Nano-bio-imaging with Radiopharmaceuticals and its Application to Health Sciences

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1. Introduction

"Nano-bio-imaging" is the entirety of various kinds of imaging technology supported by "nanotechnology", and it enables further progress of research in nanomedicine and nanotechnology. Although there are various available methods, our team is in charge of nano-bio-imaging using a nuclear medicine technique.

In the methodology of nuclear medicine, we administer various kinds of radiopharmaceuticals to investigate events taking place in a living body from the outside. The foundation of this technique could date back to the early 20th century when it was originally developed as a "tracer method". This method was first explored by Dr. George von Hevesy, a Nobel laureate in chemistry in 1943. This method continued to make progress, and it came to be applied to human studies and was then called "nuclear medicine" in the latter half of the 20th century. The initial system was called scintigraphy, and later it was combined with computed tomography at the end of the 20th century. The technique was later fused with technology of computed tomography, and has been established as the "single photon ejection dislocation method" (SPECT), and "positron emission dislocation method" (PET), both of which seemed to be the most suitable tools for "nano-bio-imaging" since they can be used to visualize pharmacodynamic/pharmacokinetic information in the body of living subjects by injecting only a small amount of radiopharmaceuticals (1 to 2 nano-moles). Here, the term "a tracer" means injected radiopharmaceuticals used for obtaining information (signals) on phenomena in the body, and sometimes can also be called "a probe", meaning that we can probe the presence of extremely small amounts of biological substances. Thus, in the nuclear medicine technique, radiolabelling with high specific activity is very important to visualize the presence of very small amounts of materials in a "nano-" to "pico-" mole order. Therefore, it can be said that this technique is the right tool optimized for nano-bio-imaging.

Our group has been seeking further potential and new applications of this radionuclide technique to clinical evaluation/diagnosis and health promotion science.

We are aiming at promoting the medical use of the radionuclide technique and its further applications to health promotion science; mainly in terms of image analysis and medical engineering research and development as follows:

[1] modeling in neural transmission function nano-bio-imaging and temporary establishment of an assay,

[2] application of nano-bio-imaging technology to preventive medicine/health generation science,

[3] development of research software hardware related to cancer examination of 3 focus, and promotion of related studies. In 2007, we mainly promoted the following study themes, particularly on PET studies.

2. Nano-bio-imaging of a Neural Transmission Function and Establishment of a Simple Quantification Method

2.1. Bio-information obtainable from the living human brain

Human mental function is based on the action of our brain. On one hand, one ultimate and fundamental aim of this study topic is "elucidation of psychiatric functions of human brain". On the other hand, in modern society, the incidence of neuropsychiatric disorders including depression, anxiety disorder and cognitive disorder (dementia) as well as physical disorders such as metabolic disorder is constantly increasing. Various factors such as "stress" and "lifestyle" have been regarded as among the main causes of the current situation of our society. The large amount of stress in our life has been associated with increased rate of various disorders. When we review such problems, nano-bio-imaging technology could be expected to offer basic data potentially useful for establishing practical strategies.

As for the available methodology for nano-bio-imaging, we can use PET to measure cerebral energy (glucose) metabolism by injecting a small amount of radio-labeled glucose ([^{18}F]fluorodeoxyglucose: FDG) (Fig. 1). Due to the activated regional brain metabolism, demand for glucose and oxygen is increased, inducing dilation of brain capillaries, which is observed as an increase in regional cerebral perfusion. Cerebral perfusion can be measured using radio-labeled water ([^{15}O]H_2O: Figs. 1 and 2). More recently, a method using magnetic resonance imaging has also been applied

to the measurement of brain regional perfusion (functional MRI: fMRI). In addition, another technique using near-infrared light (NIRS) has been introduced for measuring brain regional perfusion. PET is still used very often, but mainly for measuring regional brain glucose consumption and for evaluating neuro-transmission function (Fig. 2).

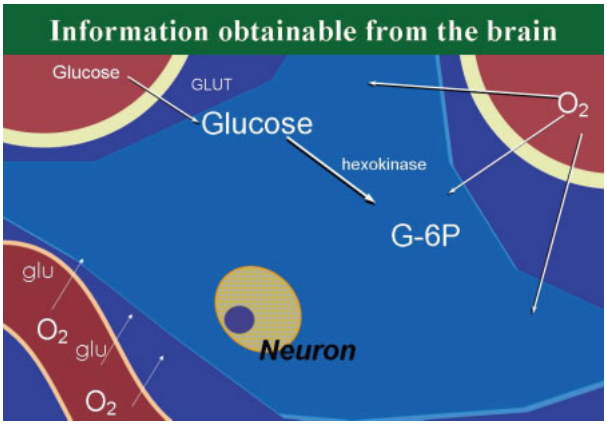

Fig. 1. Energy resources of the brain. The most important energy resource of the human brain is "glucose". Glucose and oxygen molecules necessary for glucose metabolism are supplied by the blood stream. Brain regions with increased activity are accompanied by increased regional cerebral blood flow.

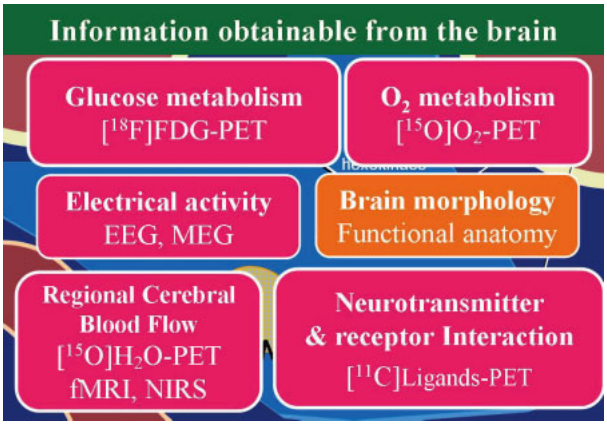

Fig. 2. Information obtainable from the living human brain. Information regarding glucose and oxygen metabolism can be obtained using PET. Presently, regional cerebral blood flow is measured using various methods. Interaction of neurotransmitters and receptors can also be measured using PET.

In the human brain, neurotransmitters can manifest their effects even in very small amounts. It is not easy to visualize the actions of neurotransmitters in the living human brain externally without using a highly sensitive technique such as PET [1]. In addition, with PET, it is possible to quantify interactions between neurotransmitters and neuroreceptors as well as tissue metabolism in the living brain using the time course data of radioactivity in the blood (plasma time activity curve: pTAC) and in the brain tissue (tissue time activity curve: tTAC). So far, our group has studied neurotransmission of the histaminergic and dopaminergic neuronal systems, by constructing a suitable model and a simplified quantification method that can be applied to further clinical studies [2].

2.2. Imaging study on functions of the histaminergic nervous system

We have conducted studies regarding quantitative measurement of neural transmission in the histaminergic and dopaminergic nervous systems non-invasively using various models [2,3]. [^{11}C]Doxepin, a tracer for histamine H1 receptors (H1Rs), is a good example of the medical application of the tracer method to clinical medicine. One of the most frequently used therapeutic drugs for "pollinosis" (or "hay fever") is a H1R antagonist (antihistamine). There are many available antihistamines but some of them have sedative side effects. Therefore, it is important to develop an objective and reliable method for measuring the strength of such sedative side effects.

To date, we have studied the mechanism of functional suppression in signal transmission through H1Rs in the brain. Usually, antihistamines are used to suppress the actions of mast cells in the peripheral blood and to control allergic reactions. However, part of these drugs may enter the brain and suppress the signal transmission of intra-cerebral H1Rs. As a result, it becomes difficult to maintain arousal (sedative effects), and sometimes these drugs might cause us to make mistakes during work or while driving, resulting in decreased work efficiency or traffic accidents. Considering such a background, objective measurement of the sedative effects of these drugs becomes very important.

We succeeded in quantifying the strength of the sedative effects of antihistamines in terms of H1R occupancy rate in the brain using PET, and we have measured this clinically (in collaboration with Professor Kazuhiko Yanai at the Department of Pharmacology, Graduate School of Medicine, Tohoku University). Previously, investigators have performed macroscopic behavioral techniques such as cognitive examinations and subjective sleepiness measurement using many volunteer subjects to evaluate drug sedative effects.

In 2007, we performed a clinical test to evaluate the sedative profiles of "bepotastine", a new antihistamine developed in Japan. It was thought that the basic pharmaceutical classification of this antihistamine was a mildly sedative antihistamine. Then, we compared the effects of this drug with those of diphenhydramine, which has been classified as a sedative antihistamine and whose sedative characteristics were previously confirmed. We obtained supporting data regarding the classification of bepotastine as a mildly sedative antihistamine also by PET [4] (Fig. 3).

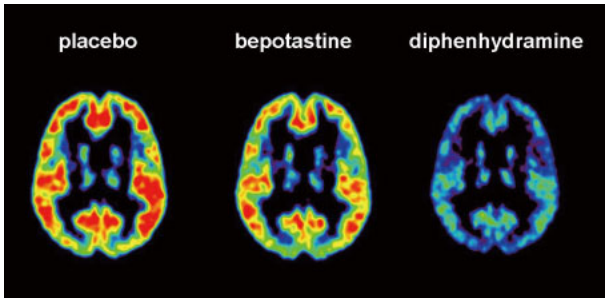

Fig. 3. Binding potential images of human brain following oral administration of placebo, bepotastine (a mildly sedative antihistamine), and diphenhydramine (a sedative antihistamine). Values of binding potential or brightness of images can indicate the strength of sedative side effects.

From the viewpoint of cognitive neuroscience, the category of cognitive function (psychomotor performance) measured in antihistamine studies is mainly "vigilance and attentive function" of the human brain. Such function can be suppressed with the presence of two different tasks at the same time (dual tasks). The mechanism of the interference phenomenon has not yet been elucidated physiologically, and such a study theme could be a good topic for nano-bio-imaging study. We therefore attempted to elucidate the brain mechanism of interference created by dual tasking using [^{15}O]H_2O PET [5].

It was thought that the action of histamine in the central nervous system contributed to the recognition of pain; almost nothing was revealed regarding the brain mechanism of itching sensation. We induced pseudo-allergic reaction using stimulation with histamine solution of the peripheral tissue (skin) and showed using functional MRI that it was very likely that the central nervous system also contributes to the recognition of the itching sensation [6]. In addition, the difference in the recognition of the itching sensation in the regional brain mechanism compared with the pain sensation was elucidated.

Moreover, we also performed studies related to recognition and memory of color [7], and subjective feeling of beauty ("a kansei" function) and ugliness of a chord [8]. We therefore hope that, ultimately, human psychiatric functions can be elucidated based on many accumulated investigational facts.

2.3. Usefulness of nanobioimaging on evaluation of drug transporter proteins and effects of their genetic polymorphisms

The Human Genome Project (HGP), a 13-year international project, was completed in 2003. This project identified approximately 20,000-25,000 genes in human DNA and determined the sequences of 3 billion chemical base pairs of human DNA. Since then, many people have expected the establishment of a system for "individualized or personalized medicine". However, this is still a long way off; there are huge numbers of transporters and enzymes contributing to every process of drug absorption, distribution, metabolism and excretion.

In the human body, for instance, there are many drug transporters, including p-glycoprotein (P-gp) (Fig. 4), multi-drug resistance protein (MRP), and organic anion transporting polypeptide (OATP) in various organs. It is not easy to determine the functional effects of various genetic mutations. The field of "pharmaco-genomics" or "pharmaco-genetics" has explored the relationship between single nucleotide polymorphisms (SNPs) and pharmaco-kinetic/-dynamic outcomes (Fig. 5). The merit of using molecular imaging in this field is that we can obtain biological information regarding changes in an intermediate "endo-phenotype", lying between changes in genotype and phenotype.

As an example, P-gp, a gene product of multidrug resistance gene 1 (MDR1) in humans, is one of the most important transporters contributing to drug transport in the human body. It works like a cellular pump equipped by a battery, transporting various xenobiotics (biologically active substances from the outside) that are energized by ATP-binding cassettes (ABC) (Fig. 4). P-gp was first discovered as the causative substance for multidrug-resistance of cancer cells, which altered membrane permeability of anticancer drugs. Then, P-gp was later identified in various normal tissues as well. Currently, it is known that P-gp is expressed in cells of various organs such as the intestinal tract, liver, kidney, placenta, and brain (blood-brain barrier: BBB). Most of these organs have secreting function where cells transport xenobiotics actively from the inner part of endothelial cells of capillaries to the capillary lumen (Fig. 4).

So far, the effect of MDR-1 polymorphism on BBB permeability has been studied in humans using PET and [^{11}C]verapamil between SNPs such as C1236T and C3435T. These previous studies demonstrated that there was no difference in BBB permeability where no differences among different polymorphisms were observed. However, there have been no studies to evaluate such differences using drugs at clinical doses (Fig. 5).

We have measured variation of H1R occupancy following oral administration of various antihistamines. Variation in cerebral H1R occupancies due to antihistamines may be in part a result of their different BBB permeabilities, demonstrated as H1R occupancy using PET and [^{11}C]doxepin. In clinical settings, however,

permeability at the gut level would also affect net antihistamine transport to the brain.

Thus, the purpose of this study was to examine whether H1R occupancy due to fexofenadine, a non-sedative antihistamine, varies between different genetic types, using a non-invasive technique such as PET. For this purpose, the authors tried to compare the amount of antihistamines transported to the brain tissue within 3 hours following medication. Fexofenadine is also a substrate of P-gp, and it is thought that BBB permeability is low even at an exceeded dose.

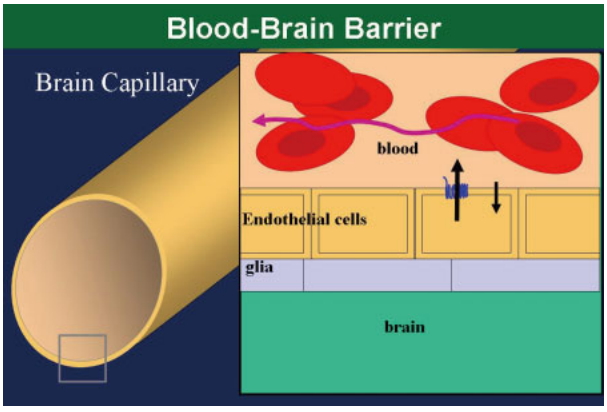

Fig. 4. Basic structure of blood-brain barrier (BBB) consisting of endothelial and glia cells. An efflux transporter (blue) actively transports specific substrates outward to the blood stream.

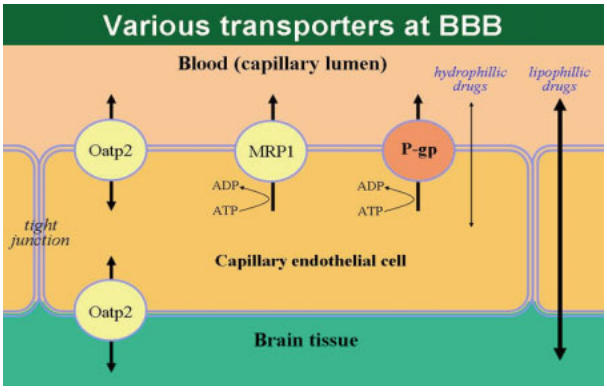

Fig. 5. Various transporters located at the BBB. P-gp transports specific substrates outward using the energy supplied by ATP. Lipophillic drugs can enter the brain tissue easily. Hydrophilic drugs have difficulty in entering the brain tissue.

The result of the PET investigation is presented in Fig. 4, where almost negligible differences were found between FEX and placebo in some subjects. Further analysis demonstrated the following H1R occupancy rates after FEX treatment calculated based on the placebo data in the anterior cingulated gyrus, frontal cortex, occipital cortex, orbitofrontal cortex, and temporal cortex: -5.41%, -3.6%, -0.05%, -8.20%, and -1.12%, respectively. In addition, the overall cortical mean value was -3.67%.

Comparison of H1R occupancy rates averaged across the cortex among the subgroups compared between the polymorphism types (C3435T mutation) revealed a trend toward increased H1R occupancy in volunteers having mutated genes although there was no statistical significance in these rates among the subgroups. This is preliminary research regarding variation in receptor occupancy of psychoactive drugs such as an antihistamine associated with genetic polymorphisms in the human MDR1 gene.

First, H1R occupancy rates of fexofenadine in the present study were negative in many brain regions. The rates calculated in our previous study [5] were also negative in some brain regions such as the anterior cingulate, where baseline data obtained from different subjects was used. In the present study, however, H1R occupancy was calculated using the baseline (placebo condition) data obtained from the same subjects. Thus, it is difficult to explain the negative values from the inter-individual difference.

Second, the present PET study demonstrated relatively higher H1R occupancy rates in holders of mutant genes, although these results were not statistically significant. The effect of MDR polymorphisms on BBB permeability of fexofenadine has never been studied using PET. The PET results might suggest the presence of a slight decrease in efflux function of P-gly in BBB among holders of mutations in comparison to wild-type gene holders. However, it is not known whether there is any BBB permeability variation among other drugs.

To draw a definitive conclusion, further investigation using a larger sample size is needed. Molecular imaging seems to be very useful for the establishment of the field of individualized or personalized medicine. Importantly, molecular imaging enables access to biological information on endophenotype. Observation of the endophenotype makes it possible to predict and explain possible mechanisms of drug side effects.

2.4. A Study on image analysis and early diagnosis of dementia including Alzheimer's disease

Dementia study has become a very important in our modern society. As for PET imaging of Alzheimer's disease, it has been widely recognized that decreases in regional brain metabolism in the posterior cingulate gyrus and temporal-parietal corticies are typical patterns of Alzheimer's disease, which can be visualized with FDG. In such demented brains, many nerve cells are already destroyed and the cell population in the brain is decreased, manifesting as considerably decreased nervous activity. It is thought that the neuronal damage is associated with accumulation of β-amyloid protein in the brain, and early diagnosis of Alzheimer's disease can be realized if we use a tracer specifically binding to β-amyloid proteins (amyloid imaging). Currently, we are

establishing a suitable pharmacokinetic model for quantification of β-amyloid deposits in the brain of Alzheimer's disease patients (Fig. 6), as well as modeling of neural transmission in the cholinergic neuronal system.

At Tokoku University, we performed the first clinical examination of Alzheimer's disease employing a new tracer, [^{11}C]BF-227, which can be used for direct imaging of amyloid deposits in the brain (a collaborative study with Professor Y. Kudo of the Tohoku University Biomedical Engineering Research Organization (TUBERO), Professor K. Yanai of the Department of Pharmacology, Graduate School of Medicine, and Professor H. Arai of the Departments of Gerontology and Geriatrics and Alternative and Complementary Medicine, Graduate School of Medicine). The Division of Cyclotron Nuclear Medicine is in charge of the analysis and construction of a useful model in studies of [^{11}C]BF-227 data as well as enforcement of further clinical studies in all laboratories [9] (Fig. 6).

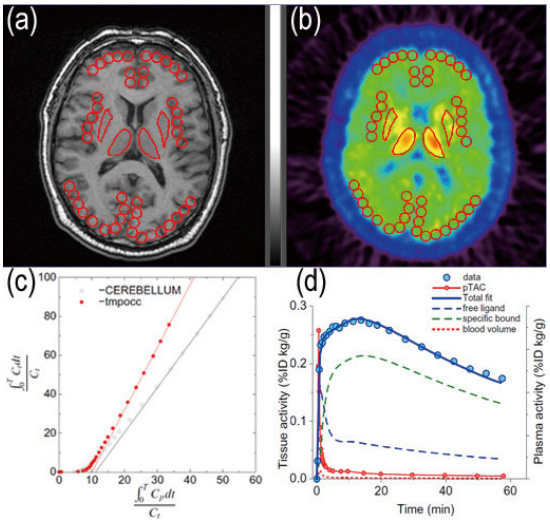

Fig. 6. Examples of pharmacokinetic analysis showing basic procedures of quantification. Regions of interest (ROIs) defined for various brain structures in co-registered MR (a) and PET (b) images. Example of quantification using graphical analysis (c). Time activity curves in plasma and brain tissue for compartmental model analysis (d).

We succeeded in visualizing the clear contrast between "healthy elderly volunteers" and " patients with Alzheimer's disease" using a cerebellar ratio of standardized uptake value (SUV), a simplified semi-quantitative index for clinical diagnosis [9]. We can also collect numerical clinical data (arterial blood samples). Linearization of the data, such as with the use of the Logan method (Fig. 6c), was applied, and it was confirmed that adequate values could be obtained. We can also use the data of time-activity curve in plasma (pTAC) and time-activity curve in tissue (tTAC) obtained through sequential blood sampling and dynamic PET scanning.

Furthermore, at the Cyclotron and Radioisotope Center and in collaboration with Professor K. Yanai,, we are using another novel tracer, [^{11}C]donepezil, which is a radio-labeled donepezil, to evaluate neural transmission in an acetylcholine nervous system. In Alzheimer's disease, it is well known that signal transduction in an acetylcholine nervous system is disordered. As a result of our recent study, it was confirmed in the brain of an Alzheimer's disease patient that the number of binding sites of donepezil decreased markedly [10]. We plan to observe whether we can use this [^{11}C]donepezil as a marker for evaluating therapeutic efficacy of treatment using acetylcholine esterase inhibitors of Alzheimer's disease in the future. In addition, we are in charge of the construction of a calculation model regarding this tracer, and analysis is now under way.

2.5. Study of image information engineering

Development of new image processing methods is also important, such as more efficient software for co-registration of MR and PET images (Fig. 1). We are also working in this field of information science. The recent results indicate that we have succeeded in algorithmic development to accelerate transaction speed to about 10 times while having maintained precision of image processing to some extent. It is expected that the application of this method can shorten working hours for imaging.

3. Preventive Medicine of Nanobioimaging Technology Application to Normal Generation Science

3.1. Background of the study: What is health?

According to the definition by the World Health Organization (WHO), "health" is "a complete state of physical, mental and social well-being, and not merely the absence of disease or infirmity." Needless to say, quality of life (QOL) is very important in all procedures of medical treatment and care. The definition may suggest that attention should also be paid to QOL in daily lives.

In general, there appears to be greater anxiety about the issue of radioactivity in Japan than in Western countries. A highly-sensitive PET scanner has enabled examinations at minimal radiological doses, far below the annual environmental exposure.

This has allowed PET to be applied to elucidate the mechanism of our bodily functions that achieve and maintain a healthy state. This could be viewed as a new application of PET to the field of preventive medicine and health promotion.

Our studies of the brain activities of patients who suffer from malignant diseases have yielded interesting results. The brain metabolic pattern of cancer patients

show abnormalities that correlate to the intensity of depressive mood. Also psychological state correlates to immune functions possibly via the regional brain functions (Fig. 7). PET appears to be useful not only for diagnosis of cancer but also for evaluation of the psychological status of cancer patients. Furthermore, we have conducted studies regarding whole-body exercise such as running and bicycle riding to observe regional activities of skeletal muscles, heart muscles, and brain. PET was useful for evaluating the effects of various therapeutic interventions including exercise for metabolic disorders such as diabetes mellitus, hypertension, cerebro- and cardiovascular diseases in terms of interaction between the mind, brain and body. Recently, alternative medicine has become popular among patients, and the scientific evaluation of these therapeutic techniques would be of clinical importance. PET can be very useful for evaluations based on scientific evidence.

We plan to investigate the relationship between psycho-behavioral factors and achieving a healthy state. Our ultimate goal is to establish a model of whole-body organ interactions.

3.2. Brain imaging study for mental care and QOL improvement of cancer patients

Functional imaging techniques such as PET have been used for detecting malignant tumors at early stages and for differentiating malignant from benign tissues. PET has been also used for studies of neurological and psychiatric disorders. Brain PET study in oncology seems to have been exclusively focused on brain tumors thus far. Although there are many reasons that would lead us to believe that a cancer patient's brain is not functionally normal, the use of PET imaging to evaluate the psychological and behavioral aspects of such patients has been rare. Rather, it seems that FDG brain images of cancer patients have been added to a resting normal control database, based on a belief that a cancer patient's brain without metastasis should be normal. This may be true in terms of a rough anatomical evaluation, but such a belief cannot be firmly held in terms of functional imaging because many cancer patients tend to have psychological abnormality that is sometimes at a subclinical level, as mentioned above. Such a relatively mild abnormality also could be detected by means of functional imaging. Because cancer and cancer treatments have various effects on the central nervous system, the diagnosis of psychiatric symptoms in cancer patients is problematic. Nano-bio-imaging could be used as a supplementary diagnostic tool. Previously, we have proposed the use of FDG-PET in the neuropsychiatric evaluation of cancer patients, and have been performing a series of studies to examine whether the images of a cancer patient's brain are in fact normal or not.

It is now widely accepted that psychological factors are equally important to external factors in disease progression. Some studies have shown that cancer patients with attitudes of "helplessness" and "hopelessness" had a shorter survival period than those with "denial" and "fighting spirit" attitudes [11]. They confirmed the reproducibility of their past study by demonstrating again the negative effect of helplessness, hopelessness and depression [12]. Thus, psychological evaluation and patient care are very important not only for improving quality of life (QOL) but also for prolonging survival. If we suppose a certain psychological disturbance truly exists to the extent of affecting systemic functions of patients, it is also possible for their brain activity to have significant alterations.

Derogatis and colleagues conducted an epidemiological study, in which they diagnosed psychiatric illnesses among cancer patients [13]. They reported that approximately 47% of cancer patients were categorized into certain criteria of the Diagnostic and Statistical Manual, third edition (DSM-III). To date, depression in cancer patients has been reported to range from 4.5% to 50%, depending on the diagnostic scales used [14]. Thus, it seems reasonable to think that cancer patients may manifest a corresponding abnormality in their functional brain images. Our preliminary works demonstrated regional hypometabolic findings mainly in the prefrontal cortex, limbic structures and striatum of Japanese cancer patients [15]. Although the results were slightly surprising, they were however in accordance with those of many previous neuroimaging studies on major depression.

In our previous studies, both Japanese [15] and German patients [16] manifested abnormal regional metabolism compared with benign disease patients. Common findings in these studies were hypometabolism in the prefrontal cortex, anterior and posterior cingulate gyri, insular cortex and striatum. These regions were similar to those demonstrated in previous neuroimaging studies of patients with major depression showing commonly repeated findings of hypometabolism in the prefrontal cortex, anterior cingulate gyrus and basal ganglia [17,18]. Typical findings of hypometabolism are observed in the anterior cingulate gyrus, prefrontal cortex, lateral prefrontal cortex, basal ganglia as well as in the temporoparietal regions. Thus, considering the similarity to known lesions in major depression, it should be possible to postulate that the regional metabolic reduction in cancer patients starts at very mild stages of depression. Even relatively mild disorders such as adjustment disorder would be accompanied by hypometabolism. The present study also suggests that the depth of depression has good correlation with the regional metabolic reduction in relatively mild stages of depressive disorders, although it seems that such correlation is not evident in major depression.

Our additional cross-sectional study in Japanese patients showed that the depth of hypometabolic findings tended to fluctuate in some regions and constantly decreased in other regions. The hypometabolic levels of

the orbitofrontal, basolateral prefrontal, and ventral anterior cingulated cortices and insula tended to be constantly low in all phases [19]. Those of other regions, such as the prefrontal, anterior cingulated, and posterior cingulated cortices, as well as that of the subcortical nuclei tended to fluctuate. The fluctuation gave us an impression that these findings were state-dependent and were more likely caused by non-organic factors. Finally, we demonstrated that regional hypometabolism in the prefrontal cortex negatively correlated with the subjective measure of depression (Zung's Self-Rating Depression Scale: SDS) in cancer patients. Although patients with negligible SDS scores manifested negligible hypometabolism in FDG brain images, those with mild or moderate SDS scores manifested significant hypometabolism in wide areas in the frontal, temporo-parietal, and cingulated cortices among others.

Our previous findings are summarized as follows:

(1) Cancer patients manifest clearly distinguishable regional metabolic abnormality in the limbic structures and frontal cortex (mainly metabolic decline) measurable by FDG PET. If cancer patients are included in the so-called normal control database, detection sensitivity will be lowered especially in detecting decreased regional metabolism in Alzheimer's disease, Parkinson's disease with affective disorders, inter-ictal epilepsy, and so on. Also, our results suggest that even in completely healthy volunteers, mild depression and anxiety might affect brain metabolic pattern.

(2) This metabolic abnormality seems to be associated with psychological factors such as depression. Chemotherapy and paraneoplastic factors also affect metabolic activity but presumably to a lesser extent based on our preliminary study. Replication with a large number of patients is necessary.

(3) Since FDG PET can detect the effect of relatively mild depression, it might be applicable to the objective evaluation of the psychological aspect of cancer patients as a supplementary evaluation technique. Nowadays, whole-body FDG PET is a commonly used routine diagnostic procedure. If this technique can be applied to the objective evaluation of QOL in combination with brain PET, we might open a door into a new field of whole-person medicine addressing the physical to spiritual dimensions of a human being.

Thus, functional and morphological neuroimaging studies in cancer patients have produced novel findings revealing the mechanism of psychiatric disorders related to cancer. Medical technology is continuously progressing and other techniques, such as magneto encephalography (MEG) and near-infrared spectroscopy (NIRS), have recently been introduced for carrying out further research. Thus, noninvasive neuroimaging techniques show promise in contributing more to human welfare in the future.

In particular, metabolic brain activity negatively correlated with SDS score. Thus, PET is expected to be a useful tool for further evaluating psychological and behavioral aspects of cancer patients. Replications from other Japanese groups based on refined protocols are presently available. PET has shown its usefulness in the observation of effective therapy considering a psychosomatic, and especially a psycho-immune, correlation [21] (Fig. 7). The purpose of this study was to examine the relationship between psychological factors, regional brain activity and natural killer cell activity (NKA). Eight patients with malignant diseases were studied by FDG PET under a resting condition. NKA and the degree of depression was measured using SDS, and anxiety was measured using Taylor's manifest anxiety scale (MAS). Linear correlation of NKA and psychological measures to the regional brain metabolism in cancer patients was examined. Positive linear correlation between NKA and regional metabolic rate ratios was identified in the visual cortex, anterior cingulate gyrus and sensorimotor area. Negative correlation was identified in the prefrontal cortex, orbitofrontal cortex and anterior temporal cortex. The NKA and MAS scores positively correlated with each other ($p<0.001$) [21].

The result might serve as supporting data for a hypothesis that psycho-immune interaction is also mediated by the cerebral cortex and limbic system. More subject data suggests we can observe the relationship between natural killer cell activity and regional brain activity in a cancer patient (now in preparation for submission).

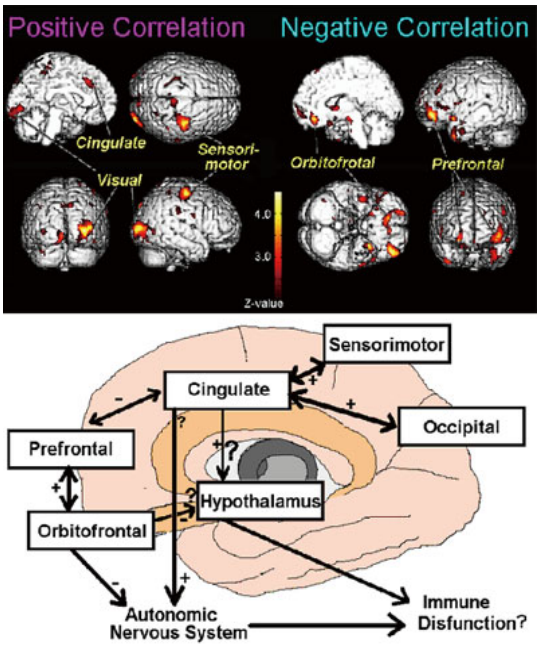

Fig. 7. Brain regions of positive and negative correlation to cellular immunity (natural killer cell activity) in cancer patients (Top). A hypothesized model of neuro-immune interaction in human (Bottom).

3.3. Exercise and brain imaging study related to "physical and mental health"

In addition, in the scope of applying PET to health promotion science, we have performed imaging studies during various forms of exercise, including running and bicycle riding, scanning not only the brain but also cardiac and skeletal muscles [22]. By conducting the whole-body scanning, we can obtain a whole-body map of energy metabolism in the human body [23]. To date, there are few study groups using PET for health promotion science, and this topic will have great relevance in the future. We are currently collaborating with Professor Toshihiko Fujimoto at the Center for the Advancement of Higher Education / Department of Medicine and Science in Sports and Exercise in this new area of research.

In 2007, we have analyzed regional brain activities with an emphasis on the brain's special role as the important center controlling the interaction between muscle action and immune functions. Our series of exercise studies have attracted the attention of overseas researchers. As an example, Professor Arne Dietrich (Department of Social and Behavioral Psychology, American University of Beirut: AUB) has shown his interest in our research. His attention is focused on the importance of a brain energy metabolism distribution mechanism during exercise, and he established the "transient hypofrontality theory" (THT) [24,25]. As a method to investigate his theory, we have started new collaborative work to determine directly using PET with FDG (exercise PET) the importance of measuring energy consumption during exercise, running a joint-protocol with CYRIC, Tokoku University and AUB.

3.4. Scientific observation of alternative medicine

As mentioned above, exercise contributes to health promotion and disease prevention. However, in modern society, interest in the therapeutic efficacy of alternative medicine is growing stronger. Not only exercise but also alternative therapy has attracted public attention and, from the viewpoint of evidence-based medicine (EBM, PET can be used for producing supporting data for the efficacy of alternative medicine). PET offers us a means of obtaining physiology data that cannot be obtained by other methods.

We have reported a PET study regarding the effects of aromatherapy. We performed PET examinations using FDG in 10 women under two conditions of "resting" and "aroma patch stimulation". Monitored autonomic nervous activity showed changes corresponding to the subjects' autonomic nerve activity of parasympathetic nerve predominance [26].

4. Research and Development of Software and Hardware for Cancer Detection

4.1. Development of a whole-body automated diagnostic system

In recent years, malignant tumor (cancer) has become the leading cause of death in Japan. Against this background, the Japanese Government introduced a new law to promote the improvement in the quality of cancer diagnosis and treatment in 2007 [27].

In general, cancer examination using PET with FDG is supposed to be a whole-body scan. If we can develop an automated diagnostic program through simulating the cognitive tasks performed in the brain of radiologists, we may be able to use the results of the diagnostic system as supporting information for the diagnosis, and also as a tool for double-checking. We are currently examining the possibility of making such a system.

4.2. Development of a new PET system (positron emission mammography) for exclusive use in high resolution diagnosis of breast cancer

In Japan, incidence and mortality from cancer has been increasing partly because of westernization of the population's eating habits. For instance, the incidence of breast cancer has been constantly increasing among Japanese women. Our group has started to develop positron emission mammography (PEM), a new PET system specialized for the diagnosis of breast cancer, with excellent spatial resolution of 1 mm.

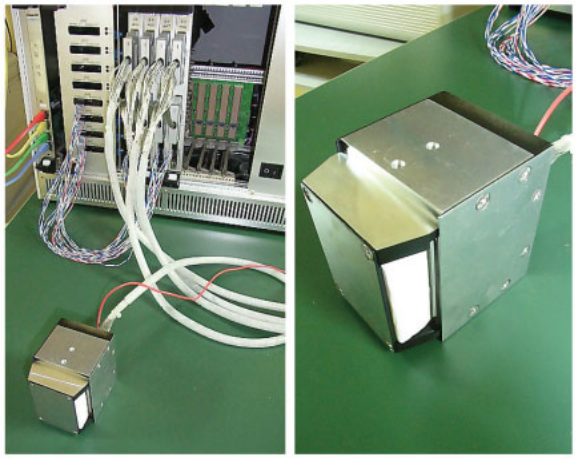

Fig. 8. Test device system of PEM scanner and block detector device (left), and crystal block opened (right).

Of the various cancers cancers, breast cancer can show complete recovery following early detection and treatment. However, diagnosis currently relies on cancer screening that involves mammography and echography. General PET using FDG is also available for diagnosis and is covered by insurance for mammary cancer, but the technique has limited spatial resolution at 4-6 mm, is influenced by respiratory fluctuation, and small tumor can be easily missed. In addition, the price of the scanner is very expensive. Therefore establishment of more effective diagnostic procedure is needed (Fig. 8).

We are now looking to develop nano-bio-imaging for such application in the near future, in collaboration with Masatoshi Itoh, Specially Approved Visiting Professor of Tohoku University, Professors Mamoru Baba and Yoshikawa Akira).

5. Summary

The potential for further application of nano-bio-imaging technology using tiny amount of radiopharmaceuticals is clear. We should also look to develop nano-bio-imaging by continuing collaboration across the various fields of medical science, pharmaceutical science, engineering, information engineering, etc.

Tokoku University has started "a molecule imaging education course" for master and doctoral students at the Graduate Schools of Tohoku University, under the auspices of the "Section for molecule imaging research and education", a part of the whole-school organization established in 2006 (in collaboration with the National Institute of Radiological Science, Molecule Imaging Research Center) [28]. In this research and education program, the Cyclotron and Radioisotope Center provides education and training in molecule imaging. Here we can promote the training of specialist personnel while performing maintenance of the various equipment needed to further promote active research. Nano-bio-imaging is essentially an interdisciplinary field and its development requires dynamic interaction between young researchers. There is considerable potential for nano-bio-imaging techniques using minimal-dose radiopharmaceuticals and the interaction and collaboration of young researchers having a wide variety of academic backgrounds will help to achieve this. The author hopes that the present global COE program can offer an ideal environment for such fruitful interactions.

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