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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Recommended Citation

Singh, Jagmohan; Mehendiratta, Vaibhav; Jimenez, Sergio A.; Cohen, Sidney; DiMarino, Anthony J.; and Rattan, Satish, "Effect of Pooled Human Intravenous Globulin (IVIG) on the Reversal of Cholinergic Inhibition of Smooth Muscle by Immunoglobulins (IgGs) from Patients with Scleroderma (SSc)" (2012). *Division of Gastroenterology and Hepatology Faculty Papers*. Paper 11.

https://jdc.jefferson.edu/gastro_hepfp/11
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 (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

Figure 1. (A) M3-R occupancy with SScIgGs (ss. NIGG and IVIG) in the SMC membrane as determined by IF and wire (B) Graph showing SScIgGs binding to SMC membrane. (C) Schematic of m3-R occupancy calculation.

Figure 2. (A) Immunocytochemical co-localization of different IgGs (ss. ss. IVIG and IVIG) in the SMC membrane as determined by IF and wire. (B) Labeling of co-localization of SScIgGs and M3-R.

Figure 3. SScIgGs cause Functional Displacement of M3-R; Reversed by IVIG

IVIG Blocks SScIgG Binding with M3-R

Figure 4. IVIG Reverses the binding of SscIgG with second Loop of M3-R (M3-R2/3).

Summary

1. SScIgGs 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) reverses the M3-R occupancy and inhibition primarily by neutralizing circulating the SScIgGs.

Conclusions

IVIG alleviates 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 manifestations.