

IMMUNOSUPPRESSOR RESPONSE TRIGGERS BY THE INTERACTION OF
LYMPHOCYTES WITH CHAGASIC IgG.

ENRI S. BORDA and LEONOR STERIN-BORDA

CEFAPRIN, CONICET, Serrano 665, 1414 BUENOS AIRES, ARGENTINA.

Alter immunity has been proposed as a mechanism for the pathogenesis of chronic Chagas' disease. Evidence for an immunological role in chagasic myocarditis in general is limited, but includes the presence of circulating and bound antimyocardial antibody, the presence of myocardial lymphomononuclear cell infiltration and abnormalities in circulating lymphocyte subpopulations and the absence of etiologic agent in myocardial tissue.

In studies of the immunological aspect of Chagas' disease the role of lymphocytes is important. We have demonstrated that peripheral chagasic human lymphocytes are active upon contact with cardiac antigens altering normal myocardial contractility, behaving in a similar way to mitogenic lectin activated-normal lymphocytes or to ionophore, sodium arachidonate or adrenergic agonist activated lymphocytes. Furthermore, chagasic lymphocytes do not require any activation with mitogen and they appear to be in an "active state" before further manipulations.

In this work we demonstrated an alteration in the biological behaviour of T-lymphocytes (T-suppressor (Ts) or T-helper (Th)) by the interactions of chagasic IgG with the attachment membrane β -adrenergic and cholinergic receptor, inducing an immunosuppressor response.

Figure 1 shows the interference of T cells β adrenergic and cholinergic receptors ligand occupancy by chagasic IgG and the correspondent F(ab)'₂. It can be seen a concentration-dependent inhibition of (-)-³H-DHA binding (Panel A) and (-)-³H-QNB (Panel B) on T cells β adrenoceptors and muscarinic receptors respectively by chagasic IgG or chagasic F(ab)'₂.

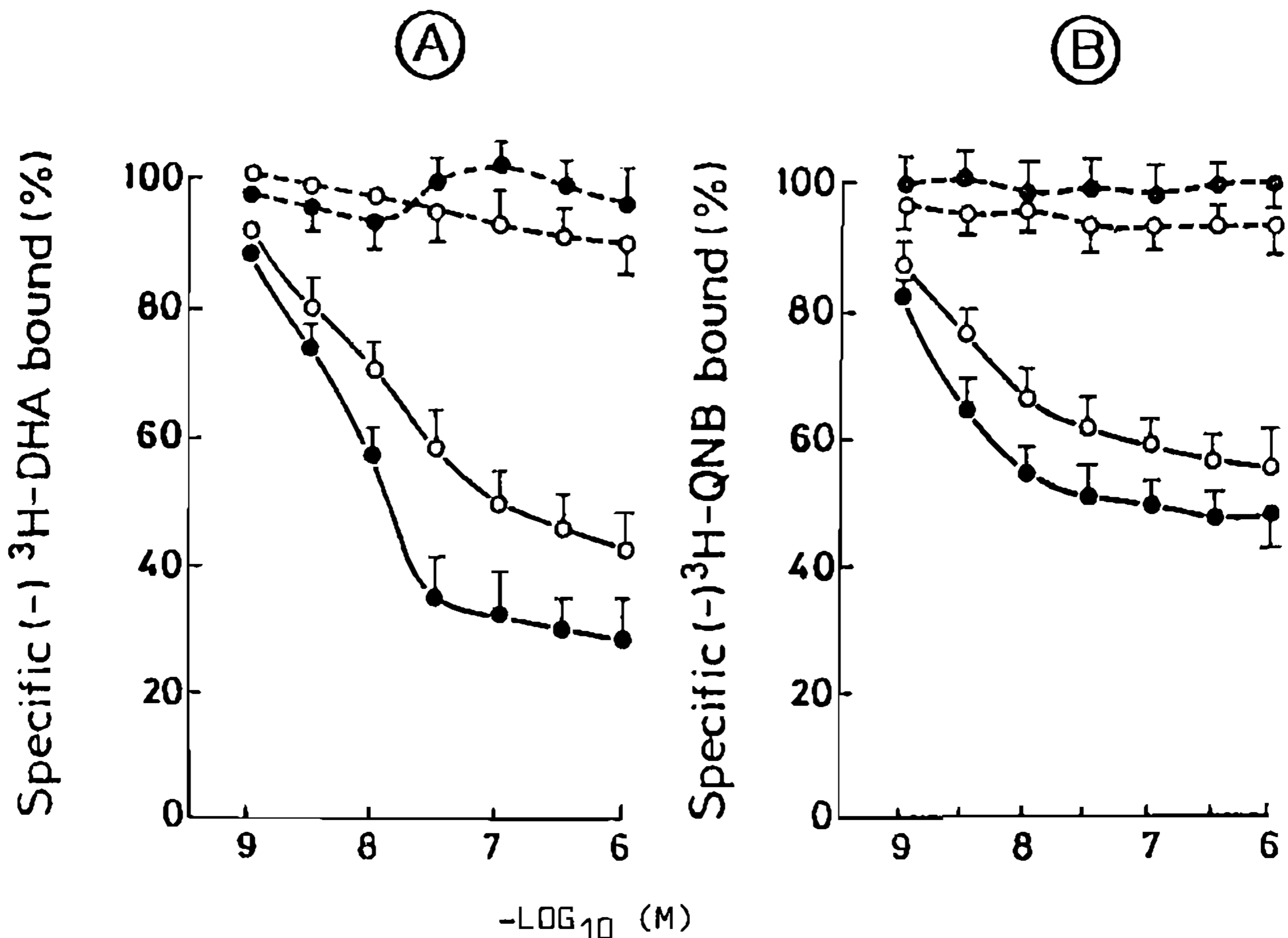


Figure 1: Inhibition of binding of (-)3H-DHA (Panel A) and (-)3H-QNB (Panel B) on T-cell enriched populations of murine chagasic IgG (●—●), chagasic F(ab)'2 (●—●), normal IgG (●---●) or normal F(ab)'2 (○---○).

To evaluate if during the interaction of chagasic IgG with lymphocyte neurotransmitter receptors triggers same biological effect, the action of chagasic IgG on the intracellular cAMP and cGMP levels of respective target cells were explored. We measured cAMP and cGMP levels on B cells, Tt cells, Th and Ts lymphocytes, before and after treatment with propranolol or atropine followed by treatment with $5 \times 10^{-7} \text{M}$ chagasic IgG at different incubation time. The results are plotted in Figure 2. When cAMP was measured on Tt cells a byphasic action of the IgG was observed: first there was a significant decrease of intracellular levels which was followed by an increase. When cAMP levels was measured on Th

lymphocytes only a gradual increase of the nucleotide was obtained. On the contrary, a significant decrease of cAMP intracellular levels was observed by the action of chagasic IgG on Ts (Figure 2, Panel A). The maximal increment induced by chagasic IgG on Th lymphocytes cAMP levels was similar to that observed with $5 \times 10^{-9}M$ isoproterenol and was blunted by propranolol treatment while the inhibition in the cyclic nucleotide levels of Ts cells was prevented by atropine. Values of cGMP on different cells exposed to chagasic IgG are also shown in Figure 2 (Panel B). It can be seen that cGMP levels increased in Tt cells and in Ts cells when they reacted with chagasic IgG. The maximal effect induced by chagasic IgG was similar to that observed with acetylcholine $10^{-7}M$ and was abrogated by atropine confirming a muscarinic cholinergic effect.

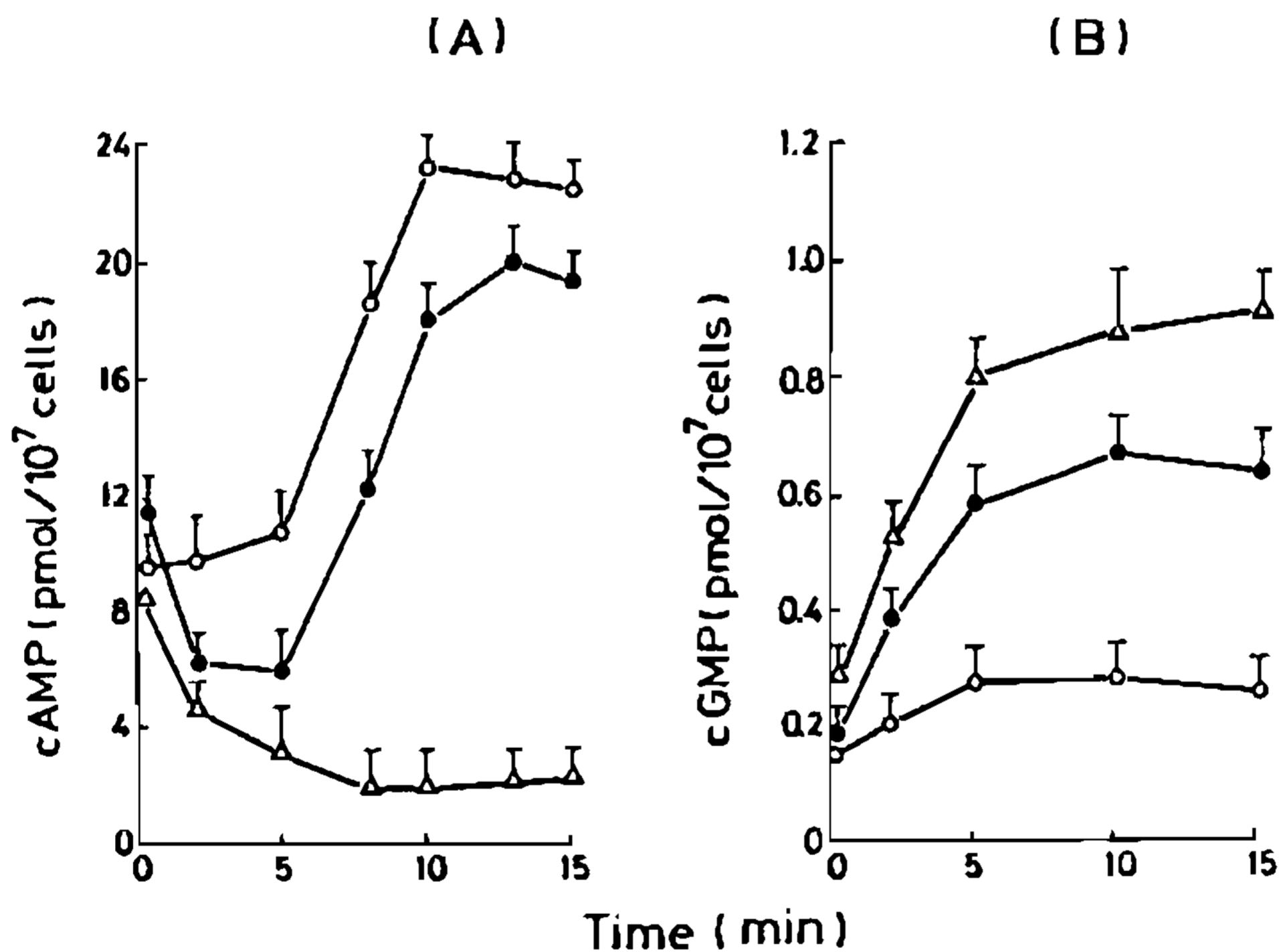


Figure 2: Time course of cAMP (Panel A) and cGMP (Panel B) effect of chagasic IgG on Tt (●—●), Th (○—○), and Ts (△—△) cells.

To evaluate if during the interaction of the chagasic IgG with lymphocytes, β adrenergic and cholinergic receptor, some immuno-

suppressor substance is released, PGE₂ was assayed on supernatants from different subsets of T cells that had been incubated with chagasic IgG. Supernatants from Tt cells and Ts cells exposed to chagasic IgG higher amounts of PGE₂ than that no exposed to chagasic IgG. Atropine inhibited the stimulatory action of the IgG on PGE₂ release by Tt and Ts cells, while propranolol did not produce any effect. The stimulatory action of chagasic IgG on PGE₂ release by Ts cells was similar to that observed by 10⁻⁷M acetylcholine. On the contrary, Th cells failed to show increased of PGE₂ release in the presence of chagasic IgG.

We demonstrated that human chagasic IgG exerted an immunosuppressor action acting on both Th and Ts lymphocytes, simulating a β adrenergic and muscarinic cholinergic agonism respectively. From the interaction of chagasic IgG with lymphocytes neurotransmitters receptors, signal transduction resulting in increase production of intracellular Th cAMP and Ts cGMP is generated. The stimulation by chagasic IgG of Ts cells muscarinic cholinergic receptors triggers the release of PGE₂. This is of particular interest because we proposed that a specific sort of IgG fulfills the criteria of a β adrenergic neurotransmitter in lymphoid organs; indicating that the specific recognition of lymphocytes attached neurotransmitter receptors by the antibody could induce an immunomodulation of the immunoresponse in Chagas' disease. Elevation of cGMP by stimulation of muscarinic cholinergic receptors of Ts cells or elevation of cAMP by stimulation of β adrenergic receptor of Th cells, served as a simple negative regulatory signal of the immune response. Another factor that confirms immunosuppressor action of the chagasic IgG is shown through its ability to trigger the release of PGE₂ from Ts cells. This release seems to be related to the stimulatory action of chagasic IgG on muscarinic cholinergic receptors. We propose that the recognition of chagasic IgG upon lymphocytes neurotransmitter receptors may induce an immunosuppressor response, that contributes to the chronic course of Chagas' disease.