

A. Outline of activities (chronologically)

Friday October 9:

Departure from Copenhagen for Osaka.

Saturday October 10:

Arrival in the morning at Osaka, Kansai International Airport, and transportation to Masumi Sou Hotel, Ikeda City. In the evening we (my wife, my daughter and I) had dinner with Dr. Shigeri, who nicely introduced us to Japanese cooking and culture.

Sunday October 11:

Visit together with Dr. Shigeri to historical Nara seeing the impressive Todai-ji and Horyu-ji Temples.

Monday October 12:

Participation in the Japanese Alcohol, Nicotine and Drug Addiction Conference 2015 in Kobe. I gave a talk in the symposium entitled, "Homeostatic mechanism of dopaminergic function against the damage by psychostimulant". Before the symposium I met for scientific discussions with the other speakers, who presented their interesting work to me. The Chairs of the symposium, Dr. Atsumi Nitta, Laboratory of Pharmaceutical Therapy & Neuropharmacology, University of Toyama and Dr. Ichiro Sora (The president of the 27th JSND), Department of Psychiatry, Kobe University), also participated in the discussion. Dr. Yoshiyuki Kasahara showed studies on serotonin (SERT) and dopamine transporter (DAT) knock-out (KO) mice. Specifically, he showed data demonstrating that SERT KO mice did not get sensitized to metamphetamine; however, a 5-HT1B receptor antagonist restored sensitization and moreover, sensitization was found to be enhanced in 5-HT1B receptor KO mice. The results led to an interesting discussion about the role of the serotonin system in the actions of metamphetamine. Dr. Takatoshi Hikida showed an exciting series of data based on expression of tetanus toxin in striatal dopamine D1 receptor neurons or dopamine D2 receptor neurons. Remarkably, the data showed that D1 receptor activation (direct pathway) and inactivation of D2 receptors (indirect pathway) critically determine reward-based and avoidance learning, respectively. Finally, Dr. Yoshiaki Miyamoto discussed intriguing data relating to the N-acetyltransferase, Shati/Nat8l, that the group has identified in the nucleus accumbens (NAc) of mice and shown to be critical for the behavioral effects of metamphetamine.

In the evening we participated in the excellent galla dinner/reception. This was a brilliant opportunity to further interact with Japanese scientists.

Tuesday October 13:

Participation in the Japanese Alcohol, Nicotine and Drug Addiction Conference 2015 in Kobe. I gave a plenary lecture entitled 'The dopamine transporter: a key player in psychostimulant addiction and dopaminergic pathologies'. The lecture was well received and the audience had several interesting and thought-provoking questions.

Wednesday October 14:

Traveling to Hiroshima by 'Shinkansen' to visit the laboratory of Professor Norio Sakai, Department of Molecular and Pharmacological Neuroscience, Institute of Biomedical & Health Sciences, Hiroshima University. Importantly, just after arrival laboratory we had the

opportunity to see the Hiroshima Peace Memorial Park and Hiroshima Peace Memorial Museum.

In the laboratory, Professor Sakai and his colleagues presented recent results based on which we had a stimulating scientific discussion. First we discussed data showing how chemical chaperones could enhance surface expression of SERT and SERT mutations, and the implications of these data for understanding biosynthesis and targeting of this important transport protein. Second, we discussed how the constitutively active G protein coupled receptor GPR3 plays a putative role in neurite outgrowth and neuron maturation, as well as in protection of neurons from apoptosis, via activation of the ERK and Akt signaling pathways. I presented my research both informally during our scientific discussions and in a formal seminar.

In the evening we had dinner with Professor Sakai and his son, experiencing the Hiroshima cousin including okonomiyaki.

Thursday October 15:

Together with Professor Sakai and three of his students, we went to see the famous and beautiful Itsukushima Shrine on Miyajima Island. In addition to learn more about the fascinating culture and history of Japan, the trip was an excellent opportunity for continuing the scientific discussions from the day before. It was very nice to talk to the students, although they were not completely fluent in English.

In the afternoon, we returned by 'Shinkansen' to Osaka and Ikeda City.

Friday October 16:

Visit to Osaka University and the laboratory of Professor Yoshikatsu Kanai. Before presenting my research at a formal seminar, I had very good discussions with three of Professor Kanai's colleagues. In particular, I had a very fruitful and inspiring interaction with Dr. Shushi Nagamori on several timely topics. These included i) what we can learn from rare coding variants in transport proteins in relation to disease mechanisms; ii) "Transportsome" as functional units of transporters; and iii) how e.g. amino acid transporter not only operate to supply amino acids for the cell but also play a role in cellular signaling by taking up amino acids that may activate intracellular signaling cascades. My formal seminar also generated interesting questions and a good scientific discussion. Altogether, the visit at Professor Kanai's laboratory was very stimulating and has inspired new angles on projects in my own laboratory relating to the monoamine transporters.

In the evening, we had a very nice dinner together with Professors Kanai and three of his colleagues while continuing our scientific discussions.

Saturday and Sunday, October 17-18:

Dr. Shigeri and his son kindly took us to Yoshino where we had a fantastic opportunity to get further acquainted with Japanese history and culture. We stayed in a 'Ryokan', saw Kimpusen-ji, went to a Buddhist ceremony early Sunday morning and experienced the 'Hōnen Matsuri', the Japanese harvest festival.

Sunday evening we had a wonderful Japanese dinner in Dr. Shigeri's home.

Monday, October 19:

Visit to my host, Dr. Shigeri's Institute (AIST). Dr. Shigeri and I had long and interesting discussions about the wide spectrum of application of MALDI-TOF. Dr. Shigeri also told me about his very interesting work on frog skin peptides and we discussed the many utilities of these peptides. Overall, I was very impressed about the high technical quality, the expertise available and the level of science in Dr. Shigeri's group and at AIST in general.

Tuesday, October 20:

Visit to Kyoto guided by a postdoctoral fellow from the group of Dr. Shigeri. We were very impressed about the cultural heritage present in Kyoto where we visited magnificent places such as the Golden Pavillon, Kiyomizu-dera and Nijojo. During the day I also had discussions with Dr. Shigeri's postdoc about scientific career possibilities in Japan compared to Europe and the importance of being trained also abroad. Unfortunately, I learned that many Japanese students do not want to go to Europe or USA for a postdoc but prefer to stay in Japan.

In the evening we returned to Ikeda City where Dr. Shigeri took us to an outstanding Sushi restaurant.

Wednesday, October 21:

Visit to Suntory Foundation for Life Sciences together with my host, Dr. Shigeri. Dr. Keioko Shimamoto, who showed us around in the remarkable research facility, received us. During the tour, different researchers described their work. I was very impressed about the levels of science conducted, the people working at the institute and the top class equipment available for the researcher to perform their studies. After the tour of the research center, we had lunch together with Director, Professor Shigetada Nakanishi. I have had the pleasure to know Professor Nakanishi since the early nineties when we collaborated on identification of ligand binding sites in the tachykinin receptors. As a result we co-authored a paper in Nature and in PNAS. It was a great honor to meet him again and discuss the latest developments in science. Strikingly, Professor Nakanishi has recently – like me - had great interest in the dopamine system.

After the visit we traveled by 'Shinkansen' to Tokyo.

Thursday, October 22:

Visit to the laboratory of Professor Kazu Ikeda at Tokyo Metropolitan Institute of Medical Science. First, Professor Ikeda invited my family and I on a beautiful harbor cruise, which gave a great impression of the city of Tokyo. We had a nice lunch and informal scientific discussions. After the lunch I visited the Institute where I gave a formal seminar before having further discussions with Dr. Ikeda as well as with different laboratory members. Specifically, we had discussions about the use of genome-wide association studies in the study of drug action and drug addiction. These discussions were very fruitful and we discussed different possibilities of future collaboration. In the evening, Professor Ikeda took us out for an excellent dinner.

Friday, October 23:

Visit to the laboratory of Professor Kohichi Tanaka, Medical Research Institute, Tokyo Medical & Dental University. In the morning, three students of Professor Tanaka took us sightseeing in Tokyo. This gave us the opportunity to see both Asakusa and the Skytree. The Skytree was an exceptional experience with outstanding views of the Tokyo metropol. The

students were excellent guides and, also, we had plenty of time to discuss and compare graduate student programs in Denmark and Japan. One of the students was excellent in English and asked many very good questions. In the afternoon, I presented my work at a formal seminar that was followed by several interesting questions. Following my seminar, I had the chance to have informal discussions with Professor Tanaka and other members of his laboratory. I was very impressed about their work on glutamate transporters using inducible knock-outs. It was also interesting to discuss the prospect of implementing the use of the CRISPR/Cas system for generation of genetic mouse models.

In the evening we had a great dinner together with Professor Kohichi Tanaka and four laboratory members.

b. Thoughts on the present state of transporter biology in Japan.

I was overall very impressed about the level of science carried out in the laboratories I visited. It was great to see how different laboratories were undertaking many different approaches in their research. I noticed that many of the laboratories had really excellent facilities and access to state-of-the-art equipment. The group members in the different laboratories also impressed me, although several had some troubles speaking English. It was also interesting to learn how Japanese laboratories are organized with a full Professor often having several Assistant and Associate Professors working under him/her. The system appeared to work efficiently but it is different from the Danish and American system where the department often is split up in smaller groups with one principal investigator per group. Working under a full Professor as an Assistant/Associate Professor could be challenging when attempting to demonstrate your scientific independence. I noticed moreover that, with a few exceptions, there were very few foreigners working in the laboratories. In the laboratories I almost exclusively met Japanese except in a couple of places where one or two either Chinese or Taiwanese were working in the laboratory. Most of the laboratories I visited were not only focused on transporters but also had interests in related areas of neurobiology. For me, this was really interesting by enabling discussions of e.g. use of genetics and genetic tools as well as several other approaches. However, still some of the groups I visited are central to the transporter field. For example, I would like to emphasize the work carried out in the laboratory of Professor Kanai, which was really impressing and very inspiring to me. Altogether, it is my impression that science in Japan is doing extremely well but that it could benefit from more 'internalization' including recruiting foreigners to Japan as well as encouraging more young Japanese to go Europe, USA or other parts of the world during their scientific career. Indeed, especially after meeting so many excellent students, I would more than welcome applications from Japanese students wanting to join my laboratory.

c. Comments to JSPS

I am very grateful to the JSPS for giving me this outstanding possibility for leaning about Japanese science, culture and history. Meeting so many great scientists and interacting with them would otherwise have been impossible. My visit has led to many valuable contacts in Japan that I am convinced will be of benefit for my research many years ahead. It is also my sincere hope that my visit not only will generate possibilities for collaboration but also will generate possibilities for having Japanese students coming to my laboratory and for me to send Danish students to Japanese laboratories.