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FPR2 antagonism inhibited preventive effect of pro-resolving mediators or hydroalcoholic crude extract from *Casearia sylvestris* in an animal model of Complex Regional Pain Syndrome - Type I.

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Complex Regional Pain Syndrome Type I (CRPS-I) has a relatively high prevalence (~26/105 habitants [Netherland study]) in humans, with symptoms that include edema and pain, specifically allodynia (sensing as painful an otherwise non-noxious stimulus) (1). Among the main mechanisms associated with its pathophysiology is inflammation and drugs currently used to treat it have produced little effectiveness (2). Our group registered preliminary data using a model of ischemia-reperfusion (IR) induced CRPS-I where LXA4 analog, BML-111, and hydroalcoholic extract from *Casearia sylvestris* (HCE-CS), a plant with anti-inflammatory and antioxidant properties (3), reduced edema and mechanical allodynia of inflammatory origin (evident 3 days after IR) at same extents. The aim of this study was to investigate the possible involvement of formyl-peptide receptor type 2 (FPR2) to the effects promoted by BML-111 and HCE-CS on this model.

Male Swiss mice (25–30 g) are anesthetized and submitted to ischemia of the right hind paw using a tourniquet for 3 h, then reperfusion is allowed (4). Different groups of animals were treated with vehicle (sterile saline, 10ml/kg), FPR2 (WRW4) or FPR1 (BOC-2) antagonists, both 10µg/animal, subcutaneously (s.c.) and 15 min after they received vehicle, BML-111 (1µg/animal, s.c) or HCE-CS (30mg/kg, orally). BOC-2 treatments were performed at 10 min, 24h and 48h after reperfusion is allowed, while WRW4 was used 24h and 48h after this procedure. Edema was measured as changes in paw thickness (in µm, compared to basal values) and mechanical allodynia was assessed by paw withdrawal in response to 10 applications of a von Frey filament (0.4 g) from 1-72h after reperfusion (AR). Data are presented as mean±SEM (n= 6-12 animals), Two-way ANOVA followed by Bonferroni ($p \leq 0.05$).

Pharmacological delivery of WRW4 abrogated the protective action of HCE-CS (55.6±9.3% of response) or BML-111 (62.5±11.6% of response) against mechanical allodynia (vehicle groups: 22.9±8.1 and 22.0±9.6 % of response, respectively) in the model of CRPS-I, while no substantial effects were observed on edema (not shown). In the contrary, antiallodynic effect for HCE-CS (26.0±9.0% of response) or BML-111 (28.0±8.0% of response) in relation to control group (vehicle+vehicle: 82.0±4.7%

of response) was not affected in animals treated with BOC-2 (HCE-CS: 23.3±8.0 or BML-111: 24.0±9.8% of response).

In summary, animal treatment with FPR2 antagonist, WRW4, inhibited preventive effect of BML-111 or HCE-CS on mechanical allodynia associated to the inflammatory phase in a model of CRPS-I induced by IR in mice. These data indicate pro-resolving mediators as candidates for its potential benefits on symptoms related to CRPS-I in humans, as well as a likely modulation of resolution of inflammation pathways (possibly centred on AnxA1-LXA4-FPR2) following HCE-CS application to the animals.

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