Role of 5-HT in intestinal ischemia-reperfusion: suppression of inflammatory events by 5-HT_{1A} blockade in mice

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Background and Aim Intestinal ischemia and reperfusion (I/R) is a potentially life-threatening disease, ensuing from various clinical conditions (1). Experimentally, either protective or detrimental roles have been attributed to 5-HT in the functional and morphological injury caused by mesenteric I/R (2,3). Recently, we proved the involvement of 5-HT_{2A} receptors in the intestinal dysmotility and leukocyte recruitment induced by 45 min occlusion of the superior mesenteric artery (SMA) followed by 24 hours reperfusion in mice (4). The aim of our present work was to investigate the role played by endogenous 5-HT in the same experimental model where 45 min SMA clamping was followed by 5 hours reflow.

Materials and Methods The effects produced by intravenous administration of 5-HT_{1A} ligands (full agonist 8-OH-DPTA 1 mg×Kg^{-1}, partial agonist buspirone 10 mg×Kg^{-1}, antagonist WAY100135 5 mg×kg^{-1}), 5-HT_{2A} antagonist sarpogrelate (5 mg×kg^{-1}), 5-HT_3 antagonist alosetron (0.1 mg×kg^{-1}), 5-HT_4 antagonist GR12548 (5 mg×kg^{-1}), 5-HT re-uptake inhibitor fluoxetine (10 mg×kg^{-1}) or saline (10 ml×kg^{-1}) on I/R-induced inflammatory response were investigated in I45/R5h mice (IR) and compared to those obtained in sham-operated animals (S). Moreover, α_7 nicotinic receptor (α7nAchR) antagonist methyllycaconitine (5 mg×kg^{-1}), alone or in association with buspirone, was subcutaneously administered 30min before SMA occlusion. All experiments were performed according to Guiding Principles in the Care and Use of Animals (DL116/92).

Results Mesenteric I/R significantly increased intestinal myeloperoxidase activity (MPO) ($P<0.001$), index of leukocyte infiltration, malondialdehyde levels (MDA) ($P<0.001$), index of lipoperoxidation, and plasma extravasation (wet to dry weight ratio) ($P<0.001$), compared to S mice. Buspirone and WAY100135 markedly attenuated neutrophil recruitment (16.2±3.7 and 15.6±4.0 vs 29.1±3.9 U MPO/g dry tissue, $P<0.01$), oxidative stress (289.3±23.9 and 204.6±23.8 vs 477.8±59.7 nmol MDA/g dry tissue, $P<0.01$ and $P<0.001$ respectively) and edema (3.5±0.1 and 3.5±0.1 vs 3.9±0.1, $P<0.05$) induced by SMA occlusion; buspirone protective effect on leukocytes activation was prevented by methyllycaconitine treatment (27.9±8.5 vs 15.8±6.4 U MPO/g dry tissue). Sarpogrelate was effective in reducing neutrophils recruitment (9.8±3.1 vs 29.1±3.9 U MPO/g dry tissue, $P<0.05$), while none of the other tested serotoninergic ligands was able to counteract the increase of inflammatory parameters elicited by mesenteric I/R.

Conclusions Our results confirmed the role played by 5-HT_{2A} receptors in I/R-induced leukocytes infiltration and demonstrated the critical contribution brought by 5-HT_{1A} receptors to the intestinal inflammatory response triggered by SMA occlusion and reflow; the ability of α7nAchR antagonist methyllycaconitine to revert the protection provided by buspirone on neutrophil infiltration suggests that the ameliorative effect produced by 5-HT_{1A} receptor antagonism could be partly ascribed to the indirect activation of α7 nicotinic receptors.

References

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