第326回 大阪大学神経科学懇話会

日時：平成**26**年**10**月**3**日（金）17：00 – 19:00

場所：医学部附属病院 １４階 会議室２（会場が変更になりました）

演題Ⅰ：***Dorsal raphe VGluT3-containing neurons provide a glutamatergic reward input to ventral tegmental area mesoaccumbens dopamine neurons***

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Electrical stimulation of dorsal raphe (DR) and ventral tegmental area (VTA) activates fibers of the same reward pathway (Simon *et al.* 1976; Wise and Rompre, 1989), but the phenotype of this pathway and the direction of the reward-relevant fibers have not been determined. Here, we report that DR neurons expressing the vesicular glutamate transporter 3 (VGluT3) provide a glutamatergic input to VTA dopaminergic neurons that project to the nucleus accumbens (nAcc), and that activation of this DR-VTA pathway is rewarding. Utilizing retrograde tracing, *in situ* hybridization and immunohistochemistical techniques, we found that the majority of inputs from DR to VTA have the capacity to accumulate glutamate into synaptic vesicles via VGluT3. Synapses between DR VGluT3-expressing terminals and VTA dopamine (DA) neurons were examined using double VGluT3 and tyrosine hydroxylase (TH) immuno-electron microscopy. We found that DR-VGluT3 terminals mostly synapse on the DA neurons, including those that innervate the nAcc. In order to examine the function of the VGlut3-expressing fibers, we targeted expression of channelrhodopsin2 (ChR2) in DR-VGluT3 neurons by injecting an adeno-associated virus vector encoding Cre-inducible ChR2 into DR of VGluT3::Cre (VGluT3-ChR2-eYFP) mice. Light activation of VGluT3-ChR2 fibers within the VTA elicited AMPA-mediated synaptic excitatory currents in VTA mesoaccumbens DA neurons, and resulted in DA release in nAcc. In optical intracranial self-stimulation experiments, VGluT3-ChR2-eYFP mice quickly established instrumental responding in response to VTA light activation of DR-VGluT3 fibers. In place preference experiments, VGluT3-ChR2-eYFP mice spent significantly more time in the light-paired chamber than VGluT3-eYFP controls. In addition, they also acquired a preference for the stimulation-associated chamber as reflected by the time spent there on the subsequent day, when light stimulation was no longer available. The place preference induced by light activation of DR-VGluT3 inputs to VTA was blocked by intra-VTA administration of an AMPA receptor antagonist, or by intra-nAcc administration of D1 receptor antagonist. These findings indicate that the DR-VGluT3 pathway to VTA utilizes glutamate as a neurotransmitter and is a substrate linking the DR—one of the most sensitive reward sites in the brain—to mesoaccumbens VTA DA neurons. Support: NIDA Intramural Program.

演題Ⅱ：***Time and space in the hippocampal chronocircuits***

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Co-ordinated neuronal activity is intrinsically linked with behaviour and malfunction of neuronal coordination results in psychiatric and neurological disorders. Timing is crucial for neuronal integration including events lasting from milliseconds up to several seconds. Much of the neuronal activity is rhythmic in the brain, as rhythmicity facilitates local and global interactions and enables the representation of temporal sequences. Rhythmicity provides flexibility by resetting the frequency, amplitude and phase of population activity for encoding and delivering information in support of behavioural needs. Importantly, firing of single and groups of neurons can change systematically relative to the population rhythm and reflect temporal coding of information.

We have explored how distinct cell types change their firing rates in the hippocampus by recording and labelling single neurons of freely moving and naturally sleeping rats. During spatial navigation, or the offline replay of spatial representations, pyramidal cell firing is rhythmic and phase-related to the local field potential in the theta, gamma and sharp wave related ripple (SWR) frequency ranges. The rhythmic firing of GABAergic interneurons in the hippocampus contributes to the synchronization of neuronal activity. Distinct types of interneuron can be defined by the combined exploration of molecular components, synaptic connections and spike patterns in different brain states. I recognise 21 types of GABAergic interneruon in the CA1 hippocampal area, innervating 4 types of pyramidal cells. Distinct types of interneuron innervate specific postsynaptic domains, selectively discharge at different rates, phase-locked to network oscillations in a cell type specific manner. All parts of pyramidal cells, except the axon initial segment, receive GABA from multiple interneuron types, each with distinct firing dynamics. Parvalbumin-expressing basket cells fire phase locked to field theta and gamma activity in both CA1 and CA3, and also strongly increase firing during SWRs in slow wave sleep, as do dendrite-innervating bistratified cells in CA1. Some other GABAergic cell types decrease their firing rate during sleep. The axon initial segment is exclusively innervated by axo-axonic cells, which preferentially fire after the peak of pyramidal layer theta when pyramidal cells are least active. The evolution of domain-specific GABAergic innervation was probably driven by the need of coordinating multiple glutamatergic inputs to pyramidal cells through temporally-distinct GABAergic interneurons, which independently change firing during different network states. I will demonstrate the key mechanism of coordination: a *network state-dependent temporal redistribution of inhibition over distinct subcellular domains of pyramidal cells.*

※本講演は、医科学修士課程系別セミナーとして単位が認定されます。

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