Immunological study in molecular pathophysiology of ion channel

1997 Fiscal Year Final Research Report Summary

IMMUNOLOGICAL STUDY IN MOLECULAR PATHOPHYSIOLOGY OF ION CHANNEL

Research Project

Project/Area Number

07457154

Research Category

Grant-in-Aid for Scientific Research (B)

Allocation Type

Single-year Grants

Section

一般

Research Field

Neurology

Research Institution

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Keywords

Lambert-Eaton myasthenic syndrome / Myasthenia gravis / Calcium channel / Acetylcholine / Ryanodine receptor / synaptotagmin / Autoimmunity

Research Abstract

(1) Lambert-Eaton myasthenic syndrome (LEMS) LEMS,often ssociated with small cell lung carcinoma (SCLC), impairs the quantal release of acetylcholine (ACh) by antibodies against voltage-gated calcium channel (VGCC) in the motor nerve terminal. We focused attention on the P/Q-type VGCC,against which a majority of LEMS patients carry the specific antibody. This type of VGCC expresses in the motor nerve terminal and also in SCLC.In search of antigenic sites in the P/Q-type VGCC molecular structure, we synthesized peptides corresponding to the extracellular region (S5-S6 linker) of each of the four domains that form the alpha1A subunit of VGCC and tested their antigenicity. In LEMS patients' sera, some were positive for anti-domain II,and the other were positive for anti-domain IV.Lewis rats immunized with domain II and III peptides, each being conjugated with KLH,showed such characteristic LEMS features as presence of antibodies to P/Q-type VGCC and reduced ACh quantal release. In additio n, the possible role of synaptotagmin, a Ca^<++> sensor for exocytosis of synaptic vesicles taking place prior to ACh release, in the pathogenesis of LEMS was studied. The peptide corresponging to the extracellular region of synaptotagmin was found antigenic for the induction of an animal model of LEMS.A proportion of human LEMS antibodies reacted with the recombinant synaptotagmin in immunoblot.
(2) Myasthenia gravis (MG) In MG in which muscle anti-ACh receptor antibodies play a crucial role, we focused attention on an additional impairment of excitation-contraction coupling in muscle, attributable to a defect caused by antibodies against ryanodine receptor (RyR). Many of MG patients with thymomas contained anti-RyR antibodies in serum ; these sera inhibited the calcium-induced release of calcium in response to caffeine in human muscle cell line. The Buffalo/Mna rat with spontaneous benign thymoma was shown as an animal model of impaired subcellular machineries in MG muscle as evidenced by RyR expressed in thymic epithelial cells, anti-RyR antibodies in serum and reduced contractile forces without abnormality in synaptic transmission and muscle membrane properties.▲ Less

Research Products (112 results)

All | Other

All | Publications (112 results)

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