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Autoimmunity against the β_2 adrenergic receptor and muscarinic-2 receptor in complex regional pain syndrome

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ABSTRACT

Complex regional pain syndrome (CRPS) is a painful condition affecting one or more extremities of the body, marked by a wide variety of symptoms and signs that are often difficult to manage because the pathophysiology is incompletely understood. Thus, diverse treatments might be ineffective. A recent report revealed the presence of autoantibodies against differentiated autonomic neurons in CRPS patients. However, it remained unclear how the antibodies act in the development of CRPS. We therefore aimed to characterize these antibodies and identify target antigens. Functional properties of affinity-purified immunoglobulin G of control subjects or CRPS patients were assessed using a cardiomyocyte bioassay. Putative corresponding receptors were identified using antagonistic drugs, and synthesized peptide sequences corresponding to segments of these receptors were used to identify the target epitopes. Chinese hamster ovary cells were transfected with putative receptors to ensure observed binding. Further, changes in the intracellular Ca^{2+} concentration induced by agonistic immunoglobulin G were measured using the Ca^{2+}-sensitive fluorescent dye fura-2 assay. Herein, we demonstrate the presence of autoantibodies in a subset of CRPS patients with agonistic-like properties on the β_2 adrenergic receptor and/or the muscarinic-2 receptor. We identified these autoantibodies as immunoglobulin G directed against peptide sequences from the second extracellular loop of these receptors. The identification of functionally active autoantibodies in serum samples from CRPS patients supports an autoimmune pathogenesis of CRPS. Thus, our findings contribute to the further understanding of this disease, could help in the diagnosis in future, and encourage new treatment strategies focusing on the immune system.

1. Introduction

Complex regional pain syndrome (CRPS) is a painful condition that can develop after peripheral limb trauma, either without (CRPS 1) or with a clinically evident peripheral nerve lesion (CRPS 2). The main clinical features are pain and hyperalgesia, vasomotor, pseudomotor, and trophic changes in the affected limb. In addition, motor symptoms can be present from the beginning, and may progress with longer duration [5,47]. The pathophysiology of CRPS appears to be multifactorial and complex and therefore not completely understood. A sum of possible mechanisms responsible for the clinical signs of CRPS have been identified: exaggerated inflammation after trauma, in particular neurogenic inflammation and/or hypoxic changes at the site of the lesion, dysfunctions of the peripheral or central sympathetic nervous system, and/or profound cortical reorganization processes [12,28,33,36,53]. Certain mechanisms predominate depending on clinical presentation or CRPS stage [15]. Recent evidence has begun to focus research on the involvement of immune system in CRPS pathogenesis. The human leukocyte antigen alleles DQ1, DR13, DR15, and the centromeric

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