A virtual reality system to study social interaction in adult zebrafish

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Abstract

The essence of social interaction is the exchange of information between individuals. During this reciprocal process, the response timing and the response predictability play an important role. However, as social stimulus is the behavior of another animal, these parameters of the stimulus are difficult to manipulate. To enable a systematic control of the social stimulus, we are developing 3D models of adult zebrafish with controllable behaviors. The virtual fish, which is displayed on a computer monitor, performs naturalistic swimming patterns and adjusts its locomotion according to the behavior of a real animal swimming in an adjacent tank. The virtual and real animals thus establish a close-loop interaction in which experimenters have a full access to manipulate the response of the virtual animal through computer programing. To enable measurements of brain activity during behavior, we are also developing a VR system using a 6-axis force/torque sensor that in principal enables a head-restrained zebrafish to navigate in a 3D virtual space. This VR system is integrated into a two-photon microscope for non-invasive measurements of activity throughout the dorsal telencephalon. In addition, the respiration and the eye angle of the adult animal are simultaneously monitored, which enables us to correlate neural activities to behaviors driven by emotions and visual attention. Overall, this ongoing project demonstrates the potential of using virtual reality techniques to investigate the role of reciprocal interaction during social behavior.

Investigating the circatidal rhythm in vertebrates using Periophthalmus modestus (Shuttles Hoppfish)

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Abstract

The behavior of intertidal organisms may be affected by the sun or the moon. For example, circadian rhythm, annual rhythm, and seasonal rhythm are modulated by the sun. In contrast, circalunar rhythm, circasemilunar rhythm, and circatidal rhythm may be regulated by the moon. Current research primarily focuses on the circatidal rhythm of invertebrates such as crustaceans, mollusks, and insects. However, whether circatidal rhythm exists in other intertidal vertebrates is unclear. Thus, we investigate the circatidal rhythm of an intertidal vertebrate Periophthalmus modestus in a stimulated tidal environment. Using video cameras to monitor and analyze the activity individually, we found that P. modestus has tidal rhythmic behaviors such as movement time, dry, and wet zone location preference under both 6.5:6.5 high-low tide cycle and constant conditions. Furthermore, the circadian rhythm is relatively weak compared to the circatidal rhythm. Together, our results suggest that the circatidal clock may be a conserved biological clock in animals, including osteichthyes.

Optogenetic inhibition of vCA1 suppresses LH-related sleep disturbance induced by footshock in mice

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Abstract

Sleep disturbance troubles hundreds of people every night over the world. These sleepless experiences sometimes are related to unpleasant daytime experience. Recent studies have showed that ventral hippocampus CA1 (vCA1), known as a critical brain area that process memory, is enriched in anxiogenic experience-sensitive cells. Meanwhile, lateral hypothalamus (LH) has been implicated in wakefulness promotion and also mediated stress response. In previous studies done by our lab team, we found a significant increase of wakefulness ratio in TRAP(Fos2A-iCreER) mice during their resting phase, following chemogenetic activation of LH neurons that had been“Trapped”after giving inescapable footshock stimuli (IFS). We proposed that there is a direct neuron activation route from vCA1 to LH activated during IFS conditioning. In following researches, we extended the previous experiments by application of optogenetic techniques, using virus-carried light-activated membrane chloride pump Halorhodopsin (NpHR) to locally inhibit the activation of vCA1 neurons during IFS conditioning. At the LH we injected Cre-DIO (double floxed inverse open reading frame) hM3Dq virus with mCherry reporter gene to stimulate IFS-activated cells. The effects to sleep disturbance was observed by electroencephalography (EEG) 12 hours sleep recording after different doses of clozapine (CLO) intraperitoneal injection. The preliminary results show that although wakefulness ratio is notably higher in the first 2 hours of the resting phase, there are no significant difference of wakefulness, NREM sleep and REM sleep ratios in following hours between different groups of CLO doses. Fluorescent microscope image results show that the expression of hM3Dq is remarkably reduced compared to previous experiments.

CPEB2-Activated Axonal Translation of VGLUT2 mRNA Promotes Glutamatergic Transmission and Presynaptic Plasticity

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Abstract

Remodeling the synaptic proteome to sustain long-term plasticity and memory can depend on locally translated mRNAs. However, the regulatory mechanisms have been biasedly discovered in postsynaptic (dendritic) rather than presynaptic (axonal) compartments due to the lack of distinct polyribosomes in the tiny domain of adult mammalian forebrain axons. Cytoplasmic polyadenylation element binding protein 2 (CPEB2)-controlled translation is important for postsynaptic function and spatial memory. We therefore investigated the presynaptic role of CPEB2 in Schaffer collateral-CA1 and temporoammonic-CA1 circuits and found defective fiber volley amplitude and paired-pulse facilitation in CPEB2-deficient presynaptic afferents. By cross-comparing CPEB2-immunoprecipitated transcriptome with a learning-associated axonal translatome in the adult cortex, we identified and validated that Slc17a6, encoding vesicular glutamate transporter 2 (VGLUT2), is translationally upregulated by CPEB2. Blocking activity-induced axonal Slc17a6 translation by CPEB2 deficiency or cycloheximide diminished the releasable pool of VGLUT2-containing vesicles. Collectively, CPEB2-regulated presynaptic translation supports glutamatergic transmission, long-term potentiation and memory.

Involvement of ASIC1a in ASIC4-positive BNST/amygdala neurons in modulating anxiety and fear

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Abstract

ASIC4 is a member of acid-sensing ion channels and widely expressed in the CNS. However, the physiological function of ASIC4 remains unclear. Previous studies have shown that ASIC4 can interact with ASIC1a and counteract the ASIC1a-mediated anxiety-like responses. Here we used genetic approaches to probe the role of ASIC4 in anxiety-associated nuclei in mouse models. We discovered that chemo-optogenetically activating ASIC4-positive cells induced anxiety-like responses in mice. Studies of mice with a disrupted ASIC4 gene in specific brain regions suggested that ASIC4 in the amygdala and the bed nucleus of the stria terminalis (BNST) are implicated in fear and anxiety. Interestingly, conditional knockout of ASIC1a in ASIC4 positive cells resulted in reduced anxiety behavioral phenotypes in both fear and anxiety. In situ hybridization data suggested a possible surface membrane protein modulation role for ASIC4 in regulating ASIC1a, so we performed point-mutations on two glycosylation sites, Asn191 and Asn341, which resulted in differential effects on ASIC4 biogenesis. Furthermore, these Asn191 and Asn341 mutations increased ASIC1a surface protein expression and current density. More importantly, expression of ASIC4 in the amygdala and bed nucleus of the stria terminalis of ASIC4 knockout mice using viral vector-mediated gene transfer resulted in rescue of the anxious phenotypes. Together, these data suggest ASIC4 plays an important role in fear and anxiety-related behaviors, with the glycosylation of ASIC4 as one of the possible mechanisms.

Exploring Sng Behavior in Mouse Gait

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李杰威、李政翰、陳志成

Abstract

Sngception (痠覺) describes the response of the somatosensory nervous system to tissue acidosis and is closely related to nociception. This ambiguity has condemned it to remain neglected in neuroscience studies causing its underlining mechanism largely undiscovered. Sngception has been shown to be a central concern in fibromyalgia, radiculopathy and other related somatosensorial conditions. To pave the way for the understanding of sngception's molecular mechanism, it's urgent to develop and establish a monitoring system for sngception-related behaviors in animal models. Sngception is thought to be caused by tissue acidosis, which is, in term, induced by inflammation, ischemia, fatiguing exercise, and the like. When people suffer from unpleasant sensations, gait is usually modified in order to guard the uncomfortable tissue. Gait analysis is widely used in monitoring nociception in clinical and animal models of pain. We hypothesize that this system may also be valuable in monitoring sngception-related behaviors. Our preliminary results, analyzed from mice paw imaging show that spatial, structural, and temporal gait parameters have a tendency to change after temporary muscle acidosis induced through intramuscular acidic saline injection. This suggests that the technique has potential in monitoring sng behavior, which could lead to the discovery of its molecular mechanism. In this study, we will analyze sng- and pain-induced gait change and further investigate the involvement of acid sensing ion channels through both pharmacological and genetic approaches.

An unexpected role of proprioceptors in the development of chronic muscle pain

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Abstract

Fibromyalgia affects 2% to 8% of the adult population with high prevalence in women. Patients always suffer from chronic widespread musculoskeletal pain. However, how FM pain developed is still a mystery. Clinical studies demonstrated that intramuscularly injection of acidic solution would cause pain. In fibromyalgia mouse model, repeated acid injection in muscle, further developed long-lasting mechanical hyperalgesia. This highlights the importance of peripheral acid signaling in chronic muscle pain development. Previous findings point out the critical role of Acid-Sensing Ion Channel 3 (ASIC3) in development of acid-induced mechanical hyperalgesia. ASIC3 predominately expresses in peripheral sensory neurons including nociceptors and proprioceptors. It's worth to discover the contribution of each population of ASIC3-expressing sensory neurons in development of acid-induced chronic pain. We first test the mechanical hyperalgesia level in nociceptors or proprioceptors ASIC3 conditional knockout mouse (Asic3Pv, proprioceptors or Asic3Nav1.8, nociceptors) after acid induction. Surprisingly, Asic3Pv but not Asic3Nav1.8 mice showed no prime responses after acid induction. This indicated that proprioceptors may play an additional role in sensing muscle acidosis, which mediated by ASIC3. Further, we use optochemogenetic tool (CTZ-LMO3 system) to specific activate Nav1.8+ and Pv+ muscle afferents to address the population of muscle afferents in acid-induced chronic hyperalgesia. Excitingly, specific activate Pv+ muscle afferents, mice were primed to induce mechanical hyperalgesia, but not Nav1.8+. Further, we explored a subtype of metabotropic glutamate receptor, mGluR5-PLD, mediates the Pv+ neuron-dependent prime effect and cellular neuronal activation (monitored by phosphorylated ERK level) by the mGluR5-PLD inhibitor, PCCG13. To further understand proprioceptor ASIC3-mediated, acid-induced chronic hyperalgesia is developed through glutamate-mGluR5 signaling. We modified the recipe of acid-induced hyperalgesia in following up first inject pH6.4 and ASIC3 potenciator, RPRFamide, with an acid injection one day apart in wild type mice. Exhilaratingly, PCCG13 blocks ASIC3-mediated, acid-induced chronic hyperalgesia. Further, in acid-induced chronic hyperalgesia in Asic3Nav1.8 mice, supposed ASIC3 expression is normal in proprioceptors, PCCG13 also blocks the development of chronic hyperalgesia. Taken all together, proprioceptors may contribute to acid induced-priming during development of chronic muscle hyperalgesia through ASIC3 and peripheral mGluR5-dependent glutamate signaling.

Basal forebrain glutamatergic neurons inhibit reward-seeking behavior and the activity of bursting neurons

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Abstract

Basal forebrain (BF) is one of the most prominent neuromodulatory systems and plays key roles in attention, arousal and decision making. While most BF studies have focused on its cholinergic and GABAergic neurons, the functions of BF glutamatergic (Vglut2) neurons remain largely unknown. Recent studies have found that subcortical glutamatergic neurons in several brain regions, including the BF, send prominent projections to the lateral habenula (LHb), a critical hub of the brain's aversion circuitry. Moreover, many such glutamatergic neurons inhibit reward-seeking behavior and encode negative valence. These observations raise the question of whether BF glutamatergic neurons may serve a similar role in the processing of aversive information and oppose the processing of reward information by another group of BF neurons, the BF bursting neurons. Using cell-type specific optogenetic manipulations and neuronal recording in head-fixed Vglut2-cre mice, here we show that BF Vglut2 neurons transiently inhibit reward-seeking behavior and inhibit the activity of BF bursting neurons. Mice were trained to perform a reward-seeking task, in which an auditory cue is paired with water reward in two-thirds of trials. We found that photostimulation of BF-LHb Vglut2 neurons led to a biphasic effect of the reward-seeking licking response, which was composed of an initial transient inhibition followed by a rebound facilitation. At the neuronal activity level, photostimulation of BF Vglut2 neurons biphasically modulated the activity of BF bursting neurons, starting with a transient inhibition phase followed by a rebound excitation. Moreover, photostimulation of BF-LHb Vglut2 neurons led to consistent effects on bursting neurons with those described above. These results indicated that the modulation of BF Vglut2 neurons on reward-seeking processing was mainly via the LHb. Together, our results reveal a novel biphasic modulation of BF-LHb Vglut2 neurons at both behavioral and neural activity levels, and suggest that BF-LHb Vglut2 neurons play an opposing role to the BF bursting neurons. The opponent interactions between BF bursting neurons and Vglut2 BF neurons suggest that positive and negative valence information converge and interact within the BF.

Functional coupling between midbrain dopamine neurons and basal forebrain bursting neurons in the encoding of reward prediction error

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Abstract

Reward prediction error (RPE), the difference between received and predicted reward, has been traditionally associated with neuronal activity in midbrain dopaminergic (DA) neurons. However, recent studies from our group have demonstrated that a special subset of noncholinergic neurons in the basal forebrain (BF), which we refer to as BF bursting neurons, are similarly modulated by RPE. Both neuronal populations show synchronous phasic activities relative to reward delivery and reward-predicting cues, with responses modulated by subjective value and reward expectations. These observations raise the important question of whether the highly similar neural profiles in midbrain DA neurons and BF bursting neurons represent the same RPE information and result from functional coupling. To answer this question, we simultaneously recorded DA and BF activities while rats perform a licking-based delayed reward task. Here we show that the activities of DA and BF bursting neurons were tightly coupled, with DA neurons temporally leading BF bursting neurons by 10ms. We found that the responses of BF bursting neurons and DA neurons toward various behavioral events were highly similar. Moreover, the trial-by-trial fluctuation of neuronal activities in both regions were strongly coupled with each other even after the influence of common behavioral events were taken into account. Spike timing cross-correlation analysis further revealed a consistent temporal delay, with midbrain DA neurons temporally leading BF bursting neurons by ~10ms. Together, these results suggest that BF bursting neurons similarly encodes RPE information and challenges the canonical view that RPE is solely encoded by DA neurons. These results also serve as a starting point to further investigate why and how the brain uses two major neuromodulatory systems to jointly encode RPE. In the accompanying poster, we investigate the causal interactions between the two neuronal populations by optogenetically activating DA neurons.

Distinct subsets of hypothalamic SF-1 expressing neurons encode an exploratory internal state that drives animals' investigative behaviors

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Abstract

The Steroidogenic factor 1 expressing neurons in the dorsomedial/central parts of the ventromedial hypothalamus (VMH-SF1 neuron) are regarded as an essential pivot for maintaining energy homeostasis and driving several innate behaviors. Previous studies have suggested that VMH-SF1 neurons encode a predator-orientated defensive state: optogenetic and pharmacogenetic stimulation of the VMH-SF1 neurons evoked an anxious-like state that further elicited various defensive behaviors. On the other hand, silencing these neurons rendered the animal less anxious while encountering predatory cues. Nevertheless, whether the VMH-SF1 neurons would respond to hostile conditions and their behavioral relevance remain mostly elusive. We performed in vivo calcium imaging with fiber photometry and a head-mounted miniature microscope (miniscope) to monitor the real-time activities of the VMH-SF1 neurons in response to predatory- or conspecific-cues in freely-roaming mice. We found that the VMH-SF1 neurons were robustly activated by conspecific exposure, yet encountering predatory cues induced relatively moderate neural responses. Moreover, VMH-SF1 neuronal activities showed a strong temporal correlation with exploratory but not defensive behaviors. The miniscope recording further revealed that conspecific- and predatory cues recruited distinct subsets of VMH-SF1 neurons, and the stimulus-induced calcium dynamics of these distinct subpopulations reliably encode the identity of the stimulus. However, artificially manipulating all VMH-SF1 neurons robustly altered animals' defensive states. This discrepancy implied that functional interpretations derived from conventional manipulations without selectivity to stimulus-selective subsets might not truly reflect the behaviors controlled by these neurons in vivo. Altogether, we suggest that the VMH-SF1 neurons are heterogeneous and can be further classified into several functionally distinct groups based on their stimulus selectivity. A distinct subset of VMH-SF1 neurons could prompt animals' investigative behaviors upon detecting the presence of their preferred external stimulus, yet another subset facilitates defensive state-related behaviors.

Generational synaptic functions of GABAA receptor β3 subunit deteriorations in an animal model of social defcit

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Abstract

Disruption of normal brain development is implicated in numerous psychiatric disorders with neurodevelopmental origins, including autism spectrum disorder (ASD). Widespread abnormalities in brain structure and functions caused by dysregulations of neurodevelopmental processes has been recently shown to exert adverse effects across generations. An imbalance between excitatory/inhibitory (E/I) transmission is the putative hypothesis of ASD pathogenesis, supporting by the specific implications of inhibitory γ-aminobutyric acid (GABA)ergic system in autistic individuals and animal models of ASD. However, the contribution of GABAergic system in the neuropathophysiology across generations of ASD is still unknown. Here, we uncover profound alterations in the expression and function of GABAA receptors (GABAARs) in the amygdala across generations of the VPA-induced animal model of ASD. The F2 generation was produced by mating an F1 VPA-induced male offspring with naïve females after a single injection of VPA on embryonic day (E12.5) in F0. Autism-like behaviors were assessed by animal behavior tests. Expression and functional properties of GABAARs and related proteins were examined by using western blotting and electrophysiological techniques. Social deficit, repetitive behavior, and emotional comorbidities were demonstrated across two generations of the VPA-induced offspring. Decreased synaptic GABAAR and gephyrin levels, and inhibitory transmission were found in the amygdala from two generations of the VPA-induced offspring with greater reductions in the F2 generation. Weaker association of gephyrin with GABAAR was shown in the F2 generation than the F1 generation. Moreover, dysregulated NMDA-induced enhancements of gephyrin and GABAAR at the synapse in the VPA-induced offspring was worsened in the F2 generation than the F1 generation. Taken together, these findings revealed the E/I synaptic abnormalities in the amygdala from two generations of the VPA-induced offspring with GABAergic deteriorations in the F2 generation, suggesting a potential therapeutic role of the GABAergic system to generational pathophysiology of ASD.

Dopamine signaling in the regulation of neuroinflammation and glymphatic dysfunction during chronic feeding with high fat diet

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Abstract

Depression is associated with the change of functional connection between the frontal cortex and the striatum, which is called fronto-striatal (FS) circuit in the central nervous system (CNS). The disruption of dopamine (DA) transmission in. Neuroinflammation in the CNS is triggered by different types of stimuli, such as peripheral inflammation, traumatic brain injury, viral infection, chronic stress, etc. Glia, astrocytes, and microglia, play the major inducers in the initiation and progress of neuroinflammation. Obesity is due to metabolic abnormalities and becomes one of the risks of depression and metabolic disorders. It is an increasing interest in examining the role of the glymphatic system in the development of neurodegenerative diseases. We have previously demonstrated that the reactivity of glia in the CNS was induced in the hypothalamus and striatum by chronic feeding with high fat diet (HFD). Based on the role of the DA signaling in adaptive immunity, we attempted to define the involvement of DA and its receptors (D1R and D2R) in HFD-induced glial reactivity in the FS circuit and the glymphatic deregulation. At first, the regional change in DR gene expression was examined at the different time points of HFD feeding. D1R expression was insignificantly altered in the analyzed brain regions. Yet, the temporal and spatial changes of D2R expression by HFD feeding were observed. Moreover, HFD feeding reduced the gene expression of aquaporin 4 (AQP4), a water channel protein that is intensively present at the vascular astrocytic endfeet and promotes lymphatic transport. Furthermore, the in vitro experiments showed that AQP4 expression was downregulated by the addition of DA or D2R antagonist trifluoperazine (TFP) in inflammagen-stimulated striatal astrocytes. These results indicate that chronic feeding by HFD could cause glymphatic dysfunction. Thus, DA/D2R signaling in the regulation of glial function in the FS is to be determined in chronically HFD-fed mice. We are also to determining the mechanisms underlying the regulation of AQP4 expression by chronic HFD feeding and the imbalance of the glymphatic system in obese mice.

Effects of sleep restriction on brain function and cognition-enhancing protein klotho

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Abstract

Sleep is a physiologic state that performs an essential restorative function and facilitates memory consolidation. Sleep restriction may impair hippocampal neuronal plasticity and memory process. Klotho is initially identified as an anti-aging protein. Recent studies have found that klotho improves cognition through enhancing long-term potentiation and enriching the synaptic NR2B and NMDA receptors. Although klotho is viewed as a potential treatment for cognitive and neurodegenerative disorders, whether it is able to alleviates the detrimental effects induced by sleep restriction remains elusive. Therefore, the objective of this study is to explore whether sleep restriction causes cognitive impairment by regulating klotho protein. Male C57BL/6 mice were randomly assigned to control and sleep restriction (SR) groups after evaluating behavior by using open field and Morris water maze. Mice of SR group were placed into the SR box for 20 hrs per day. After 7-day sleep restriction, both groups were conducted in the behavioral tests again to investigate the effects of sleep restriction on locomotion and cognition. The levels of klotho and its downstream NR2B protein expression in the cognition-related brain regions were analyzed by western blotting. The results demonstrated that mice of SR group spent more time to find the platform in the test trial in Morris water maze, indicating that sleep restriction impairs spatial memory. However, SR treatment didn’t affect locomotor activity in the open field. SR treatment induced down-regulation in klotho and NR2B protein levels in the prefrontal cortex. Taken together, sleep restriction impairs spatial memory, but has no effects on locomotion. The impaired spatial memory induced by sleep restriction might due to the regulation of klotho levels and related pathway.

Impact of information transfer in Periplaneta group dynamics and aggregation behaviour

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Abstract

Optimal foraging theory, Selfish Herd, and several top-down models fall short of explaining the factors that determine group movement and decision-making for animals that do not follow rigid hierarchies or centralised control. These models define intergroup relations as immutable rules based on proximity, without considering an animal's sensory system or information gained from conspecifics. Thus, animal groups are modelled as an aggregation of particles, disregarding new properties that emerge as members cooperate or compete. The American cockroach (\textit{Periplaneta Americana}) does not exhibit rigid patterns of social hierarchy or task allocation. They seem to rely on `collective wisdom' and show a preference for aggregating with peers rather than venturing alone into unbeknownst territories in search of food. The simplicity and horizontality of their social interactions make them an ideal organism for studying information dissemination and its impact on system-wide behavioural patterns. This study draws on models and techniques used in network and information theory and trajectory forecasting to understand the factors that modulate information exchange and group decision-making in moving insects. It contrasts cockroach group movement in an open space, where they can interact freely, with their dynamics in a maze that restricts their interactions. We described and explained collective movement using mathematical and computational tools by using prediction models and mutual information to identify the most useful features to forecast individual and group behaviour. Then, we determined the impact of information transfer in insect groups by contrasting group behaviour against the non-interacting aggregation of individual behaviours. Finally, we concluded that communication between Periplaneta acts as a weak attractive force, that influences their decisions only when in close proximity of their peers. Thus, communication ensures that groups of animals maintain cohesiveness that protects individuals from predators or environmental hazards.

Investigating the role of Cap-methyltransferase 2 in cerebellar development and neurodegeneration

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Abstract

Methylation of messenger RNA (mRNA) is an abundant event in the central nervous system, but its effects on regulating gene expression and biological processes are poorly understood. A pre-mRNA undergoes post-transcriptional processing and modification (i.e., splicing, polyadenylation and 7-methylguanosine capping) before becoming a mature mRNA to be translated in the cytoplasm. In higher eukaryotic organisms, the first and second nucleotide are methylated at the 2' O-ribose position by cap methyltransferase (CMTR) 1 and 2, respectively. CMTR1 regulates brain development and neuromorphogenesis, but the role of CMTR2 in the brain remains completely unexplored. To understand the physiological function of CMTR2, we generated Cmtr2 global knockout mice and found them unable to develop beyond the gastrulation stage. Thus, we used Nestin-Cre mice to generate conditional knockout of Cmtr2 (Cmtr2-cKO) in neural and glial progenitor cells and investigated Cmtr2 function in the nervous system. Cmtr2-cKO mice with mild cerebellar atrophy showed severe motor incoordination in beam walking and rotarod assays. Histological analyses showed reduced thickness of the cerebellar molecular layer, which is the dendritic layer of Purkinje cells (PCs). Inositol 1,2,3-triphosphate receptor type (ITPR1) immunohistochemistry, which labels PCs, revealed increased axonal swellings (torpedoes) and dendritic swellings in Cmtr2-Cko PCs. Notably, evident neurodegeneration and death of PCs especially in Lobules IV-V were observed in aging Cmtr2-cKO mice (18-25 months). Using Visium spatial transcriptomics analysis, we identified differential expression of mitochondrion-related, genes in Cmtr2-cKO PCs. Together, we hypothesize that CMTR2 deficiency-induced mitochondrial stress and dysfunction result in abnormal axonal and dendritic swellings of PCs, thereby leading to age-dependent neurodegeneration. The mitochondria functional assay will be performed to validate our hypothesis. Moreover, we will also identify the target mRNAs regulated by CMTR2 in PCs to better understand the molecular action of CMTR2 in the cerebellum.