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Effect of Pooled Human Intravenous Globulin (IVIG) on the Reversal of Cholinergic Inhibition of Smooth Muscle by Immunoglobulins (IgGs) from Patients with Scleroderma (SSc)

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Backgrounds & Aims

The gastrointestinal (GI) tract is the most common internal organ system affected in SSc. We and others have shown before that the SSc immunoglobulins (IgGs) cause selective blockade of muscarinic type-3 cholinergic (M3-R) in the GI tract. Presently, there is no effective treatment for SSc although numerous cytolytic and immunomodulatory agents have been employed with limited success and are marred with serious side effects. Present studies investigated the reversibility of SScIgGs-caused M3-R blockade by the pooled Intravenous immunoglobulins (IVIG).

Methods

Effects of SScIgGs and IgGs from normal individuals (NigGs) on M3-R activation by betahanechol (BeCh) were determined in human internal anal sphincter (IAS) smooth muscle cells (SMCs), before and after IVIG. M3-R occupancy and binding by the SScIgGs was determined via immunofluorescence (IF), Western blotting, and ELISA, respectively. Functional displacement of M3-R occupancy by the SScIgGs was determined employing different concentrations of the IgGs during the sustained phase of the BeCh-induced contraction of rat IAS smooth muscle strips.

Results

Fig. 1. (A) M3-R occupancy with SScIgGs (ss, NigGs and IVIG) in the SMC membrane as determined by I-FACS and western blotting (B) Schematic showing SScIgG binding to SMC membrane. (C) Schematic of microtubule intensity calculation.

Fig. 2. (A) Immunocytochemical localization of different IgGs (a,b,c,d) (FITC-conjugated) and M3-R (TRITC-conjugated) on HUVEC cells. (B) Western blot showing SScIgG binding to SMC membrane.

Fig. 3. SScIgG cause Functional Displacement of M3-R: Reversed by IVIG

Summary

1. IgG from scleroderma patients (SSC IgGs) inhibit muscarinic type-3 (M3-R) activation, as shown by the data in human IAS smooth muscle cells and rat smooth muscle strips.
2. SscIgG inhibits M3-R occupation as shown by immunofluorescence and ELISA studies.
3. Pooled Intravenous globulin (IVIG) reverses the M3-R occupancy and inhibition primarily by neutralizing circulating the SScIgG.

Conclusions

1. IVIG alleviates SScIgG-mediated block of M3-R by blocking the circulating SScIgGs.
2. This mechanism may be partly responsible for the restoration of M3-R-mediated cholinergic dysfunction in SSc-related GI manifestations.