

Department of Internal Medicine

Division of Neurology

Kiyoharu Inoue, *Professor*
Hidehiko Honda, *Associate Professor*
Akira Kurita, *Associate Professor*
Hironori Sato, *Lecturer*

Soichiro Mochio, *Professor*
Hisayoshi Oka, *Associate Professor*
Kazutaka Matsui, *Lecturer*
Masahiko Suzuki, *Lecturer*

General Summary

Clinical research in 2006 was performed in the following areas: 1) spinocerebellar degeneration (SCD), 2) autonomic nervous system, 3) neurophysiological studies in dementia and diabetic neuropathy, 4) neuroradiological studies with nuclear medicine, 5) neuroimmunological disorders, 6) cerebrovascular disorders, and 7) neuropathological studies.

Research Activities

SCD

Taltirelin hydrate has recently been used to treat patients with SCD, but a better understanding of its effects is needed. The effects of taltirelin hydrate on cerebellar limb ataxia were evaluated quantitatively over the course of 4 years in 20 patients with SCD by means of a finger-tapping device containing a pressure sensor. We found neither improvement nor aggravation of symptoms over the course of 4 years. However, because the signs and symptoms of SCD gradually worsen in most patients, our results suggest that taltirelin hydrate is useful for the management of SCD.

Autonomic nervous system

Cardiovascular autonomic dysautonomia was investigated in patients with Lewy body disease (LBD), such as Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Autonomic function was evaluated with cardiac ^{123}I -metaiodobenzylguanidine (MIBG) scintigraphy, hemodynamic function testing with the Valsalva maneuver, and orthostatic tolerance testing. We investigated whether PD can be distinguished from multiple system atrophy (MSA) on the basis of the results of cardiac ^{123}I -MIBG scintigraphy and testing of cardiovascular autonomic function, including baroreceptor reflex sensitivity. Latent sympathetic nervous dysfunction without parasympathetic dysfunction, especially that involving the sinus node, is already present in early de novo PD. However, whether the responsible lesion is central or peripheral remains unclear. Our results suggest that assessment of baroreceptor reflex sensitivity may be useful for differentiating between PD and MSA, 2 conditions in which ^{123}I -MIBG scintigraphy yields similar results.

Neurophysiological studies of dementia and diabetic neuropathy

Neurophysiological studies of visual information processing functions were evaluated in patients with DLB, PD, or Alzheimer's disease (AD) by means of visual event-related potential analyses. The author of these studies was invited as a guest speaker at a symposium at the 14th International Pharmacoo-EEG Society symposium.

The clinical utility of nerve conduction studies and of neurological examination of the feet with newly established techniques was assessed in patients with diabetic neuropathy, in collaboration with the Department of Diabetes, Metabolism, and Endocrinology. The findings of the study suggest that neurological examinations and nerve conduction studies of the feet are useful for detecting early changes of diabetic neuropathy.

Neuroradiological studies with nuclear medicine

Cardiac sympathetic dysfunction was studied in mice with parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. The clinical utility of myocardial ^{123}I -MIBG scintigraphy and of ^{123}I -isopropylidoamphetamine brain single-photon emission computed tomography studies was examined in parkinsonism and dementia. Early differential diagnosis in parkinsonian and dementing disorders was studied with positron emission tomography (PET) at the Positron Medical Center, Tokyo Metropolitan Institute of Gerontology. A significant Correlation was observed between presynaptic and postsynaptic nigrostriatal dopaminergic functions in MSA. The regional correlation between presynaptic and postsynaptic nigrostriatal dopaminergic functions in the MSA suggested pathophysiological mechanisms for responsiveness to levodopa. Intracerebral functional connectivity associated with occipital hypometabolism was evaluated in DLB. The results indicated that the visual hallucinations in DLB may be related to the hyperactivity of remote areas, such as limbic and brainstem regions.

Neuroimmunological disorders

The relationship between multiple sclerosis and Sjögren syndrome with neurological manifestations is controversial. To assess the prevalence of Sjögren syndrome in multiple sclerosis, the criteria of the American-European Consensus Group for Sjögren syndrome were used to study patients with multiple sclerosis. The authors questioned all patients about xerophthalmia and xerostomia. The following examinations were performed: measurements of anti-Ro/SS-A and anti-La/SS-B antibodies, antinuclear antibodies, and IgG in serum; the Schirmer test; salivary gland scintigraphy; and minor salivary gland biopsy.

Cerebrovascular disorders

In cerebrovascular disorders, a study of the utility of platelet-derived microparticles was performed in patients with cerebral infarction.

Neurosonological research concerning cerebral hemodynamics was performed with transcranial color flow imaging and carotid ultrasonography in patients with ischemic stroke. The hemodynamic state of intracranial arteries and the relationship between intracranial and extracranial arteries were evaluated with transcranial color flow imaging

and carotid ultrasonography. Stiffness parameter beta of the common carotid artery was measured with the echo-tracking method in patients with ischemic stroke and in healthy adults. One quantitative index of the elastic properties of large arteries was useful for evaluating early atherosclerotic changes before structural changes occur.

Neuropathological studies

Lewy body (LB)-related pathology (LBP) in the olfactory bulbs in human aging was evaluated. The olfactory bulbs are the target of neural progenitor cells and olfactory dysfunction in Parkinson's disease or AD, but few pathological studies have been performed. Pathological studies of the brain were performed in 270 consecutive autopsy cases by means of immunohistochemical staining for phosphorylated α -synuclein. LBP was found in 83 (30.7%) of 270 cases; in addition, LBP was found in the olfactory bulbs in 66 cases (24.4%) and in the amygdala in 76 cases (28.1%). The cases with LBP in the olfactory bulbs also showed LBP in the amygdala. All cases that showed degeneration with LB of the substantia nigra or locus ceruleus also showed LBP in the olfactory bulbs. In only 5 of 270 cases were LBs found only in the olfactory bulbs. Three of these cases also showed AD-type pathologic changes. These cases showed only Lewy neurites or dots in the amygdala without LBs. One case showed LBP only in the amygdala without other senile changes. In the central nervous system, the olfactory bulbs are one of the regions that show LBs at the initial stage of LBD with or without tau pathology in human aging.

Basic research

Deficiency in energy supply, like that which occurs during hypoxia, anoxia, metabolic stress, and mitochondrial failure, strongly affects the excitability of central neurons. Such lowered energy supply evokes various changes in spontaneous synaptic input to hippocampal and cortical neurons. However, how this energy deprivation affects synaptic input to motor neurons, which are also vulnerable to energy deprivation, has not been addressed. We examined the effect of metabolic stress on synaptic input to motor neurons by recording postsynaptic currents in the hypoglossal nucleus. We found that, in hypoglossal motor neurons, chemical anoxia and anoxia increase the current mediated by N-methyl-D-aspartate (NMDA) receptors through activation of their glycine-binding sites by facilitated release of glycine in the absence of action-potential generation. To our knowledge, this study is the first to provide direct evidence linking metabolic disturbances and NMDA receptor potentiation through release facilitation of glycine and its spillover in motor neurons.

The caudal nucleus tractus solitarius (cNTS), in the dorsal medulla, specifically integrates respiratory, cardiovascular, and gastrointestinal afferents. Efferents from the cNTS are regulated by γ -aminobutyric acid (GABA) synapses within the cNTS. The proper function of the brain depends on a precise arrangement of excitatory and inhibitory synapses. The number of axosomatic GABA synapses decreases during postnatal development. Such a morphologic change could cause changes in electrophysiological activity and might contribute to reorganization of the local network within the cNTS from the neonatal to the adult type. These postnatal changes in the cNTS

local network might be required for the cardiorespiratory reflexes of the adult type.

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