3P254 PS2 遺伝子変異導入アルツハイマーモデルマウスにおける瞬目反射条件付けの解析
Classical eyeblink conditioning in mouse model of Alzheimer's disease expressing the mutant human presenilin 2

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Mutations in presenilin-1 (PS1) and presenilin-2 (PS2) cause familial Alzheimer's disease (FAD). Accordingly, it is quite important to elucidate the function of presenilin for understand the molecular mechanism of Alzheimer's disease (AD). Thus, the purpose of this research is to analyze the physiological role of PS2 in cognitive function by using mouse models of Alzheimer's disease expressing the mutant human PS2. We focus on especially the performance of classical eyeblink conditioning, which has been used as clinical psychological test for human dementia including AD. First, we investigated eyeblink conditioning in PS2M MI Hemi mice (PS2M mice; purchased from IBL Japan), expressing the mutant human PS2. In this strain, an AD-associated mutant variant of human PS2 (N141I) is expressed. This N141I mutation in PS2 is tightly linked with a form of autosomal dominant familial AD in the Volga German families. PS2M mice at the age of 2 months showed normal acquisition of conditioned response during eyeblink conditioning. Furthermore, we are now trying to investigate the eyeblink conditioning in Amyloid Precursor Protein (APP) Transgenic Mice (Tg2576 Mice) and PS2M×APP-Tg2576 mice. In Tg2576 Mice, an AD-associated mutant variant of human APP (Lys⁶⁷⁰→Asn⁶⁷⁰, Met⁶⁷¹→Leu⁶⁷¹) is overexpressed and the variant was found in a Swedish family with early-onset AD. To generate PS2M×APP-Tg2576 mice, male APP Tg2576 mice were crossed with female PS2M mice, producing 25 PS2/Tg2576 double transgenic mice.

3P255 男性ホルモンによる海馬スパインの急性的増加とその細胞内情報伝達経路の解析
Androgen rapidly increases the density of dendritic spines in the hippocampus via kinase pathways

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The concentration of androgen in the hippocampus is much more than that in blood circulation, and rapid modulation of hippocampal synaptic plasticity by androgen has long been a hot topic. However, molecular mechanisms of rapid androgen action has been uncovered. Here, we investigated morphological plasticity of dendritic spines in response to dihydrotestosterone (DHT) and testosterone (T) using hippocampal slices from adult male rats. We demonstrated androgen rapidly change the number and morphology of dendritic spines in rat dorsal hippocampus within 2h. We observed that androgen increased spine density by approximately 1.3- and 1.5-fold in hippocampal CA1 (spatial memory) and CA3 (associative memory) region, respectively. In CA1, while DHT increased large-head spine, T increased middle-head spine selectively. We uncovered that MAP kinase superfamily, such as ERK1/2 and p38 were involved in this effect. It should be noted that PKA was included in the intracellular signaling of androgen only in CA1 but not in CA3. Androgen receptor (AR) was located not only in cytoplasm but also just beneath the postsynaptic membrane. These results imply that membrane associated AR activates several kinases and induces spinogenesis rapidly. Androgen has been known to change the synaptic plasticity by modulating gene transcription, but its effects were very slow. We revealed a novel effect of androgen which acts as a neuroprotective factor.

3P256 GABAA 受容体の側方拡散動態が抑制性シナプス足場タンパク質の安定性を決める
The lateral diffusion dynamics of GABAA receptors determines the stability of an inhibitory synaptic scaffold protein

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The lateral diffusion dynamics of neurotransmitter receptors is one of the key factors controlling the synaptic receptor number that determines synaptic transmission efficacy. Receptor diffusion generally depends on the interaction between the receptor and its scaffold protein accumulating at the post-synapse. GABA_A receptor (GABA_AR) is the neurotransmitter receptor that plays a crucial role in inhibitory neurotransmissions. It has long been considered that one of the inhibitory synaptic scaffold proteins is responsible for the regulation of GABA_AR diffusion dynamics, however, there is no direct evidence. The stability of GABA_AR and the scaffold protein cluster depends on the elevation intracellular Ca²⁺ concentration. In this study, we monitored the time course of Ca²⁺-dependent changes in the size of GABA_AR and the scaffold

protein clusters by quantitative immunocytochemistry. We found that the Ca²⁺-dependent changes in GABA_AR cluster size was observed ahead of that of the scaffold protein cluster size. We also found that the artificial inhibition of the lateral diffusion of GABA_ARs by surface receptor cross-linking technique totally abolished the Ca²⁺-dependent changes in the cluster size of the scaffold protein. These results indicate that the stability of this inhibitory scaffold protein is determined by the lateral diffusion dynamics of GABA_ARs, and suggest the existence of unidentified scaffold proteins for GABA_ARs.

3P257 モノアラガイの中樞神経系においてインスリン様ペプチドによって引き起こされる長期増強現象
Lon-term potentiation induced by insulin-like peptide in the central nervous system of a snail

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The pond snail *Lymnaea stagnalis* is capable of learning conditioned taste aversion (CTA) and consolidating this CTA into long-term memory (LTM). Previous studies showed that the molluscan insulin-related peptide II (MIP II) was up-regulated in snails exhibiting CTA-LTM. We thus hypothesized that MIP II plays an important role at the synapses underlying the LTM consolidation process. To examine this hypothesis, 1) we observed the distribution of MIP II and the MIP receptor and determined the amounts of their mRNAs in the central nervous system (CNS) of *Lymnaea*; and 2) we investigated the effects of CNS secretions that are expected to include MIP II on the change in synaptic transmission that is thought to underlie CTA-LTM. We show here that MIP II was only observed in the cerebral ganglia, but the MIP receptor was distributed throughout the entire CNS including the buccal ganglia. The application of exogenous mammalian insulin or the secretions from *Lymnaea* MIP II-containing cells evoked long-term potentiation at the synapses between the cerebral giant cell (a key interneuron for CTA) and the B1 motoneuron (a buccal motoneuron). These data are suggestive that MIP II triggers changes in synaptic connectivity that are correlated with CTA learning and its consolidation into LTM in the *Lymnaea* CNS.

3P258 Magnetized water improves cognitive function in mice by increasing insulin-like growth factor-I production in the hippocampus

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Insulin-like growth factor-I (IGF-I) has beneficial effects on the cognitive function. Magnetized water (MW) has biological effects similar to those of IGF-I. In the present study, we examined whether MW may increase IGF-I production in the hippocampus by stimulating sensory neurons in the gastrointestinal tract, thereby improving the cognitive function in mice. MW increased calcitonin gene-related peptide (CGRP) release from dorsal root ganglion (DRG) neurons isolated from wild-type (WT) mice. Increases of the tissue levels of CGRP, IGF-I, and the immunohistochemical expression of IGF-I were observed in the hippocampus at 4 weeks after oral administration of MW in WT mice. Significant enhancement of angiogenesis and neurogenesis was observed in the dentate gyrus of the hippocampus of the WT mice after administration of MW. Oral administration of MW to WT mice resulted in an increase in the expression of c-fos in the spinal dorsal horn, the parabrachial nuclei, solitary tract nucleus and the hippocampus. Significant improvement of spatial learning in the Morris water maze was observed in the WT mice after administration of MW. None of effects of MW in the WT mice were observed following the administration of MW in CGRP-knockout (CGRP-/-) mice. These observations strongly suggest that MW may increase the hippocampal IGF-I production via sensory neuron stimulation in the gastrointestinal tract, thereby improving the cognitive function in mice.

3P259 デジタルミラーデバイス (DMD) によるランダムアクセス型光刺激装置をそなえた膜電位感受性色素 (VSD) 神経回路活動可視化顕微鏡
A new VSD imaging microscope for neural circuit analysis with a random-access-photo-stimulator using a digital-mirror (DMD) device

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Neuronal computation depends on the temporal spike sequences conveyed by different pathways in the brain, which eventually converge into a cell. In the neural circuit of the hippocampus, cells of area CA1 receive oscillatory information from 2 major pathways: the Schaffer collateral (Sch) pathway and the temporoammonic (TA) pathway. The Sch pathway from CA3 cells make