ВЛИЯНИЕ ИНГИБИТОРОВ ГИСТОНДЕАЦЕТИЛАЗ НА ФОРМИРОВАНИЕ ПАМЯТИ

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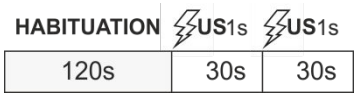
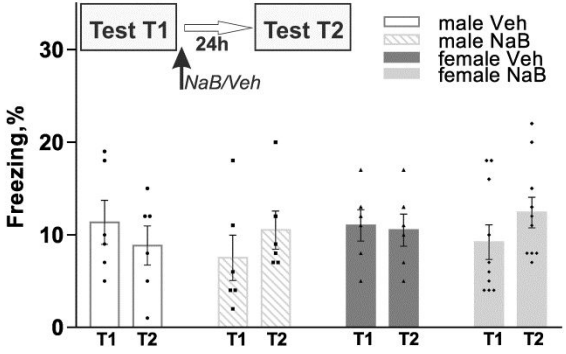
Sodium butyrate as a selective cognitive enhancer for weak or impaired memory in rats

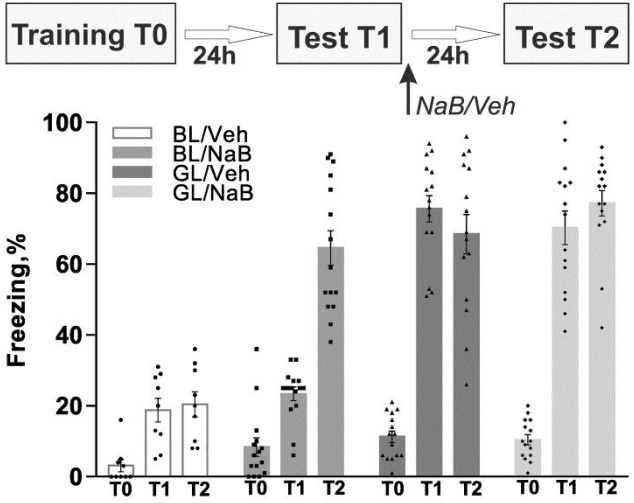


Scheme of the contextual fear conditioning protocols.

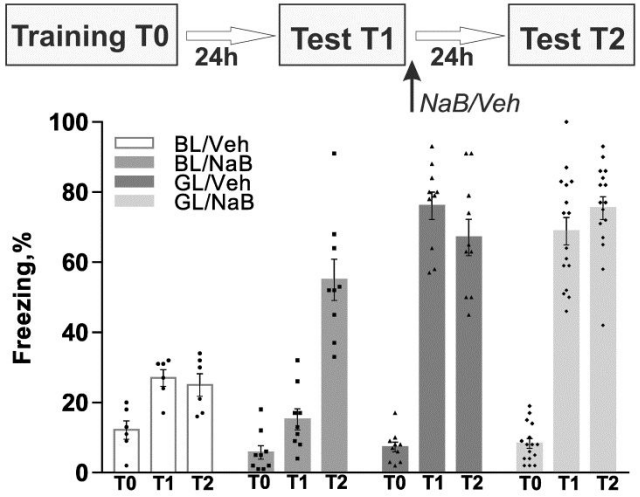
US: unconditioned stimulus, foot shock.



Averaged changes in freezing four groups of naïve rats were tested in the conditioning context before (T1) and 24 hr after (T2) sodium butyrate injections. Sodium butyrate injections had no effect on freezing responses in naïve animals ($p>0.05$). Inset – protocol of the experiment. On the ordinate the conditioned response – freezing, %.



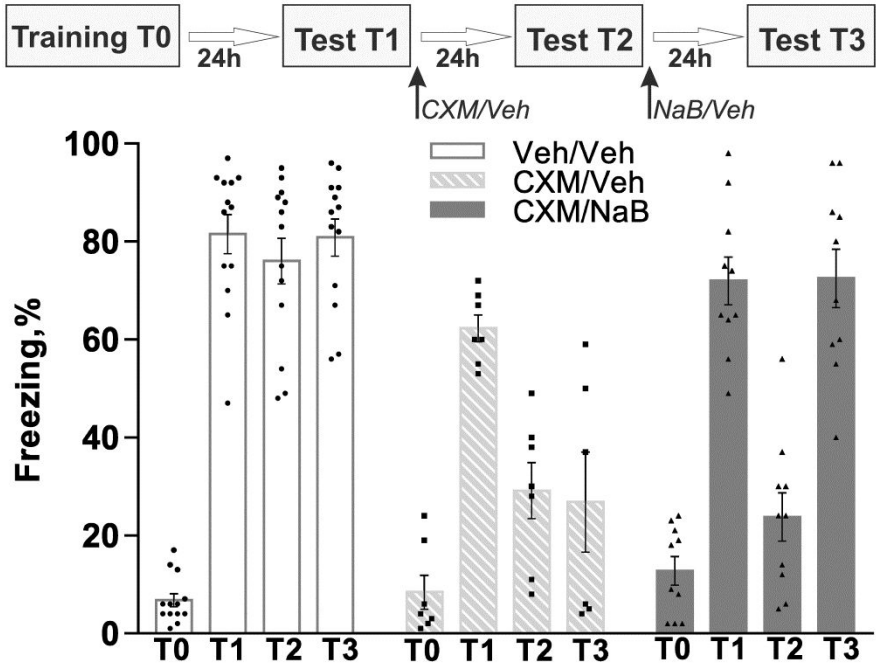
Sodium butyrate administration led to significant increase of responses in the conditioning context in sodium butyrate-treated bad learners ***males*** (BL/NaB, n=15) compared with the vehicle-treated group (BL/Veh, n=9; BL/NaB relative BL/Veh, $p<0.0001$), but no significant changes in sodium butyrate-treated good learners (GL/NaB relative GL/Veh).



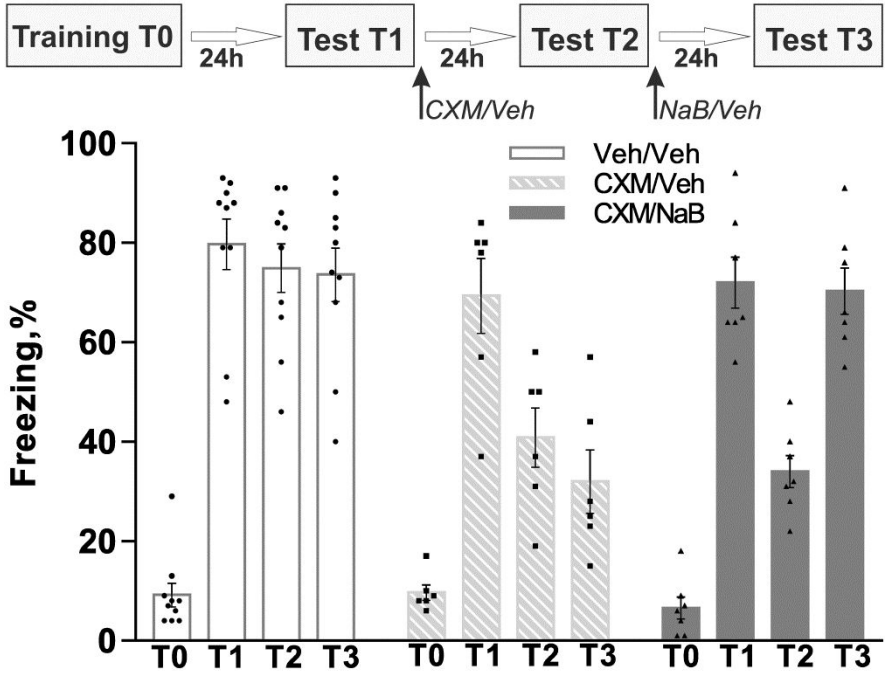
Sodium butyrate administration led to significant increase of responses in the conditioning context in sodium butyrate-treated bad learners ***females*** (BL/NaB, n=9) compared with the vehicle-treated group (BL/Veh, n=6; BL/NaB relative BL/Veh, $p<0.0001$), but no significant changes in sodium butyrate-treated good learners (GL/NaB relative GL/Veh).

butyrate

MALES. Group Veh/Veh served as a control that was injected at all stages with vehicle, and groups CXM/Veh and CXM/NaB were injected with cycloheximide (CXM) immediately after the test session T1 (protocol on the inset). Groups CXM/Veh and CXM/NaB demonstrated memory deficit at test session T2 due to impairment of reconsolidation with CXM. Immediately after the test session T2, groups Veh/Veh (n=13) and CXM/Veh (n=7) were injected with vehicle; CXM/NaB (n=10) was injected with sodium butyrate. Next day test (T3) showed that impaired memory was reinstated under the presence of sodium butyrate (CXM/NaB), however, there was no reinstatement in the absence of sodium butyrate (CXM/Veh).

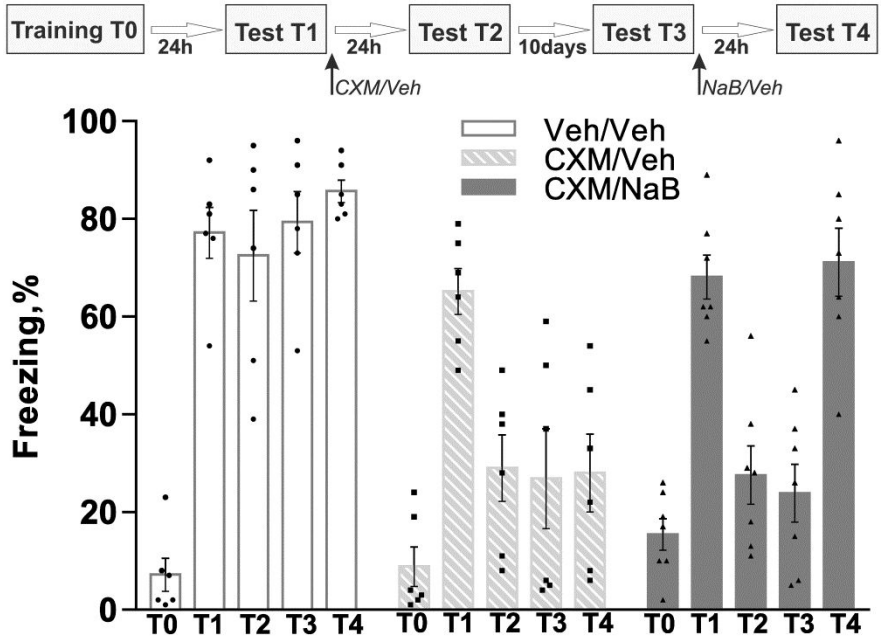


FEMALES. Group Veh/Veh served as a control that was injected at all stages with vehicle, and groups CXM/Veh and CXM/NaB were injected with cycloheximide (CXM) immediately after the test session T1 (protocol on the inset). Groups CXM/Veh and CXM/NaB demonstrated memory deficit at test session T2 due to impairment of reconsolidation with CXM. Immediately after the test session T2, groups Veh/Veh (n=10), CXM/Veh (n=6) were injected with vehicle; CXM/NaB (n=7) was injected with sodium butyrate. The test on the next day (T3) showed that impaired memory was reinstated under the presence of sodium butyrate (CXM/NaB), but there was no reinstatement in the absence of sodium butyrate (CXM/Veh).

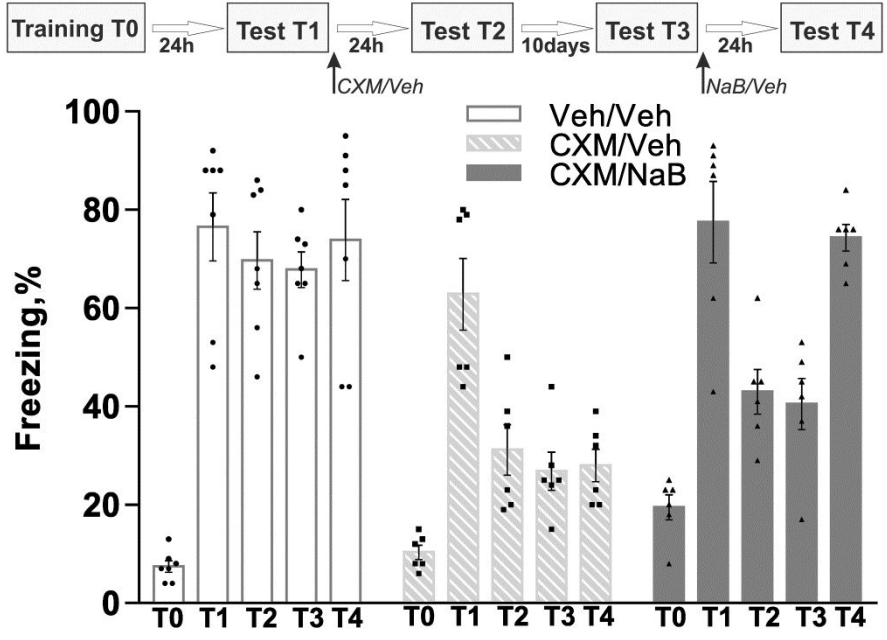


butyrate

MALES. Group Veh/Veh (n=6) served as a control, injected at all stages with vehicle, and groups CXM/Veh (n=6), CXM/NaB (n=7) were injected with cycloheximide (CXM) immediately after the test session T1 (protocol on the inset). Groups CXM/Veh and CXM/NaB demonstrated a memory deficit at test session T2, due to impairment of reconsolidation with CXM. 10 days later (day 13) all groups were tested (T3). Immediately after T3, groups Veh/Veh and CXM/Veh received sham injections of saline, whereas group CXM/NaB received injection of sodium butyrate. Next day test (T4) showed that impaired memory was reinstated under the presence of sodium butyrate (CXM/NaB), but there was no reinstatement in the absence of sodium butyrate (CXM/Veh)

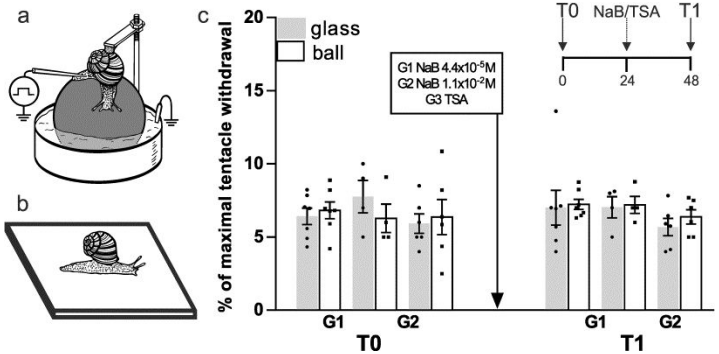


FEMALES. Group Veh/Veh (n=7) served as a control, injected at all stages with vehicle, and groups CXM/Veh (n=6), CXM/NaB (n=6) were injected with cycloheximide (CXM) immediately after the test session T1 (protocol on the inset). Groups CXM/Veh and CXM/NaB demonstrated a memory deficit at test session T2, due to impairment of reconsolidation with CXM. 10 days later (day 13) all groups were tested (T3). Immediately after T3, groups Veh/Veh and CXM/Veh received sham injections of saline, whereas group CXM/NaB received injection of sodium butyrate. The test on the following day (T4) showed that impaired memory was reinstated under the presence of sodium butyrate (CXM/NaB), although, there was no reinstatement in the absence of sodium butyrate (CXM/Veh).

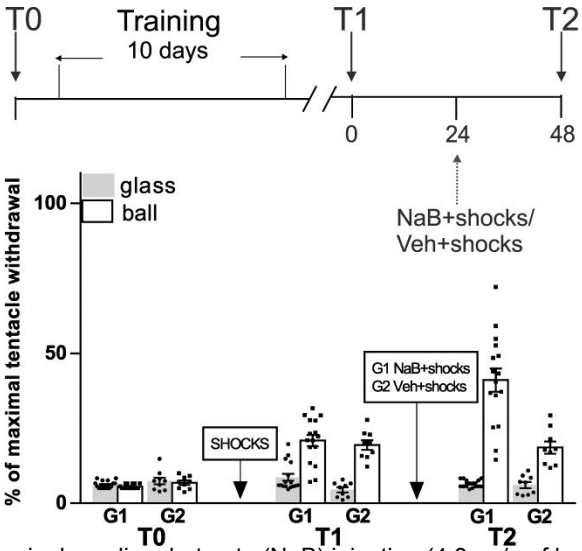


Histone deacetylase inhibitors rescue the impaired memory in terrestrial snails

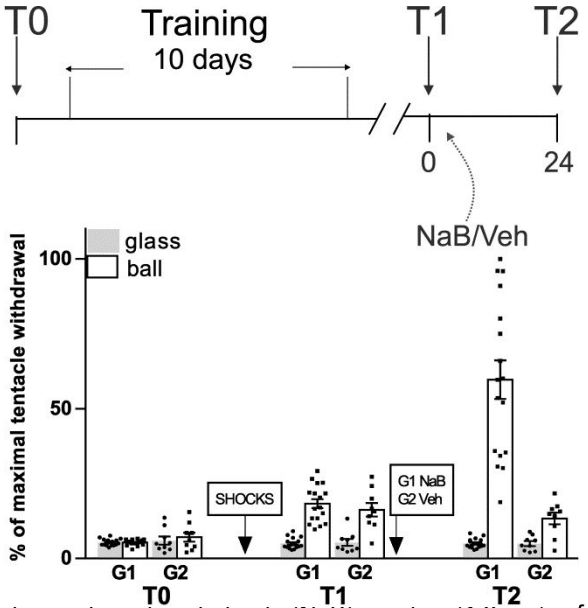
NaB facilitated the acquisition of context fear memory in “bad learners”



Schematic drawing of two contexts in behavioral experiments: a – context 1 (ball), b – context 2 (flat glass). c – averaged changes in amplitude of tentacle withdrawal in three groups of naïve snails tested in two contexts (glass, ball) before (T0) and 24 hrs after (T1) sodium butyrate (NaB) (4.4×10^{-5}M, group G1, n=7), NaB (1.1^{-2}M, group G2, n=6) or *trichostatine A* (TSA) (9×10^{-6}M, group G3, n=4) injections. *NaB and TSA injections had no effect on baseline of withdrawal responses in* naïve snail *(p*>0.05*)*. Inset – protocol of the experiment. On the ordinate amplitude of tentacle withdrawal as a percentage of maximal value is shown

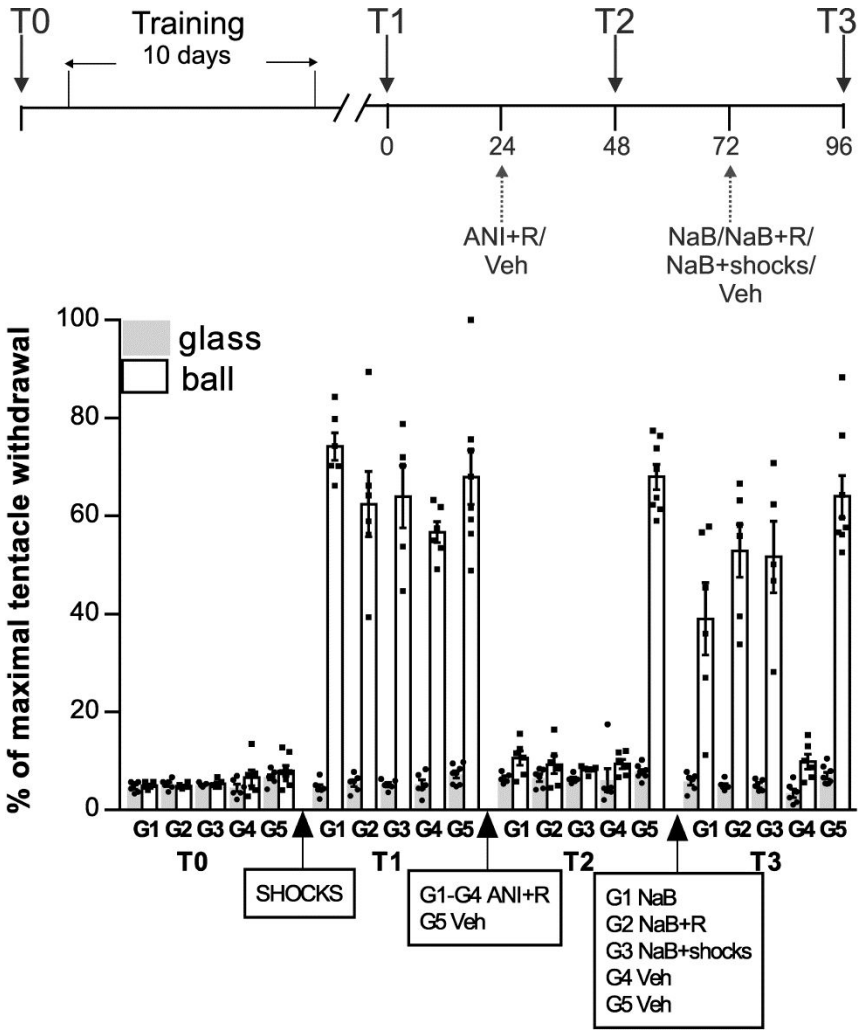


Effect of a single sodium butyrate (NaB) injection (4.8 μg/g of body weight) on the tentacle withdrawal amplitude in trained snails. NaB administration led to significant increase of responses in a reinforced context in NaB-treated group (G1, n=16) compared with vehicle-treated group (G2, n=9)



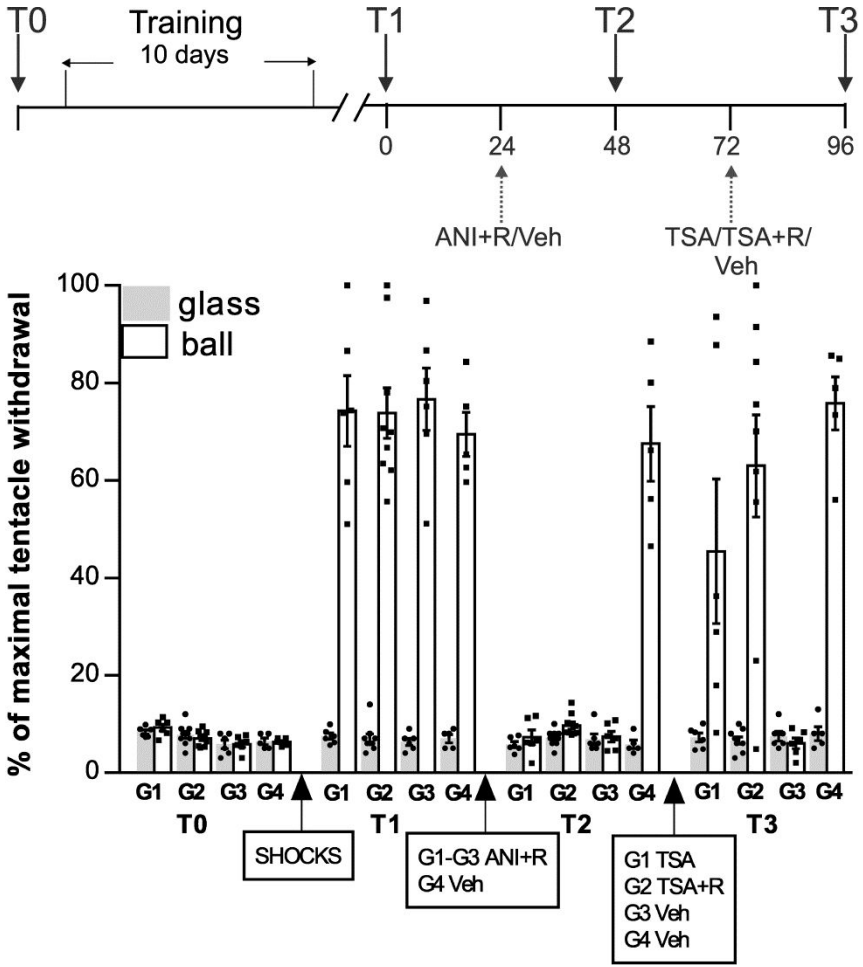
Effect of a single sodium butyrate (NaB) injection (1.2 mg/g of body weight) on the tentacle withdrawal amplitude in trained snails. NaB administration led to significant increase of responses in a reinforced context in NaB-treated group (G1, n=17) compared with vehicle-treated group (G2, n=9)

Reinstatement of the anisomycin-impaired context memory under *sodium butyrate* injections



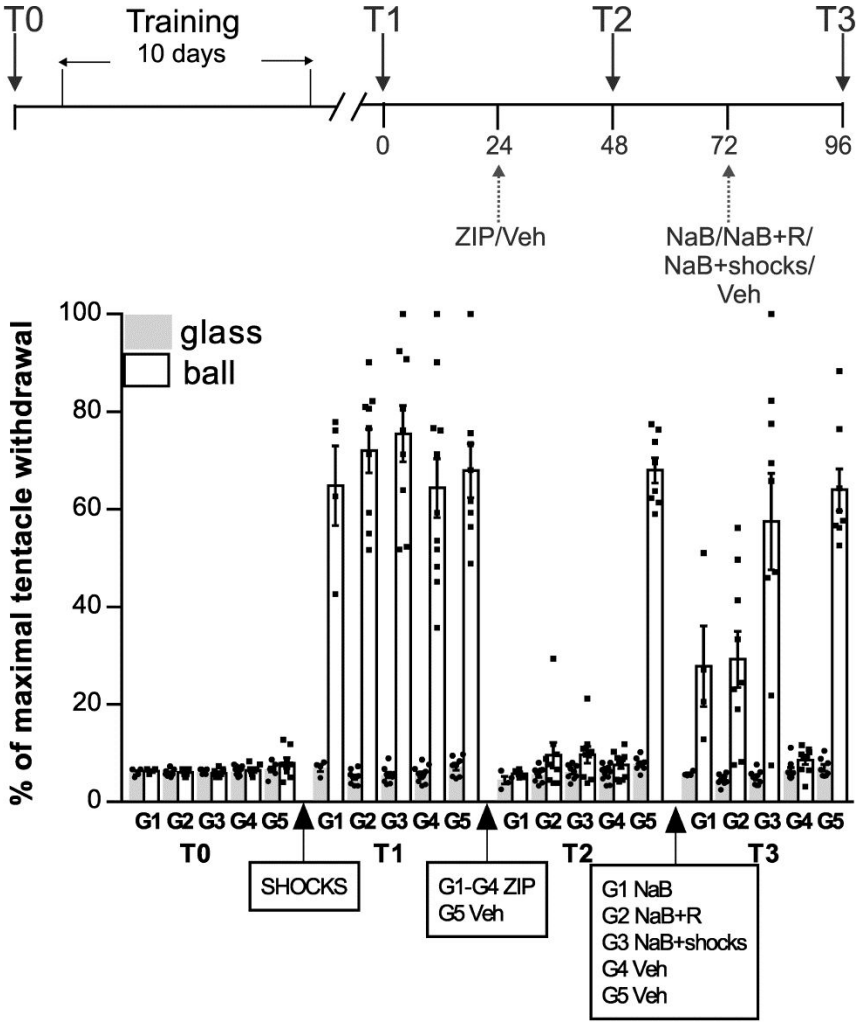
Groups G1-G4 demonstrated absence of memory at test session T2 due to impairment of reconsolidation with ANI (no difference between contexts). Next day after the test session T2, group G1 (n=6) was injected with NaB (4.8 μg/g of body weight) without reminding; G2 (n=6) was injected with NaB plus reminding (R); G3 (n=5) was injected with NaB 1hr before an additional training session (shocks), G4 (n=6) and G5 (n=8) were given vehicle injection. Next day test (T3) showed that impaired due to presence of ANI memory was reinstated under the presence of NaB independently of memory reactivation (G1, G2, G3, no significant difference between groups), but there was no reinstatement in the absence of NaB (G4)

Reinstatement of the anisomycin-impaired context memory under *trichostatin A* injections



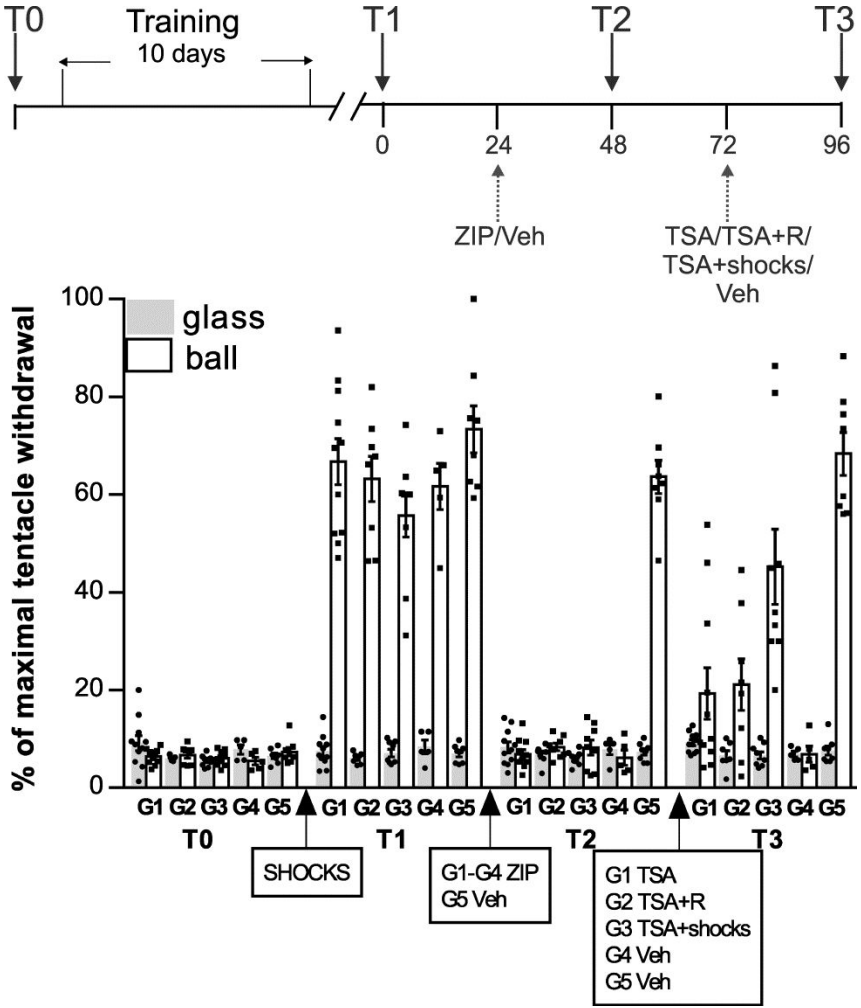
Groups G1-G3 demonstrated absence of memory at test session T2 due to impairment of reconsolidation with ANI (no difference between contexts). Next day after the test session T2, group G1 (n=6) was injected with TSA without reminding; G2 (n=9) was injected with TSA plus reminder (R); G3 (n=6) and G4 (n=5) were given vehicle injection. Next day test (T3) showed that impaired due to presence of ANI memory was reinstated under the presence of TSA independently of memory reactivation (G1, G2, no significant difference between groups), but there was no reinstatement in the absence of TSA (G3)

Reinstatement of the ZIP-impaired context memory under *sodium butyrate* injections



Groups G1-G4 demonstrated absence of memory at test session T2 (no difference between contexts). Next day after the test session T2, group G1 (n=4) was injected with NaB (4.8 μg/g of body weight) without reminding; G2 (n=9) was injected with NaB plus reminder (R); G3 (n=9) was injected with NaB 1hr before training session (shocks), G4 (n=11), and G5 (n=8) was given vehicle injection. Next day test (T3) showed that ZIP-impaired context memory was reinstated under the presence of NaB in an activation-dependent manner (most effectively in G3 subjected to an additional training session)

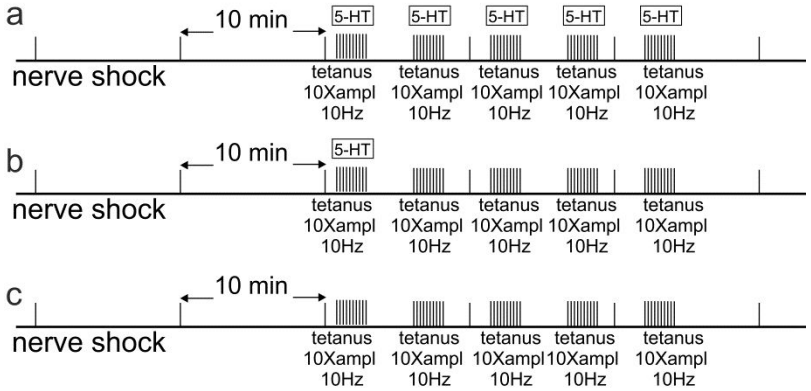
Reinstatement of the ZIP-impaired context memory under *trichostatin A* injections



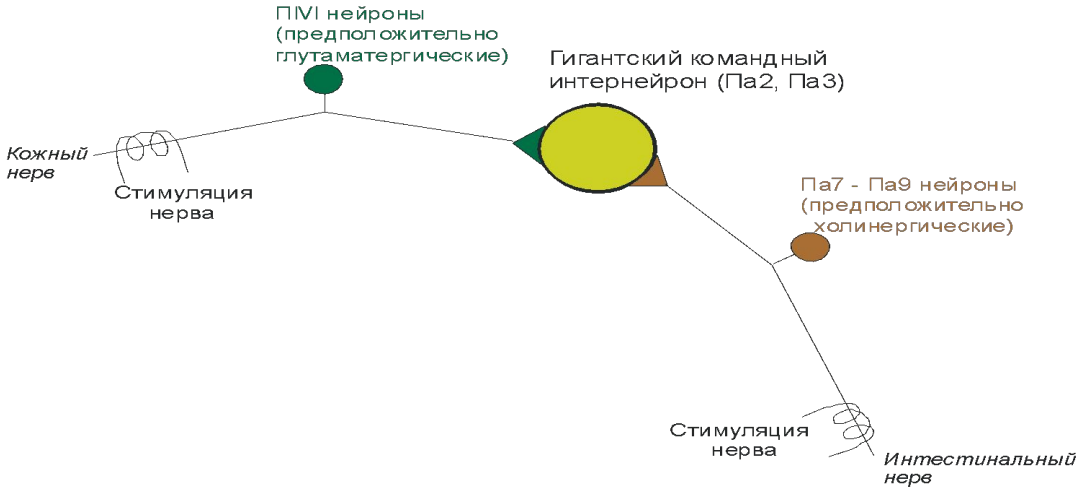
Groups G1-G4 demonstrated absence of memory at test session T2 (no difference between contexts). Next day after the test session T2, group G1 (n=11) was injected with TSA without reminding; G2 (n=8) was injected with TSA plus reminder (R); G3 (n=9) was injected with TSA 1hr before additional training session (shocks), G4 (n=5) and G5 (n=8) were given vehicle injections. Next day test (T3) showed that ZIP-impaired context memory was reinstated under the presence of TSA in an activation-dependent manner: less effectively in the absence of memory activation (G1), most effectively during an additional training session (G3)

Contribution of histone acetylation to the serotonin-mediated long-term synaptic plasticity in terrestrial snails

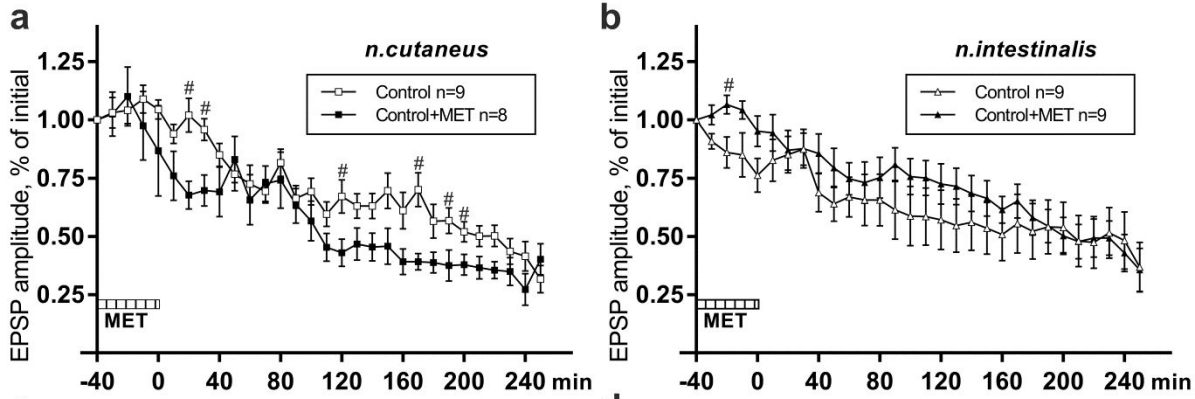
Schematic representations of protocols

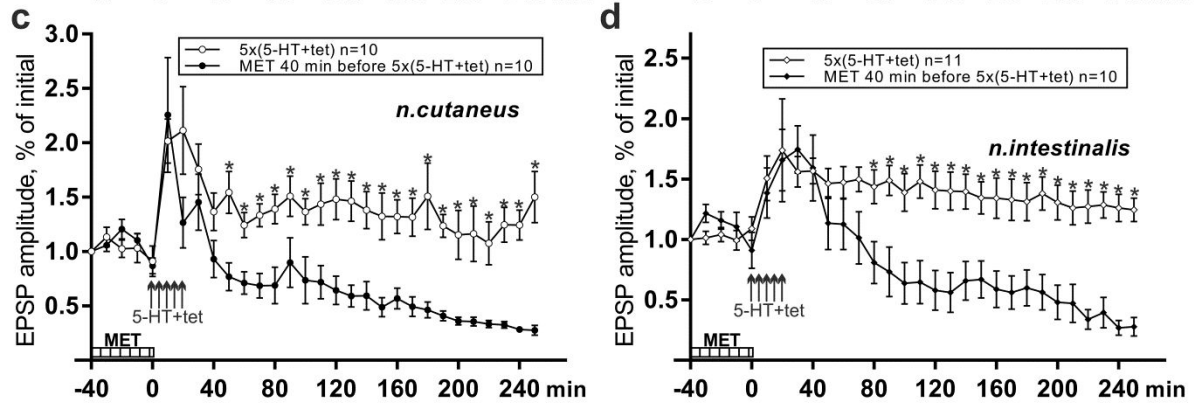


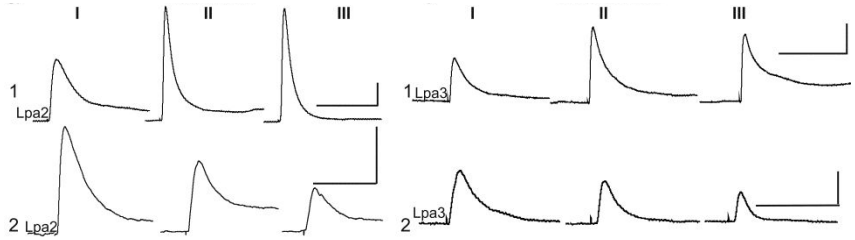
a – Strong training protocol (five tetanizations combined with five serotonin applications). b – Weak training protocol (five tetanizations+single serotonin application). c – Weak training protocol (five tetanizations only)



Effects of the serotonergic receptors blocker methiothepin on synaptic plasticity



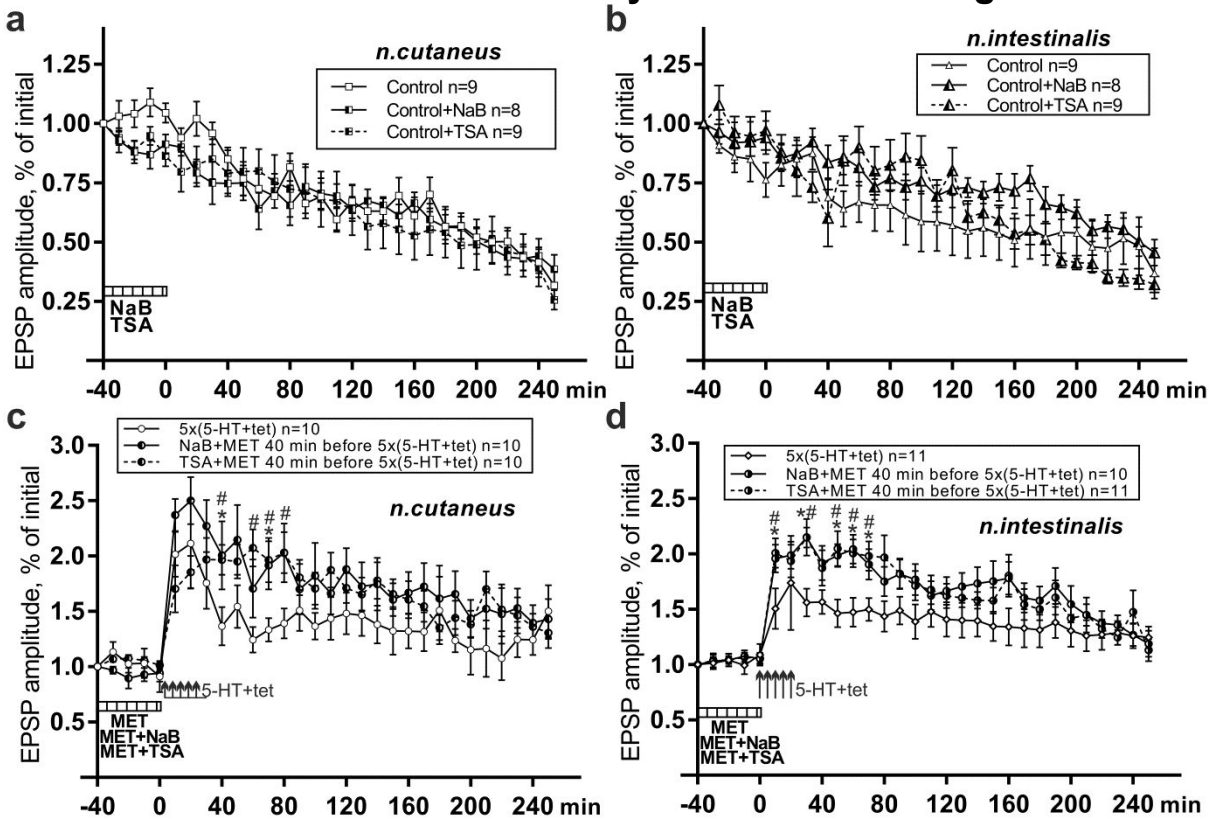




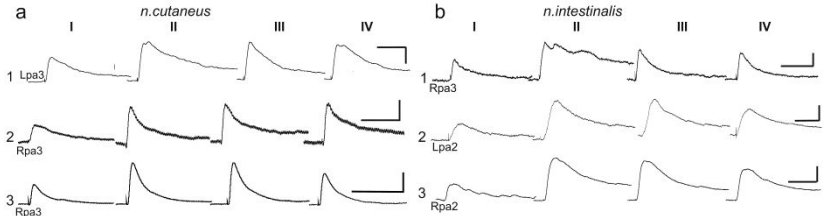
a, b – the untetanized inputs (Control, n.cutaneus, n = 9, n.intestinalis, n = 9) showed no significant changes in synaptic transmission under MET administration (Control+MET, n.cutaneus, n = 8, n.intestinalis, n = 9). c, d – MET blocked the induction of long-lasting LTP: MET application significantly impaired the increase in the EPSPs amplitudes in MET+5x(5-HT+tet) groups (n.cutaneus, n = 10, n.intestinalis, n = 10) in comparison to the control 5x(5-HT+tet) groups (n.cutaneus, n = 10, n.intestinalis, n = 11). The duration of drug infusion is shown as a rectangle at the bottom. The arrows (0 min at the scale) mark the the timing of the tetanic stimulations and serotonin applications. All data are presented as mean ± SEM. * denotes $p < 0.05$ MET+5x(5-HT+tet) vs. 5x(5-HT+tet); # denotes $p < 0.05$ Control+MET vs. Control

Examples of complex EPSPs in withdrawal interneurons (LPa2, LPa3) evoked by stimulation of cutaneous (a) or intestinal (b) nerves. 1 – group 5x(5-HT+tet). 2 – group MET+5x(5-HT+tet). For every neuron the responses at time points 40 min (left panel I), 120 min after the last tetanic stimulation (middle panel II), and 230 min after the last tetanic stimulation (right panel III) are shown. Scale bars=5 mV, 500 ms

Histone acetylation inhibitors regulate the long-term plasticity

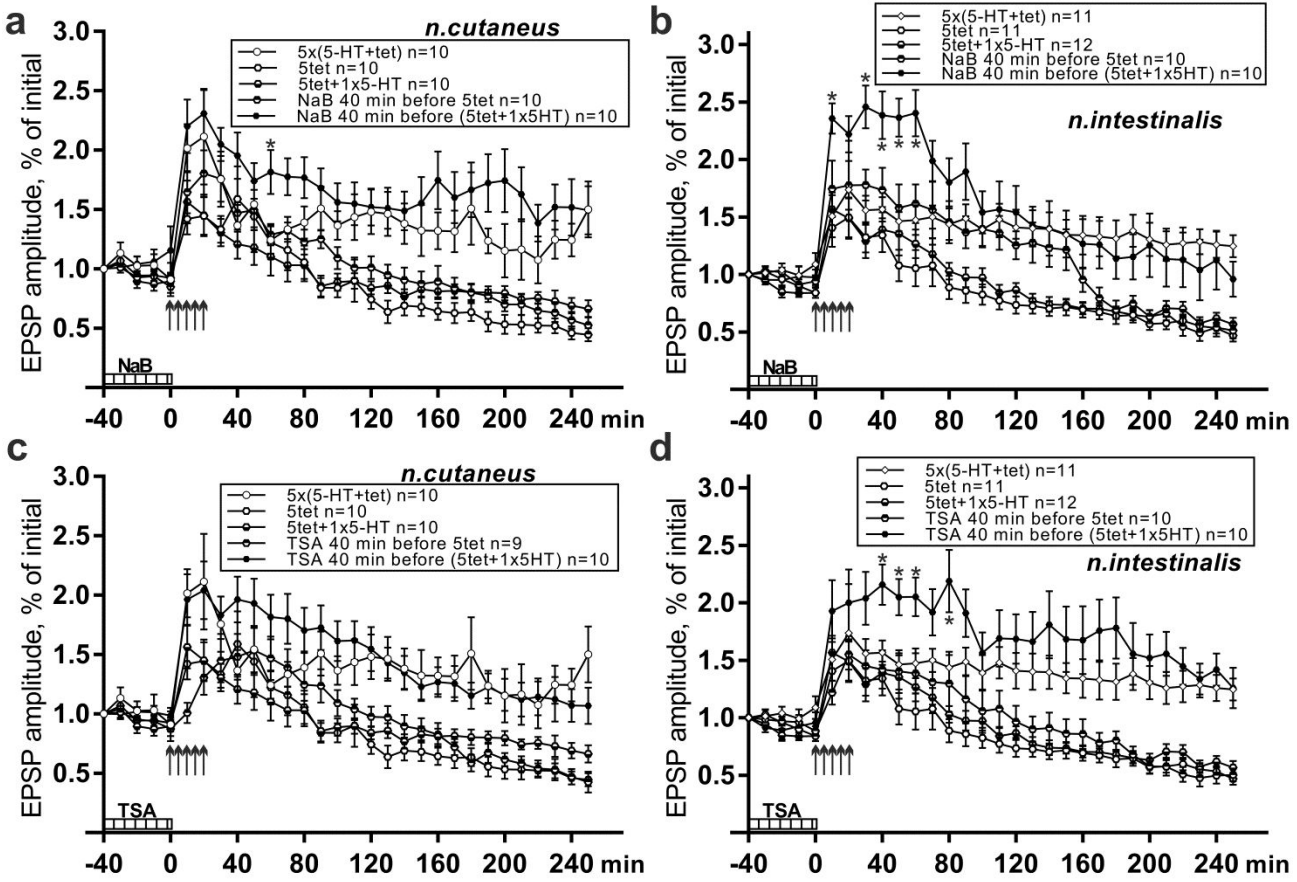


a, b – the untetanized inputs (Control, n.cutaneus, n = 9, n.intestinalis, n = 9) showed no significant changes in synaptic transmission under NaB or TSA administration (Control+NaB, n.cutaneus, n = 8, n.intestinalis, n = 8; Control+TSA, n.cutaneus, n = 9, n.intestinalis, n = 9). c, d – simultaneous administration of NaB or TSA and a blocker of serotonin receptors MET before LTP initiation prevents weakening of the potentiation in mollusk. NaB or TSA led to potentiation of the EPSPs amplitudes during the early phase of potentiation in NaB+MET+5x(5-HT+tet) groups (n.cutaneus, n = 10, n.intestinalis, n = 10)/ TSA+MET+5x(5-HT+tet) groups (n.cutaneus, n = 10, n.intestinalis, n = 11) in comparison to control 5x(5-HT+tet) groups (n.cutaneus, n = 10, n.intestinalis, n = 11), while there was no differences at time points corresponding to the late phase of potentiation. The duration of drugs infusion is shown as a rectangle at the bottom. The arrows (0 min at the scale) mark the timing of the tetanic stimulations and serotonin applications. All data are presented as mean ± SEM. * denotes $p < 0.05$ NaB+MET+5x(5-HT+tet) vs. 5x(5-HT+tet), # denotes $p < 0.05$ TSA+MET+5x(5-HT+tet) vs. 5x(5-HT+tet)



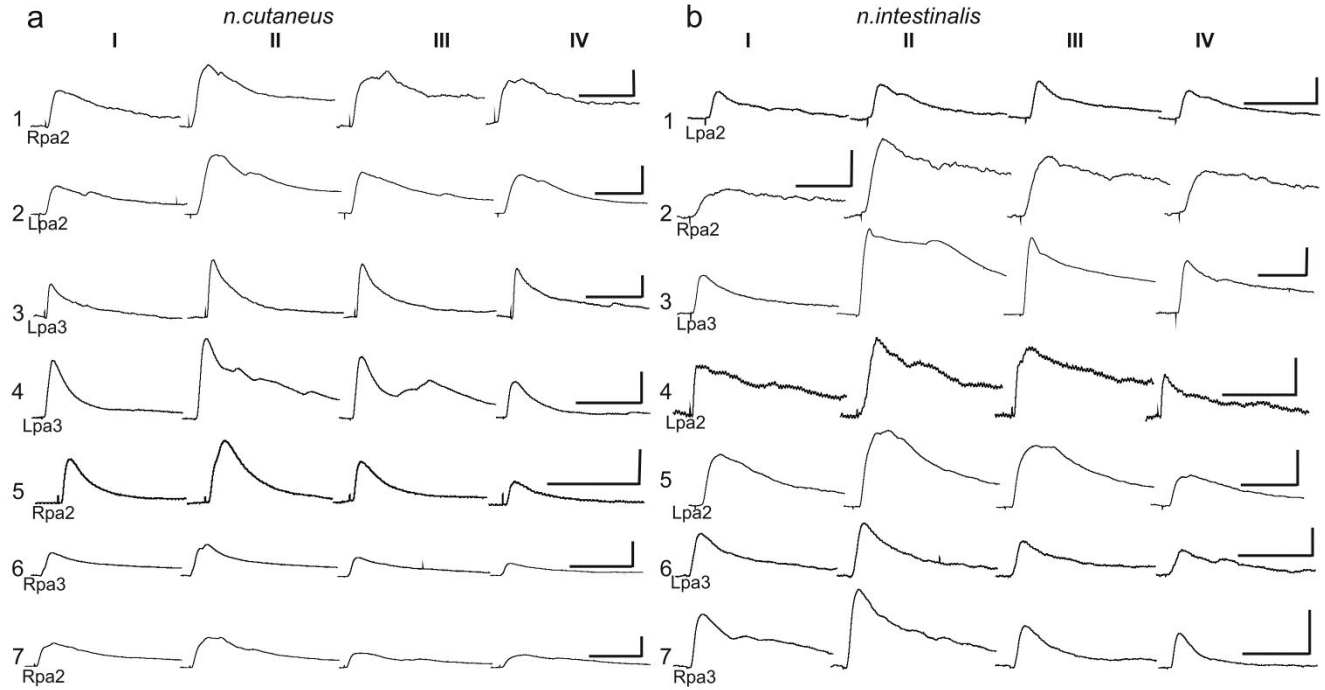
Examples of complex EPSPs in withdrawal interneurons evoked by stimulation of cutaneous (a) or intestinal (b) nerves. 1 – group 5x(5-HT+tet). 2 – group NaB+MET+5x(5-HT+tet). 3 – group TSA+MET+5x(5-HT+tet). For every neuron the responses at time points -40 min (left panel I), 70 minutes after the first tetanus (middle panel II), 120 min after the last tetanic stimulation (middle panel III), and 230 min after the last tetanic stimulation (right panel IV) are shown. Scale bars=5 mV, 500 ms

HDAC inhibition affects the potentiation induced by the weak training protocols



Weak training protocols (five tetanizations only or five tetanizations+single serotonin application) induced a transient early potentiation (5tet, n.cutaneus, n = 10, n.intestinalis, n = 11; 5tet+1x5-HT, n.cutaneus, n = 10, n.intestinalis, n = 12) that significantly decreased at the time points corresponding to the late phase of LTP if compared to 5x(5-HT+tet) groups (n.cutaneus, n = 10, n.intestinalis, n = 11). Preincubation for 40 min with NaB/ TSA paired with five tetanizations and one pulse of 5-HT (NaB+5tet+1x5-HT, n.cutaneus, n = 10, n.intestinalis, n = 10; TSA+5tet+1x5-HT, n.cutaneus, n = 10, n.intestinalis, n = 10) induced the LTP comparable to that induced by five pulses of 5-HT+five tetanizations. However, exposure to NaB/ TSA paired to five tetanizations without serotonin had no long-term effect on potentiation (NaB+5tet, n.cutaneus, n = 10, n.intestinalis, n = 10; TSA+5tet, n.cutaneus, n = 9, n.intestinalis, n = 10). The duration of drugs infusion is shown as a rectangle at the bottom. The arrows (0 min at the scale) mark the timing of the tetanus and serotonin application. All data are presented as mean ± SEM. * denotes $p < 0.05$ NaB+5tet+1x5-HT or TSA+5tet+1x5-HT vs. 5x(5-HT+tet)

HDAC inhibition affects the potentiation induced by the weak training protocols



Examples of complex EPSPs in withdrawal interneurons evoked by stimulation of cutaneous (a) or intestinal (b) nerves. 1 – group 5x(5-HT+tet). 2 – group NaB+5tet+1x5-HT. 3– group TSA+5tet+1x5-HT. 4 – group NaB+5tet. 5 – group TSA+5tet. 6 – group 5tet. 7 – group 5tet+1x5-HT. For every neuron the responses at time point -40 min (left panel I), 60 minutes after the first tetanus (middle panel II), 120 min after the last tetanic stimulation (middle panel III), and 230 min after the last tetanic stimulation (right panel IV) are shown. Scale bars=5 mV, 500