Imperial Prize and Japan Academy Prize to:

Haruo Kasai
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for "Discovery of Principles of Structural Plasticity in Brain Spine Synapses"

Outline of the work:

Most excitatory synapses are formed on small appendages of dendrites, characterized by a submicron head and a narrow neck structure, called dendritic spines, in the brain. The highest density of dendritic spines on dendrites are found in the principal neurons of the forebrains. The shapes and densities are highly diverse and are often affected in mental disorders. Despite their attractive features, intensive investigations in the 20th century have failed to elucidate the pivotal role of dendritic spines; mainly because there was no appropriate method for the stimulation of single spines (Refs. 1 and 3).

1. Investigation of spine synapses with two-photon glutamate uncaging

In 2001, Dr. Haruo Kasai developed two-photon uncaging of glutamate, enabling the stimulation of visually identified spines. This revealed that spine-head sizes are closely correlated with their glutamate sensitivity, a determinant of synaptic connections (Ref. 15). Moreover, Dr. Kasai discovered that repetitive glutamate uncaging induces enlargement of spine heads when applied together with membrane depolarization. Spine enlargement has both transient and sustained phases and is confined to the stimulated spines. Glutamate sensitivity is increased during the sustained phase of spine enlargement (Ref. 18), which is dependent on BDNF (Brain-Derived Neurotrophic Factor) and protein synthesis (Ref. 22). Spine enlargement is necessary in many scenarios, such as in motor learning (Ref. 30).

2. Dopamine and psychosis

Dopamine is a crucial modulator of brain function. Dr. Kasai found that increases in dopamine concentrations potentiated spine enlargement only within the precise time window up to 2 s after excitatory input (Ref. 29), consistent with the reward timing of conditioned learning and the eligibility trace in reinforcement learning. Reward timing is formed by the Ca/calmodulin-induced conformation change of adenylate cyclase 1 (AC1), following which AC1 can more efficiently generate cAMP. In contrast, decreases in dopamine concentrations during conditioned learning promoted punishment learning and spine enlargement in the neurons expressing the dopamine D2 receptor. Thus, his studies clarified that D2 receptor antagonists (antipsychotic drugs) facilitate punishment learning and prevent psychotic symptoms (delusion and hallucination) (Ref. 33).

3. Fluctuations and statistical properties of dendritic spines in memory functions and mental disorders

How long does plasticity last? Dendritic spines restore the stationary condition a certain duration after plasticity. The spines display day-by-day spontaneous fluctuations (intrinsic dynamics) even in static conditions, which regularize the spine size distributions and facilitate the elimination and generation of spines (Refs. 3 and 23). Consequently, new and small spines are predominant in the spine population. These features conform to the inexhaustibility of new memories in daily life, most of which are forgotten within a few days (Ebbinghaus). Repeated recall improves memory via spine enlargement. In autism spectrum disorders (ASD), the stability of synaptic contact is impaired, the intrinsic dynamics are exacerbated, and small spines prevail, yielding spine dysgenesis. In such cases, dendritic spines show excess fluctuations and fail to elaborate the communicational skills; a significant hurdle even for contemporary artificial intelligence (Ref. 3).

4. Mechanical actions of dendritic spine enlargement on presynaptic exocytosis.

Additionally, Dr. Kasai found that the force of rapid spine enlargement is equal to that of smooth muscle contraction (0.5 kg/cm^2). This force is primarily used to expand the spine space for stable spine growth, but further acts on the presynaptic terminals to enhance evoked release 2–3 times for 20 min. This transmission is neither chemical nor electrical and represents the third form of synaptic transmission. Pressure sensation and transduction (PREST) is new in mechanobiology but may be widely utilized in various cell functions. PREST represents the increases in SNARE assembly induced by the approach of SNAREs in the plasma membrane toward SNAREs on the vesicles, which are supported by actin scaffolds. It is the best candidate for short or working memory substrates for the brain because it is rapid, synapse-specific, short-lasting, and naturally extended into long-term memory (Ref. 34).

Dr. Kasai has, thus, revealed the structure–function relationship of dendritic spines, the enlargement during long-term memory, purposive modulations by dopamine, spontaneous slow fluctuations (intrinsic dynamics), and mechanical transmission. These newly found principles are essential for the roles of dendritic spines in rapid and long-lasting mental functions and their disorders.

List of Main Publications

Review Articles

1. Kasai, H., Matsuzaki, M., Noguchi, J., Yasumatsu, N. and Nakahara, H. Structure-stability-function relationships of dendritic spines. ***Trends Neurosci.*** 26; 360–368, 2010.
2. Kasai, H., Takahashi, N. and Tokumaru, H. Distinct initial SNARE configurations underlying the diversity of exocytosis. ***Physiol. Rev.*** 92; 1915–1964, 2012.
3. Kasai, H., Ziv, N. E., Okazaki, H., Yagishita, S. and Toyoizumi, T. Spine dynamics in the brain, mental disorders and artificial neural networks. ***Nat. Rev. Neurosci.*** 22; 407–422, 2021.

Research Articles

4. Kasai, H. and Augustine, G. J. Cytosolic Ca^{2+} gradients triggering unidirectional fluid secretion from exocrine pancreas. ***Nature*** 348; 735–738, 1990.
5. Kasai, H. Tonic inhibition and rebound facilitation of a neuronal calcium channel by a GTP-binding protein. ***Proc. Natl. Acad. Sci. U.S.A.*** 88; 8855–8859, 1991.
6. Kasai, H., Li, Y. and Miyashita, Y. Subcellular distribution of Ca^{2+} release channels underlying Ca^{2+} waves and oscillations in exocrine pancreas. ***Cell*** 74; 669–677, 1993.
7. Takahashi, N., Kadowaki, T., Yazaki, Y., Miyashita, Y. and Kasai, H. Multiple exocytotic pathways in pancreatic β-cells. ***J. Cell Biol.*** 138; 55–64, 1997.
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9. Takahashi, N., Kadowaki, T., Yazaki, Y., Ellis-Davies, G.C.R., Miyashita, Y. and Kasai, H. Post-priming actions of ATP on Ca^{2+}-dependent exocytosis in pancreatic beta cells. ***Proc. Natl. Acad. Sci. U.S.A.*** 96; 760–765, 1999.
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15. Matsuzaki, M., Ellis-Davies, G.C.R., Nemoto, T., Miyashita, Y., Iino, M. and Kasai, H. Dendritic spine geometry is critical for AMPA receptors expression in hippocampal CA1 pyramidal neurons. ***Nat. Neurosci.*** 4; 1086–1092, 2001.
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