

Japan-US Brain Research Cooperative Program

The Report of Information Exchange Seminar in 2008 fiscal year

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1. The Seminar Title:

Steroid Hormone Action and Sex Differences in Brain Function

2. The Term: From 2008. 09. 08 To 2008. 09. 11

3. The Location:

2695-2 Nagarafukumitsu, Gifu City, Gifu Prefecture, Japan
Nagaragawa Convention Center, International Conference Room

4. The Representative's Name, Title and Affiliation:

Japanese Coordinator:

Nobuhiro Harada, Professor, Fujita Health University

US Coordinator:

Robert J. Handa, Professor, Colorado State University

5. The Participants:

Japan: The Invited participants 22 people The others 35 people

Name, Title and Affiliation of the Invited participants

Shinji Hayashi, Ex-Professor, Ex-Yokohama City University

Shogo Haraguchi, Doctoral Fellow, Waseda University

Kazuyoshi Tsutsui, Professor, Waseda University

Yoshihisa Uenoyama, Assisitant Professor, Nagoya University

Masakatsu Kato, Associate Professor, Nippon Medical School

Hiroyuki Minakata, Division Chief, SuntoryInstitute for Bioorganic Research

Yoshitaka Oka, Professor, University of Tokyo

Yuji Mori, Professor, University of Tokyo

Koh Shinoda, Professor, Yamaguchi University

Suguru Kawato, Professor, University of Tokyo

Nobuhiro Harada, Professor, Fujita Health University

Shinji Tsukahara, National Institute for Environmental Studies

Masugi Nishihara, Professor, University of Tokyo

Kataaki Okubo, Associate Professor, University of Tokyo

Dai Mitsushima, Associate Professor, Yokohama City University

Ken-ichi Matsuda, Associate Professor, Kyoto Prefectural University of Medicine

Yasuo Sakuma, Professor, Nippon Medical School

Sonoko Ogawa, Professor, University of Tsukuba

Yasuhiko Kondo, Assistant Professor, Nippon Medical School

Takefumi Kikusui, Associate Professor, Azabu University
 Hirotaka Sakamoto, Assistant Professor, Kyoto Prefectural University of Medicine
 Mitsuhiro Kawata, Professor, Kyoto Prefectural University of Medicine

US: The Invited participants 21 people The others 16 people

Name, Title and Affiliation of the Invited participants

Arthur Arnold, Professor, University of California
 Marc Tetel, Assistant Professor, Wellsley College
 Melinda E. Wilson, Assistant Professor, University of Kentucky
 Shaila Mani, Assistant Professor, Baylor University
 Paul Micevych, Professor, University of California
 Paul Mermelstein, Associate Professor, University of Minnesota
 Martin Kelly, Professor, Oregon Health & Science University
 George Bentley, Assistant Professor, University of California
 Donald Skinner, Assistant Professor, University of Wyoming
 T. John Wu, Assistant Professor, Uniformed Services University
 Ei Terasawa, Professor, Wisconsin National Primate Research Center
 Suzanne Moentor, Associate Professor, University of Virginia
 Patrick Chappell, Assistant Professor, University of Oregon
 Robert J Handa, Professor, Colorado State University
 Charles Roselli, Professor, Oregon Health & Science University
 Geert DeVries, Professor, University of Massachusetts
 Stuart Tobet, Professor, Colorado State University
 Nancy Forger, Professor, University of Massachusetts
 Kim Wallen, Professor, Emory University
 Tracy Bale, Assistant Professor, University of Pennsylvania
 Anthony Auger, Assistant Professor, University of Wisconsin

6. The Abstract and the Significance of this seminar:

Steroid hormones are key modulators of the intercellular communications network used by the central nervous system. These hormones, although simple in structure, have the capacity to influence virtually all neural functions; from the maintenance and organization of neurons and their connections during development, to the activity and function of neurons in adulthood, to the death of neurons during aging and neuropathology. Steroid sensitive neural circuits are implicated, not only in the control of reproductive hormone secretion and behaviors, but also non-reproductive functions such as hormonal responses to stressors, emotion, aggression, cognition, activity, feeding and others. Thus, an understanding of the molecular mechanisms of steroid hormone action, the location of their receptors, and the factors which regulate their synthesis and secretion both in the brain (neurosteroids) and the periphery (gonadal and adrenal steroids) are of paramount importance for determining how the brain can integrate diverse information and the pathological consequences that arise when this integration goes away.

Since the early '60s there have been extensive interactions among U.S. and Japanese neuroendocrinologists studying the action of steroid hormones in the brain. Consequently, several US/Japan joint meetings concerning neurosteroids (for example, JSPS/NSF sponsored US/Japan symposia at 1994 and 2000) have been successfully held, and then a number of fruitful collaborative studies between US and Japanese scientists have established. Although a number of interactions between

US and Japanese neuroendocrinologists still remain, but have been recently declining. So, it was our hope that this meeting involving in neuroscientists from US and Japan would again increase the opportunity for cooperative research between these two countries, particularly between young scientists.

The focus of this meeting was in elucidating the mechanisms of actions of steroid hormones on neuroplastic changes in the brain during development and adulthood and thereby point towards some of the future directions that this currently burgeoning field should take. The invited speakers from both the US and Japanese sides have contributed tremendously to this field.

The cellular and molecular mechanisms through which steroid hormones act to regulate physiology and behavior have been becoming increasingly complex. Consequently, one goal of this meeting was to bring together scientists from the US and Japan who have approached related topics from a number of overlapping perspectives, in cutting edge research areas. The speakers were selected from scientists who have used molecular, anatomical, physiological, biochemical and behavioral approaches as well as a variety of animal models. These have been mixed into each individual session. A second goal of this meeting was to promote interaction and discussion in the hopes of facilitating scientific exchange and promoting international collaborative efforts. Although there have been interactions between neuroendocrinologists from the US and Japan in the past, this meeting further strengthened the tie between scientists of these two countries to help facilitate new discoveries. Diversity of the speaker population was directly considered. Furthermore, session chairs were selected who have been knowledgeable in the area and who have demonstrated ability to promote discussion with questions and counterpoints. A number of observers from both the US and Japan were invited, the goal of these observers being to present alternate points of view during discussion. A poster session was also held where exciting new research from Japanese and U.S. laboratories were presented.

7. The result of this seminar and its implication for future perspective:

The meeting were arranged for 7 sessions to focus on the mechanisms of actions of neurosteroids on neuroplastic changes or synaptic networks during perinatal development and adulthood and to share the scientific information between the US and Japan scientists through thorough discussion on the topics in the cutting edge research areas. The sessions were composed of **(1) Classical mechanisms of sex steroid hormone action in the brain: transcriptional regulation and cellular functions, (2) Alternative mechanisms of steroid hormone action in the brain: rapid membrane responses, (3) Novel neuropeptides and their receptors in the control of reproduction, (4) Regulation of GnRH neurons and central control of steroid hormone secretion, (5) Steroid hormone metabolism and novel mechanisms of steroid hormone action, (6) Developmental effects of steroid hormones: sexual differentiation of the brain, (7) Steroid hormones and sex differences in behavior.**

In the session 1, it was shown that steroid hormone action can be modulated by nuclear receptor coactivators of SRC-1 and CBP in specific brain regions to influence a variety of steroid-dependent behaviors, and also by methylation of ER in the neuroprotective and anti-apoptotic effects of E2. In the session 2, rapid E2 signaling in the specific brain regions or physiological events was indicated to be mediated by membrane ER in contrast to classical intracellular ER-mediated E2 signaling. This membrane ER was demonstrated to directly interact with a G protein coupled receptor, the mGluR1a. A unique neural activator, 7 α -hydroxypregnenolone was reported to acutely stimulate locomotor activity. In the session 3, gonadotropin-releasing hormone (GnRH) and gonadotropin-inhibitory hormone were reported and characterized as a new key neurohormone controlling reproduction. In the session 4, the role of calcium channel, potassium channel, and GPR30 in GnRH neurons in rapid non-genomic action of E2 was reported and discussed. The neurological mechanisms underlying negative and positive feedback regulation by E2 in GnRH neurons was also reported. The control mechanisms of GnRH neurons by metastin (kisspeptin) neurons, one of the hottest topics in the field of reproductive neuroendocrinology, were suggested and discussed. An endogenous circadian clock and pheromone was identified as a modulator of GnRH pulse generation. In the session 5, a role for the androgen metabolite, 3 β -androstenediol was

identified as a bioactive ligand of ER β and suggested to mediate brain functions through its binding to ER β . The correlation between brain aromatase and nuclear/membrane sex-steroid receptors in expression and regulation was suggested on the brain sexual differentiation. The physiological importance of aromatase/estrogen system in the brain functions was demonstrated by analyses of synaptic plasticity and by sexual/locomotive behaviors using aromatase transgenic and knockout mice. In the session6, aromatase/estrogen system in the brain was discussed in relation to its involvement in the sexual differentiation of behaviors, in the formation of sexually dimorphic nuclei ,and in the neurogenesis. In the session 7, it was reported that sex differences in social behavior and stress response were organized and activated by neurosteroid.

In this meeting, 5 of 22 Japanese invited speakers and 9 of 21 US invited speakers were doctoral fellows or assistant professors, and furthermore, there were many Japanese and US young participants in the poster presentation. Both leading researchers and young newcomer researchers have joined in the meeting and contributed together to the development of new perspectives. We, participants in the meeting could also share up-to-date scientific information. Now, we hope young newcomers will continuously pursue several open issues raised in the meeting.

8. The Others (Other Comments):

The proceedings of this meeting have already been published in the special issue of “Journal of Neuroendocrinology” (volume 21, number 4, April 2009) and opened for researchers in the related field.