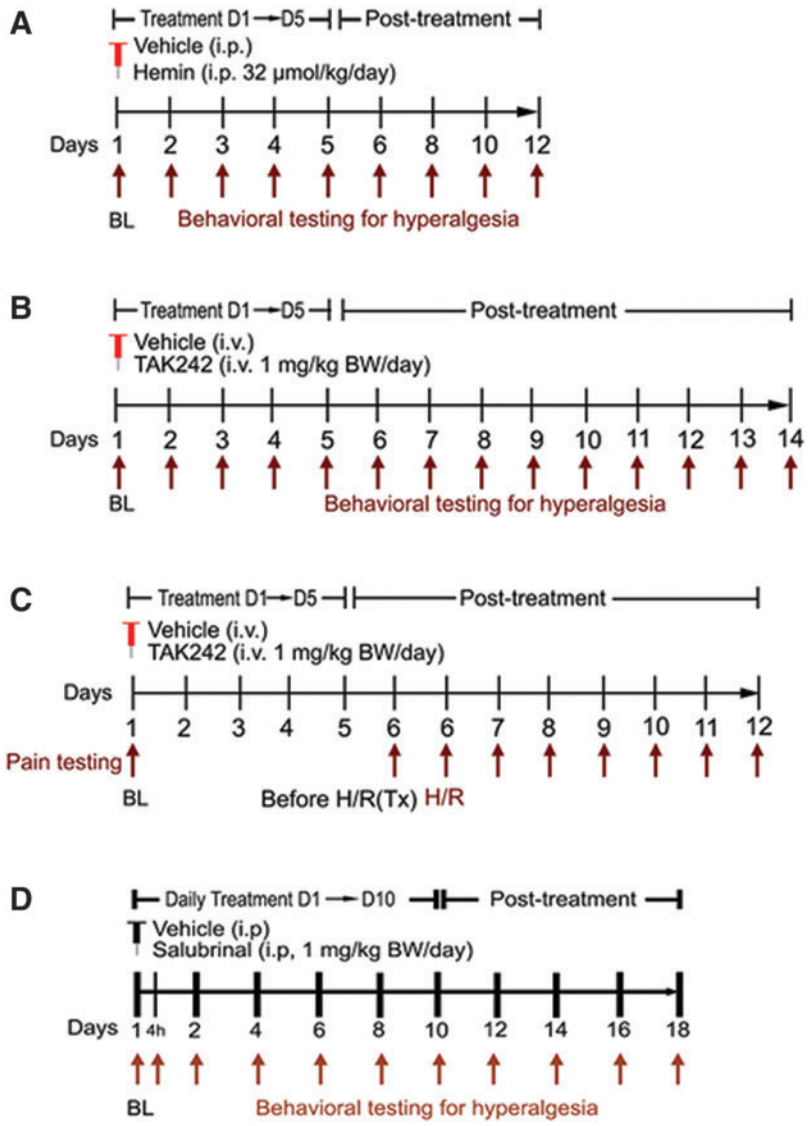


**SUPPLEMENTARY FIG. S5. Animal treatment protocol and pain assessment schema**. **(A)** After BL pain determination, HbSS-BERK and HbAA-BERK mice received vehicle solvent (Veh) or hemin (32 $\mu$mol/kg of BW) by i.p. injection for 5 days. Pain testing was performed 20 h after each injection during the period of treatment and every other day during the period of post-treatment. **(B)** After BL pain determination at day 1, HbSS-BERK and HbAA-BERK mice received intralipid Veh or TAK242 (1 mg/kg/day) by i.v. injection for 5 days. Pain testing was performed 20 h after each injection during the treatment and daily post-i.v. for 9 days. **(C)** After BL pain determination, HbSS-BERK mice were administered intralipid Veh or TAK242 (1 mg/kg/day) by i.v. injection for 5 days. Twenty-four hours after the last injection, mice were subjected to H/R Tx. Pain behaviors were measured before injection (BL), under normoxia before H/R (Tx, pre-H/R), immediately after H/R, and daily post-H/R. **(D)** After BL pain determination, HbAA-BERK and HbSS-BERK mice were treated with i.p. injection of vehicle (0.2% DMSO in saline) or salubrinal (1 mg/kg/day) for 10 days. Pain measures were recorded 4 h after first injection and every other day during injection and postinjection. DMSO, dimethyl sulfoxide; i.p., intraperitoneal.