Middle molecular weight heparinylphenylalanine, an RAGE blocker, prevents oxaliplatin-induced peripheral neuropathy and butyrate-induced colonic pain in mice

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We have shown that activation of the receptor for advanced glycation end-products (RAGE) by all-thiol (at)-HMGB1 participates in pathological pain. Interestingly, low molecular weight heparin (LMWH) blocks RAGE and reduces the HMGB1-dependent pain, although it has potent anti-Xa and moderate anti-IIa activities. In the present study, we assessed the anti-RAGE, anti-Xa and anti-IIa activity of middle molecular weight heparinylphenylalanine (MMWH-F), in comparison with LMWH, MMWH and heparin (HP), and tested whether it prevented the at-HMGB1-induced allodynia, oxaliplatin-induced peripheral neuropathy (OIPN) and butyrate (Bu)-induced colonic pain/hypersensitivity in mice. The RAGE-binding affinity of heparinoids was LMWH ≈ MMWH ≈ HP << MMWH-F. The potency of anti-Xa and anti-IIa activities was MMWH-F << LMWH ≈ MMWH < HP and MMWH-F (not detectable) << LMWH < MMWH < HP, respectively. LMWH, MMWH or MMWH-F, preadministered i.p. at 2.5 mg/kg, partially blocked the intraplantar at-HMGB1-induced allodynia in mice. MMWH-F as well as LMWH, but not MMWH, at 2.5 mg/kg, almost completely prevented OIPN. LMWH, MMWH or MMWH-F at 2.5 mg/kg largely prevented or reversed the Bu-induced colonic pain and hypersensitivity. Together, MMWH-F is considered a potent RAGE blocker, and useful to prevent or treat neuropathic and visceral pain without causing hemorrhage.