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Antinociceptive effect of dipyrone and its metabolites on hyperalgesia induced by endothelin-1

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Introduction: Dipyrone is a pro-drug with potent analgesic and antipyretic effects. After its administration, dipyrone is rapidly hydrolysed to 4-methylaminoantipiryne (4-MAA), which is further metabolized to 4-formylaminoantipiryne (4-FAA), 4-aminoantpiryne (4-AA) and 4-acetylaminoantipiryne (4-AAA). Differently from non steroidal antiinflammatory drugs, dipyrone's antinociceptive effect is not related only to inhibition of prostaglandin E_2 (PGE_2) synthesis, but also involves other incompletely understood mechanisms. Endothelin-1 (ET-1)-induced hyperalgesia depend importantly on signaling pathways involving phospholipase (PL) PLC, adenylyl cyclase (AC), and mitogen-activaded protein kinases (MAPK). Moreover, the ET-1-induced hyperalgesia are not blocked by indometacin and dexamethasone. The aim of the experiment is to better understand dipyrone antinociceptive effects, the present study assessed the analgesic effect of dipyrone and its metabolites on hypernociception induced by ET-1.

Methods: Male Wistar rats weighing 180 to 200 g were habituated to the test room for at least 1 h prior to experiments. Mechanical hyperalgesia was assessed by electronic von Frey apparatus. Dipyrone (60-120 mg/kg) and its metabolites 4-MAA (15 - 120 mg/kg), 4-AAA (180 mg/kg), 4-AA (120 mg/kg) and saline (control group) were given intraperitoneally 30 min before ET-1 (30 pmol/paw) or saline injection. Hypernociception was evaluated on 1-5 hours after injecting the nociceptive stimuli (N=6 for all groups). Data are expressed as mean ± S.E.M. and were statistically evaluated using ANOVA followed by Tukey test, $p < 0.05$. This study was approved by the Ethic Committee of FMRP/USP (process n° 019/2012).

Results: Dipyrone (DIP) and it metabolite 4-MAA, but no its metabolites 4-AA and 4-AAA, showed analgesic effect against ET1-induced hyperalgesia. The intensities of hyperalgesia (Δ withdrawal threshold, in g (Δ g)) were: saline + saline: 0.60 ± 0.14; saline + ET-1: 6.07 ± 0.96; DIP + ET-1: (60mg/kg: 3.75 ± 0.82), (90mg/kg: 1.74 ± 0.53), (120mg/kg: 0.90 ± 0.24); 4-AA + ET-1: (60mg/kg: 4.79 ± 1.35; 120 mg/kg: 3.05 ± 1.13); 4-MAA + ET-1: (15mg/kg: 3.22 ± 1.08; 30mg/kg: 1.89 ± 0.61; 60mg/kg: 2.05 ± 0.44; 120mg/kg: 0.57 ± 0.18); 4-AAA + ET-1: (120 mg/kg: 3.04 ± 0.72; 240mg/kg: 3,36 ± 0,89.

Discussion: These results show for the first time that, like dipyrone, it metabolite 4-MAA reduced ET-1-induced hyperalgesia, suggesting that this metabolite may be responsible for the analgesic effect independent of inhibition of PGE_2 synthesis pathways may participate in the signaling involving PLC, AC and MAPK. Both 4-AA and 4-AAA had no effect on ET-1-induced hyperalgesia. Financial support: CNPq and FAPESP.