Xenon plays inhibition roles on the neuronal network activities
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Summary: To identify the xenon (Xe)-induced inhibition effect on the neuronal network activities, we examined two experimental approaches. One of them is the Raman spectroscopic observations of the membrane structure change due to the dissolution of Xe. Obtained peak shifts of membrane molecules indicated the amount of Xe in the membrane linearly depended on the structure change of the membrane. Another is the direct observation of the electrical activity change of neuronal networks under Xe pressure by using the multi-electrode arrays. When Xe gas was applied at 0.3 MPa on this system, the synchronized bursts cease within several minutes although single spikes were retaining during the suspension of the synchronized bursts. We discuss about the specific molecular mechanisms of Xe-inducing inhibition effect from these experimental evidences.

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Introduction: General anesthesia is a physiological state characterized by loss of consciousness, loss of sensation through analgesic effects, immobilization, and temporary amnesia [1]. These physiological effects are thought to be caused by a depressant effect on the central nervous system from the anesthetic agent. However, the specific molecular mechanisms by which anesthetic agents in the gaseous state, such as xenon (Xe), induce anesthesia remain unclear. Despite the uncertain mechanism, however, Xe is used clinically as a general anesthetic without causing undesirable side effects [2].

The narcotic effect of Xe was attributed to its high fat solubility and high oil/water coefficient, and following the Meyer-Overton correlation, thought to act via the lipid-dissolution hypothesis [3-5]. Although that correlation is not accepted as the main mechanism for the general anesthesia, a certain amount of Xe is thought to be dissolved in the lipid bilayer of neurons, so we tried to observe its experimental evidence in the plasma membrane of neurons as well as its model material of liposome [6]. The results indicated that the effect of Xe dissolved in the plasma membrane on the electric activities of neurons should not be neglected.

To study the Xe-induced narcotic effect on the neuronal network at the mesoscopic scale (between single-neuron and tissue scale), multi-electrode arrays (MEAs) can provide a good in vitro model. Ito et al. [7] studied the electric activity development by both MEA measurements and immunofluorescent staining observations. They clearly showed that the electric activities of neuronal networks develop from the random-spontaneous firing to the synchronized bursting (SB). Later, by applying a gas pressure system to a neuronal network on a MEA, Uchida et al. [8] found that the SB of a mature neuronal network was inhibited by applying 0.3 MPa Xe, whereas spontaneous firings remained. The inhibited SBs, however, recovered after depressurization of the Xe gas.
As the retaining of single spikes during the suspension of SB did not fit the lipid-dissolution hypothesis, we considered that the suspension was due to inhibition of the synapse transmission by the dissolved Xe. In this presentation, we show these experimental approaches to examine the Xe-induced narcotic effect on the in-vitro neuronal networks.

**Raman spectra measurements on DEPC liposome and cell membrane of living neuron under xenon pressure** [6]: Raman spectra of liposomes were measured under xenon pressures and low temperatures to observe the spectra changes accompanying the gel to liquid crystalline phase transition of the liposomes. C-H stretching bonds of the lipids in the liposome were slightly red shifted at approximately 285 K and atmospheric pressure, which coincided well with the phase transition condition. This Raman-peak shift was observed at lower temperatures and related linearly to the xenon pressures. The xenon pressure dependence on the phase transition temperature was in good agreement with the DSC measurements [9], and the red shifts of Raman peaks supported the molecular mechanism of interaction between xenon and phospholipid bilayers suggested by the MD simulations. The phase-transition measurements under xenon pressure with the microscopic Raman spectroscopy were applied to cultured neuronal networks to observe the interaction of dissolved xenon with the cell membrane and the surrounding water.

**Model system of general anesthesia by xenon in a rat cortical neuronal network cultured on multi-electrode arrays** [8]: Electrical activities of mature neuronal networks cultured on multi-electrode arrays show synchronized bursts accompanied by single spikes. When Xe gas is applied at 0.3 MPa on this system, the synchronized bursts cease within several minutes. After depressurization to atmospheric pressure of the same gas composition, the synchronized bursts gradually recover but are infrequent. Purging with Xe-free air accelerates the recovery of synchronized bursts. In contrast, applying 0.3 MPa air pressure does not produce such inhibition-recovery of synchronized bursts. We will show additional experimental data expressing the inhibition effect of Xe on the neuronal network activities depending on pressure and Xe concentrations.

**References:**