

Responses of withdrawal interneurons to serotonin applications in naïve and learned snails are different

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Abstract

© 2017 Bogodvid, Andrianov, Deryabina, Muranova, Silantyeva, Vinarskaya, Balaban and Gainutdinov. Long-term changes in membrane potential after associative training were described previously in identified premotor interneurons for withdrawal of the terrestrial snail *Helix*. Serotonin was shown to be a major transmitter involved in triggering the long-term changes in mollusks. In the present study we compared the changes in electrophysiological characteristics of identifiable premotor interneurons for withdrawal in response to bath applications of serotonin (5-HT) or serotonin precursor 5-hydroxytryptophan (5-HTP) in preparations from naïve, neurotoxin-injected or associatively trained snails. It was found that 5-HT or 5-HTP applications caused a significant decrease of membrane potential in premotor interneurons of naïve snails, associatively trained snails and snails with impaired serotonergic system by injection of a selective neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) 1 week before the experiments. Applications of 5-HT or 5-HTP did not cause significant changes in the action potential (AP) threshold potential of these neurons in naïve snails. Conversely, applications of 5-HT or 5-HTP to the premotor interneurons of previously trained or 5,7-DHT-injected snails caused a significant increase in the firing threshold potential in spite of a depolarizing shift of the resting membrane potential. Results demonstrate that responsiveness of premotor interneurons to extracellularly applied 5-HT or 5-HTP changes for days after the associative training or serotonin depletion. Similarity of the effects in trained and 5,7-DHT-injected animals may be due to massive release of serotonin elicited by 5,7-DHT injection. Our results suggest that serotonin release due to aversive conditioning or elicited by the neurotoxin administration triggers similar changes in resting membrane potential and AP threshold in response to bath applications of 5-HT or its precursor 5-HTP.

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Keywords

5-hydroxytryptophan, Associative learning, Identified neurons, Membrane potential, Serotonin, Snail, Threshold potential

References

- [1] Abramova, M. S., Nistratova, V. L., Moskvitin, A. A., and Pivovarov, A. S. (2006). Methiothepin-sensitive serotonin receptors are involved in the postsynaptic mechanism of sensitization of the withdrawal response of the common snail. *Neurosci. Behav. Physiol.* 36, 589–596. doi: 10.1007/s11055-006-0062-4

- [2] Albert, P. R., Vahid-Ansari, F., and Luckhart, C. (2014). Serotonin-prefrontal cortical circuitry in anxiety and depression phenotypes: pivotal role of preand post-synaptic 5-HT1A receptor expression. *Front. Behav. Neurosci.* 8:199. doi: 10.3389/fnbeh.2014.00199
- [3] Alkon, D. L. (1984). Changes of membrane currents during learning. *J. Exp. Biol.* 112, 95–112.
- [4] Andrianov, V. V., Bogodvid, T. Kh., Deryabina, I. B., Golovchenko, A. N., Muranova, L. N., Tagirova, R. R., et al. (2015). Modulation of withdrawal reflex conditioning in snails by serotonin. *Front. Behav. Neurosci.* 9:279. doi: 10.3389/fnbeh.2015.00279
- [5] Bailey, C. H., Giustetto, M., Zhu, H., Chen, M., and Kandel, E. R. (2000). A novel function for serotonin-mediated short-term facilitation in *Aplysia*: conversion of a transient, cell-wide homosynaptic hebbian plasticity into a persistent, protein synthesis-independent synapse-specific enhancement. *Proc. Natl. Acad. Sci. U S A* 97, 11581–11586. doi: 10.1073/pnas.97.21.11581
- [6] Balaban, P. (1993). Behavioral neurobiology of learning in terrestrial snails. *Prog. Neurobiol.* 41, 1–19. doi: 10.1016/0301-0082(93)90038-t
- [7] Balaban, P. M. (2002). Cellular mechanisms of behavioral plasticity in terrestrial snail. *Neurosci. Biobehav. Rev.* 26, 597–630. doi: 10.1016/s0149-7634(02)00022-2
- [8] Balaban, P. M. (2017). Molecular mechanisms of memory modifications. *Zh. Vyssh. Nerv. Deiat. Im. I P Pavlova* 67, 131–140. doi: 10.7868/S0044467717020046
- [9] Balaban, P. M., Bravarenko, N. I., Maksimova, O. A., Nikitin, E., Ierusalimsky, V. N., and Zakharov, I. S. (2001). A single serotonergic modulatory cell can mediate reinforcement in the withdrawal network of the terrestrial snail. *Neurobiol. Learn. Mem.* 75, 30–50. doi: 10.1006/nlme.1999.3953
- [10] Balaban, P. M., Roshchin, M., Timoshenko, A. K., Gainutdinov, K. L., Bogodvid, T. K., Muranova, L. N., et al. (2014). Nitric oxide is necessary for labilization of a consolidated context memory during reconsolidation in terrestrial snails. *Eur. J. Neurosci.* 40, 2963–2970. doi: 10.1111/ejn.12642
- [11] Balaban, P. M., Vehovzsky, A., Maksimova, O. A., and Zakharov, I. S. (1987). Effect of 5,7-dihydroxytryptamine on the food-aversive conditioning in the snail *Helix lucorum* L. *Brain Res.* 404, 201–210. doi: 10.1016/0006-8993(87)91371-0
- [12] Balaban, P. M., Vinarskaya, A. K., Zuzina, A. B., Ierusalimsky, V. N., and Malyshev, A. Y. (2016). Impairment of the serotonergic neurons underlying reinforcement elicits extinction of the repeatedly reactivated context memory. *Sci. Rep.* 6:36933. doi: 10.1038/srep36933
- [13] Balaban, P. M., and Zakharov, I. S. (1992). *Learning and Development: Common Basis of Two Phenomena.* Moscow: Nauka, 151.
- [14] Barbas, D., DesGroseillers, L., Castellucci, V. F., Carew, T. J., and Marinesco, S. (2003). Multiple serotonergic mechanisms contributing to sensitization in evidence of diverse serotonin receptor subtypes *Aplysia*. *Learn. Mem.* 10, 373–386. doi: 10.1101/lm.66103
- [15] Bao, J. X., Kandel, E. R., and Hawkins, R. D. (1998). Involvement of presynaptic and postsynaptic mechanisms in a cellular analog of classical conditioning at *Aplysia* sensory-motor neuron synapses in isolated cell culture. *J. Neurosci.* 18, 458–466.
- [16] Baxter, D. A., Canavier, C. C., Clark, J. W. Jr., and Byrne, J. H. (1999). Computational model of the serotonergic modulation of sensory neurons in *Aplysia*. *J. Neurophysiol.* 82, 2914–2935.
- [17] Boyer, E. W., and Shannon, M. (2005). The serotonin syndrome. *N. Engl. J. Med.* 352, 1112–1120. doi: 10.1056/NEJMra041867
- [18] Burrell, B. D., and Sahley, C. L. (2005). Serotonin mediates learning-induced potentiation of excitability. *J. Neurophysiol.* 94, 4002–4010. doi: 10.1152/jn.00432.2005
- [19] Byrne, J. (1987). Cellular analysis of associative learning. *Physiol. Rev.* 67, 329–439.
- [20] Catterall, W. A. (2012). Voltage-gated sodium channels at 60: structure, function and pathophysiology. *J. Physiol.* 590, 2577–2589. doi: 10.1113/jphysiol.2011.224204
- [21] Cavallo, J. S., Hamilton, B. N., and Farley, J. (2014a). Behavioral and neural bases of extinction learning in *Hermisenda*. *Front. Behav. Neurosci.* 8:277. doi: 10.3389/fnbeh.2014.00277
- [22] Cavallo, J. S., Hamilton, B. N., and Farley, J. (2014b). In vitro extinction learning in *Hermisenda*: involvement of conditioned inhibition molecules. *Front. Behav. Neurosci.* 8:354. doi: 10.3389/fnbeh.2014.00354
- [23] Clark, G. A., and Kandel, E. R. (1993). Induction of long-term facilitation in *Aplysia* sensory neurons by local application of serotonin to remote synapses. *Proc. Natl. Acad. Sci. U S A* 90, 11411–11415. doi: 10.1073/pnas.90.23.11411
- [24] Cleary, L. J., Lee, W. L., and Byrne, J. H. (1998). Cellular correlates of long-term sensitization in *Aplysia*. *J. Neurosci.* 18, 5988–5998.
- [25] Crow, T. (2004). Pavlovian conditioning of *Hermisenda*: current cellular, molecular, and circuit perspectives. *Learn. Mem.* 11, 229–238. doi: 10.1101/lm.70704
- [26] Crow, T., and Tian, L. M. (2009). Polysensory interneuronal projections to foot contractile pedal neurons in *Hermisenda*. *J. Neurophysiol.* 101, 824–833. doi: 10.1152/jn.91079.2008

- [27] Daoudal, G., and Debanne, D. (2003). Long-term plasticity of intrinsic excitability: learning rules and mechanisms. *Learn. Mem.* 10, 456–465. doi: 10.1101/lm.64103
- [28] Debanne, D., and Poo, M.-M. (2010). Spike-timing dependent plasticity beyond synapse - pre- and post-synaptic plasticity of intrinsic neuronal excitability. *Front. Synap. Neurosci.* 2:21. doi: 10.3389/fnsyn.2010.00021
- [29] D'iakonova, V. E. (2007). Behavioral functions of serotonin and octopamine: some paradoxes of comparative physiology. *Usp. Fiziol. Nauk* 38, 3–20.
- [30] Dumitriu, B., Cohen, J. E., Wan, Q., Negroiu, A. M., and Abrams, T. W. (2006). Serotonin receptor antagonists discriminate between PKA- and PKC-mediated plasticity in *Aplysia* sensory neurons. *J. Neurophysiol.* 95, 2713–2720. doi: 10.1152/jn.00642.2005
- [31] Dyakonova, V., Hernádi, L., Ito, E., Dyakonova, T., Zakharov, I., and Sakharov, D. (2015). The activity of isolated snail neurons controlling locomotion is affected by glucose. *Biophysics (Nagoya-shi)* 11, 55–60. doi: 10.2142/biophysics.11.55
- [32] Farley, J., and Wu, P. (1989). Serotonin modulation of *Hermisenda* type B photoreceptor light responses and ionic currents: implications for mechanisms underlying associative learning. *Brain Res. Bull.* 22, 335–351. doi: 10.1016/0361-9230(89)90061-0
- [33] Fickbohm, D. J., Spitzer, N., and Katz, P. S. (2005). Pharmacological manipulation of serotonin levels in the nervous system of the opisthobranch mollusc *triton* *diomedea*. *Biol. Bull.* 209, 67–74. doi: 10.2307/3593142
- [34] Fioravante, D., Liu, R.-Y., Netek, A. K., Cleary, L. J., and Byrne, J. H. (2007). Synapsin regulates basal synaptic strength, synaptic depression, and serotonin-induced facilitation of sensorimotor synapses in *Aplysia*. *J. Neurophysiol.* 98, 3568–3580. doi: 10.1152/jn.00604.2007
- [35] Frysztak, R. D., and Crow, T. (1997). Synaptic enhancement and enhanced excitability in presynaptic and postsynaptic neurons in the conditioned stimulus pathway of *Hermisenda*. *J. Neurosci.* 17, 4426–4433.
- [36] Gadotti, D., Bauce, L. G., Lukowiak, K., and Bulloch, A. G. M. (1986). Transient depletion of serotonin in the nervous system of *Helisoma*. *J. Neurobiol.* 17, 431–447. doi: 10.1002/neu.480170507
- [37] Gainutdinov, Kh. L., Andrianov, V. V., and Gainutdinova, T. K. (1999). The action of the neurotoxins 5,6-dihydroxytryptamine and p-chlorophenylalanine on the electrical activity parameters of the command neurons during long-term sensitization and learning in the snail. *Zh. Vyssh. Nerv. Deiat. Im. I P Pavlova* 49, 48–58.
- [38] Gainutdinov, Kh. L., Andrianov, V. V., and Gainutdinov, T. K. (2011). Changes of the neuronal membrane excitability as cellular mechanisms of learning and memory. *Usp. Fiziol. Nauk.* 42, 33–52.
- [39] Gainutdinova, T. K., Andrianov, V. V., Gainutdinov, Kh. L., Mukhamedshina, D. I., and Tagirova, R. R. (2003). Duration of changes in electrical characteristics of command neurons after defensive conditioning in snails. *Zh. Vyssh. Nerv. Deiat. Im. I P Pavlova* 53, 379–382.
- [40] Gainutdinov, Kh. L., Andrianov, V. V., Gainutdinova, T. K., and Tarasova, E. A. (2000). The electrical characteristics of command and motor neurons during acquisition of a conditioned defensive reflex and formation of long-term sensitization in snails. *Neurosci. Behav. Physiol.* 30, 81–88. doi: 10.1007/bf02461395
- [41] Gainutdinov, Kh. L., Chekmarev, L. J., and Gainutdinova, T. H. (1998). Excitability increase in withdrawal interneurons after conditioning in snail. *Neuroreport* 9, 517–520. doi: 10.1097/00001756-199802160-00026
- [42] Gillette, R. (2006). Evolution and function in serotonergic systems. *Integr. Comp. Biol.* 46, 838–846. doi: 10.1093/icb/icl024
- [43] Glanzman, D. L. (2010). Common mechanisms of synaptic plasticity in vertebrates and invertebrates. *Curr. Biol.* 20, R31–R36. doi: 10.1016/j.cub.2009.10.023
- [44] Glanzman, D. L., and Krasne, F. B. (1986). 5,7-Dihydroxytryptamine lesions of crayfish serotonin-containing neurons: effect on the lateral giant escape reaction. *J. Neurosci.* 6, 1560–1569.
- [45] Glanzman, D. L., Mackey, S. L., Hawkins, R. D., Dyke, A. M., Lloyd, P. E., and Kandel, E. R. (1989). Depletion of serotonin in the nervous system of *Aplysia* reduces the behavioral enhancement of gill withdrawal as well as the heterosynaptic facilitation produced by tail shock. *J. Neurosci.* 12, 4200–4213.
- [46] Greenier, E., Lukyanova, V., and Reede, L. (2014). Serotonin syndrome: fentanyl and selective serotonin reuptake inhibitor interactions. *AANA J.* 82, 340–345.
- [47] Grinkevich, L. N., and Vorobiova, O. V. (2014). The role of the modulator transmitter serotonin in induction epigenetic processes at the formation of long-term memory in *Helix*. *Vavilovsky J. Genet. Selections* 18, 298–307.
- [48] Habertztl, R., Berta, B., Fink, H., and Fox, M. A. (2013). Animal models of the serotonin syndrome: a systematic review. *Behav. Brain Res.* 256, 328–345. doi: 10.1016/j.bbr.2013.08.045
- [49] Hart, A. K., Fioravante, D., Liu, R.-Y., Phares, G. A., Cleary, L. J., and Byrne, J. H. (2011). Serotonin-mediated synapsin expression is necessary for long-term facilitation of the *Aplysia* sensorimotor synapse. *J. Neurosci.* 31, 18401–18411. doi: 10.1523/jneurosci.2816-11.2011
- [50] Hawkins, R. D., Kandel, E. R., and Bailey, C. H. (2006). Molecular mechanisms of memory storage in *Aplysia*. *Biol. Bull.* 210, 174–191. doi: 10.2307/4134556

- [51] Hernádi, L., Hiripi, L., Vehovszky, A., Kemenes, G., and Rózsa, K. (1992). Ultrastructural, biochemical and electrophysiological changes induced by 5,6-dihydroxytryptamine in the CNS of the snail *Helix pomatia* L. *Brain Res.* 578, 221-234. doi: 10.1016/0006-8993(92)90251-4
- [52] Hernádi, L., Kárpáti, L., Gyori, J., Vehovszky, A., and Hiripi, L. (2008). Humoral serotonin and dopamine modulate the feeding in the snail, *Helix pomatia*. *Acta Biol. Hung.* 59, 39-46. doi: 10.1556/abiol.59.2008.suppl.6
- [53] Hirayama, K., Moroz, L. L., Nathan, G., Hatcher, N. G., and Gillette, R. (2014). Neuromodulatory control of a goal-directed decision. *PLoS One* 9:e102240. doi: 10.1371/journal.pone.0102240
- [54] Hu, J.-Y., Baussi, O., Levine, A., Chen, Y., and Schacher, S. (2011). Persistent long-term synaptic plasticity requires activation of a new signaling pathway by additional stimuli. *J. Neurosci.* 31, 8841-8850. doi: 10.1523/jneurosci.1358-11.2011
- [55] Ierusalimskii, V. N., and Balaban, P. M. (2010). Serotonergic system of neurons in the CNS of terrestrial snail: morphology, ontogenesis, control of behavior. *Zh. Vyssh. Nerv. Deiat. Im. I P Pavlova* 60, 515-524.
- [56] Il-Han, J., Janes, T., and Lukowiak, K. (2010). The role of serotonin in the enhancement of long-term memory resulting from predator detection in *Lymnaea*. *J. Exp. Biol.* 213, 3603-3614. doi: 10.1242/jeb.048256
- [57] Jin, N. G., and Crow, T. (2011). Serotonin regulates voltage-dependent currents in type Ie(A) and Ii interneurons of *Hermisenda*. *J. Neurophysiol.* 106, 2557-2569. doi: 10.1152/jn.00550.2011
- [58] Jin, N. G., Tian, L.-M., and Crow, T. (2009). 5-HT and GABA modulate intrinsic excitability of type I interneurons in *Hermisenda*. *J. Neurophysiol.* 102, 2825-2833. doi: 10.1152/jn.00477.2009
- [59] Jing, J., and Gillette, R. (2003). Directional avoidance turns encoded by single interneurons and sustained by multifunctional serotonergic cells. *J. Neurosci.* 23, 3039-3051.
- [60] Kandel, E. R., and Schwartz, J. H. (1982). Molecular biology of learning: modulation of transmitter release. *Science* 218, 433-443. doi: 10.1126/science.6289442
- [61] Kemenes, G. (1997). In vivo neuropharmacological and in vitro laser ablation techniques as tools in the analysis of neuronal circuits underlying behaviour in a molluscan model system. *Gen. Pharmacol.* 29, 7-15. doi: 10.1016/s0306-3623(96)00520-4
- [62] Kemenes, G., Hiripi, L., and Benjamin, P. R. (1990). Behavioural and biochemical changes in the feeding system of *Lymnaea* induced by the dopamine and serotonin neurotoxins 6-hydroxydopamine and 5,6-dihydroxytryptamine. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 329, 243-255. doi: 10.1098/rstb.1990.0168
- [63] Khodorov, B. I. (1974). *The Problem of Excitability: Electrical Excitability and Ionic Permeability of the Nerve Membrane*. New York, NY: Plenum Press, 301.
- [64] Kiss, T. (2003). Evidence for a persistent Na-conductance in identified command neurones of the snail, *Helix pomatia*. *Brain Res.* 989, 16-25. doi: 10.1016/s0006-8993(03)03316-x
- [65] Kiss, T., Hiripi, L., Papp, N., and Elekes, K. (2003). Dopamine and serotonin receptors mediating contractions of the snail, *Helix pomatia*, salivary duct. *Neuroscience* 116, 775-790. doi: 10.1016/s0306-4522(02)00754-6
- [66] Kiss, T., Pirger, Z., and Kemenes, G. (2009). Food-aversive classical conditioning increases a persistent sodium current in molluscan withdrawal interneurons in a transcription dependent manner. *Neurobiol. Learn. Mem.* 92, 114-119. doi: 10.1016/j.nlm.2009.03.001
- [67] Klein, M., Camardo, J. S., and Kandel, E. R. (1982). Serotonin modulates a new potassium current in the sensory neurons that show presynaptic facilitation in *Aplysia*. *Proc. Natl. Acad. Sci. U S A* 79, 5713-5717. doi: 10.1073/pnas.79.18.5713
- [68] Lee, Y.-S., Choi, S.-L., Lee, S.-H., Kim, H., Park, H., Lee, N., et al. (2009). Identification of a serotonin receptor coupled to adenylyl cyclase involved in learning-related heterosynaptic facilitation in *Aplysia*. *Proc. Natl. Acad. Sci. U S A* 106, 14634-14639. doi: 10.1073/pnas.0907502106
- [69] Leon-Pinzon, C., Cercós, M. G., Noguez, P., Trueta, C., and De-Migue, F. F. (2014). Exocytosis of serotonin from the neuronal soma is sustained by a serotonin and calcium-dependent feedback loop. *Front. Cell. Neurosci.* 8:169. doi: 10.3389/fncel.2014.00169
- [70] Levenson, J., Byrne, J. H., and Eskin, A. (1999). Levels of serotonin in the hemolymph of *Aplysia* are modulated by light/dark cycles and sensitization training. *J. Neurosci.* 19, 8094-8103.
- [71] Liao, X., Brou, C. G., and Walters, E. T. (1999). Limited contributions of serotonin to long-term hyperexcitability of *Aplysia* sensory neurons. *J. Neurophysiol.* 82, 3223-3235.
- [72] Lin, A. H., Cohen, J. E., Wan, Q., Niu, K., Shrestha, P., Bernstein, S. L., et al. (2010). Serotonin stimulation of cAMP-dependent plasticity in *Aplysia* sensory neurons is mediated by calmodulin-sensitive adenylyl cyclase. *Proc. Natl. Acad. Sci. U S A* 107, 15607-15612. doi: 10.1073/pnas.1004451107
- [73] Malyshev, A. Yu., Bravarenko, N. I., Pivovarov, A. S., and Balaban, P. M. (1998). Effects of serotonin levels on postsynaptically induced potentiation of snail neuron responses. *Neurosci. Behav. Physiol.* 28, 556-563. doi: 10.1007/bf02463017

- [74] Marinesco, S., Wickremasinghe, N., Kolkman, K. E., and Carew, T. J. (2004). Serotonergic modulation in *Aplysia*. II. Cellular and behavioral consequences of increased serotonergic tone. *J. Neurophysiol.* 92, 2487–2496. doi: 10.1152/jn.00210.2004
- [75] Mauelshagen, J., Sherff, C. M., and Carew, T. J. (1998). Differential induction of long-term synaptic facilitation by spaced and massed applications of serotonin at sensory neuron synapses of *Aplysia californica*. *Learn. Mem.* 5, 246–256.
- [76] Mozzachiodi, R., and Byrne, J. H. (2010). More than synaptic plasticity: role of nonsynaptic plasticity in learning and memory. *Trends Neurosci.* 33, 17–26. doi: 10.1016/j.tins.2009.10.001
- [77] Mozzachiodi, R., Lorenzetti, F. D., Baxter, D. A., and Byrne, J. H. (2008). Changes in neuronal excitability serve as a mechanism of long-term memory for operant conditioning. *Nat. Neurosci.* 11, 1146–1148. doi: 10.1038/nn.2184
- [78] Nagakura, I., Dunn, T. W., Farah, C. A., Hepner, A., Li, F. F., and Sossin, W. S. (2010). Regulation of protein kinase C Apl II by serotonin receptors in *Aplysia*. *J. Neurochem.* 115, 994–1006. doi: 10.1111/j.1471-4159.2010.06986.x
- [79] Nikitin, E. S., Balaban, P. M., and Kemenes, G. (2013). Nonsynaptic plasticity underlies a compartmentalized increase in synaptic efficacy after classical conditioning. *Curr. Biol.* 23, 614–619. doi: 10.1016/j.cub.2013.02.048
- [80] Nikitin, E. S., Kiss, T., Staras, K., O’Shea, M., Benjamin, P. R., and Kemenes, G. (2006). Persistent sodium current is a target for cAMP-induced neuronal plasticity in a state-setting modulatory interneuron. *J. Neurophysiol.* 95, 453–463. doi: 10.1152/jn.00785.2005
- [81] Pavlova, G. A. (2001). Effects of serotonin, dopamine and ergometrine on locomotion in the pulmonant mollusc *Helix lucorum*. *J. Exp. Biol.* 204, 1625–1633.
- [82] Petersen, A. V., Jensen, C. S., Crépe, V., Falkerslev, M., and Perrier, J.-F. (2017). Serotonin regulates the firing of principal cells of the subiculum by inhibiting a T-type Ca^{2+} current. *Front. Cell. Neurosci.* 11:60. doi: 10.3389/fncel.2017.00060
- [83] Pivovarov, A. S., Murzina, G. B., Makhnovsky, D. A., and Tret’yakova, M. S. (2014). Possibility of “comet-like” transport of acetylcholine receptors in command *Helix* neurons in cellular analog of habituation. *World J. Neurosci.* 4:45104. doi: 10.4236/wjns.2014.42016
- [84] Pivovarov, A. S., and Nistratova, V. L. (2003). Modulatory serotonin receptors on the soma of command neurons in edible snail. *Bull. Exp. Biol. Med.* 136, 114–116. doi: 10.1023/A:1026390117562
- [85] Ravinder, S., Pillai, A. G., and Chattarji, S. (2011). Cellular correlates of enhanced anxiety caused by acute treatment with the selective serotonin reuptake inhibitor fluoxetine in rats. *Front. Behav. Neurosci.* 5:88. doi: 10.3389/fnbeh.2011.00088
- [86] Riad, M., Zimmer, L., Rbah, L., Watkins, K. C., Hamon, M., and Descarries, L. (2004). Acute treatment with the antidepressant fluoxetine internalizes 5-HT_{1A} autoreceptors and reduces the in vivo binding of the PET radioligand [¹⁸F]MPPF in the nucleus raphe dorsalis of rat. *J. Neurosci.* 24, 5420–5426. doi: 10.1523/jneurosci.0950-04.2004
- [87] Saar, D., and Barkai, E. (2009). Long-lasting maintenance of learning-induced enhanced neuronal excitability: mechanisms and functional significance. *Mol. Neurobiol.* 39, 171–177. doi: 10.1007/s12035-009-8060-5
- [88] Sakharov, D. A. (1990). Integrative function of serotonin in primitive Metazoa. *Zh. Obshch. Biol.* 51, 437–449.
- [89] Sakharov, D. A. (2012). The biological substrate for the generation of behavioral acts. *Zh. Obshch. Biol.* 73, 334–348.
- [90] Shevelkin, A. V., Nikitin, V. P., Kozyrev, S. A., Samoilov, M. O., and Sherstnev, V. V. (1998). Serotonin imitates several of the neuronal effects of nociceptive sensitization in the common snail. *Neurosci. Behav. Physiol.* 28, 547–555. doi: 10.1007/bf02463016
- [91] Shevelkin, A. V., Nikitin, V. P., and Sherstnev, V. V. (2009). Intravital investigation of the effects of serotonin and glutamate on the dynamics of DNA activity in L-RP1 neurons of edible snail. *Bull. Exp. Biol. Med.* 148, 563–567. doi: 10.1007/s10517-010-0766-x
- [92] Sugita, S., Baxter, D. A., and Byrne, J. H. (1997). Differential effects of 4-aminopyridine, serotonin, and phorbol esters on facilitation of sensorimotor connections in *Aplysia*. *J. Neurophysiol.* 77, 177–185.
- [93] Sun, Z. Y., and Schacher, S. (1998). Binding of serotonin to receptors at multiple sites is required for structural plasticity accompanying long-term facilitation of *Aplysia* sensorimotor synapses. *J. Neurosci.* 18, 3991–4000.
- [94] Timoshenko, A. K., Shevelkin, A. V., Nikitin, V. P., and Sherstnev, V. V. (2014). Live-cell imaging microscopy and quantitative analysis of Ca^{2+} -dependent effects of neurotransmitters on DNA in snail neurons. *Biophysics* 59, 91–97. doi: 10.1134/s0006350914010229
- [95] Vasil’yeva, N. A., Murzina, G. B., and Pivovarov, A. S. (2015). Habituationlike decrease of acetylcholine-induced inward current in *Helix* command neurons: role of microtubule motor proteins. *Cell. Mol. Neurobiol.* 35, 703–712. doi: 10.1007/s10571-015-0165-y
- [96] Whitaker-Azmitia, P. M. (1999). The discovery of serotonin and its role in neuroscience. *Neuropsychopharmacology* 21, 2S–8S. doi: 10.1016/s0893-133x(99)00031-7

- [97] Zakharov, I. S., Ierusalimsky, V. N., and Balaban, P. M. (1995). Pedal serotonergic neurons modulate the synaptic input of withdrawal interneurons of *Helix*. *Invert. Neurosci.* 1, 41-52. doi: 10.1007/bf02331831
- [98] Zenke, F., Gerstner, W., and Ganguli, S. (2017). The temporal paradox of Hebbian learning and homeostatic plasticity. *Curr. Opin. Neurobiol.* 43, 166-176. doi: 10.1016/j.conb.2017.03.015