(a) Outline of academic activities

a1. Experimental research

Cannabinoid signalling system is widespread in the central nervous system. Neuroglial cells that represent the main homeostatic and defensive system of the CNS have been demonstrated to express functional CB1/CB2 and CB-like cannabinoid receptors (Stella, 2010, Glia, 58:1017). In particular astroglial CB1 receptors mediate neuronal-glial communications in hippocampus (Navarrete & Araque, 2010, Neuron 68: 113), whereas CB2 receptors are up-regulated in activated microglia in a pathology-specific manner (Zhang et al., Eur J Neurosci. 2003, 17:2750); with cannabinoid signalling system being arguably involved in promoting neuroprotective microglial phenotype. Furthermore, both CB1 and CB2 receptors were detected in cells of oligodendroglial lineage; activation of these receptors was proposed to regulate oligodendrocytes differentiation.

The main aim of this proposal was to collect preliminary data, which may provide a background for an extended collaboration on the role of cannabinoid receptors in neurodegeneration with a particular emphasis on Alzheimer's disease (AD). To that end we studied expression of CB1 and CB2 receptors in neuroglial cells, including hippocampal and cortical astrocytes, hippocampal and cortical microglia (in cooperation with Professor Mami Noda), and hippocampal NG2 glial cells. We used immunocytochemistry to identify cell type specific expression of cannabinoid receptors, using CB1 and CB2 specific antibodies in combination with glial cell specific markers (astrocytes: GFAP and glutamine synthetase; microglia: tomato lectin and Iba-1, NG2 cells - NG2 proteoglycan). We confirmed expression of CB1 receptors in astrocytes, CB2 receptors in activated microglia and detected CB1 receptors in NG2 cells.

In a separate series of experiments performed in visitor scientist laboratory in Manchester (immediately prior to visit) using antibodies and staining protocols provided by the project host (Professor Masanobu Kano) we studied expression of CB1 receptors in astrocytes associated with senile plaques in a triple transgenic mouse model of AD (this model carries 3 disease-specific mutated genes for amyloid precursor protein, presenilin 1 and tau protein and has a manifest histopathology including accumulation of senile plaques and intraneuronal tangles - see Oddo, 2003, Neuron, 39:409). As we have demonstrated previously (Olabarria et al., 2010, Glia, 58:831) astroglial cells in these Ad mice undergo two types of pathological remodelling resulted in an appearance of two distinct cellular phenotypes. Astrocytes associated with senile plaques demonstrate signs of mild (isomorphic) reactivity,

whereas cells distant to amyloid deposition display reduction in morphological profiles and down-regulation of glutamine synthetase these being regarded as a sign for atrophy/asthenia. We found reduction in expression of CB1 positive astroglial profiles specifically in the cells surrounding senile plaques, whereas astrocytes distant to plaques are not much differenet from the cells in control(non-Ad) tissues..

Based on these preliminary data we may suggest that AD progression affects CB1 receptor expression in astroglia and therefore we now plan future collaboration aimed at in depth investigation of CB1 receptors expression and functional properties in hypertrophic/reactive astrocytes in animal models of neurodegeneration.

a2. Discussions

In the course of visit several in depth scientific discussions were held with Professor Masanobu Kano (the host PI on the project), with Professors Hiroshi Kawasaki, Osamu Hori, Noriyuki Ozaki, Takeshi Sakurai, Takako Ohno-Shosaku and Haruhiro Higashida in Kanazawa University, with Professor Mami Noda in Kyushu University. During these discussions various aspects of neuropathology of glial cells were analysed, and plans for future research outlined.

a3. Research visits

During the period of my stay in Japan I have visited Kyushu University (collaboration with Professor Mami Noda; we performed staining of microglia with CB1 and CB2 antibodies) and Kanazawa University (collaboration with Professor Takako Ohno-Shosaku). In both Universities I have delivered seminars (lecture titles: in Kyushu University “Physiology and pathophysiology of neuroglia”, in Kanazawa University “Astroglia in Ageing and Alzheimer's disease).

In the University of Tokyo I delivered 8 lectures to postgraduate students of the Medical school. Lecture titles were:

1. History of Neuroscience and Introduction to neuroglia
2. Neuroglia: Definition, Classification, Evolution
3. Cell biology and physiology of astroglia
4. Neuronal-glial chemical transmission mediated by glutamate and ATP
5. Glial calcium and sodium signalling
6. Glia in neuropathology
7. Astroglia in ageing and Alzheimer's disease

8. Microglia in physiology and pathophysiology

(b) Impressions and thoughts on the present state of science in Japan in your field.

The neuroglial research in Japan is strong and there are numerous groups focusing on various aspects of glial physiology and pathophysiology. Japanese laboratories have well deserved international reputation and publication in the most prestigious journals. At the same time educational curriculum for both under and postgraduates is almost completely devoid of glial part, which can somewhat jeopardise future developments in the field.

(c) A list of papers published during or after the fellowship period and the names of the journals in which they appeared.

Because of the very limited time spent in Japan (3 weeks) no papers have been produced; nonetheless the preliminary results obtained may initiate future collaborative research that can identify the role of cannabinoid signalling system in neurodegeneration.

(d) Comments or suggestions to JSPS, especially concerning the Fellowship program

The JSPS fellowship scheme is a very important programme that is vital for international collaboration and increase of visibility of Japanese science.

(e) Other comments

I am very grateful to Professor Masanobu Kano for his continuous support during my visit.