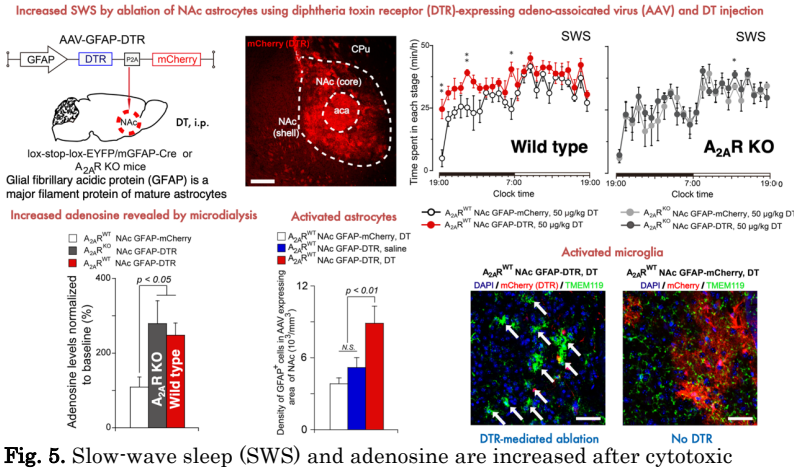

Fig. 5. Slow-wave sleep (SWS) and adenosine are increased after cytotoxic ablation of NAc astrocytes.

５．主な発表論文等

〔雑誌論文〕　計13件（うち査読付論文　13件／うち国際共著　12件／うちオープンアクセス　5件）

１．著者名 Li Ya-Dong、Luo Yan-Jia、Xu Wei、Ge Jing、Cherasse Yoan、Wang Yi-Qun、Lazarus Michael、Qu Wei-Min、Huang Zhi-Li	４．巻 -
２．論文標題 Ventral pallidal GABAergic neurons control wakefulness associated with motivation through the ventral tegmental pathway	５．発行年 2020年
３．雑誌名 Molecular Psychiatry	６．最初と最後の頁 1-17
掲載論文のDOI（デジタルオブジェクト識別子） 10.1038/s41380-020-00906-0	査読の有無 有
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１．著者名 Takato Honda, Yohko Takata, Yoan Cherasse, Seiya Mizuno, Fumihiro Sugiyama, Satoru Takahashi, Hiromasa Funato, Masashi Yanagisawa, Michael Lazarus, Yo Oishi	４．巻 23
２．論文標題 Ablation of Ventral Midbrain/Pons GABA Neurons Induces Mania-like Behaviors with Altered Sleep Homeostasis and Dopamine D2R-mediated Sleep Reduction	５．発行年 2020年
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３．雑誌名 Frontiers in Neuroscience	６．最初と最後の頁 -
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2．論文標題 Gating and the need for sleep: dissociable effects of adenosine A1 and A2A receptors	5．発行年 2019年
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2．論文標題 Enhancing endogenous adenosine A2A receptor signaling induces slow-wave sleep without affecting body temperature and cardiovascular function	5．発行年 2019年
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3．雑誌名 Brain Structure and Function	6．最初と最後の頁 2907～2915
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2．論文標題 Slow-wave sleep is controlled by a subset of nucleus accumbens core neurons in mice	5．発行年 2017年
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2．論文標題 Adenosine and Sleep	5．発行年 2017年
3．雑誌名 Handbook of Experimental Pharmacology	6．最初と最後の頁 1～23
掲載論文のDOI（デジタルオブジェクト識別子） 10.1007/164_2017_36	査読の有無 有
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1．著者名 Oishi Yo、Lazarus Michael	4．巻 118
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3．雑誌名 Neuroscience Research	6．最初と最後の頁 66～73
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２．論文標題 報酬系と睡眠・覚醒	５．発行年 2017年
３．雑誌名 医学のあゆみ	６．最初と最後の頁 761～764
掲載論文のDOI（デジタルオブジェクト識別子） なし	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 －

〔学会発表〕　計9件（うち招待講演　3件／うち国際学会　6件）

１．発表者名 Lazarus Michael
２．発表標題 Why are we sleepy when bored? The gating of sleepiness by motivation
３．学会等名 The 2020 Oriental International Sleep Medicine Summit Forum (Virtual)（招待講演）（国際学会）
４．発表年 2020年

１．発表者名 Xuzhao Zhou, Tsuyoshi Saitoh, Zhaofa Wu, Yulong Li, Michael Lazarus
２．発表標題 Why are we sleepy when bored? Astroglial regulation of sleep in the nucleus accumbens
３．学会等名 Cold Spring Harbor Laboratory Meetings - Glia in Health & Disease (Virtual)（国際学会）
４．発表年 2020年

１．発表者名 Lazarus Michael
２．発表標題 Why do we fall asleep when bored?The gating of sleep by motivated behaviors
３．学会等名 NEURO 2019 - The 42nd Annual Meeting of the Japan Neuroscience Society
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Lazarus Michael

２．発表標題
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１．発表者名
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The gating of sleep by motivated behavior

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４．発表年
2017年

〔図書〕　計0件

〔出願〕　計1件

産業財産権の名称	発明者	権利者
Heterocyclic compound as sleep-inducing agent	Nagase Hiroshi, Lazarus Michael	University of Tsukuba
産業財産権の種類、番号	**出願年**	**国内・外国の別**
特許、2019-076477	2019年	国内

〔取得〕　計0件

〔その他〕

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７．科研費を使用して開催した国際研究集会

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８．本研究に関連して実施した国際共同研究の実施状況

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