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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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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 cytotoxic 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 (NlgGs) on M3-R activation by bethanechol (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. SSc IgGs occupy M3-R thus reducing M3-R Immunofluorescence. Reversed by Pooled Human Immunoglobulin (IVIG)

Fig 2. Co-localization of SSc IgGs with M3-R is Blocked by IVIG

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

Fig 4. IVIG Reverses the binding of SScIgG with second Loop of M3-R (M3-RL2)

Summary

1. IgGs from scleroderma patients (SScIgGs) inhibit muscarinic type-3 cholinergic (M3-R) activation, as shown by the data in human IAS smooth muscle cells and rat smooth muscle strips.
2. SScIgGs inhibit M3-R occupation as shown by immunocytochemistry and ELISA-binding studies.
3. Pooled Intravenous globulin (IVIG) renews the M3-R occupation and inhibition primarily by neutralizing circulating the SScIgGs.

Conclusions

- IVIG alters SScIgGs-mediated block of M3-R by blocking the circulating SScIgGs.
- This mechanism may be partly responsible for the restoration of M3-R-mediated cholinergic dysfunction in SSc-related GI motility disorders.

Fig 5. SScIgG significantly bound to M3-R (*p < 0.05). IVIG reverses the binding (*p < 0.05)

Fig 6. Active IVIG (not inactivated) *p < 0.05) the binding of SScIgGs with M3-RL2 and the HSSMIF

Proposed Mechanism of Action of Pooled Human Immunoglobulin (IVIG)

Strengthened contractile properties of smooth muscle

Data shown in Figure 5.