NOVEL INSOMNIA TREATMENT

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1） Background

Insomnia is one of the most common sleep problems with an estimated prevalence of 10-15% in the general population and 30-60% in the older population. Due to work schedules and expectations, life-style choices, or pre-existing medical conditions, people are coping with an increasingly wide range of sleep problems, including problems with falling and staying asleep, waking up too early and poor-quality ("non-restorative") sleep. Deficiencies in sleep cause significant social losses due to increased prevalence of mood disorders, lead to decreased economic productivity, and are linked to traffic and work-related accidents due to excessive daytime sleepiness. Insufficient sleep is not only by itself a major problem in modern society, but also an established risk factor for obesity, diabetes, heart disease and other lifestyle diseases.

The most widely prescribed agents for treatment of insomnia are central nervous system depressants, known as benzodiazepines (BDZ) and non-BDZ, that enhance signaling of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). These medications are notorious for their side effects. In addition, orexin receptor antagonists, e.g., suvorexant (sold under the trade name Belsomra), have most recently been developed and approved as medication for insomnia treatment; however, orexin receptor antagonists are inefficient in a large number of people.

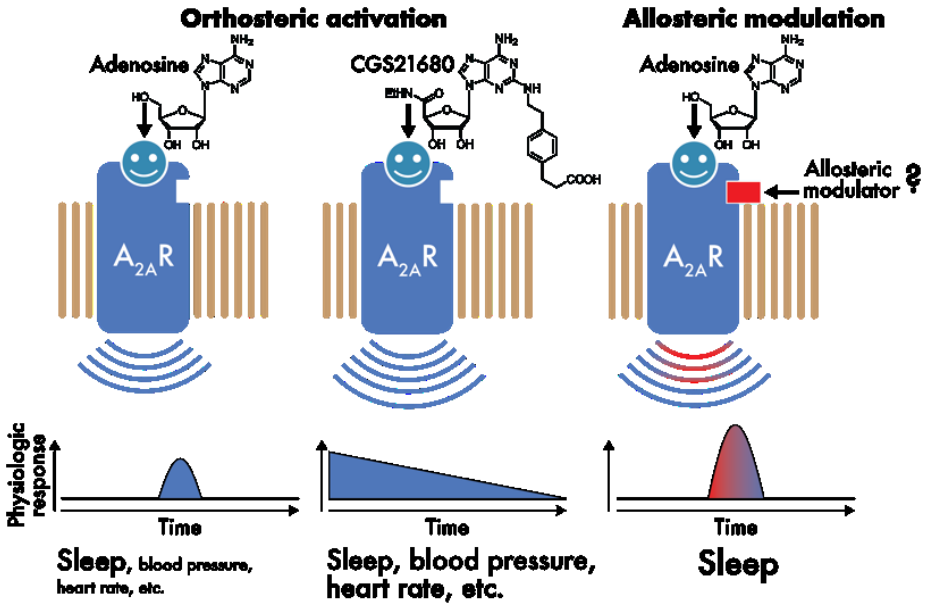

Fig. 1. Induction of selective physiologic $A_{2A}R$ responses by positive allosteric modulation.

The adenosine A_{2A} receptor ($A_{2A}R$) agonist CGS21680 strongly induces sleep when infused into the brain of rodents. However, it is commonly believed that administration of an $A_{2A}R$ agonist has no clinical

potential for treating sleep disorders, because of its cardiovascular effects, especially hypotension and tachycardia. Selective physiologic $A_{2A}R$ responses may, however, 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. 1). Therefore, $A_{2A}R$ modulating compounds may open safe therapeutic avenues for treating insomnia and poor-quality sleep. The possibility that pharmacologic $A_{2A}R$ responses, especially in the brain, can be fine-tuned using allosteric modulators has been largely ignored. Consequently, the development of $A_{2A}R$ allosteric modulators has received almost no attention.

2） Results

We identified compound 378 of the Yanagisawa-Nagase-Tsukuba (YNT) library as a positive allosteric modulator for $A_{2A}R$ (Korkutata M, et al. *Neuropharmacology*, 2019, **144**:122) (Fig. 2, left panel). We found that slow wave sleep (SWS), the major part of sleep characterized by slow and high-voltage brain waves, was induced after intraperitoneal administration of YNT-378, whereas the SWS-inducing effect of YNT-378 was abolished in $A_{2A}R$ knockout mice (Fig. 2, middle panel). Blood pressure and heart rhythm were not affected after IP administration of YNT-378, whereas an $A_{2A}R$ agonist decreased blood pressure (and caused an abnormal heart rhythm) (Fig. 2, right panel). These unexpected findings indicate that allosteric modulation of $A_{2A}R$ induces SWS without cardiovascular effects in mice.

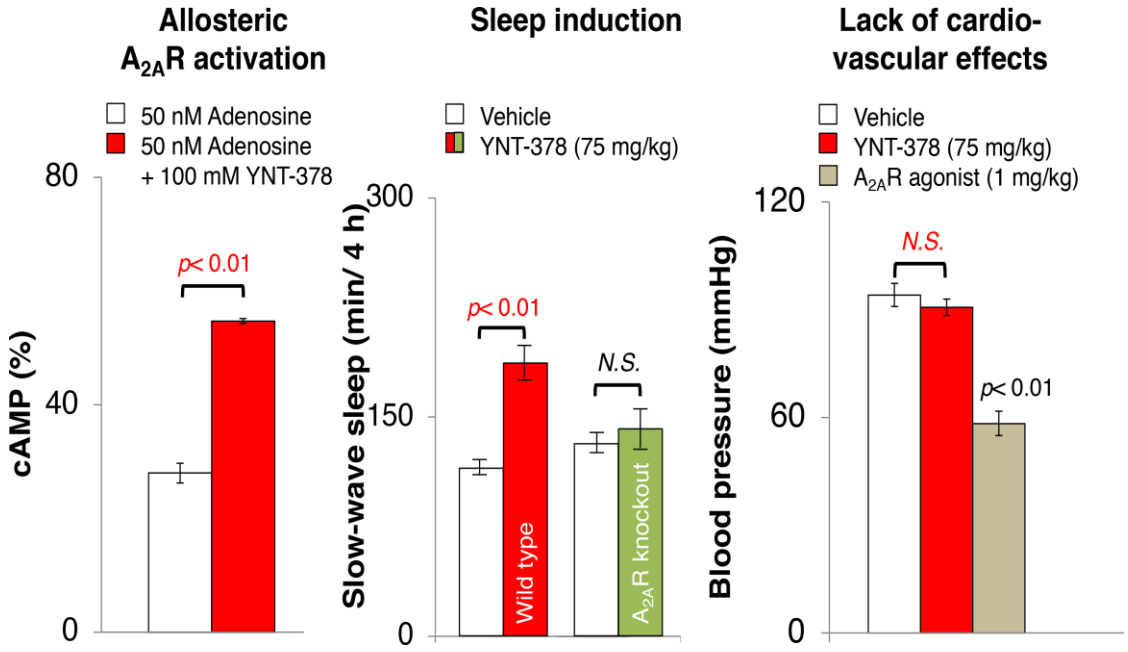

Fig. 2. YNT-378 is a sleep-inducing $A_{2A}R$ allosteric modulator lacking cardiovascular effects.

Optopharmacology may inspire the development of light-controllable drugs for the temporal and spatial control of medications to minimize side effects and maximize benefits in the treatment of disorders. Therefore, we are also developed a photocaged derivative of YNT-378 (opto-YNT-378) to facilitate an optopharmacology study of A2AR. The first generation of opto-YNT378 using 6-nitroveratryl (Nv) group as a photolabile protecting group had problematic properties such as water-insolubility, slow photo-response, and short absorption maximum. To overcome the problems of the Nv group, we developed in collaboration with Professor Manabu Abe at Hiroshima University a novel photolabile protecting group A400 based on a 3-aryl coumarine chromophore (Ioka S., et al., unpublished). The second generation opto-YNT-378 bearing A400 exhibited high water solubility, a fast photo-response, and an absorption maximum at 420 nm. Moreover, time-dependent photoactivation of opto-YNT-378 was observed in a cell-based assay.

We have previously demonstrated that $A_{2A}R$ in the nucleus accumbens (NAc) have the ability to control sleep when activated (Oishi, Y., et al., *Nat Commun*, 2017, **8**:734; Zhou X, et al., *Neurochem Int*. 2019, **124**:256). In collaboration with Professor Radhika Basheer of Harvard University, we used opto-dialysis to introduce opto-YNT378 into the NAc and illuminate simultaneously the compound with violet light for 3 hours. Preliminary data show that SWS was increased after light illumination. On-going experiments will further explore the feasibility of optopharmacology in mice.

3） Discussion

Small molecules like the $A_{2A}R$ allosteric modulator YNT-378 may help people with sleep problems to fall asleep. Although mice are the most commonly used model organism of human disease, results in mice, however, are often not always reliable for predicting human study outcomes. Therefore, many obstacles remain to be overcome in generating a novel drug for the treatment of insomnia in humans, but we believe that our discovery will unlock the development of the next-generation sleeping pill.

It should be noted that sleep disturbances are also common in schizophrenia patients. Schizophrenia is a devastating neuropsychiatric disorder that is characterized by positive symptoms (hallucinations, delusions, disorganized speech and behaviour, and agitated body movements), negative symptoms (deficits in affective and social domains), and cognitive impairment (disruptions to attention, working memory and executive function) (Ross, C.A., et al. *Neuron*, 2006, **52**:139). Approximately 1% of individuals are affected worldwide, regardless of race, age or gender. The age of onset is typically between 15 and 25 years of age (Schultz et al., *Am Fam Physician*, 2007, **75**:1821). Overactive mesolimbic dopamine D_2 receptors (D_2R) are thought to underlie a chemical synaptic dysregulation responsible for inducing psychosis in schizophrenia (Carlsson & Lindqvist, *Pharmacol Toxicol Acta*, 1963, **20**:140). Amphetamines, which increase levels of extracellular dopamine, have been shown to worsen positive schizophrenic symptoms and induce psychosis in patients without schizophrenia, mimicking paranoid symptoms.

First- and second-generation antipsychotic drugs work primarily by blocking D_2R, but these drugs are relatively ineffective for treating the negative symptoms and cognitive deficits of schizophrenia. As medications for schizophrenia can cause serious side effects, people with schizophrenia are often reluctant to take them. Psychotic symptoms such as delusion are believed to be caused by impaired discrimination of environmental cues. New findings demonstrate that discrimination learning is mediated by D_2R in the NAc and inhibition of $A_{2A}R$, which are co-expressed with D_2R in the NAc, leads to impaired discrimination learning (Iino Y, et al., Nature, 2020 **579**:555). Moreover, NMDA-type glutamate receptor hypofunction is believed to participate in schizophrenia, because NMDA receptor antagonists such as phencyclidine and dizocilpine (MK-801) induce psychotic and cognitive disturbances in humans and animals (Field JR, et al., *Trends Mol Med*, 2011, **3**:689). The deletion of $A_{2A}R$ in astrocytes exhibits motor and memory dysfunctions relevant to schizophrenia, namely the exacerbation of MK-801-induced psychomotor response and a decrease of working memory (Matos, M., et al., *Biological Psychiatry*, 2015, **78**:763).

The fact that adenosine acting via $A_{2A}R$ interacts with dopamine and glutamate has stimulated original thinking of new opportunities for schizophrenia pharmacotherapy. Although $A_{2A}R$ activation may be a potential treatment for schizophrenia, the lack of brain-permeable $A_{2A}R$ agonists hampered the verification of this hypothesis in schizophrenia animal models. Due the ability YNT-378 to cross the blood-brain barrier, it may also be useful to treat schizophrenia and other psychotic conditions by enhancing $A_{2A}R$ signaling (Fig 3). Thus, $A_{2A}R$ signaling may constitute an important molecular mechanism for sleep regulation and sound mental health. Enhancing $A_{2A}R$ signaling may not only be useful to treat sleep

disorders, but also schizophrenia and other psychotic disorders.

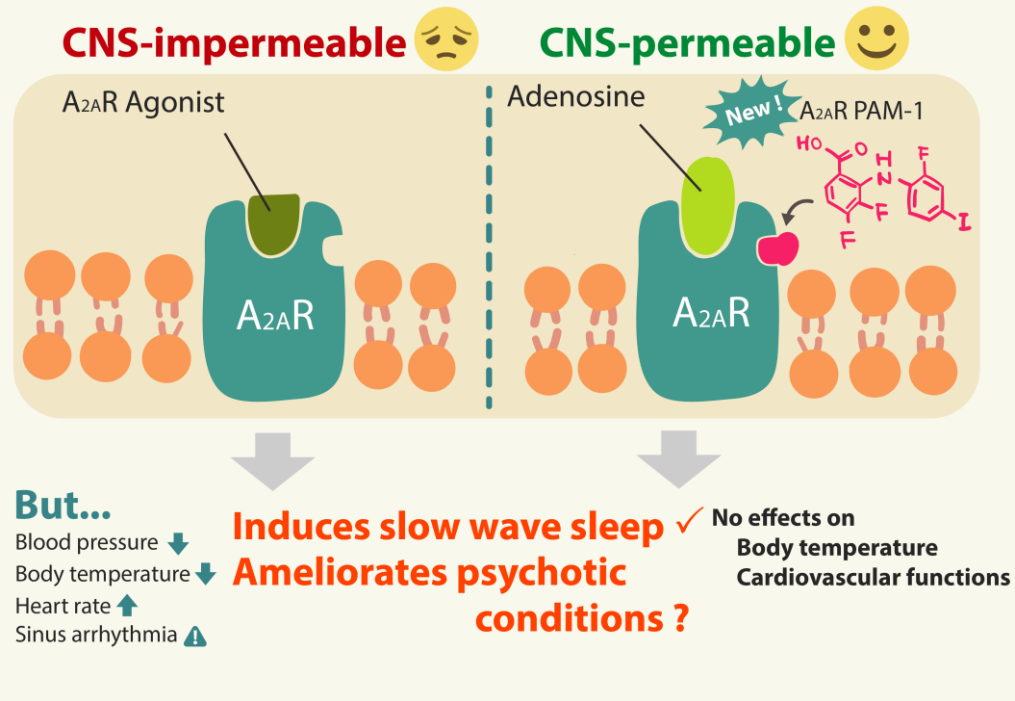

Fig. 3. First positive allosteric modulator that evokes $A_{2A}R$ responses in the brain.