Involvement of cathepsin S and protease-activated receptor-2 (PAR-2) in ciguatoxin-induced substance P (SP) release: new promising targets to treat ciguatera pruritus

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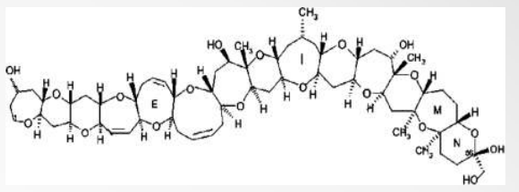


Introduction

Ciguatera :

- Characterized by **sensory symptoms** (paresthesia, cold dysesthesia, pruritus)
- Consecutive to ciguatoxin (CTX) ingestion
- Target of CTXs : voltage dependent sodium channels (Nav)
  - Membrane hyperexcitability
  - Downstream events unkown

PAR-2 activation induces SP release

Role of SP in pruritus and pain

Previous results :

- P-CTX-2 induces SP release from our co-culture

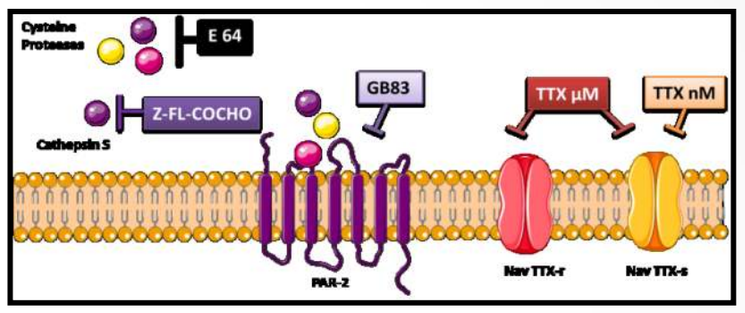
Material & methods

Rat sensory neurons → **Calcium imaging**

Human keratinocytes → **Calcium imaging & confocal microscopy**

Co-culture keratinocytes & neurons → **Cathepsin S activity & SP dosage**

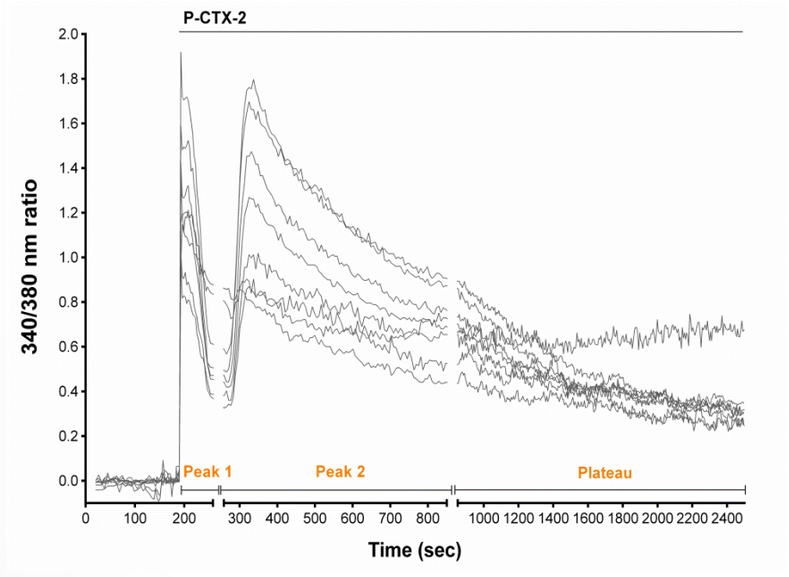
Antagonists/targets →



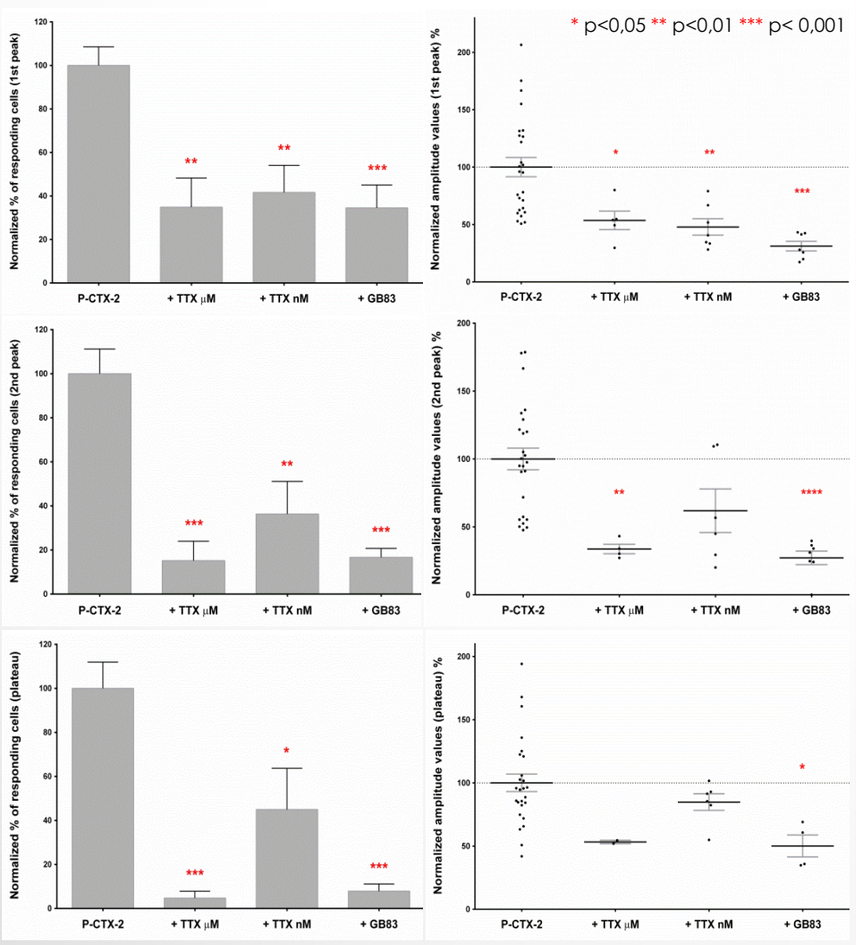
Objectives

Identification of cellular and molecular actors in CTX-induced SP release
Role of PAR-2

Rat sensory neurons

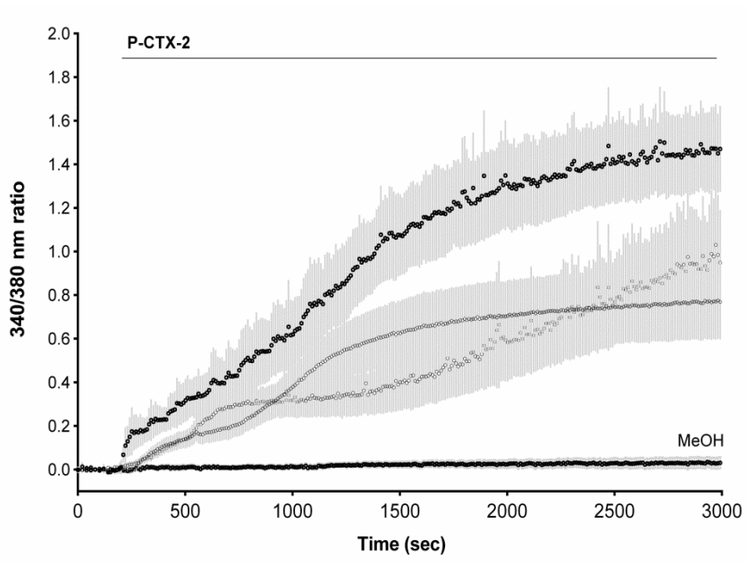


➔ Transient and sustained increase of cytosolic calcium in 3 phases

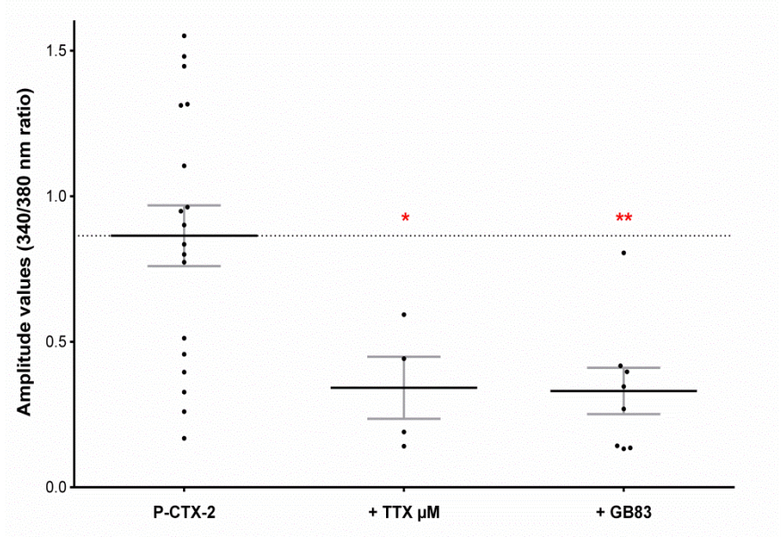


➔ Nav and PAR-2 are implicated in calcium response to P-CTX-2

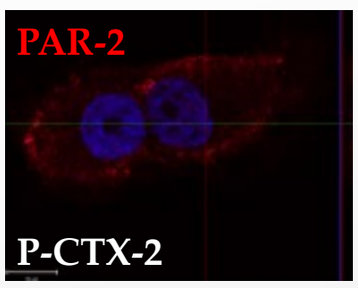
Human keratinocytes



➔ Sustained calcium increase

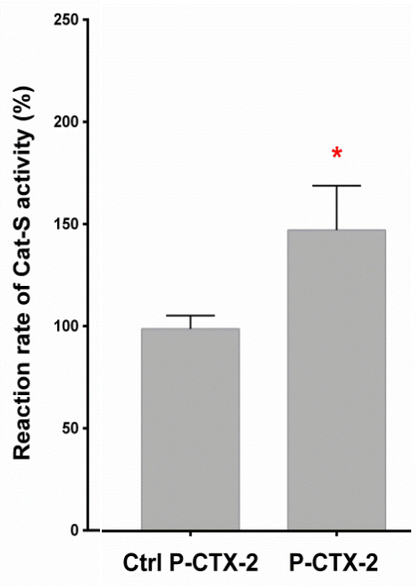


➔ Role of Nav and PAR-2 in calcium response to P-CTX-2

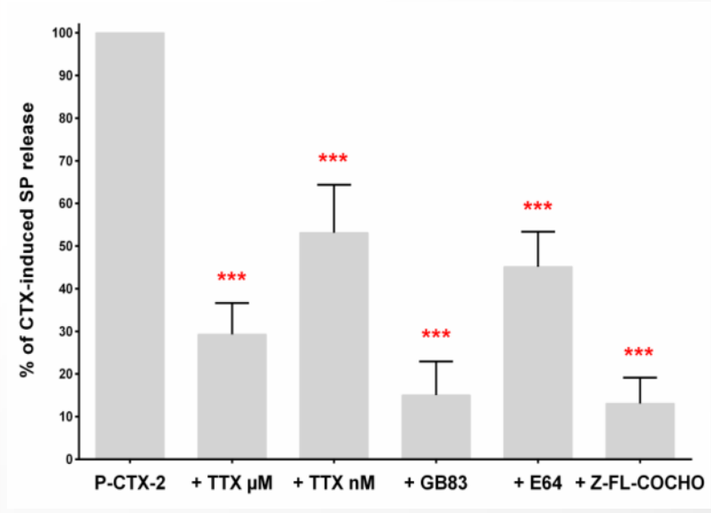


➔ P-CTX-2 internalize PAR-2

Co-culture keratinocytes & neurons



➔ P-CTX-2 increase cathepsin S activity in the supernantant



➔ Role of Nav, PAR-2, cysteine proteases, cathepsin S in the CTX-induced SP release

Conclusions

Keratinocytes, Nav channels, PAR-2, cathepsin S are key actors involved in CTX-induced SP release.

Cathepsin S and PAR-2 are promising targets to relieve sensory disorders in ciguatera.