Research on treatments for the fatigue state

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According to the latest epidemiological investigation for the fatigue (Ministry of Health and Welfare in Japan, 1999), 1/3 of Japanese people had chronic fatigue which continues more than 6 months, and the half of these people felt the loss of working ability compared with before, and says that they cannot fully be working. Therefore, chronic fatigue not only has ruined the health of Japanese people, but also poses a big social problem because of its economical impact. However, the fundamental treatment for chronic fatigue is not yet found and compensatory treatments using anti-inflammatory and psychotropic agents for their symptoms are usually used. Therefore, we have studied the following points in order to develop the new technology of treatment for the fatigue state.

1. **Epidemiological investigation for fatigue in patients treated in a general medical institution and primary care unit**
2. **Verification of the validity of a medicine which affects the brain metabolism in patients with chronic fatigue syndrome (CFS)**

   Fluvoxamine is well known as a serotonine specific reuptake inhibitor, and it was frequently used for the treatment of patients with depression. For evaluating the effect of Fluvoxamine on morbid fatigue, 39 patients with CFS were administered Fluvoxamine (initial dose: 25mg / day), and 11 patients withdrew within 2 weeks because of side effects, nausea, increase in fatigue and a loss of thinking ability. The remaining 28 were able to be given of Fluvoxamine for more than 2 months. Judging from their symptoms and performance statutes after treatment, 2 of them were cured from CFS, and 8 of them recovered enough to return to work. 5 of them indicated they were feeling better, but showed no improvement in physical activity, and 13 patients showed no improvement. Therefore, 36 % of the 28 patients who were administered Fluvoxamine had an improvement (Table 1).

   Amantadine is well known to have an effect on the release of dopamine in the brain. We enrolled 22 patients for the administration of Amantadine, and 3 with drew because of side effects, headaches, dizziness and increase in fatigue. The remaining 19 were administered Amantadine for more than 2 months. 2 of them were cured from CFS after treatment, and 8 of them recovered enough to return to work. 6 of them indicated they were feeling better, but showed no improvement in physical activity, and 4 patients showed no improvement.

Therefore, 47 % of the 19 patients who were administered Amantadine had an improvement (Table 1). Judging from these results, serotonergic and opaminergic dysmetabolism might be involved in the pathogenesis of CFS.

3. The study for brain functions (serotonergic and dopaminergic metabolism, acetylcarnitine uptake, regional cerebral blood flow) in patients with CFS using positron emission tomography

When we studied the cerebral uptake of acetylcarnitine by using [2-^{11}C]acetyl-L-carnitine in 8 patients with chronic fatigue syndrome and in 8 normal age- and sex-matched controls (Fig. 1A), a significant decrease was found in several regions of the patients group, namely, in the prefrontal (Brodmann's area 9/46d) and temporal (BA21 and 41) cortices, anterior cingulate (BA24 and 33) and cerebellum (Fig. 1B). These findings suggest that the levels of biosynthesis of neurotransmitters through acetylcarnitine might be reduced in some brain regions of chronic fatigue patients and that this abnormality might be one of the keys to unveil the mechanisms of the chronic fatigue sensation. The studies for serotonergic and dopaminergic metabolism in the brain of patients with CFS are in progress.

4. Metabolite analysis of [2-^{14}C]acetylcarnitine in the mice brain

When the time course of brain uptake was followed from 1 to 20 min after injection of [2-^{14}C]acetylcarnitine into mice, it increased gradually until 20 min (Fig. 1A). Instead, the blood curve of the radioactivity decreased with time (Fig. 1A). The metabolite analysis was performed in mice sacrificed at 20 min. Since the radioactivity of each brain was low, 3 brains were collected into one group, and a group sample from 3 brains was used for the metabolite analysis (n = 4 with 12 mice). Thin layer chromatography analysis revealed three major neurotransmitters, glutamate, aspartate, and GABA (Fig. 1B), of which glutamate accounted for 60% of the radioactivity in the brain, although the major radioactive metabolites in the plasma were mostly acetyl-carnitine itself and acetate.

Table 1. Improvement by Fluvoxamine and Amantadine on the symptoms in patients with CFS

	Fluvoxamine		Amantadine	
Entry	**39**		**22**	
Evaluated	**28**		**19**	
withdraw	**11**		**3**	
Improvement				
(++)	**2 (7 %)**	**36%**	**1 (5 %)**	**47%**
(+)	**8 (29 %)**		**8 (42 %)**	
(+/-)	**5 (18 %)**		**6 (32 %)**	
(-)	**13 (46 %)**		**4 (21 %)**	

(++): cured from CFS **(+)**: recovered enough to return to work
(+/-): feeling better **(-)**: no improvement

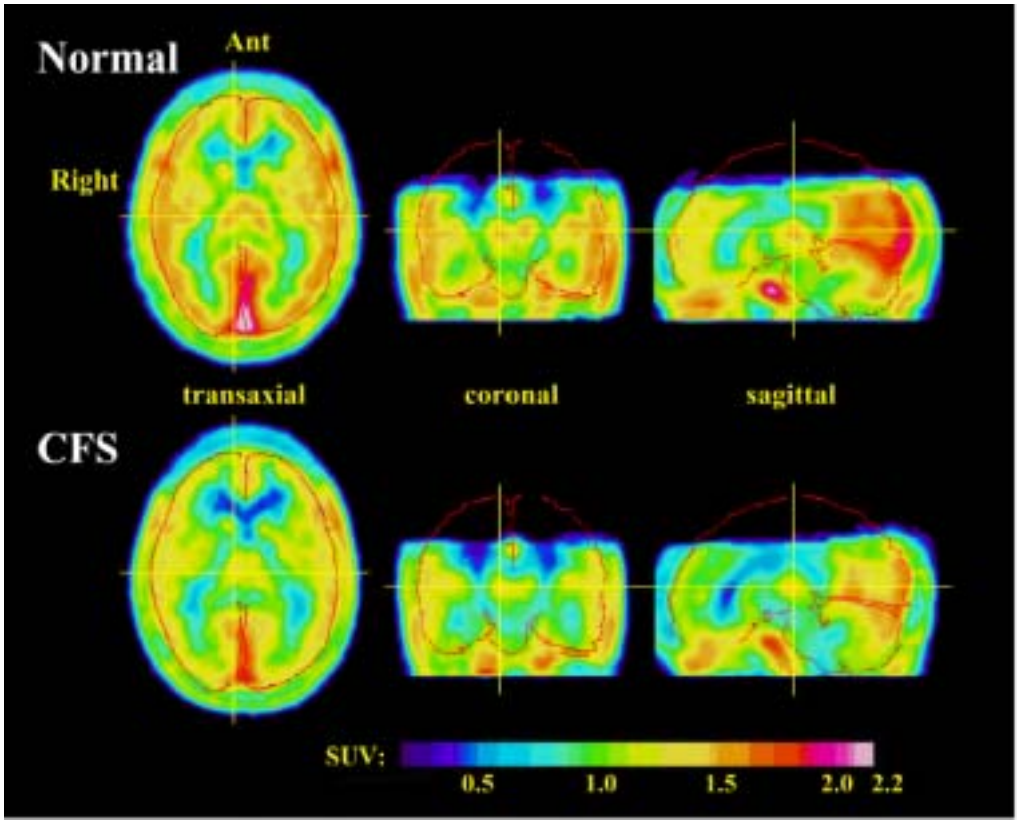

Fig. 1A. The regional standard uptake value of [2-^{11}C]acetyl-L-carnitine (rSUVacc) at the computerized brain atlas from late-phase summation images (60-90 min after injection). The group averaged images of normal controls and CFS patients at the typical transaxial, coronal and sagittal slices are presented here. Outline in red color delineates the frame work of the brain, and yellow lines show the transaxial, coronal and sagittal planes.

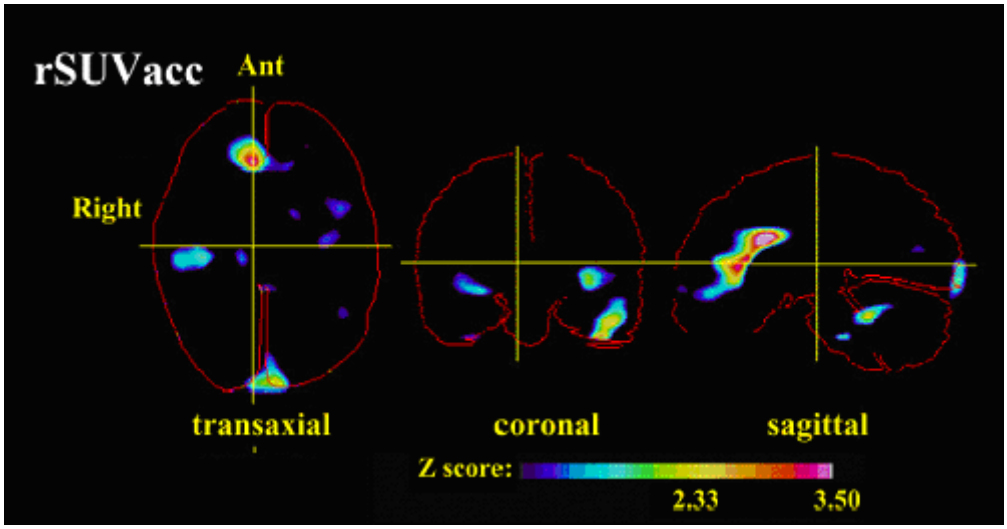

Fig. 1B. Z-score images showing decreased rSUVacc in the CFS group as compared with those for the normal control group at the same slice as used for the rSUVacc.

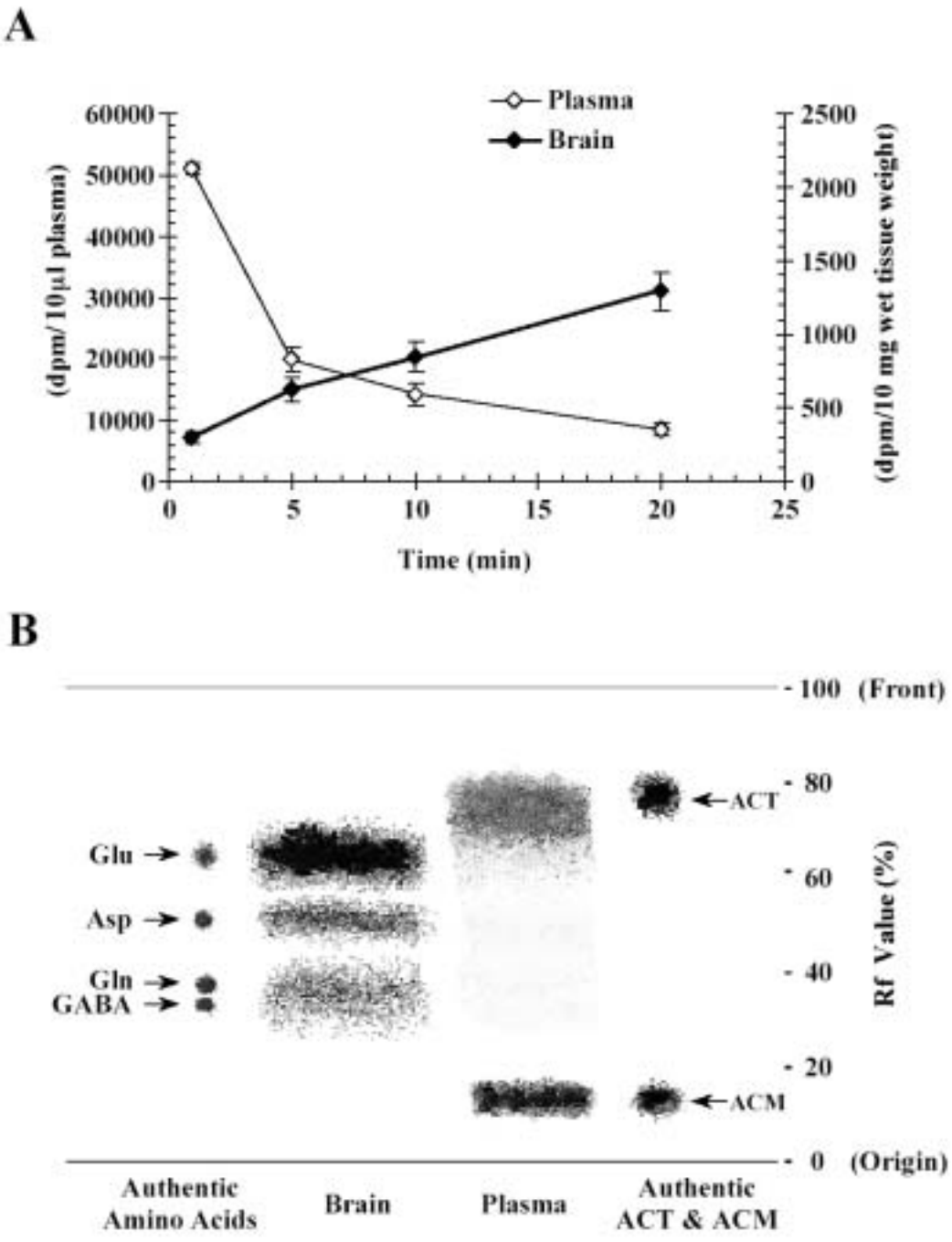

Fig. 2 Metabolite analysis of [2-^{14}C]acetylcarnitine in the mice brain