NLRP3 activation contributes to Endothelin-1-induced erectile dysfunction

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July 23, 2021

Abstract

Background and Purpose: Endothelin-1 (ET-1) and Nucleotide Oligomerization Domain-Like Receptor Family, Pyrin Domain Containing 3 (NLRP3) play an essential role in erectile dysfunction. ET-1 and NLRP3 activate inflammatory processes by increasing calcium (Ca^{2+}) and reactive oxygen species (ROS). In the present study, we hypothesized that endothelin receptors (ET_A and ET_B) stimulation, through increased calcium and ROS formation, leads to NLRP3 activation. **Experimental approach:** Intracavernosal pressure (ICP/MAP) was measured in C57BL/6 (WT) mice. Functional and immunoblotting assays were performed in corpora cavernosa (CC) strips from WT, $NLRP3^{-/-}$ and $caspase^{-/-}$ mice after ET-1 (100 nM) stimulation in the presence of vehicle, MCC950, tiron, BAPTA AM, BQ123, or BQ788. **Key Results:** ET-1 gradually reduced the ICP/MAP in WT mice, and MCC950 administration prevented the effect of ET-1. ET-1 decreased CC relaxation to ACh and sodium nitroprusside (SNP) and increased caspase-1 protein expression, effects reversed by the ET_A receptor antagonist BQ123. The ET_B receptor antagonist BQ788 also reversed the effect of ET-1 on ACh and SNP relaxation. Additionally, tiron, BAPTA AM, and NLRP3 genetic deletion prevented the ET-1-induced loss of ACh and SNP relaxation. Moreover, BQ123 diminished CC caspase-1 expression, while BQ788 increased caspase-1 and IL-1β levels in a concentration-dependent manner (100 nM to 10 μM). Furthermore, tiron and BAPTA AM prevented ET-1-induced increase in caspase-1. In addition, BAPTA AM blocked ET-1-induced ROS generation. **Conclusion and Implications:** NLRP3 activation contributes to acute ET-1-induced erectile dysfunction by mechanisms that depend on ET_A- and ET_B-induced Ca^{2+} influx and ROS generation.

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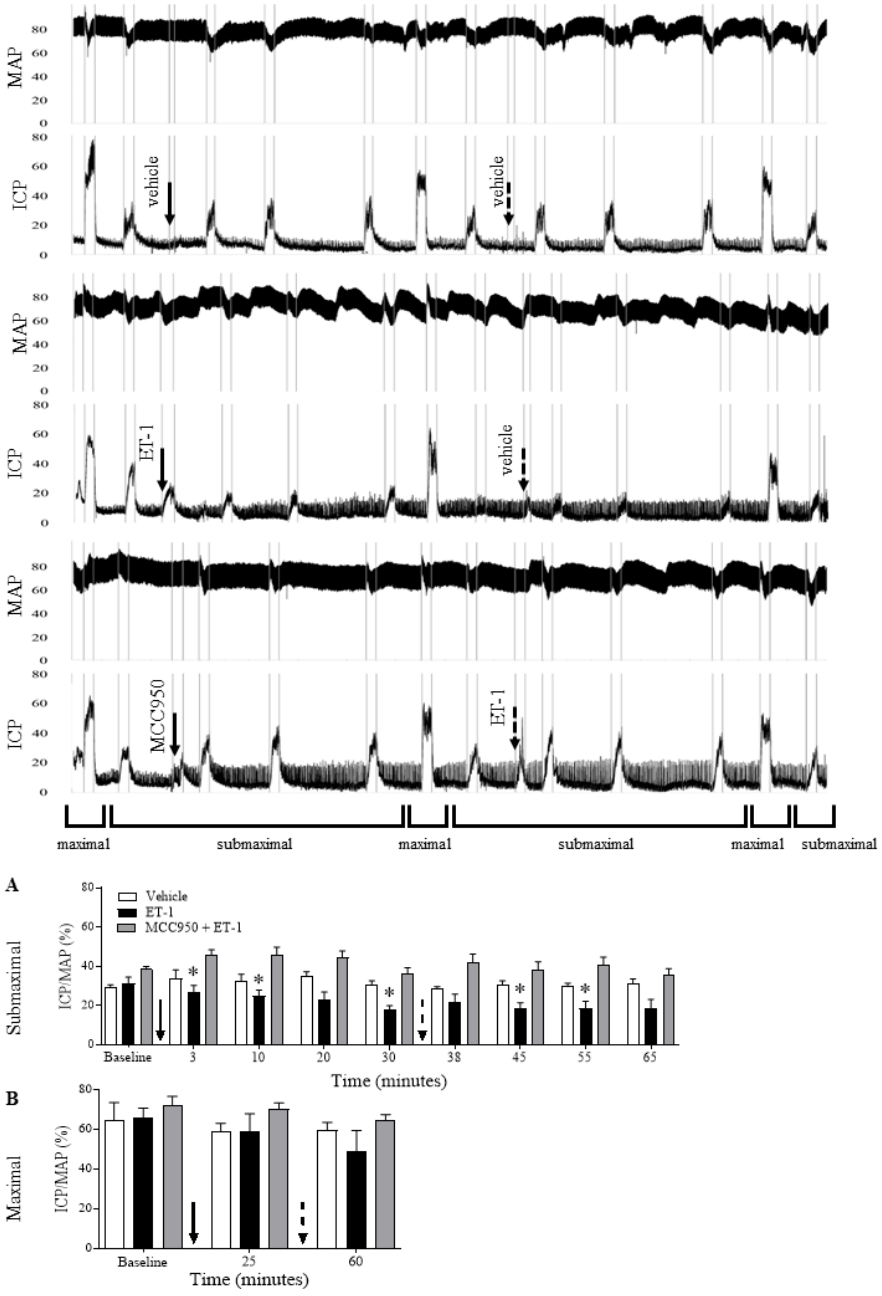

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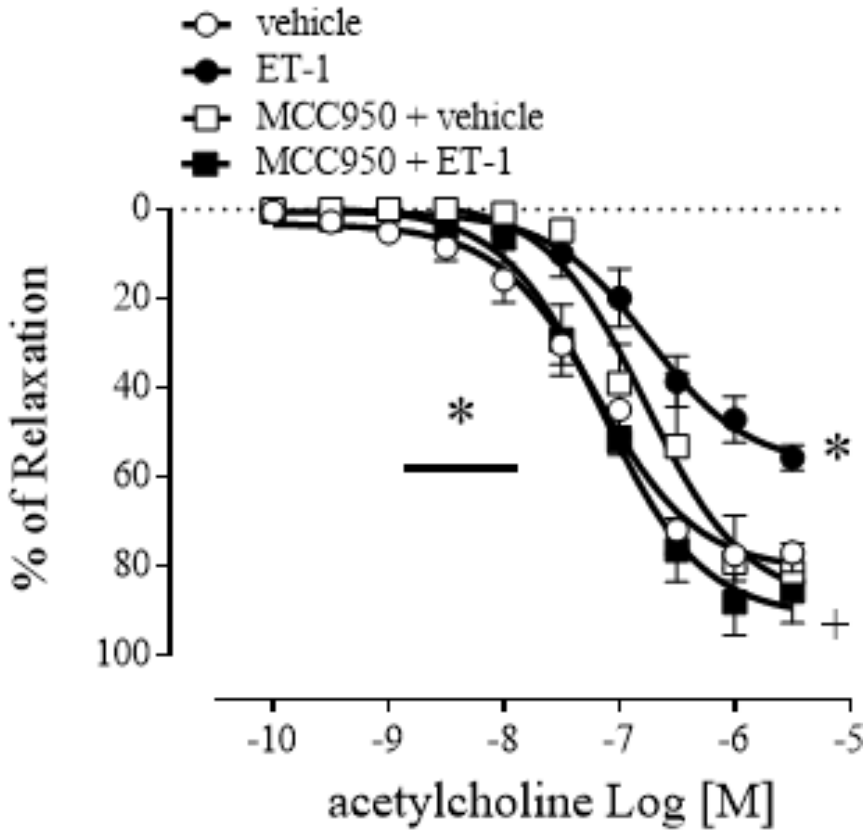

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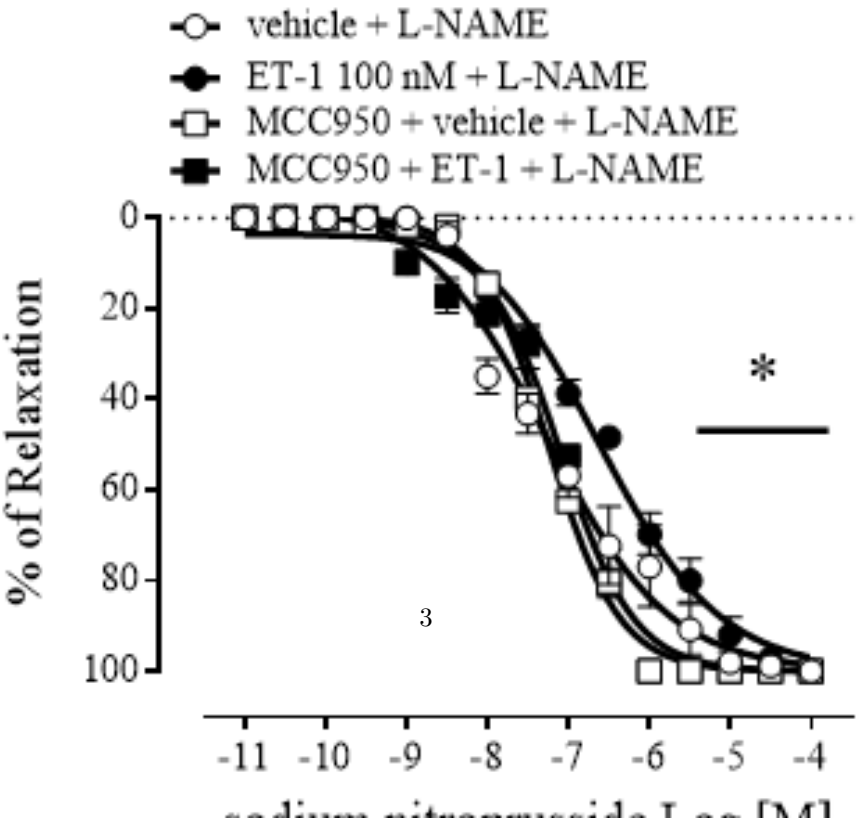

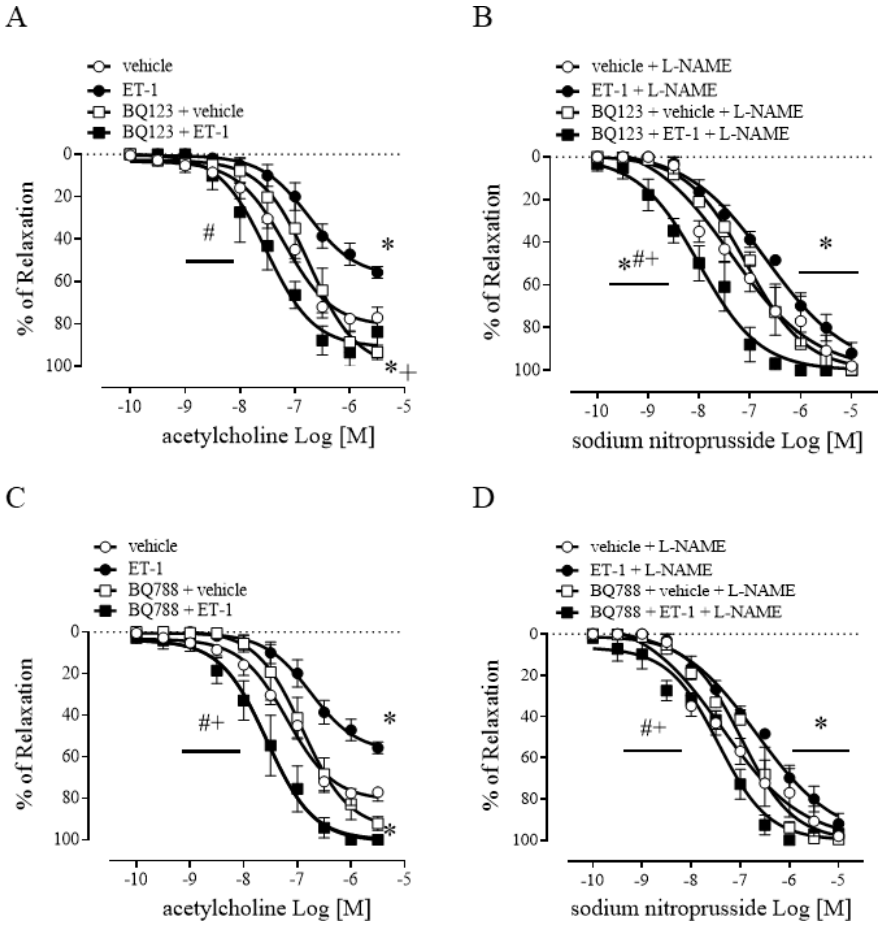

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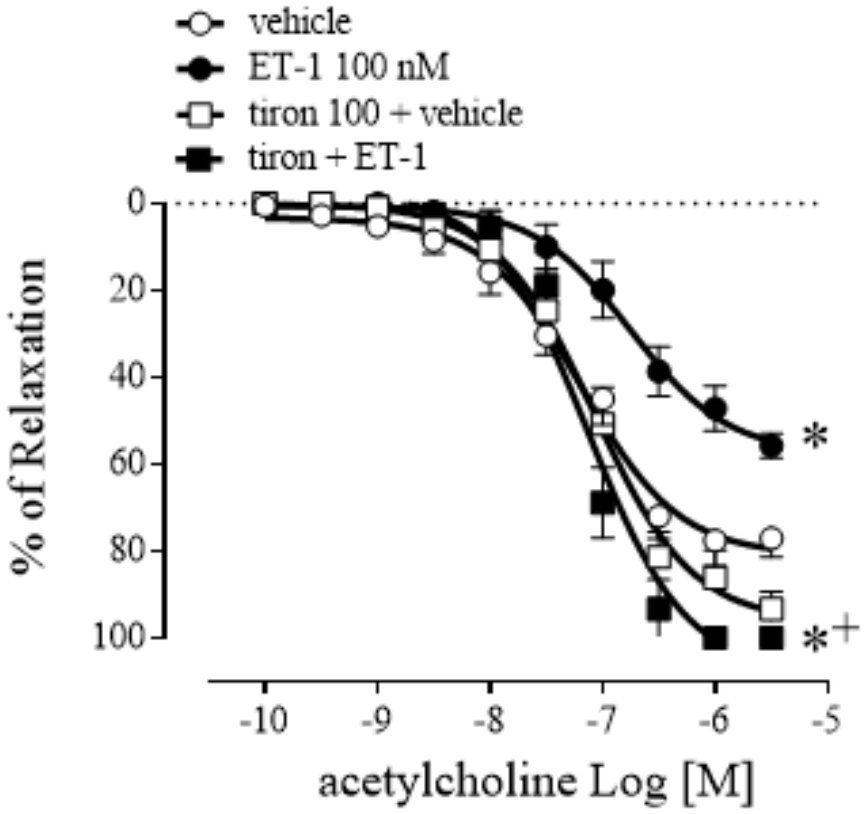

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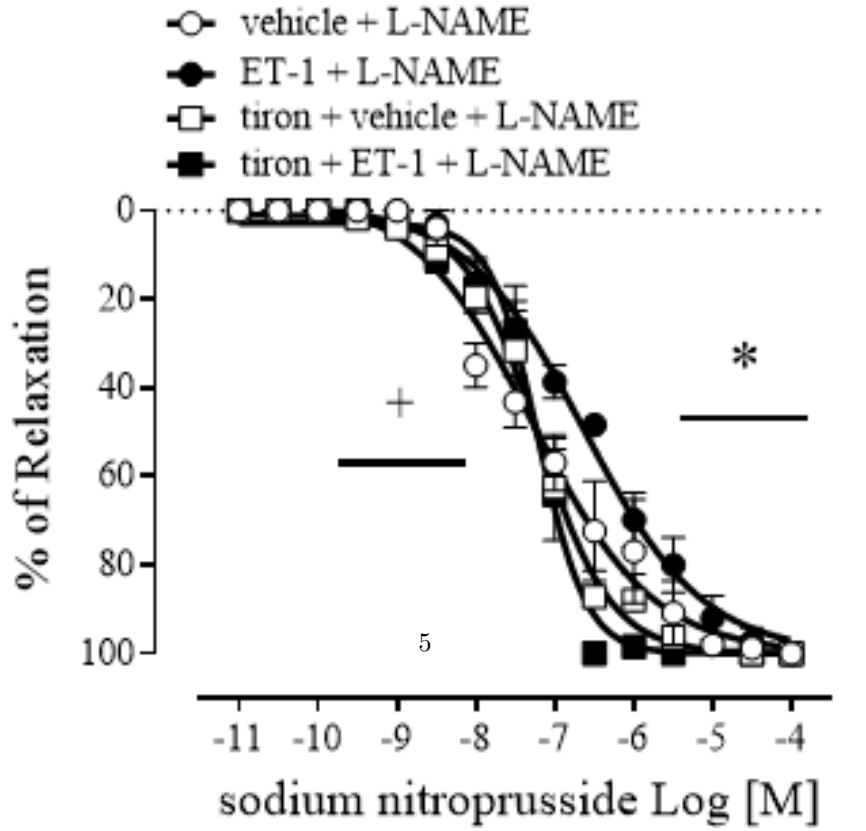

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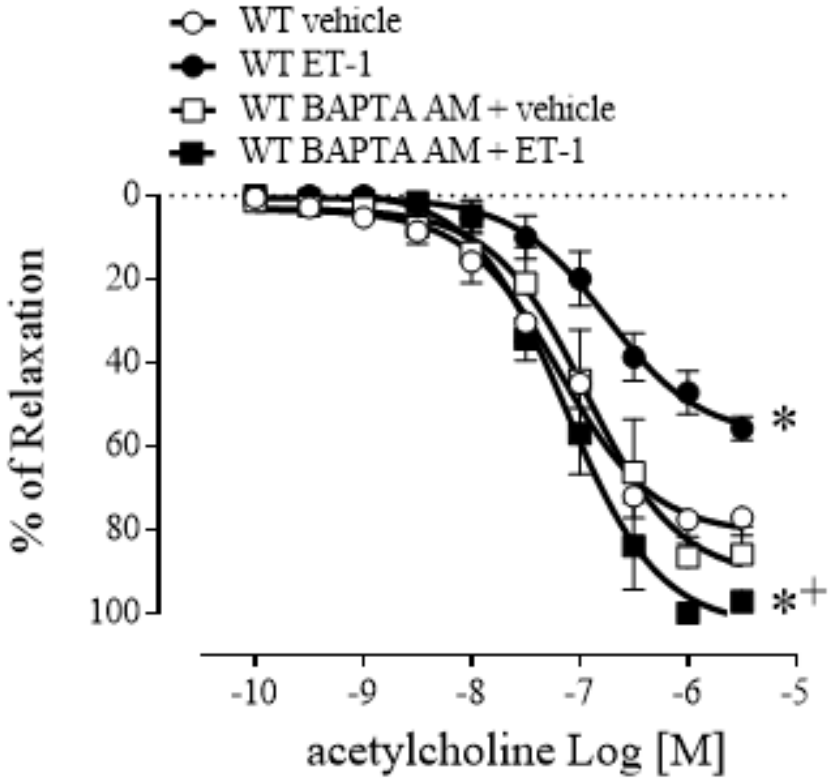

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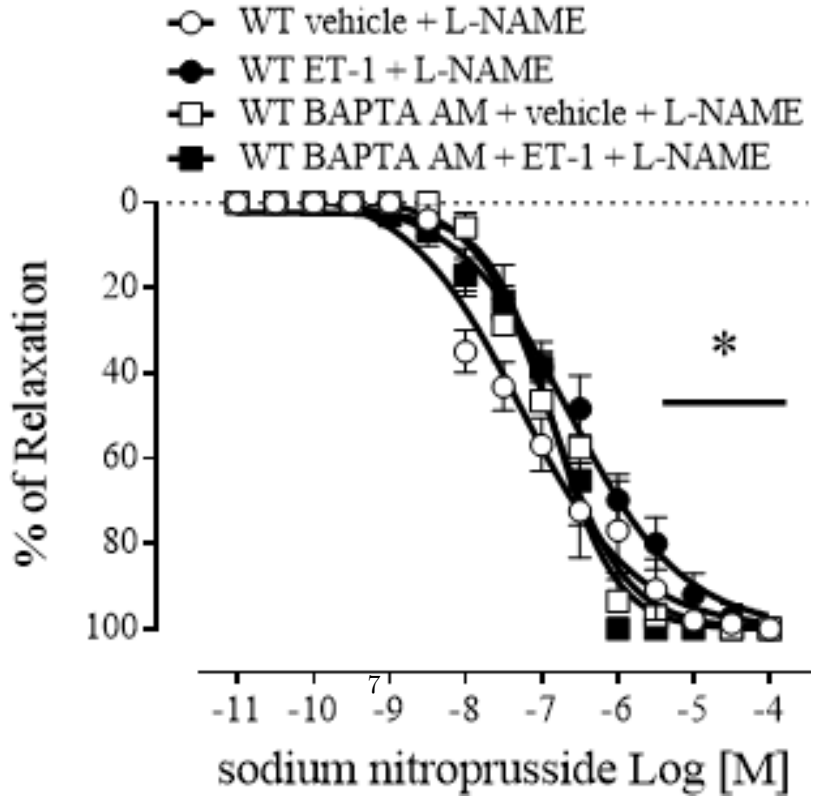

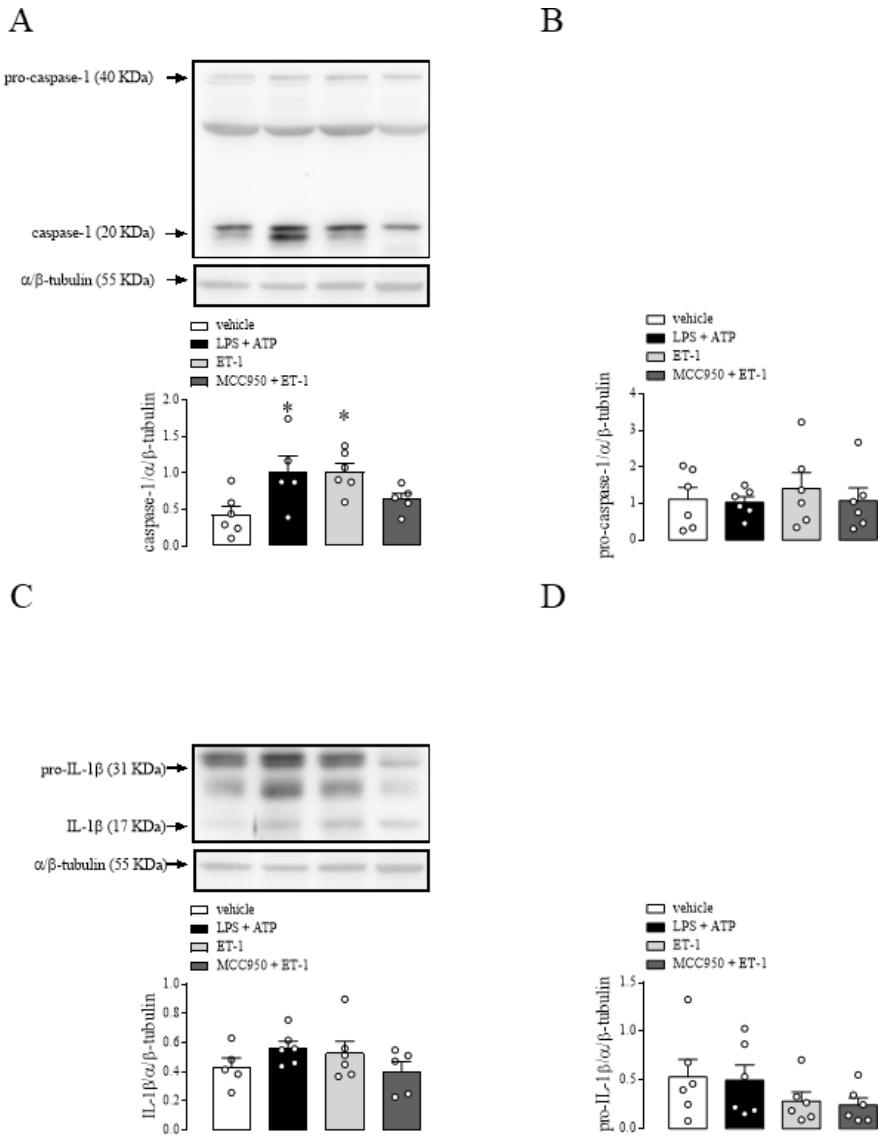

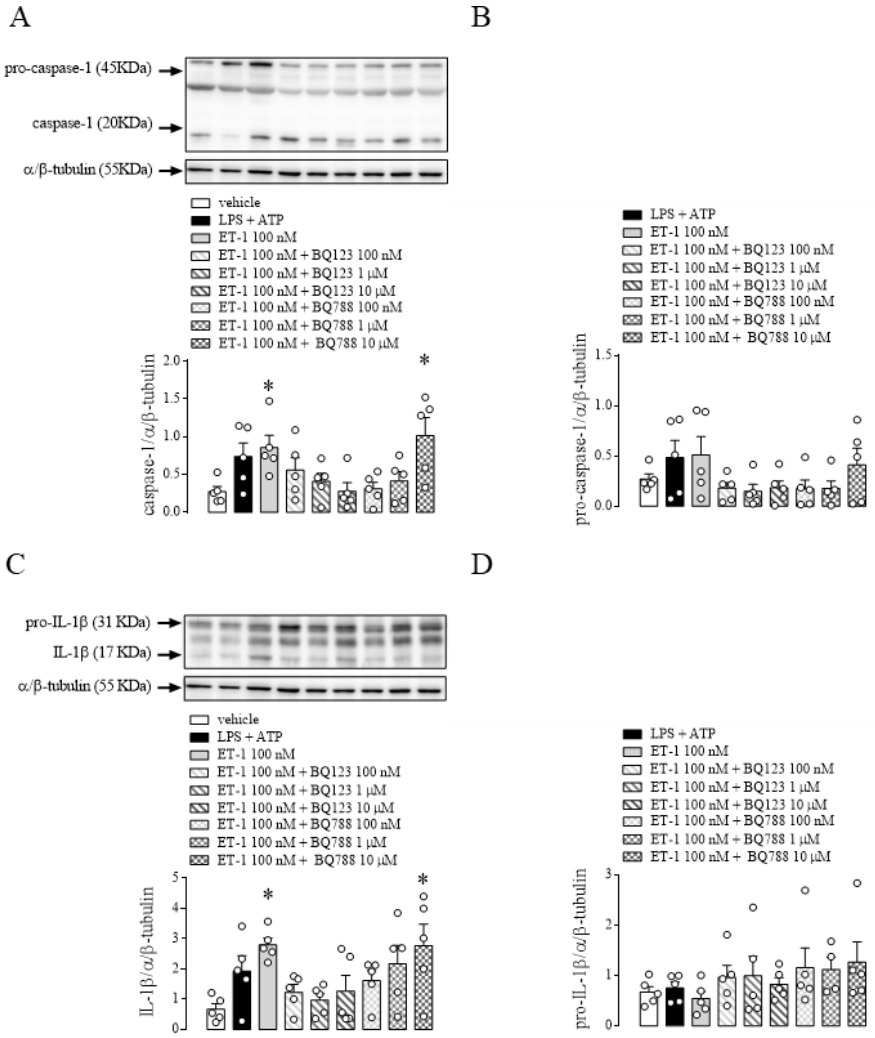

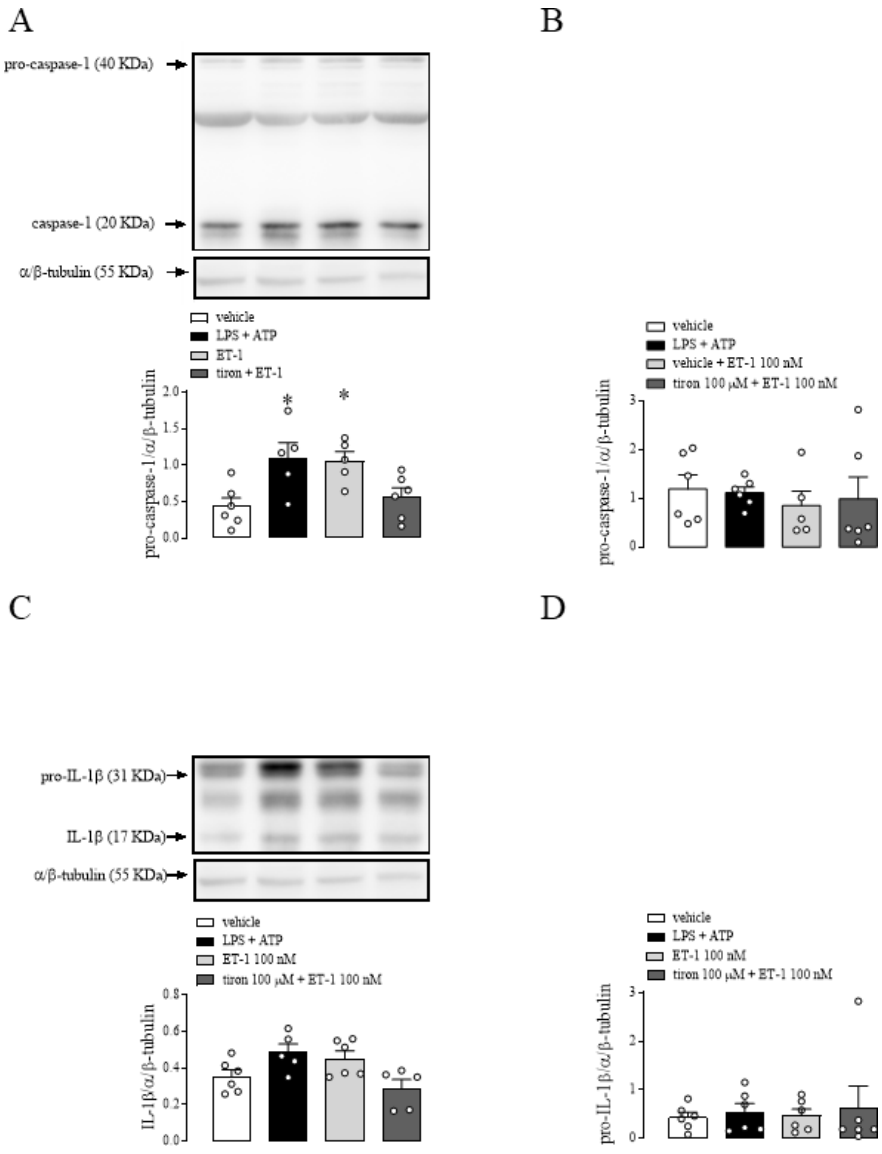

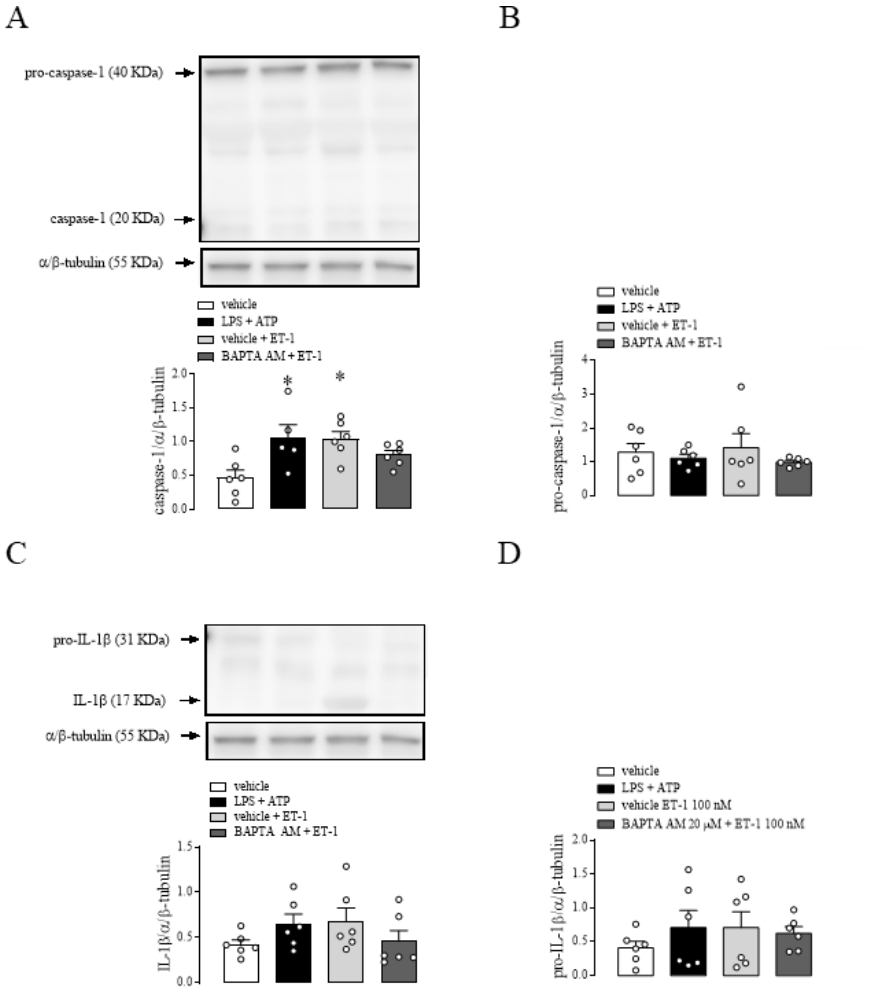

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