Endothelial Barrier Breakdown in Experimental Chagas Disease: Inflammatory Edema Propagated Via the Kallikrein-Kinin System Fuels Intracardiac Parasitism and Associated Pathology

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Trypanosoma cruzi, the protozoa that causes Chagas disease, employs multiple strategies to subvert immunity. Focusing on the Kallikrein-kinin System (KKS), here we investigated the possibility that T. cruzi exploits the formation of inflammatory edema to parasitize heart tissues via activation of bradykinin receptors (B2R/B1R). Using intravital microscopy, we found that tissue culture trypomastigotes (TCTs) topically applied to “leaky” microvascular beds (hamster cheek pouch) potently evoke microvascular leakage due to mast cell (MC)-dependent activation of the KKS/contact system. Assisted by high-resolution echocardiography, we then inoculated mice intracardiacally with TCTs (Dm28 strain) and found that heart parasitism (qPCR; 3 d p.i.) was drastically reduced in MC-deficient mice or in WT mice pretreated with cromoglycate (MC stabilizer) or infectin-4 (Factor XIIa inhibitor). Using the same model, we next found that intracardiac edema (2 h p.i.) and heart parasitism (3 d p.i.) were both inhibited by (i) subtype-specific antagonists of bradykinin receptors (B2R versus B1R) or (ii) bosentan, a non-selective antagonist of endothelin receptors (ET_AR/ET_BR). Notably, the myocarditis/fibrosis (30 d p.i.) was attenuated in mice pretreated with these GPCR blockers, implying that they exerted prolonged therapeutic effects. We next studied the impact of TCT application to LPS-treated microvascular beds (cheek pouch) and found that B1R intensified/prolonged the inflammatory edema. We next challenged C57BL/6 mice and B1R-/- mice (i.p.) and found that intracardiac parasitism was reduced in the mutant mouse (14 d p.i.), correlating with the milder myocarditis/fibrosis observed at the chronic phase (90 d p.i.). Importantly, heart parasitism was significantly inhibited in acutely infected WT mice (Colombian strain) subjected to daily treatment (45-60 d p.i.) with a specific antagonist of B1R (R-954). Our results suggest that endothelial barrier stabilizers, such as B1R antagonists, limit the extent of *T. cruzi* infectivity and the associated pathology (myocarditis/fibrosis) by inhibiting inflammatory edema orchestrated via the MC/KKS pathway. **Keywords:** Chagas disease, Kallikrein, Kinin, *Trypanosoma cruzi,*