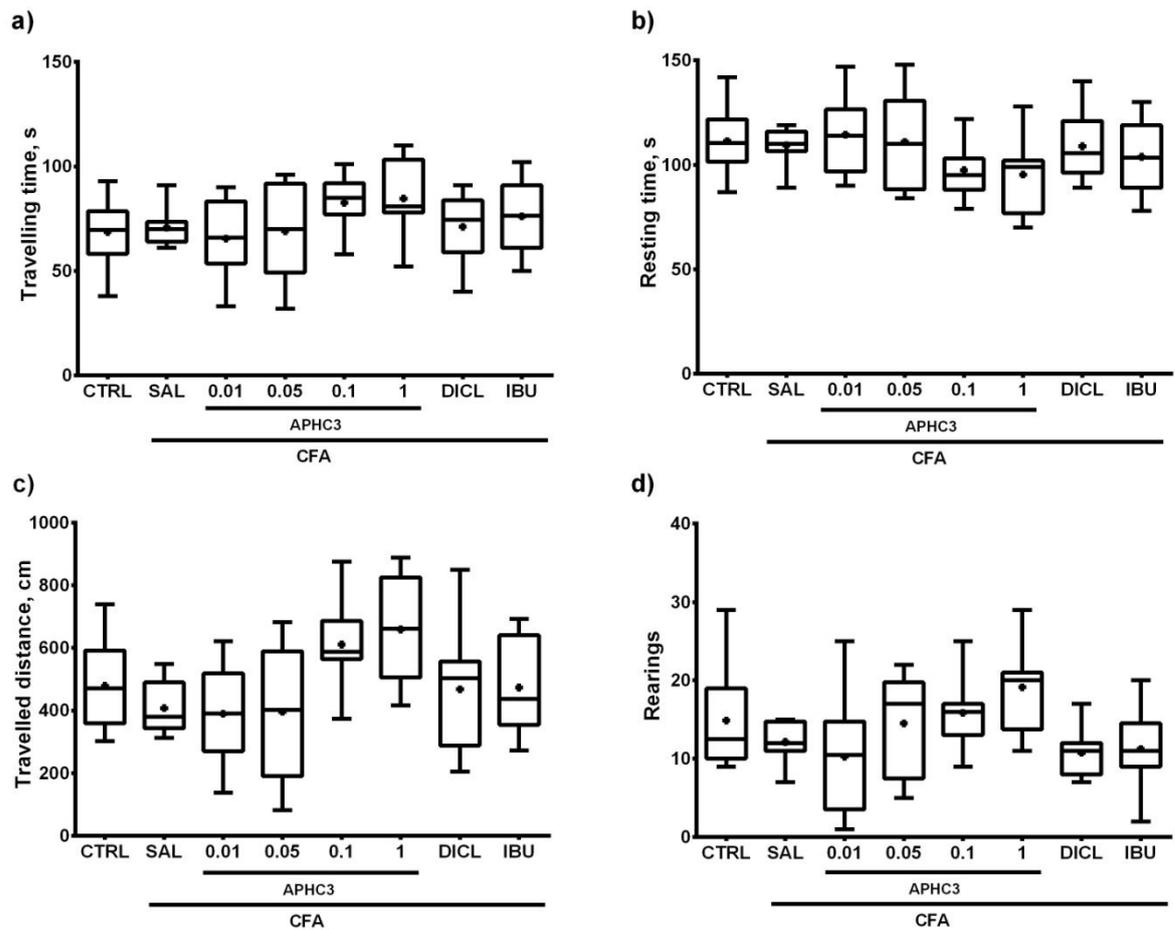
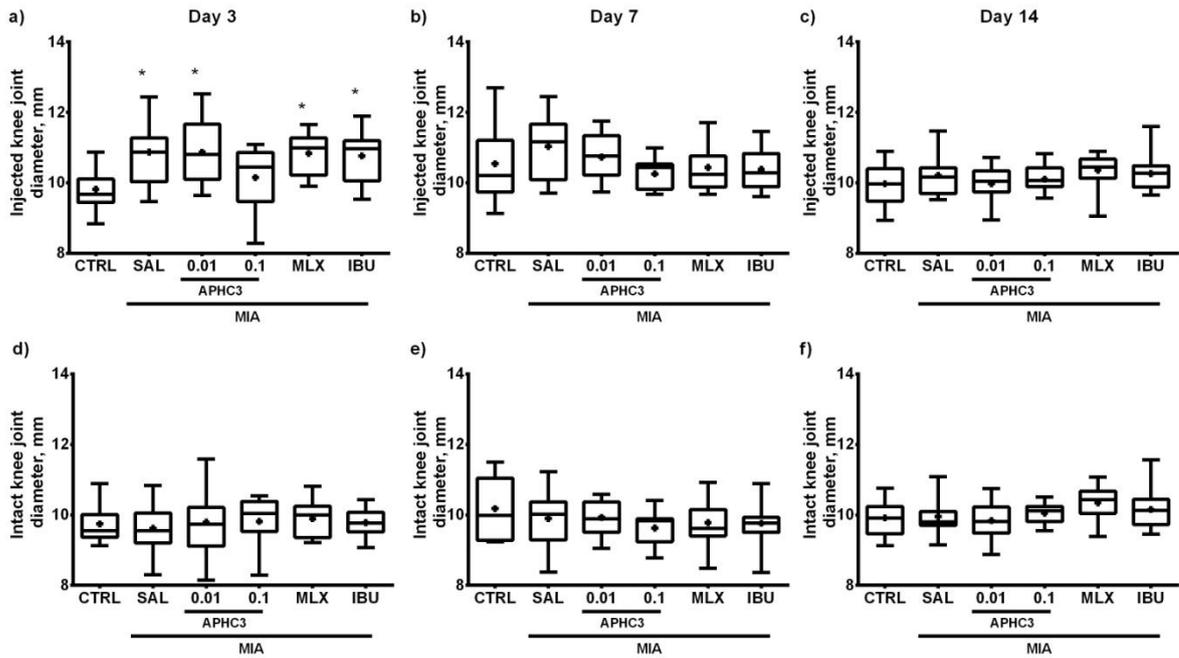


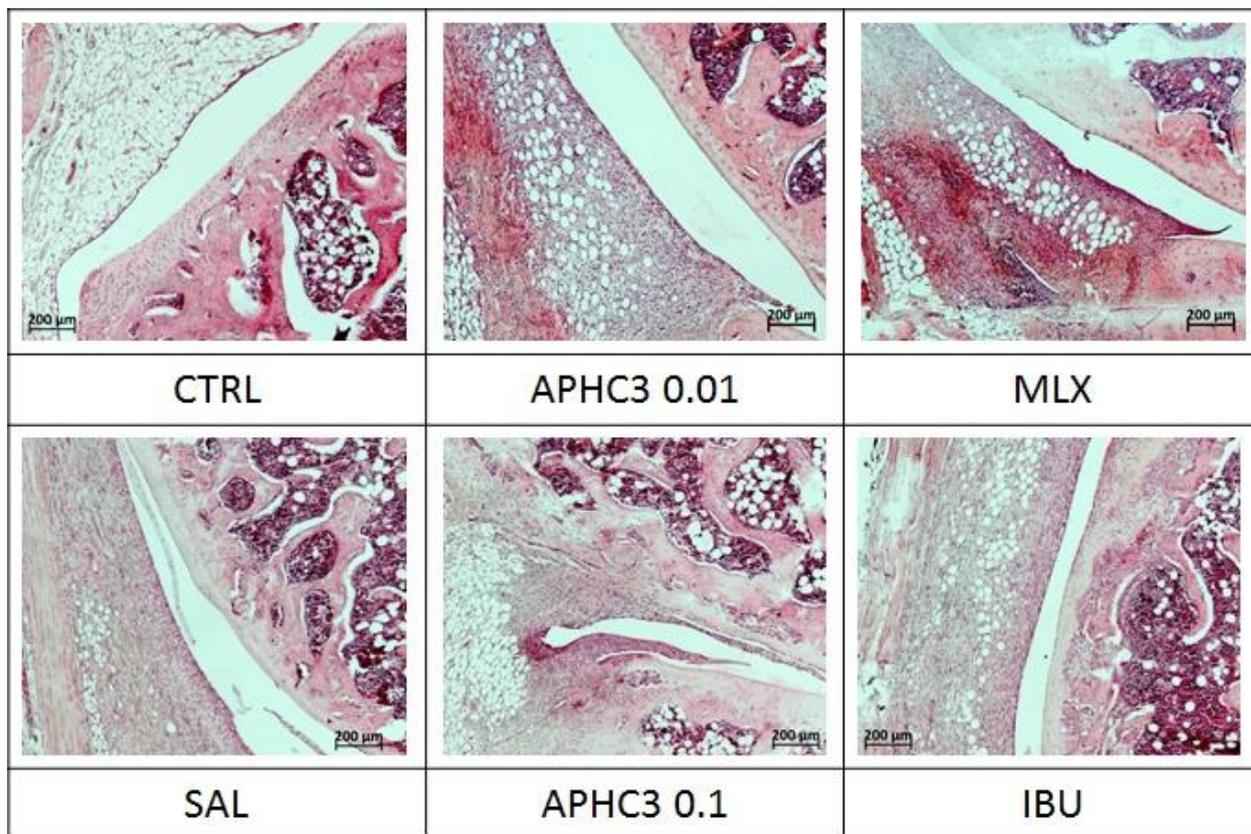
**Figure S1** Assessment of inflammation in the ankle joint on the day 3 after intra-articular administration of CFA (40 $\mu$ l) and anti-inflammatory effects of APHC3 (0.01, 0.05, 0.1 and 1 mg/kg s.c.), diclofenac (20 mg/kg i.m.) and ibuprofen (40 mg/kg p.o.). (a) diameters of the contralateral intact joints; (b) absolute and (c) local temperature of CFA-injected joint. Abbreviation CTRL designates control group, SAL - sterile saline, DICL - diclofenac, and IBU - ibuprofen. Results are presented as median and mean is shown as a cross (+), interquartile range, and minimum and maximum ( $n = 8$  for each group). Statistical analysis was performed using the Kruskal-Wallis criterion followed by Dunn's multiple comparisons test. \* -  $p < 0.05$  vs CTRL, \*\* -  $p < 0.01$  vs CTRL, \*\*\* -  $p < 0.001$  vs CTRL.



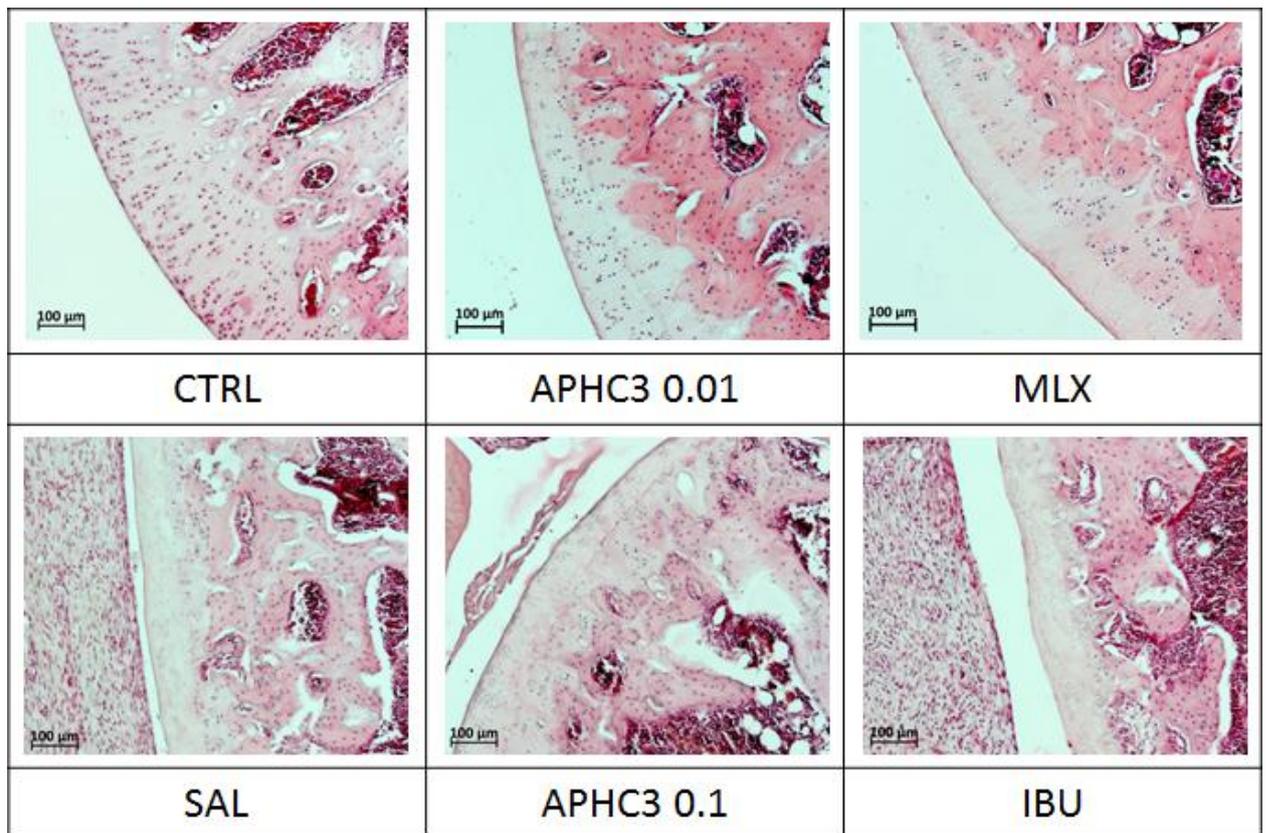
**Figure S2.** Locomotor activity in the open field on day 3 after intra-articular administration of CFA (40µl). (a) travelling time, (b) resting time, (c) travelled distance and (d) rearing count were not changed after administration of APHC3 (0.01, 0.05, 0.1 and 1 mg/kg s.c.), diclofenac (DICL, 20mg/kg i.m.) and ibuprofen (IBU, 40 mg/kg p.o.). Abbreviation CTRL designates Control group, SAL - sterile saline. Results are presented as median and mean is shown as a cross (+), interquartile range, and minimum and maximum ( $n = 8$  for each group). Statistical analysis was performed using the Kruskal-Wallis criterion followed by Dunn's multiple comparisons test.



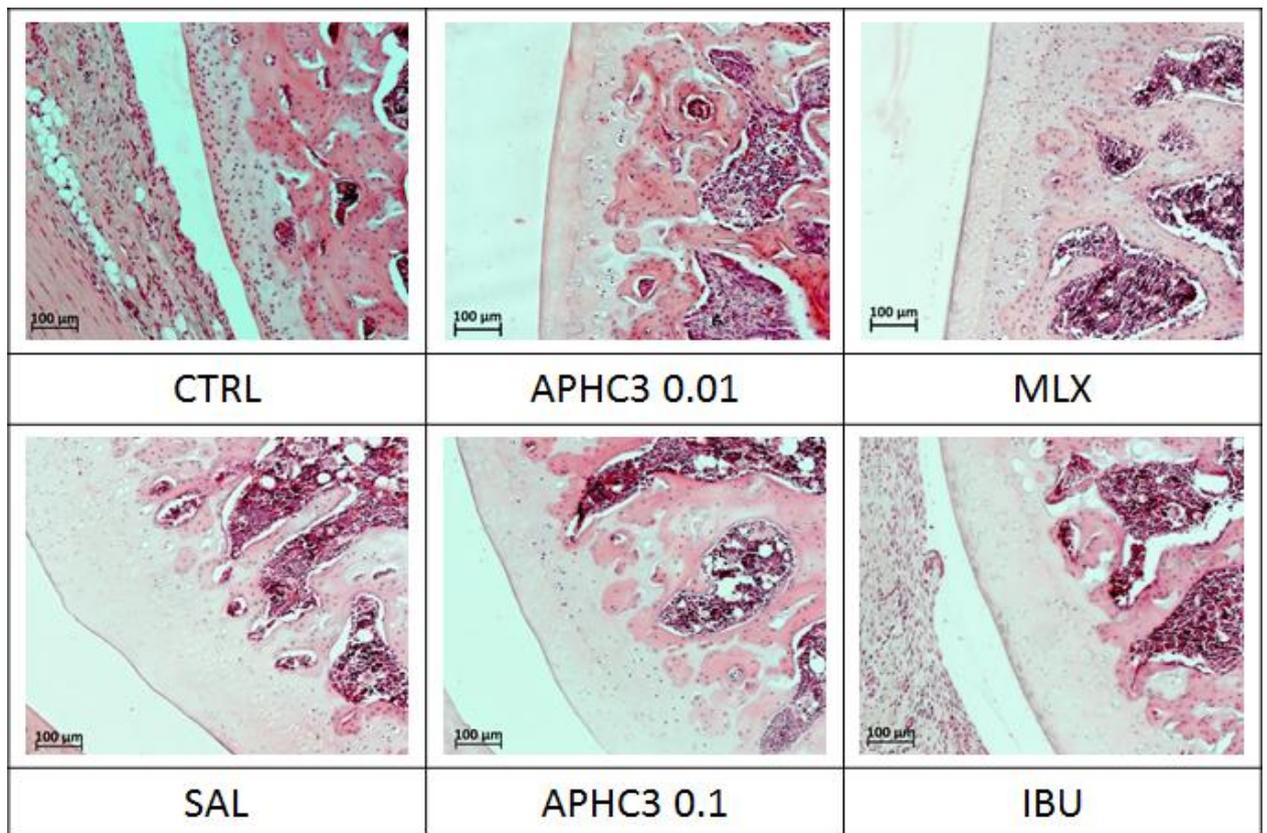
**Figure S3.** Absolute diameters of the knee joints in the MIA-induced OA model. Diameters (in mm) of the injected (a-c) and intact (d-f) joints were measured on days 3 (a, d), 7 (b, e), and 14 (c, f) after intra-articular MIA injection into the right knee joint (3 mg MIA in 50  $\mu$ l of sterile saline).. APHC3 (0.01 and 0.1 mg/kg s.c.), meloxicam (0.5 mg/kg i.m.) and ibuprofen (40 mg/kg p.o.) were administered daily on the days 3-14. Abbreviation CTRL designates control group, SAL - sterile saline, MLX - meloxicam, and IBU - ibuprofen. Results are presented as median and mean is shown as a cross (+), interquartile range, and minimum and maximum ( $n = 9-12$  for each group). Statistical analysis was performed using the Kruskal-Wallis criterion followed by Dunn's multiple comparisons test. \* -  $p < 0.05$  vs CTRL, \*\* -  $p < 0.01$  vs CTRL, \*\*\* -  $p < 0.001$  vs CTRL, # -  $p < 0.05$  vs SAL, ## -  $p < 0.01$  vs SAL, ### -  $p < 0.001$  vs SAL.



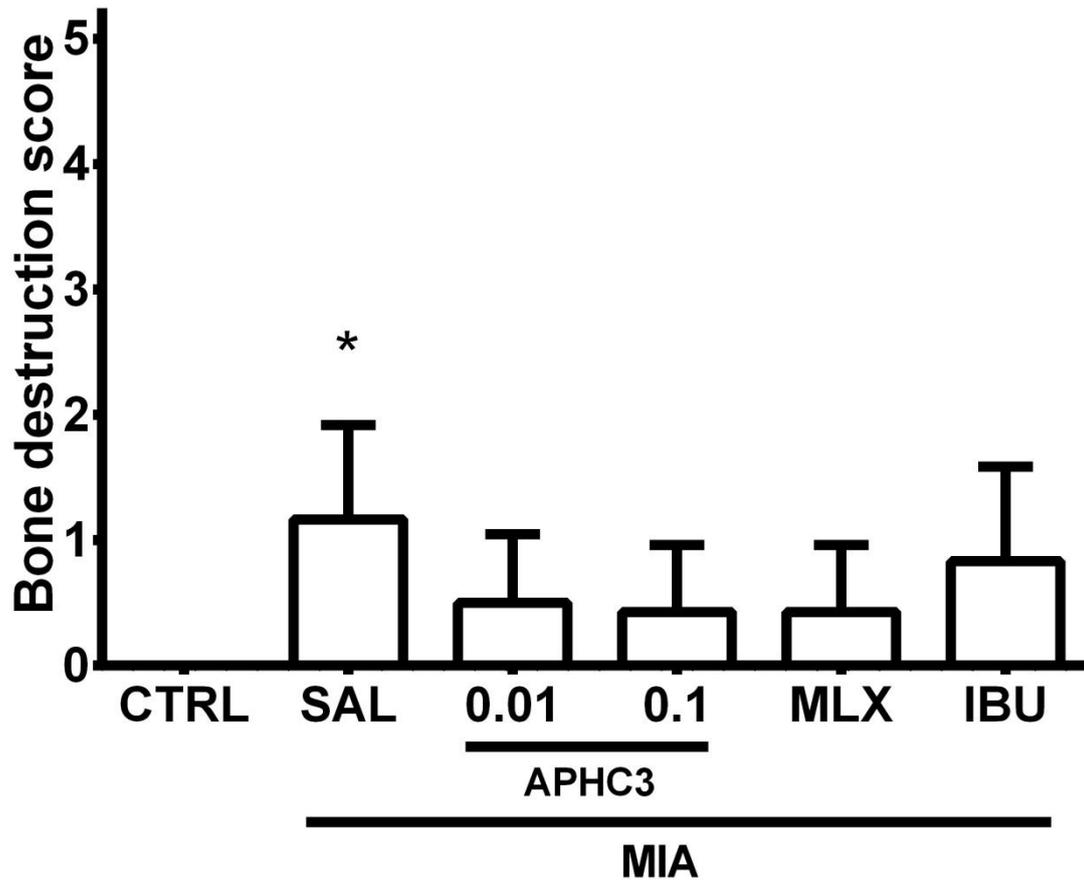
**Figure S4.** Representative images of the injected knee joint synovia in the MIA-induced OA model. Inflammatory infiltration (InIn) and synovial hyperplasia (SH) were assessed on day 8 after intra-articular MIA injection into the right knee joint (3 mg MIA in 50  $\mu$ l of sterile saline). Each sign was graded scores on a scale of 0 to 5, where 0 represents a normal tissue and 5 represents severe tissue degeneration. CTRL (control group): InIn 0, SH 0; SAL (sterile saline-treated group): InIn 4, SH 3; APHC3 0.01mg/kg: InIn 3, SH 3; APHC3 0.1mg/kg: InIn 3, SH 2; MLX (meloxicam-treated group): InIn 3, SH 2; IBU (ibuprofen-treated group): InIn 3, SH 2.



**Figure S5** Representative images of the distal femoral cartilage of the injected knee joint in the MIA-induced OA model. Cartilage (CD) and bone destruction (BD) were assessed on day 8 after intra-articular MIA injection into the right knee joint (3 mg MIA in 50  $\mu$ l of sterile saline). Each sign was graded scores on a scale of 0 to 5, where 0 represents a normal tissue and 5 represents severe tissue degeneration. CTRL (control group): CD 0, BD 0; SAL (sterile saline-treated group): CD 4, BD 1; APHC3 0.01mg/kg: CD 3, BD 0; APHC3 0.1mg/kg: CD 3, BD 0; MLX (meloxicam-treated group): CD 3, BD 0; IBU (ibuprofen-treated group): CD 4, BD 1.



**Figure S6** Representative images of the distal femoral cartilage of the injected knee joint in the MIA-induced OA model. Cartilage (CD) and bone destruction (BD) were assessed on day 15 after intra-articular MIA injection into the right knee joint (3 mg MIA in 50  $\mu$ l of sterile saline). Each sign was graded scores on a scale of 0 to 5, where 0 represents a normal tissue and 5 represents severe tissue degeneration. CTRL (control group): CD 0, BD 0; SAL (sterile saline-treated group): CD 4, BD 0; APHC3 0.01mg/kg: CD 3, BD 0; APHC3 0.1mg/kg: CD 3, BD 0; MLX (meloxicam-treated group): CD 3, BD 0; IBU (ibuprofen-treated group): CD 4, BD 0.



**Figure S7.** Histological analysis of bone destruction of the injected knee joint in the MIA-induced OA model. Destructive changes were assessed on 15 after intra-articular MIA injection into the right knee joint (3 mg MIA in 50  $\mu$ l of sterile saline). APHC3 (0.01 and 0.1 mg/kg s.c.), meloxicam (MLX, 0.5 mg/kg i.m.) and ibuprofen (IBU, 40 mg/kg p.o.) were administered daily on the days 3-14. Control and saline-administered groups are denoted as CTRL and SAL, respectively. Results are presented as mean and SD ( $n = 6-7$ ). Statistical analysis was performed using the Kruskal-Wallis criterion followed by Dunn's multiple comparisons test. \* -  $p < 0.05$  vs CTRL, \*\* -  $p < 0.01$  vs CTRL, \*\*\* -  $p < 0.001$  vs CTRL, # -  $p < 0.05$  vs SAL, ## -  $p < 0.01$  vs SAL, ### -  $p < 0.001$  vs SAL.