Relationship between Brain Activity and Natural Killer Cell Activity in Patients with Cancer

VIII. 6. Relationship between Brain Activity and Natural Killer Cell Activity in Patients with Cancer

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Introduction

Interaction between psychological factors and immune function in human has been long discussed by various investigators[1)]. Since psychological factors have been discussed in association with the prognosis of cancer patients[2-5)], explanation of how psychosocial factors result in certain physical outcomes would be of clinical importance. Nowadays, presence of psycho-neuro-immune (PNI) interaction seems to be doubtless, but its mechanism is still to be investigated. One of the possible main pathways that mediate this complex interaction would be the hypothalamic-pituitary-adrenal (HPA) axis. This hypothesis, however, does not say anything about the roles of higher brain including neocortex and limbic system. The cerebral cortex and limbic system should also be included in the pathway of psycho-immune interactions since psychosocial events should be first recognised and judged before they are felt “stressful”. Our preliminary report already demonstrated that functional neuroimaging technique would be useful in clinical research of PNI interaction though the number of subjects were rather small (n=8)[6)]. In the present report, updated results with increased number of patients are demonstrated.

Methods

Subjects were 24 patients (mean age +/- s.d., 62.5 +/- 11.5) with cancers in various organs at various stages. The study protocol was approved by the Ethics Committee for Clinical Research of Tohoku University and informed consent was obtained from each patient. After injection of [^{18}F]fluorodeoxyglucose (FDG), patients were kept under resting condition throughout uptake time and scanning periods. Details of the data acquisition and analysis are given in our previous works[7,8)]. Natural killer cell activity

(NKA) was measured using a blood sample taken from each patient just prior to injection of FDG. Then, data analysis was performed to examine linear correlation between the regional cerebral glucose uptake ratios and NKA as well as intra-group differences between high and low NKA patients, using Statistical Parametric Mapping (SPM).

Results

In the present study, 8 out of 24 patients were excluded because anti-cancer treatment including chemotherapy had already started because they demonstrated significantly low NKA (mean NKA +/- S.D.: 10.2 +/- 11.4) than the NKA of the other patients (mean NKA +/- S.D.: 24.0 +/- 14.7) ($p < 0.05$). The 16 patients were further divided into two subgroups: low and high NKA groups. Group comparison analysis was performed including the age-matched controls. Brain image analysis revealed that NKA values correlated negatively in the right lateral prefrontal cortex, temporo-parietal cortex, and in the cerebellum. No brain regions demonstrated positive correlation to NKA. Intra-group comparison demonstrated that high NKA was associated with low glucose uptake in the insula and high glucose uptake in left dorsolateral prefrontal cortex (DLPFC). Intra-group comparison also demonstrated that low NKA was associated with low glucose uptake in the thalamus and hypothalamus and high glucose uptake in occipital cortex and cerebellum.

Discussions

Links between psychosocial events and immune responses have been long studied[9.10]. However, the roles of cortical and limbic structures in a psycho-immune interaction have not been discussed into deep yet. Previous animal studies demonstrated that altered immune functions were observed following destruction of specific brain structures such as cerebral cortex, limbic structure and hypothalamus. Immune enhancement tends to follow damages to the limbic structures, suppression tends to follow damages to the cerebral cortex, and both enhancement and suppression were observed following damages to the hypothalamus[11]. The purpose of these lesioning studies was to clarify the role of specific brain regions in the neuro-immune modulation. Human studies in the same context could be achieved only with the aid of non-invasive functional imaging such as PET.

Previous works done by Wik and colleagues demonstrated correlation between the regional cerebral blood flow (rCBF) and NKA in normal volunteers and patients with

fibromyalgia[12,13]. Their studies demonstrated that NKA correlated negatively with rCBF in the somatosensory association cortex. These studies, as far as the authors know, the first studies that examined natural immunity and regional brain activity in human subjects. The findings of negative correlation between NKA and activity in the limbic structures seems to be in accordance with the previous animal studies[11].

In addition, chemotherapy might affect not only NKA but also regional brain activity. In one of our previous studies where FDG PET was performed in cancer patients[14], the patients were subgrouped by scores of Self-rating Depression Scale (SDS) and by with or without past experiences of chemotherapy. The results demonstrated that the regional brain influences of chemotherapy and depression were in part overlapping in the frontal cortex and that both would work in the same direction of decreasing brain metabolism in the cortex. Therefore, studies concerning neuro-immune interaction should employ patients before starting treatment.

In spite of the relatively small sample size and heterogeneity of the group in terms of diagnosis and history, this observation might provide supporting data for the presence of interactions between the brain and immune system. We hope that functional neuroimaging technique could provide more supporting data for cross-talk between mental, neural and immune aspects in patients.

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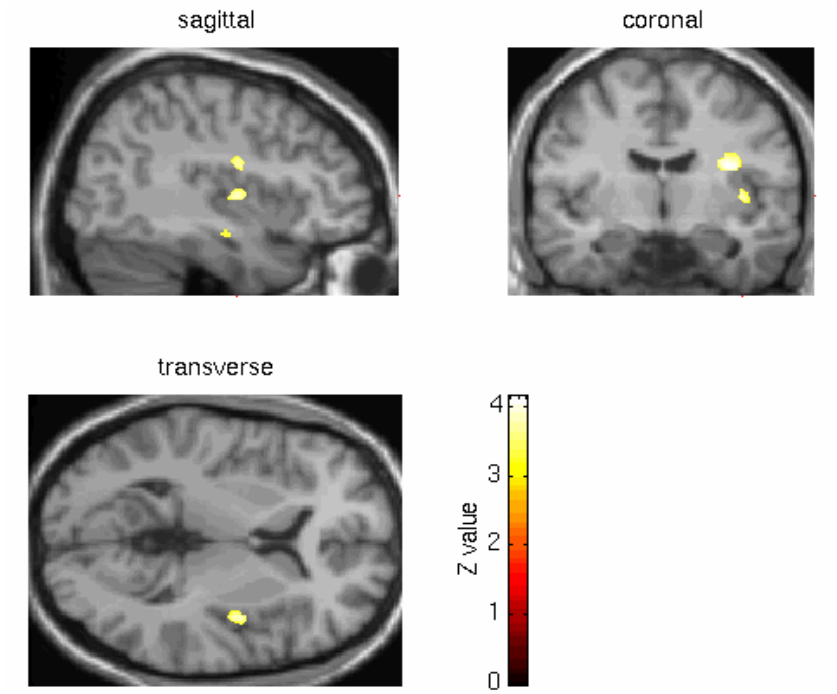

Figure 1. Regions associated with high natural killer cell activity (NKA). Decreased glucose uptake in the insular region was observed only in the high NKA subgroup (patients with cancer). In the low NKA subgroup (cancer patients), the regional glucose uptake in the insular region maintain at normal level. The statistical threshold: $p < 0.001$ (uncorrected).