Form 2-4-2

Japan-US Brain Research Cooperation Program
The Group Joint Study Report [field: ②]

1. The Representative of Group Joint Study:

Osaka Bioscience Institute / Head of Mol.Behav. Biol. / Yoshiro URADE,

2. The Project Title:

Arousal state control in histamine H_1 receptor knockout mice with prostaglandin E_2 and orexin infusion

3. Japanese Investigator 's Name, Title, Affiliation and Phone Number:

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4. U.S. Investigator 's Name, Title, and Affiliation:

①Chief;

Dr. Clifford B. Saper • Chairman • Beth Israel Deaconess Medical Center, Harvard Medical School

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Dr. Priyattam J. Shiromani, Head, VAMC West Roxbury

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5. The Term of Research: **From** 2001. 4. 1. **To** 2004. 3. 31. (3 Years)

6. The Abstract, the Result and the Significance of Research (300 Words):

We have shown that amount of wakefulness is increased by infusions of PGE_2 or orexin into the wild type mouse brains, while having no effects in the histamine H_1 receptor (H1R)-KO mice. Histamine synthesis in the hypothalamus may underlie the PGE_2-induced promotion of wakefulness and this effect is principally mediated by EP_4 subtype of PGE_2

receptor, since PGE_2 or EP_4 agonist increased histidine decarboxylase activity, histidine decarboxylase mRNA, and contents of histamine in the hypothalamus. To further analyze neuronal consequences, following studies will be examined in this year. First, conditional H1R gene knockout mouse will be made using the CRE/loxP system. Second, sleep-wake activities and orexin release form pre-synaptic terminus will be analyzed with a microdialysis probe inserted in the histaminergic tuberomammillary nucleus (TMN) of the CRE/loxP-H1R knockout mouse. In addition, activities of living TMN neurons will be visualized as a dynamics of intracellular calcium using transgenic mice expressing calcium sensitive fluorescent proteins (cameleon) in the orexin neurons. These studies will demonstrate the localization of neurons which regulate the arousal state under the control of the histaminergic and orexinergic systems in the brain.

7. The Others (Practical Issues, Special Mention Matters):