Symposium 10: Mechanisms of Innate Fear *(*Fri July 30, 9-11AM JST*)*
Chair: Reiko Kobayakawa (Kansai Medical Univ, Hirakata-Osaka, Japan)

9:00-9:30 Jeansok J Kim (Department of Psychology and Program in Neuroscience, University of Washington at Seattle, USA)
Neurobiology of Stayin' Alive

9:30-10:00 Qinghua Liu (National Inst of Biol Sciences, Beijing, China)
Posterior subthalamic nucleus (PSTh) mediates innate fear-associated hypothermia in mice

10:00-10:30 June-Seek Choi (Dept of Psychology, Korea University, Seoul, Korea)
Chasing as a psychogenic stress: implications for aging and sex differences in fear response

10:30-11:00 Ko Kobayakawa (Kansai Medical Univ, Hirakata-Osaka, Japan)
Artificial hibernation/life-protective state induced by thiazoline-related innate fear odors via sensory TRPA1 activation

Symposium 10 Speaker 1

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Neurobiology of Stayin' Alive

Fear is considered an integral part of the brain's defensive mechanism that evolved to protect animals and humans from predation and other ecological threats. Hence, it is logical to study fear from the perspective of antipredator-survival behaviors and circuits by sampling a range of threatening situations that organisms are likely to encounter in the wild. However, contemporary neurobiological models of fear stem largely from Pavlovian fear conditioning studies that focus on how a particular cue becomes capable of eliciting learned fear responses, thus oversimplifying the brain's fear system. I will present some recent systems-level data from neuroecological studies of fear in rodents and discuss whether the inferences we draw from fear conditioning studies operate in the natural world.

Symposium 10 Speaker 2

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Posterior subthalamic nucleus (PSTh) mediates innate fear-associated hypothermia in mice

Mammals normally maintain a constant body temperature irrespective of their environmental temperature. However, emotions such as fear can trigger acute changes in body temperature accompanying defensive behaviors to enhance survival in life-threatening conditions. The neural mechanisms of fear-associated thermoregulation remain unclear. Innate fear odor 2-methyl-2-thiazoline (2MT) elicits rapid hypothermia and elevated tail temperature, indicative of vasodilation-induced heat dissipation, in wild-type mice, but not in mice lacking Trpa1–the chemosensor for 2MT. Here we report that Trpa1-/- mice show diminished 2MT-evoked c-fos expression in the posterior subthalamic nucleus (PSTh), external lateral parabrachial subnucleus (PBel) and nucleus of the solitary tract (NTS). Whereas tetanus toxin light chain-mediated inactivation of NTS-projecting PSTh neurons suppress, optogenetic activation of direct PSTh-rostral NTS pathway induces hypothermia and tail vasodilation. Furthermore, selective opto-stimulation of 2MT-activated, PSTh-projecting PBel neurons by capturing activated neuronal ensembles (CANE) causes hypothermia. Conversely, chemogenetic suppression of vGlut2+ neurons in PBel or PSTh, or PSTh-projecting PBel neurons attenuates 2MT-evoked hypothermia and tail vasodilation. These studies identify PSTh as a major thermoregulatory hub that connects PBel to NTS to mediate 2MT-evoked innate fear-associated hypothermia and tail vasodilation.

Symposium 10 Speaker 3

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Chasing as a psychogenic stress: implications for aging and sex differences in fear response

Being chased by a predator or a dominant conspecific can induce significant stress. However, only a limited number of laboratory studies have employed chasing by itself as a stressor. Previously, we have developed a novel stress paradigm in which rats were chased by a fast-moving object in an inescapable maze and demonstrated that chasing stress can induce long-lasting fear memory and sensitization of defensive responses to a new aversive event as well as immediate, significant stress responses. In this presentation, I introduce several experiments where we have looked into age-dependent and sex-dependent expressions of defensive responses under chasing threat and discuss the implications of the results. Specifically, chasing stress induced distinctively different patterns of brain activation in adolescent rats from those in adult rats. In addition, behavioral response to brain-derived neurotrophic factor following chasing stress was different in adolescent rats. In a separate study, we found that the female rats responded with more active defensive responses to the chasing stress, which were rarely observed in male rats.

Symposium Speaker 4
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Artificial hibernation/life-protective state induced by thiazoline-related innate fear odors via sensory TRPA1 activation

Innate fear intimately connects to the life preservation in crises, although this relationship is not fully understood. Here, we report that presentation of a supernormal innate fear inducer 2-methyl-2-thiazoline (2MT) induced robust systemic hypothermia/hypometabolism and suppressed aerobic metabolism via phosphorylation of pyruvate dehydrogenase, thereby enabling long-term survival in a lethal hypoxic environment. These responses exerted potent therapeutic effects in cutaneous and cerebral ischemia/reperfusion injury models. In contrast to hibernation, 2MT stimulation accelerated glucose uptake in the brain and suppressed oxygen saturation in the blood. Whole-brain mapping and chemogenetic activation revealed that the sensory representation of 2MT orchestrates physiological responses via brain stem Sp5/NST to midbrain PBN pathway. Thiazoline-related innate fear-eliciting compounds (tFOs) orchestrate hypothermia, hypometabolism, and anti-hypoxia, which enable survival in lethal hypoxic conditions. Most of these effects are severely attenuated in *Trpa1* knockout mice. TFO-induced hypothermia involves the *Trpa1*-mediated trigeminal/ vagal pathways and non-*Trpa1* olfactory pathway. TFOs activate *Trpa1*-positive sensory pathways projecting from trigeminal and vagal ganglia to the spinal trigeminal nucleus (Sp5) and nucleus of the solitary tract (NTS), and their artificial activation induces hypothermia. TFO presentation activates the NTS-parabrachial nucleus pathway to induce hypothermia and hypometabolism. TRPA1 activation is insufficient to trigger tFO-mediated anti-hypoxic effects; Sp5/NTS activation is also necessary. We find a novel molecule that enables mice to survive in a lethal hypoxic condition ten times longer than known tFOs. Combinations of appropriate tFOs and TRPA1 command intrinsic physiological responses relevant to survival fate. If this system is preserved in humans, it may be utilized to give rise to a new field: “sensory medicine”.