論文の内容の要旨

Early Network Oscillations in Developing Amygdala

（発達期扁桃体における初期ネットワーク振動の解析）

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Periodic intrinsic activity is a characteristic feature of the developing nervous system. This oscillatory pattern is believed to be involved in brain maturation, including neuronal growth, synapse formation, and network construction. Several patterns of periodic activity have been described in developing structures such as cortex and hippocampus. However, intrinsic oscillatory pattern in other memory-relevant networks such as amygdala remains poorly understood. Utilizing functional multineuron calcium imaging (fMCI) to monitor the activity of amygdala neuronal populations, I discovered the earliest synapse-driven network pattern in amygdala, an almond-shape structure pivotal for emotional experience. I thus analyzed the spatiotemporal organization of these large-scale oscillatory $[Ca^{2+}]_i$ waves.

[Results **]**

1. Large-scale intrinsic oscillatory [Ca]$_i$ waves in developing amygdala

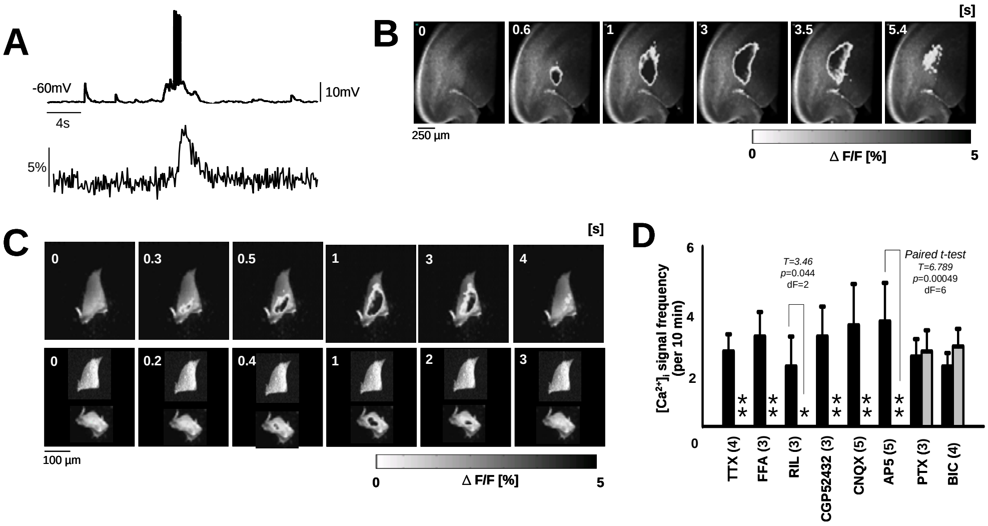

Figure 1. Amygdalar [Ca^{2+}]$_i$ waves. A, [Ca^{2+}]$_i$ signal correlated burst firing activity. B, Time-lapse imaging of amygdalar [Ca^{2+}]$_i$ wave in brain slices prepared from a newborn rat 30 min after delivery. C, Mini-slice isolation experiments. D, Pharmacological experiments. Data were obtained from slices at P0-P1 postnatal rats.

Intracellular membrane potential recording confirmed that [Ca]$_i$ increases that occurred in acute brain slices corresponded to spike bursting of neurons (Fig. 1A). I found oscillatory [Ca]$_i$ waves in the amygdala of horizontal acute slices prepared from newborn rat (Fig. 1B). The intrinsic amygdalar waves were reproducibly found in the first week of neonatal rats. Experiments using incised mini-slices revealed that the waves occurred in the posterior, but not the anterior, region of the amygdala (Fig. 1C). A series of pharmacological experiments suggests that the waves required Na$^+$ channel-dependent neural activity, glutamatergic and GABA$_B$ receptor activity (Fig. 1D).

2. Amygdalar waves propagate to surrounding networks

I next focused on the

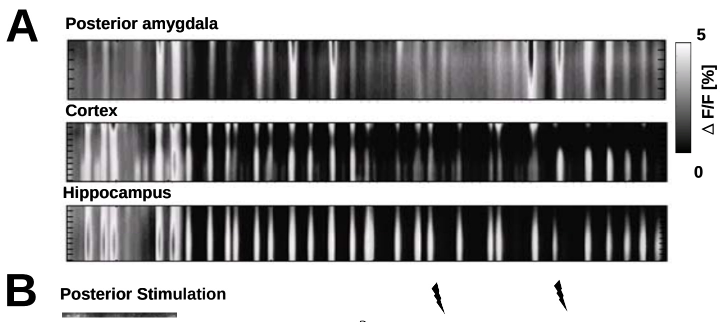

Figure 2. A, Line scanning of [Ca^{2+}]$_i$ of the posterior amygdala, the cortex, and the hippocampus in a postnatal day 2 rat. B, Electrical stimulation of the posterior part of the amygdala induced [Ca^{2+}]$_i$ waves in the cortex and the hippocampus

relationship of amygdalar $[Ca^{2+}]_i$ waves to the $[Ca^{2+}]_i$ activity of other brain regions, because the amygdala has numerous cortical projections. I observed that as the animals developed, the posterior basolateral amygdala started to generate periodic activity time-locked to other brain regions, such as the cortex and the hippocampus (Fig. 2A). Electric stimulation of the amygdala triggered $[Ca^{2+}]_i$ waves in these brain regions (Fig. 2B). Electrophysiological recording revealed that local field potential showed burst activity that persisted for 60 ms to 2 s and that the membrane potential of amygdalar neurons exhibited a bimodal distribution with inter-wave intervals showing a sharp peak at 2 s and a broad peak at 10 s. These patterns, which are prominent in the neonatal amygdala, may regulate long-distance wiring and underlie activity-dependent maturation of network formation.

3. Developmental profile of the amygdalar network oscillations

I examined the developmental change of synchronized activity. The oscillatory $[Ca^{2+}]_i$ waves in the amygdala persisted until postnatal day (P) 5. Bursting frequency is increased in later developmental age, but the wave pattern is changed. According to their initiation sites, the waves were classified into at least three spatial patterns; amygdalar waves, cortico-amygdalar waves, and hippocampo-amygdalar waves (Fig. 3A). The frequency of their emergence depended on the age of pups (Fig. 3B).

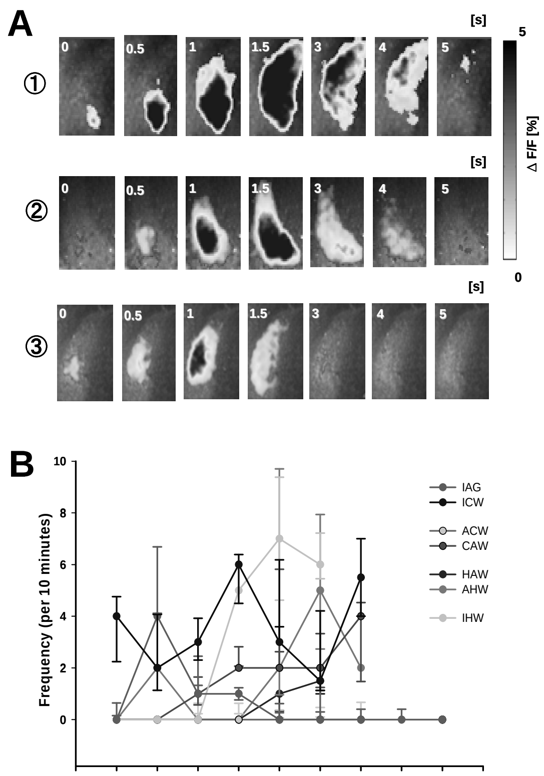

Figure 3. A, Three wave dynamics in the amygdala: amygdalar waves (top), cortico-amygdalar waves (middle), and hippocampo-amygdalar waves (bottom). B, Developmental profile of the event frequency of amygdalar waves

Amygdalar waves showed slower wave dynamics and higher $[Ca^{2+}]_i$ amplitude, compared to cortico-amygdalar waves, and hippocampo-amygdalar waves.

[Conclusion **]**

In this study, I firstly revealed a novel form of oscillatory $[Ca^{2+}]_i$ waves emerges in the amygdala at the first week of developmental stages for the first time. The wave behavior changed as the animals develop. Observations in electrophysiological and imaging techniques *in vivo* will be required to clarify more details about mapping the basic flow information in the various loops of neocortex.