Symposium 14: Hypothalamic control of behaviors and homeostasis (Sat July 31, 9-11AM JST)
Chair: Xiao-Hong Xu (Institute of Neuroscience, Chinese Academy of Sciences. Shanghai, China)

9:00-9:24 Clifford B. Saper (Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, USA
Preoptic control of sleep and body temperature

9:24-9:48 Wei Shen (Shanghaitech University, Shanghai, China)
The Brainstem-Hypothalamic circuitry controls body temperature

9:48-10:12 Sakiko Honjoh (University of Tsukuba, International Institute for Integrative Sleep Medicine, Japan)
Thalamic regulation of sleep and wakefulness

10:12-10:36 Jong-Woo Sohn (Korea Advanced Institute of Science and Technology, Daejeon, Korea)
Hypothalamic mechanisms for serotonergic regulation of feeding

10:36-11:00 Qing-Feng Wu (Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing, China)
Tbx3 dictates arcuate Tac2 neurons to control timing of puberty onset

Symposium 14 Speaker 1

Clifford B. Saper
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Preoptic control of sleep and body temperature

The preoptic area is known to play a key role in regulation of both sleep and body temperature, but the circuitry controlling these functions and how they are related remains largely unexplored. We previously found that galanin neurons in the ventrolateral preoptic nucleus (VLPO) drive sleep behavior. However, we recently found that activation of these neurons also causes hypothermia. We also found that activation of GABAergic neurons in the median preoptic nucleus (MnPO) promotes sleep, but activation of glutamatergic MnPO neurons mainly causes hypothermia. Activation of glutamatergic cells, but not GABAergic cells, in the VLPO also caused hypothermia, suggesting that the VLPO galanin population contains two types of neurons, GABAergic sleep-promoting and glutamatergic hypothermia-promoting cells. Further exploration of the preoptic glutamatergic neurons that drive hypothermia demonstrated that many of them express either PACAP or QRFP peptides, and some express the EP3R prostaglandin receptor, which inhibit the hypothermia neurons and promote fever responses. Driving these preoptic hypothermic neurons with the hM3Dq receptor for 2-4 hrs causes a prolonged state of behavioral hyporesponsiveness and deep hypothermia lasting up to several days, with complete recovery. This state of torpor or hibernation cannot be reversed by warming the animal once it has reached deep hypothermia, and probably represents a distinct self-perpetuating physiological state of extremely low metabolic rate.

Symposium 14 Speaker 2

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The Brainstem-Hypothalamic circuitry controls body temperature

The homeostatic control of body temperature is essential for survival in mammals and is known to be regulated by sophisticated neural circuits in the CNS. However, the specific neural pathways and corresponding neural populations have not been fully elucidated. To identify these pathways, we used cFos to map thermo-sensory neurons and found that induced-cFos activity by a thermal challenge resides in several subregions, including the preoptic area (POA), the dorsomedial hypothalamic nucleus (DMH), and the lateral parabrachial nucleus (LPB). Then, by using activity-dependent transcriptomic analysis (phosphor-TRAP) and optogenetics, we found that POA Vglut2, Vgat, and BDNF neurons were activated by warmth and could reduce body temperature upon activation. Next, to define key sensory inputs into the POA that finally lead to differential regulation of various thermal effector organs, we developed projection-specific and tissue-specific transcriptome analysis. We identified genetic markers that delineate the LPB-POA circuitry in regulating various aspects of thermoregulation, including BAT thermogenesis, vasodilation, and shivering activity. Also, we revealed their links to fever and body weight control. In aggregate, our data define the LPB-POA as a hub to transmit thermal signals and control body temperature and energy expenditure.

Symposium 14 Speaker 3:

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Thalamic regulation of sleep and wakefulness

Sleep is a robust and tightly regulated biological process, in which our cognitive ability reproducibly fluctuates. There are two types of sleep in mammals: REM (rapid eye movement) sleep and NREM (non-rapid eye movement) sleep. We are awake during wake, we dream during REM sleep, and we lose our consciousness during deep NREM sleep. Along with this cognitive fluctuation, the thalamo-cortical system exhibits highly dynamic changes in the activity. During wake and REM sleep, EEG (electroencephalogram) shows the low-voltage and fast frequency activity pattern, so called 'activated EEG'. In contrast, during deep NREM, EEG is dominated by the high-voltage slow frequency oscillation (0.5-4 Hz). The slow oscillation, so called 'slow wave', is the hallmark of NREM sleep and the best marker of sleep need so far.

Here we investigated potential roles of thalamic nuclei in NREM sleep. First, we examined effects of cell ablation in thalamic nuclei by AAV-mediated expression of Diphtheria Toxin Fragment A in adult mice. We performed 24 hour-sleep/wake recordings and found that postdevelopmental ablation of thalamic nuclei did not affect duration of vigilance states. However, combinational ablation of intralaminar and nonspecific nuclei significantly decreased EEG slow wave activity during NREM sleep. Next, we analyzed the firing patterns in one of the nonspecific nuclei, ventromedial nucleus (VM). Our analysis revealed that VM neurons show burst firing phase-locked to the slow wave. Lastly, we employed optogenetic stimulation to mimic their spontaneous firing pattern and found that low frequency stimulation of VM neurons induces a slow wave-like response in the cortex. Taken together, these results show that thalamic neurons play an important role in the generation of NREM sleep-specific brain state.

Symposium 14 Speaker 4:

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Hypothalamic mechanisms for serotonergic regulation of feeding

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter that contributes substantially to the regulation of feeding behavior, energy expenditure and glucose homeostasis at least in part by acting via the serotonin 2C receptor (Htr2c) within the central nervous system. Given that previously-developed anti-obesity drugs targeting central serotonin system and/or Htr2c were not very successful in clinical settings, it is important to understand how selective Htr2c agonists act in the brain to regulate food intake and body weight. Moreover, Htr2c is widely expressed in the brain and regulate a variety of physiological processes and behaviors. Thus, identification of brain regions where Htr2c regulates food intake will increase our understanding of the biological control of feeding behaviors and concurrently provide mechanistic insights to the development of safe and effective anti-obesity drugs. In this talk, I will discuss my recent findings that Htr2c activation has distinct cellular effects on two different hypothalamic neuronal populations: the pro-opiomelanocortin (POMC) neurons within the arcuate nucleus of hypothalamus (ARH) and the Htr2c neurons within the paraventricular nucleus of hypothalamus (PVH), and discuss the physiological relevance of these findings.

Symposium 14 Speaker 5:
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Tbx3 dictates arcuate Tac2 neurons to control timing of puberty onset

The timing of puberty onset is thought to be controlled by an increase in pulsatile gonadotropin-releasing hormone (GnRH)/gonadotropin secretion in mammals. However, the underlying molecular and cellular mechanism controlling puberty onset timing remains an open question. It has recently been suggested that Tac2/Kiss1 neurons in the hypothalamic arcuate nucleus play a critical role in puberty onset by triggering pulsatile GnRH/gonadotropin secretion. Here we identified a Tbx3-mediated gene regulatory network (i.e. regulon) responsible for the specification of arcuate nucleus through single-cell transcriptomic analysis. Along the developmental trajectory, transcription factor Tbx3 was expressed in neural progenitors within acroterminal domains and became restricted to selected neuronal subtypes in arcuate nucleus as development proceeds. While lineage tracing revealed that Tbx3-derived cells predominantly populated arcuate nucleus, single-cell analysis showed the loss of multiple neuronal subtypes in region-specific Tbx3-deficient brains. Given that patients with ulnar-mammary syndrome (UMS), caused by TBX3 haploinsufficiency, frequently showed delayed puberty and other signs of hypogonadism, we specifically deleted Tbx3 in Tac2/Kiss1 neurons, in which neurokinin B encoded by *Tac2* gene facilitates the synchronized discharge of neurons in autocrine and/or paracrine manners, and found that cell type-specific ablation of Tbx3 caused the loss of arcuate Tac2/Kiss1 neurons before puberty onset. Both male and female mutant mice survived to adulthood but displayed a significant delay in the timing of puberty onset, while the estrous cycle of female mice was completely disrupted. Taken together, we revealed that Tbx3 dictates arcuate Tac2/Kiss1 neurons to control the puberty onset timing, providing a molecular and cellular mechanism underlying the delayed sexual dimorphism in UMS patients.