DOXANTRAZOLE: A MAST CELL STABILIZER THAT ACTIVATES MESENTERIC AFFERENT NERVES IN RAT

Introduction

We have previously reported that *Nipponcfonias brasiliensis* (Nb) antigen activates mesenteric nerves. In an attempt to elucidate the mechanism of this Nb antigen-induced activation, the mast cell stabilizer doxantrazole was employed. This report describes initial studies with doxantrazole (DOX).

Methods

In order to confirm doxantrazole as a mast cell stabilizer, cultured RBL-2H3 cells and bone marrow-derived mast cells (BMMC) were exposed to ionomycin (1 µM) and doxantrazole (1 mM, GSK) and the supernatant collected for ELISA analysis of TNF-α and histamine. After the mast cell stabilizing properties of doxantrazole were proved by the above experiments. Mesenteric afferent recordings were obtained both in vivo from anaesthetized rats (n=12) and in vitro from rat jejunal segments (n=5) using conventional extracellular recording techniques (see the schematic illustration below). Doxantrazole was administered in vivo (n=6, 10 mg/kg i.v.) and close intrasynthetically in vitro (n=5, 0.63 µg). Cromolyn was administered in vivo (n=6, 20 mg/kg i.v.). Data are expressed as mean ± sem and analysed with One-way ANOVA or repeated-measures one-way ANOVA followed by appropriate post test.

Results

A: Histamine release from BMMC  B: TNFα release from BMMC

Figure 1 - Effects of doxantrazole on histamine and TNFα release-evoked by ionomycin in BMMC. Doxantrazole inhibited the ionomycin (Ion.)-induced release of both histamine (P<0.05, n=3) and TNFα (P<0.05, n=3). *P<0.05 vs another two groups.

Conclusions

- The mast cell stabilizing properties of doxantrazole were confirmed by the inhibition of mast cell mediators release in culture.
- Doxantrazole elicits a sustained increase in afferent nerve firing *in vivo* and this response is mimicked by another mast cell stabilizer, cromolyn.
- The nerve response to doxantrazole in *in vivo* differs as it is transient and desensitizes.
- The activating property of doxantrazole on afferent nerves may partially explain the lack of efficacy of it as an anti-allergenic agent.