Japan Academy Prize to:

Masanobu KANO
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for "Studies on Activity-Dependent Functional Adjustment of Neural Circuits"

Outline of the work:

Brain functions including human mental activity are based on the actions of neural circuits formed by synapses of many neurons. Function and connectivity of neural circuits are optimally regulated by the animal's experience, that is, neural activity, throughout life. Prototypes of neural circuits are formed primarily by genetic programs during embryogenesis, but they are modified by neural activity during postnatal development. The brain of a neonatal animal has an excess number of immature synaptic connections. During postnatal development, some are strengthened and remain while others are weakened and eventually eliminated, leading to the establishment of functional neural circuits in adult animals. This is called "synaptic pruning" and is considered to underlie reorganization of neural circuits during development.

Dr. Masanobu Kano elucidated the basic mechanism of synaptic pruning, using the postnatal development of synaptic connections from cerebellar climbing fibers to Purkinje cells as a model. Purkinje cells have two distinct excitatory synaptic inputs, namely, climbing fibers and parallel fibers. Dr. Kano clarified that climbing fiber synapse pruning is completed through the following four processes. In newborn mice, five or more climbing fibers form synaptic contacts onto the soma of Purkinje cells with almost the same strengths of synaptic inputs. During the first postnatal week, synaptic inputs from a single climbing fiber are selectively strengthened relative to those of the other climbing fibers in each Purkinje cell (selective strengthening). Subsequently, only the strengthened climbing fiber extends along the dendrites of each Purkinje cell and form synaptic contacts there (dendritic translocation). In parallel, synapses of the other weaker climbing fibers are eliminated from the soma of each Purkinje cell through two distinct processes, namely, the early and late phases of climbing fiber elimination. While the early phase is independent of parallel fiber synapse formation, the late phase is critically dependent on it. Dr. Kano elucidated the outline of the molecular mechanism of how neural activity strengthens synaptic inputs from only one climbing fiber and eliminate synapses of the other climbing fibers. He demonstrated that synaptic inputs from climbing fibers activate P/Q-type voltage-dependent calcium channels in Purkinje cells, and the resulting increase in calcium concentration is essential for all the four processes mentioned above. On the other hand, he clarified that synaptic inputs from parallel fibers activate metabotropic glutamate receptor type 1 in Purkinje cells and this process is essential for the late phase of climbing fiber elimination. Moreover, Dr. Kano identified the molecules involved in these two pathways.

In mature neural circuits, synaptic transmission is constantly modulated by neural activity. Dr. Kano discovered a completely new regulatory mechanism of synaptic transmission. When postsynaptic neurons become overactive, endocannabinoids (marijuana-like substances in the brain) are produced and released from the postsynaptic neurons, act retrogradely to presynaptic cannabinoid receptors (CB1 receptors), and suppress the release of neurotransmitters. Dr. Kano identified the three mechanisms for endocannabinoid

production in postsynaptic neurons: an increase in intracellular calcium concentration, activation of Gq-coupled receptors, or a synergistic effect resulting from the simultaneous occurrence of calcium elevation and Gq-coupled receptor activation. The endocannabinoid-mediated retrograde suppression of synaptic transmission is thought to function as a "circuit breaker" that suppresses excessive activity of neural circuits. Furthermore, Dr. Kano identified that among multiple endocannabinoids, 2-arachidonoylglycerol (2-AG), produced by the enzyme diacylglycerol lipase α (DGLα), is responsible for retrograde suppression of synaptic transmission. Through these studies, Dr. Kano revealed that endocannabinoids, which are lipids in nature, are responsible for retrograde modulation of synaptic transmission rather than classical neurotransmitters such as amino acids and amines.

Dr. Kano also made groundbreaking findings on long-term synaptic plasticity that is thought to underlie learning and memory. He clarified that metabotropic glutamate receptor type 1 and its downstream molecules in Purkinje cells are essential for "long-term depression" at excitatory synapses, which is thought to be a basis of cerebellar motor learning. He also discovered that "long-term potentiation" occurs at inhibitory synapses in Purkinje cells, establishing a new concept that long-term plasticity exists not only in excitatory synapses but also in inhibitory synapses.

In summary, Dr. Kano has made great contributions to elucidating the basic principles of neural circuit development, establishing new concepts of modification of synaptic transmission, and pioneering new fields of research of synaptic plasticity. His research has been highly regarded worldwide as being original and having influenced subsequent research trends.

List of Main Publications (*, Corresponding author)

Original Articles

1. Kano, M.* and Kato, M.: Quisqualate receptors are specifically involved in cerebellar synaptic plasticity. ***Nature*** 325, 276–279, 1987.
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4. Kano, M., Hashimoto, K., Chen, C., Abeliovich, A., Aiba, A., Kurihara, H., Watanabe, M., Inoue, Y., and Tonegawa, S.*: Impaired synapse elimination during cerebellar development in PKCγ mutant mice. ***Cell*** 83, 1223–1231, 1995.
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Book and Reviews

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