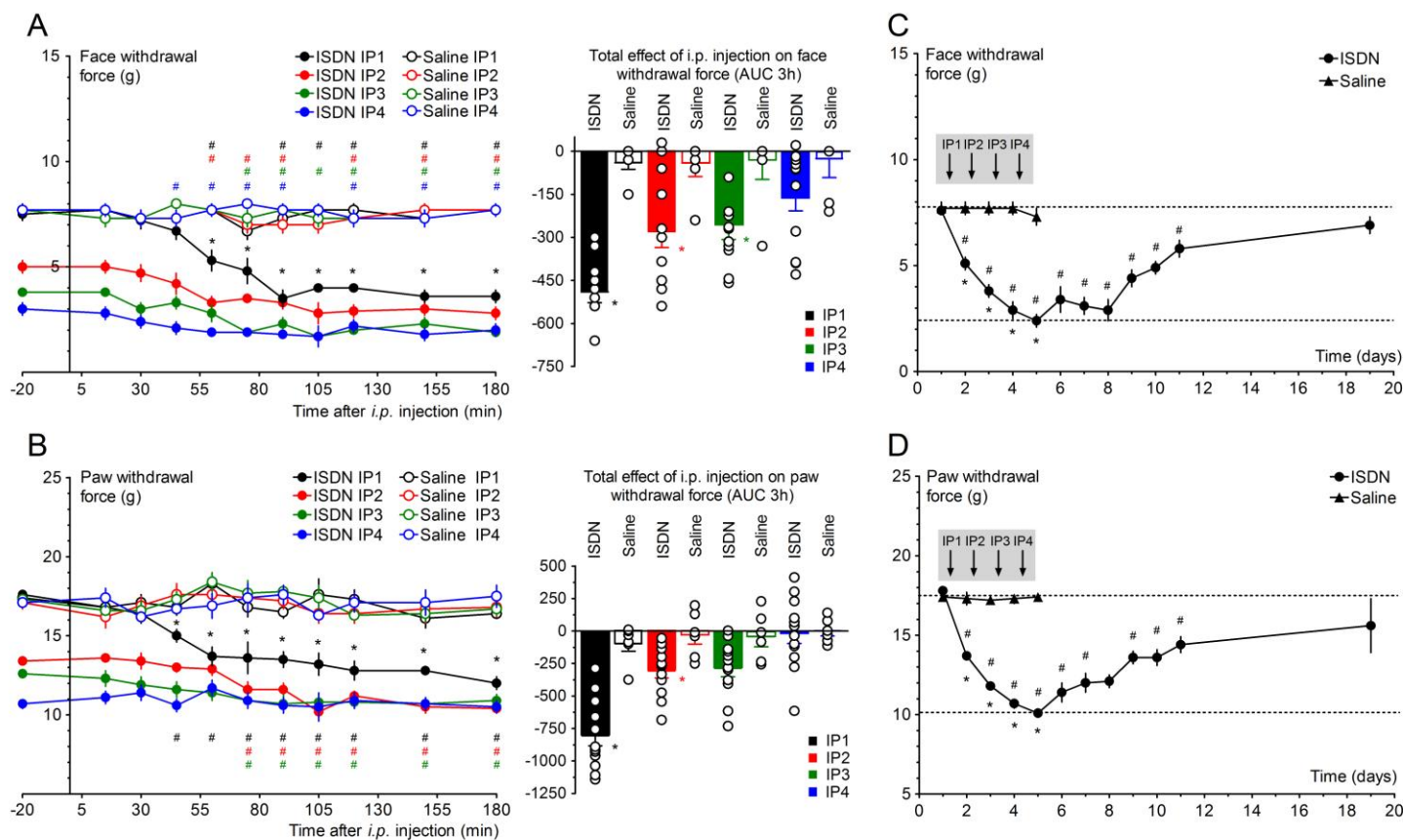


**Supplementary Fig. 1: Absence of effect of intravenous and local intraplantar injections of mambalgin-1 on paw mechanical sensitivity of naive rats.**

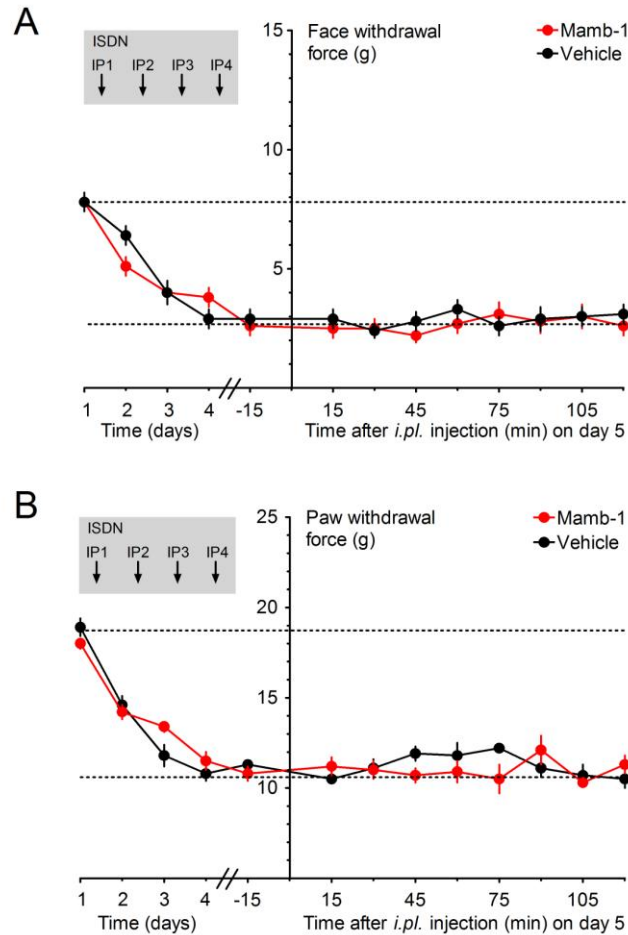
**A, B** - Effect of *i.v.* (**A**) and *i.pl.* (**B**) Mamb-1 on paw mechanical sensitivity. Paw mechanical withdrawal force (g), mean  $\pm$  SEM, n=7-14, No significant statistical difference compared to vehicle with Mann Whitney non parametric test. **C**, -Total effect of *i.v.* and of *i.pl.* Mamb-1 on paw mechanical withdrawal force calculated as the Area Under Curve (AUC) during 2 hours after the injection. Mean  $\pm$  SEM, no significant statistical difference compared to vehicle with Mann Whitney non parametric test.



**Supplementary Fig. 2: Migraine-like, ISDN-induced cephalic and extra-cephalic acute and chronic mechanical allodynia.**

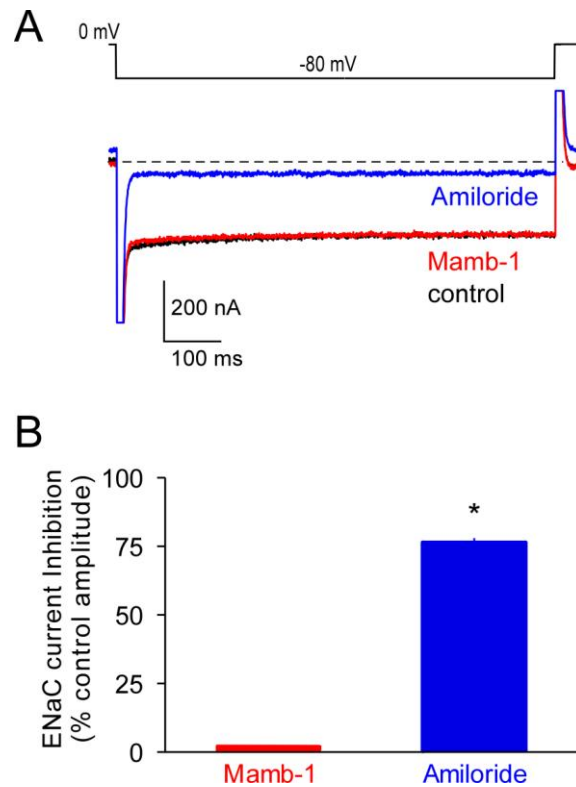
**A, B - Left panels** - Kinetics of the effects of each of the four consecutive daily *i.p.* injections of the ISDN (10 mg/kg) or of saline control on the face mechanical withdrawal threshold measured with von Frey filaments (**A**) and on the hindpaw mechanical withdrawal threshold measured with dynamic plantar aesthesiometer (**B**) on the same rats. Mean  $\pm$  SEM,  $n = 6$  and  $12$  for saline and ISDN, respectively: \*  $p < 0.05$  with Mann Whitney non parametric test compared to saline control (ISDN IP1 only), #  $p < 0.05$  with Wilcoxon matched paired test compared to basal value before ISDN. **Right panels** - Total effect on the same rats of each injection on face (**A**) and paw (**B**) withdrawal force calculated as the Area Under Curve (AUC) during 3 hours after the injection. Mean  $\pm$  SEM and individual data points, \*  $p < 0.05$  with Mann Whitney non parametric test compared to saline control.

**C, D** - Basal mechanical face (**C**) and paw (**D**) withdrawal force threshold (g) measured on the same rats before each daily injection and after the last fourth injection. Mean  $\pm$  SEM,  $n=6$  and  $12$  for saline and ISDN, respectively: \*  $p < 0.05$  with Mann Whitney non parametric test compared to saline control; #  $p < 0.05$  with Wilcoxon matched paired test compared to control before the first injection.



**Supplementary Fig. 3: Absence of effect of intraplantar injection of mambalgin-1 on ISDN-induced cephalic and extra-cephalic chronic mechanical allodynia.**

Kinetics of the effect of the local *i.pl.* injection of Mamb-1 (6.7 nmol/kg) one day after the last ISDN injection (*i.e.*, on day 5) on face (**A**) and paw (**B**) mechanical withdrawal force (g) measured on the same rats (n=9). The basal mechanical withdrawal force (g) was measured before each daily ISDN injection (left side of the y axis), showing the chronification process of cutaneous allodynia day after day. Mamb-1 effect was not significantly different ( $p > 0.05$ ) from vehicle (Mann Whitney non parametric test).



**Suppl. Fig. 4: Mambalgin-1 does not inhibit the epithelial sodium channel.**

cDNAs of the  $\alpha$ ,  $\beta$  and  $\gamma$  subunits of the epithelial sodium channel (ENaC, 10 ng/ $\mu$ l each), were co-injected into *Xenopus* oocytes (oocytes preparation and cDNA injections as previously described (Besson *et al.*, 2017)), and oocytes were kept during two days at 19°C in saline (ND96) extracellular solution (96 mM NaCl, 2mM KCl, 1.8 mM CaCl<sub>2</sub>, 2mM MgCl<sub>2</sub> and 5 mM HEPES, pH7.4 with NaOH) where Na<sup>+</sup> has been replaced by N-methyl D-glucamine, a non-permeant cation. **A**, Original traces of ENaC current recorded in Na<sup>+</sup>-containing ND96 during voltage-steps from 0 to -80 mV every 10 s, in control condition and after application of either Mamb-1 (3 $\mu$ M, a concentration that inhibits ASIC channels by 70 to 100% (Diochot *et al.*, 2012)) or amiloride (10 $\mu$ M). Dotted line: zero current level. **B**, ENaC current (% of control current amplitude) was blocked by amiloride as expected (inhibition of 77 ± 5%) but was not inhibited by Mamb-1 (2 ± 0.9%). Mean ± SEM, n=8, \* p<0.05 with Wilcoxon matched paired non parametric test.