別紙２

Results report

１． Title of Research and Development： Mechanism of circadian clock based on clock genes

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４． Results of Research and Development:

The physiological and behavioral rhythms of all life on earth are bound to the earth's rotational cycle of ~24 h. This fundamental rhythm is also affected by the planet's slanted rotational axis, which causes seasonal variations in the length of the day. How life has adapted to anticipate this yearly rhythm is still debated. The mammalian suprachiasmatic nucleus (SCN) forms not only the master circadian clock, but also a seasonal clock. This neural network of ~10,000 circadian oscillators encodes season-dependent daylength changes through a largely unknown mechanism. We show that region-intrinsic changes in the SCN fine-tune the degree of network synchrony, and reorganize the phase relationship among circadian oscillators to represent daylength. We measure oscillations of the clock gene *Bmal1*, at single-cell and regional levels, in cultured SCN explanted from animals raised under short or long days. Coupling estimation using the Kuramoto framework reveals that the network has couplings that can be both phase-attractive (synchronizing) and repulsive (desynchronizing). The phase gap between the dorsal and ventral regions increases, and the overall period of the SCN shortens with longer daylength. We find that one of the underlying physiological mechanisms is the modulation of the intracellular chloride concentration, which can adjust the strength and polarity of the ionotropic γ-aminobutyric acid receptor ($GABA_A$) mediated synaptic input. We show that increasing daylength changes the pattern of chloride transporter expression yielding more excitatory GABA synaptic input, and that blocking $GABA_A$ signaling or the chloride transporter disrupts the unique phase and period organization induced by the daylength. We test the consequences of this tunable GABA coupling in the context of excitation-inhibition balance through detailed realistic modeling. These results indicate that the network encoding of seasonal time is controlled by modulation of intracellular chloride, which determines the phase relationship among and period difference between the dorsal and ventral SCN.