Studies on drinking behavior, personality and L-dopa induced hallucination of idiopathic Parkinson's disease patients

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Introduction

Parkinson's disease (PD) is one of the common neurodegenerative disorders in elderly peoples, and idiopathic type is found in more 90% of PD. PD is caused by a progressive loss of dopaminergic neurons within the pars compacta region of the substantia nigra. More specifically, the damage within the dopaminergic nigrostriatal pathway has been associated with Lewy bodies, and with various types of neurofibrillary degeneration (Jellinger, 1986). Various physiological mechanisms have been implicated in the pathophysiology of PD including dopamine transmission, dopamine receptors, and the dopamine transporter. The major clinical symptoms of PD, which include resting tremor, rigidity, and other motor disturbances, are caused by dysfunction within the dopaminergic system. Depression, wearing-off-type motor fluctuations, dyskinesia, and hallucination are also common clinical features found in PD patients. However, these symptoms do not always occur in all patients. The etiology of PD remains unknown although it has been suggested that PD is a multifactorial disease caused by environmental and genetic risk factors (Koller et al., 1990; Hubble et al., 1993; Liou et al., 1997).

Recent familial studies of PD have suggested that a missence mutation of the alpha-synuclein gene may represent a genetic risk factor for early onset disease (Polymeropoulos et al., 1997), and Parkin gene may cause autosomal recessive juvenile parkinsonism (Kitada et al., 1998).

On the other hand, many epidemiological studies have been made from aspects of environmental factors. A discovery that the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induces Parkinsonism in human has provided a most valuable insight into biochemical processes involved in PD-like nigral cell loss (Langston et al., 1983). As well, head trauma (Cardoso et al., 1995; Seidler et al., 1996),
rural living and well-water consumption (Rajput et al., 1987; Zayed et al., 1990), herbicides and pesticides (Hubble et al., 1993; Hertzman et al., 1994), heavy metals (Fahn et al., 1992; Dexter et al., 1994; Calne et al., 1994), calcium and amalgam (Yasui et al., 1992), infections (Poskanzer et al., 1963; Sasco et al., 1985; Takahashi et al., 1995) have been suggested as risk factors in PD.

Alcohol and coffee drinking habits, and smoking (Baron, 1986; Sasco et al., 1990; Jimenez-Jimenez et al., 1992; Mayeux et al., 1994) have been studied for idiopathic PD. Carlen et al. (1981) suggested that heavy intake of alcohol provokes parkinsonism, owing to its diverse effects on dopaminergic functions under pre-existing alteration of the basal ganglia. Subsequently, a number of epidemiologic studies have shown that alcohol drinking is less common among patients with PD than healthy control subjects (Jimenez-Jimenez et al., 1992; Pollock et al., 1966; Duvoisin et al., 1981; Koller, 1983). Other reports, however, showed no significant difference in alcohol drinking habits between patients with PD and control subjects (Baumann et al., 1980; Lang et al., 1982; Bharucha et al., 1986). Genetic polymorphisms of alcohol metabolizing enzymes may be involved in the association between alcohol consumption and PD. Mitochondrial aldehyde dehydrogenase (ALDH2; EC 1.2.1.3) is a major enzyme involved in the oxidation of acetaldehyde derived from ethanol metabolism (Greenfield et al., 1977). An allelic variant (ALDH2*2) of the ALDH2 gene causes acute alcohol intoxication via accumulation of the toxic acetaldehyde. People who are heterozygous or homozygous for the ALDH2*2 allele have diminished catalytic activity (Harada et al., 1981; Yoshida et al., 1991). Many recent studies have demonstrated that catalytic deficiency of ALDH2 leads to flushing and other vasomotor symptoms after alcohol intake, owing to elevated acetaldehyde levels. Other studies have indicated that allelic
variants of ALDH2 are predominantly found in populations of Mongoloid origin (Harada et al., 1992; Goedde et al., 1985), and that people with \textit{ALDH2}^{*2} refrain from excessive alcohol drinking due to the aversive symptoms; this aversion leads to protection against alcoholism (Harada, 1982). Therefore, analysis of the association between alcohol consumption and ALDH2 polymorphisms may provide important information for understanding the alcohol consumption behaviors of patients with PD.

Recent psychological studies have suggested that there is an increased prevalence of depression amongst PD patients. Neuropsychological, metabolic, clinical, pharmacological and anatomical studies have revealed abnormalities in the frontal dopaminergic projections of both PD patients, and patients suffering from depression (Cummings, 1992). Moreover, premorbid personality traits such as overcontrol, depressiveness, positive social resonance, and social importance are common in PD patients (Poewe et al., 1983). Recently, Cloninger (1987; 1991) proposed a general biobehavioral theory of personality in which novelty seeking (NS), harm avoidance (HA), and reward dependence (RD) represent three fundamental dimensions of personality. The theory is complemented by a hypothesis that NS, HA, and RD are related to dopamine, serotonin, and norepinephrin neurotransmitter systems, respectively. Studies have shown that the Tridimensional Personality Questionnaire (TPQ) is a valid and reliable method for measuring these three personality traits (Cloninger et al., 1991; Brown et al., 1992; Cannon, et al., 1993). The validity of the TPQ test has also been confirmed in studies of Japanese subjects (Takeuchi et al., 1993). Menza et al. (1993) reported that the mean score for the NS dimension is significantly lower amongst PD patients relative to matched control subjects. Subsequent studies have suggested that allelic polymorphism of dopamine receptor (DR4) and serotonin transporter genes give a significant influence
to the score of NS and HA determined by TPQ (Ebstein et al., 1996; Benjamin et al., 1996). Based on these findings, association studies between these alleles and PD have been reported in different populations (Nanko et al., 1994; Higuchi et al., 1995; Ricketts et al., 1998).

There has been particular interest in dopaminergic-peptidergic interactions. This interest has arisen following reports demonstrating that there are changes in neuropeptide concentration within the basal ganglia of patients with extrapyramidal disorders. The coexistence of classical transmitters and neuropeptides within the same neuron has been confirmed using immunohistochemical techniques (Hokfelt et al., 1980; Schultzberg et al., 1982). Agid et al. (1985) have shown that dopamine and cholecystokinin (CCK) coexist within cells of the dopaminergic mesolimbic pathway. A significant feature of the pathophysiology of PD is the fact that the disease is associated with large fluctuations in neurotransmitter activity. Given the evidence for dopaminergic-peptidergic interactions, CCK activity may prove to be an important factor in the pathophysiology of PD.

CCK peptides exist in multiple molecular forms (for example sulfated CCK8, unsulfated CCK8 and CCK4), each resulting from distinct post-translational processing of the CCK gene product. CCK receptors are divided into two types: the CCK-A receptor and the CCK-B receptor. The CCK-A receptor mediates the action of CCK on contraction of the gall bladder, secretion of pancreatic amylase, and gastric emptying (Folsch et al., 1987; Geary et al., 1992; Liddie et al., 1985). CCK-B receptor activity is associated with increased neuronal firing, anxiety, and nociception (Lavigne et al., 1992; Orosco et al., 1986; Griebel, 1999). In addition, CCK modulates the release of dopamine and dopamine-related behaviors in the mesolimbic pathway, where CCK and dopamine have been shown to coexist (Crawley, 1991; Marshall et al. 1991). Finally, CCK immunoreactivity in
the substantia nigra is reduced in PD patients (Studler et al., 1982), and administration of CCK8 is effective in the treatment of the pathological changes in dopaminergic activity (Pioli et al., 1991; Taylor et al., 1992).

Considering the above mentioned backgrounds, the present studies were conducted to investigate the three subjects:

1) Association analysis between alcohol consumption and ALDH2 polymorphism will provide an important information to estimate alcohol drinking behaviors of patients with PD. Therefore, distributions of the three ALDH2 genotypes among PD patients and healthy control subjects, and compared the mean values of alcohol consumption were explored between PD patients and control subjects with the same ALDH2 genotype.

2) The personalities of Japanese PD patients using the TPQ test were assessed to confirm the previous report in American Caucasian, because of the possibility that psychological traits might be influenced by social and cultural factors.

3) Changes in neuropeptide concentration within the basal ganglia may play an important role in the putative dopaminergic-peptidergic interactions associated with the disease. Symptoms such as depression, dyskinesia, and hallucination do not always occur in all patients. CCK modulates the release of dopamine in the mesolimbic pathway and effects dopamine-related behavior. Therefore, systematic analyses of genetic variations in both the promoter region, and the coding region of the CCK gene were conducted to investigate the genetic backgrounds. The study involved a comparison between PD patients and control subjects. In addition, the relationships between polymorphism of the CCK gene and clinical features of the disease, including the age of onset of the disease were analyzed.