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Maternal Serotonin: Shaping Developmental Patterns and Behavioral Strategy on Progeny in Molluscs

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Serotonin is a well-known neurotransmitter and neurohormone regulating mood, sleep, feeding, and learning in high organisms. Serotonin also affects the embryonic events related to neurogenesis and maturation of hormonal systems, the underlying organism adaptation to a changing environment. Such serotonin-based mother-to-embryo signaling is realized via direct interactions in case of internal fertilization and embryonic development inside the mother body. However, the possibility of such signaling is less obvious in organisms with the ancestral type of embryogenesis and embryo development within the egg, outside the mother body. Our data, based on the investigation of freshwater gastropod molluscs (*Lymnaea* and *Helisoma*), demonstrated a correlation between seasonal variations of serotonin content within the female reproductive system, and developmental patterns and the behavioral characteristics of progeny. The direct action of serotonin via posttranslational protein modification—serotonylation—during early development, as well as classical receptor-mediated effects, underlies such serotonin-modulated developmental changes. In the present paper, I will shortly overview our results on freshwater molluscs and parallel the experimental data with the living strategy of these species occupying almost all Holarctic regions.

Keywords: adult-to-embryo chemical signaling, serotonylation, serotonin receptors, developmental dynamics, locomotion, oviposition activity

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INTRODUCTION

Serotonin (5-hydroxytryptamine, 5-HT) is a biogenic amine that can be found in most living organisms. It is a well-known neurotransmitter and neuromodulator in the nervous system of vertebrates and invertebrates, impacting such important aspects of life as learning and memory, aggression, sleep, arousal reaction, food uptake, and many others (Müller and Cunningham, 2020). It is also found in the peripheral tissues and organs where it serves as a neurohormone regulating blood pressure and platelets-dependent clotting, glucose metabolism and weight regulation in mammals (Muma and Mi, 2015; Pilowsky, 2018). The serotoninergic system includes 5-HT synthesis and degradation enzymes, receptors and coupled G-proteins, membrane, and vesicular transporters. Despite substantial variations existing across vertebrates and invertebrates, as well as

among different taxa and species (Schmidt-Rhaesa et al., 2016; Müller and Cunningham, 2020), some common organizational principles can be noted for the serotoninergic system. First, the 5-HT-containing neurons constitute a fairly small portion of neuronal elements. However, these elements provide widespread terminals contacting numerous cellular targets. Second, the serotonin receptors and transporters are present in the cell membrane of almost all tissues and organs and react to the surrounding serotonin as to hormone even far from the 5-HT released sites. Third, all components of the serotonergic systems appear to be highly plastic with both the anatomical organizations and biochemical pieces of machinery that can change at different periods of life, or under various environmental conditions. Such features of the serotonergic system allow us to speculate that 5-HT acts more as a basic modulator or integrating molecule (Sakharov, 1990; Moroz et al., 2021) at the level of the whole organism than just a local mediator transmitting a particular signal between certain cells and their targets. Moreover, serotonin has been found since the very early stage of animal development, in oocytes, zygotes, and cleaved blastomeres (Buznikov et al., 1964, 2001; Dubé and Amireault, 2007). Later in development serotonin affects the embryonic events related to neurogenesis and maturation of hormonal systems (Buznikov, 1991; Bonnin and Levitt, 2011; Bonnin et al., 2011; Vitalis et al., 2013). Serotonin appears evolutionarily before the formation of the first neurons and is a well-recognized component of ancient and archetypical signaling systems (Turlejski, 1996; Azmitia, 2010). Thus serotonin has a high potential to serve as a link between external signals, the physiological state of the maternal organism, and forming developmental and behavioral characteristics of progeny, which determine the life strategy of the generation.

To test the function of serotonin as such a broad regulating molecule we used freshwater snails: *Lymnaea stagnalis* and *Helisoma trivolvis* (Mollusca; Gastropoda), as experimental objects. These species are a popular model for neurobiology, physiology, and developmental biology. The morphology of the adult's and embryos nervous system, developmental patterns, reproduction, and behavior in normal conditions are documented in detail (Morrill, 1982; Meshcheryakov, 1990; Kemenes and Benjamin, 2009; Koene, 2010). The species are also subjects for numerous ecological and ecotoxicological studies (Morrison and Belden, 2016; Amorim et al., 2019; Fodor et al., 2020; Svigruha et al., 2020).

In this mini-review, I will compact our 20 years of research devoted to the delayed effects of serotonin shaping both the developmental patterns and behavior of progeny in gastropod molluscs. We demonstrated: (i) a correlation between season and the serotonin level in the local serotonergic network in the female reproductive system, (ii) increased intracellular serotonin during early cleavage, impacting embryonic development and juvenile behavior, (iii) the modulating role of serotonin produced by early embryonic neurons on developmental tempo and hatching. Two mechanisms underlie described long-lasting serotonin effects: (1) classical receptor-mediated regulations, and (2) the non-canonical intracellular action of serotonin as a chemical substance for transglutaminase-mediated posttranslational proteins modification (serotonylation). The combination of these mechanisms or the prevalence of one over the other varies stage-dependently at the course of embryogenesis. As a result, developing embryos demonstrate tune adaptations to the variable environmental challenges they will be faced with during their adult life, despite having no direct contact with the changing environment before birth or hatching. Such non-genetic transfer of a maternal serotonin-mediated signal provides the appropriate adaptive choice of the progeny life strategy, ensures population reproductive success and wide distribution of the species (**Figure 1**).

LOCAL SEROTONERGIC NETWORK IN THE FEMALE MOLLUSC REPRODUCTIVE SYSTEM AS THE LOCATION OF CLOSEST CONTACT BETWEEN MATERNAL TISSUES AND THE EARLY EMBRYO

One of the biggest questions is how environmental information or parents' behavioral experiences can be encoded and transmitted from the nervous system of adults to the gonads, and subsequently to progeny? Such maternal effects on offspring phenotype, particularly in how maternal experience can adaptively shape offspring behavior and the developmental state attracted the attention of evolutionary ecologists and evo-devo biologists for a long time. No single source can cover all aspects of the maternal effects. The principal topics, a number of general issues, updated coverage of problem agendas and perspectives mostly covered in comprehensive reviews (Bernardo, 1996; Rossiter, 1996; Mousseau and Fox, 1998; Bonduriansky and Day, 2009; Uller et al., 2009), with examples from mammals (Maestripieri and Mateo, 2009), maternal effects in marine environments (Marshall et al., 2008), some aspects of the evolution of maternal effects from a developmental perspective (Uller, 2012) and ecological and evolutionary implications, in particular, for plants (Sultan, 2015). In our work we concentrated in one possible particular underlying mechanism of adult-to-embryo signaling—the serotonin-mediated maternal effect—in a limited group of aquatic molluscs. We demonstrated that in freshwater gastropods' serotonin is a key player providing a link between generations by affecting the oocyte and fertilized zygote within the mother reproductive system.

In addition to neurons located within the central ganglia and rich peripheral innervation, the local network of 5-HT-containing cells located in the female part of the *Lymnaea* reproductive system. *L. stagnalis* is a hermaphroditic gastropod snail and the reproductive system contains both male and female parts. Oocytes start their way along the oviduct in response to the signals from the neuroendocrine cells. Ripe oocytes are fertilized in the fertilization pouch and supplied with perivitelline fluid secreted by the albumen gland. Then the zygote starts to move through the folded muscular uterus (pars contorta) and there it is enveloped in two membranes and forms the egg. The muciparous gland secretes mucus that fuses the eggs together, the oothecal gland surrounds the whole

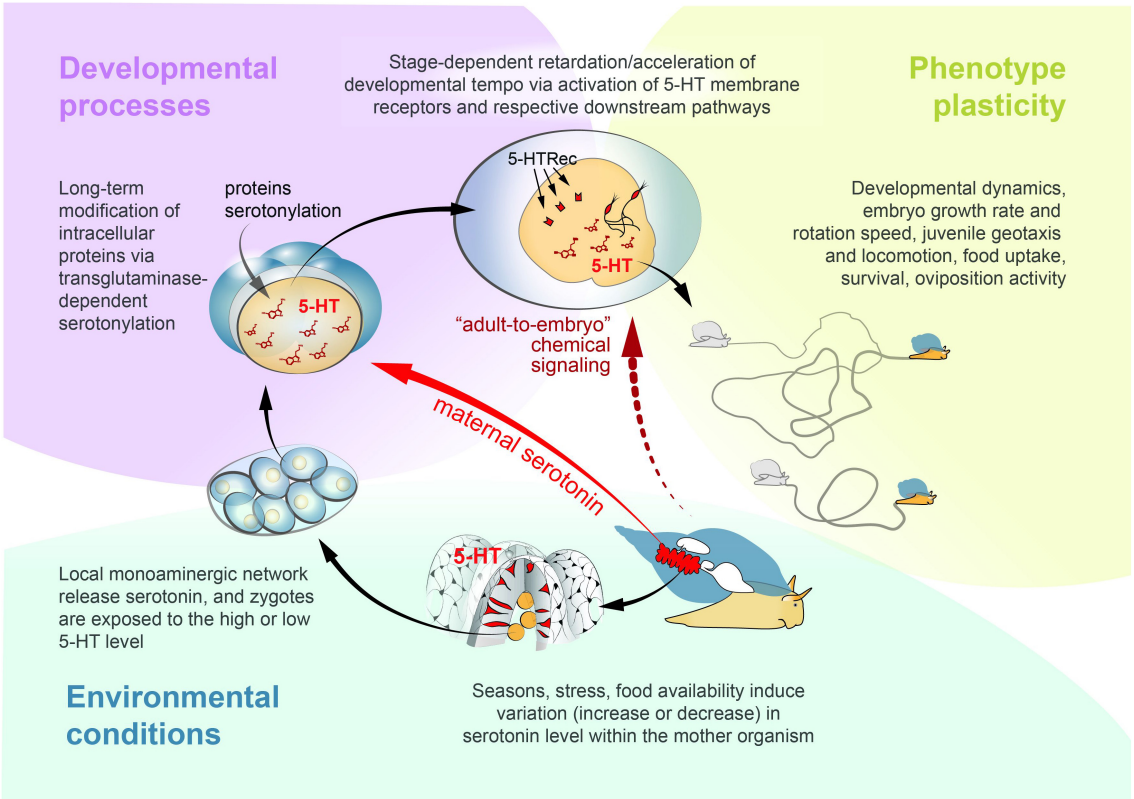

FIGURE 1 | Schematic representation of the tune adaptations in progeny live strategies based on serotonin-mediated regulatory mechanisms during the freshwater gastropod mollusc life cycle. The solid red arrow represents the direct effect of mother serotonin to the developing oocytes and zygotes. The dashed red arrow represents chemical water-born signaling from adults, which activates the serotonin release from specific embryonic sensory neurons. 5-HTRec—specific serotonin receptors in embryonic tissues. The female reproductive system represents a location of the closest contact between the mothers' serotonin releasing network with oocyte and zygote (maternal serotonin arrow). The seasonal and environmental factors lead to modulation of the serotonin level in the mother organism and subsequent changes within the developing embryo. High serotonin within cleaved blastomeres provides a substrate for the serotonylation of specific proteins, and appearance of the progeny with faster development and locomotion, raised survival and productivity. Embryonic apical neurons react to water-born chemical signals emitted by adults in unfavorable conditions ("adult-to-embryo" chemical signaling dashed arrow). Serotonin released from the apical neurons activate specific serotonin receptors located in embryonic cells and stage-dependently retard or accelerate the developmental tempo and juvenile behavior. Combinations of serotonin-dependent mechanisms in the course of development underlay the appropriate adaptive choice of the progeny life strategy, ensures the population reproductive success and the wide distribution of the species.

egg mass with tunica capsulis, and the complete egg mass leave the mother organism to the environment via female gonopore (Koene, 2010). Most aforementioned parts of the reproductive system are innervated by 5-HT-immunopositive fibers. However, only the uterus possesses the intensive local network of 5-HT-containing elements.

The dense network of 5-HT-immunoreactive cells and their processes in the epithelium, and in the muscular layer of the uterus, represent the key location where maternal serotonin contacts with zygotes (Ivashkin et al., 2017). Numerous multipolar 5-HT-containing cells are located between the epithelial cells in the folded part of the uterus (convoluted part of the pars contorta). Their thick bulb-shaped apical processes contact the inner lumen of the duct and the basal varicose fibers organize a basket-shape network on the surface of the folded epithelium. The morphology of multipolar 5-HT-containing cells suggested their exocrine function, and active release of their transmitter content –serotonin—into the reproductive tract lumen. The extensive folding of the uterus indicates that the fertilized egg spends a long time moving along this part of the reproductive system. And during all that time the zygote is exposed to serotonin which is released by the serotonergic cells of the mother's organism.

Direct measurements of 5-HT content in the *Lymnaea* confirmed the high level of 5-HT in the female part of the reproductive system, especially within the pars contorta region. The important fact is that serotonin level within this particular region of the reproductive system is season-dependent: 5-HT content within the uterus gradually increased from winter through spring to summer, then falls dramatically in the autumn (Ivashkin et al., 2015). Pharmacological experiments with the application of 5-HT immediate biochemical precursor—5-HTP—result in an enhanced serotonin level similar to in summertime while the application of chlorpromazine leads to serotonin depletion similar to the autumn condition. These pharmacological approaches allowed us to experimentally mimic

the natural seasons in the laboratory and follow the induced changes in progeny development and behavior under various conditions (see detailed description below).

SEASON-DEPENDENT TUNING OF PROGENY DEVELOPMENT AND BEHAVIOR AND THE UNDERLYING SEROTONIN-MEDIATED MECHANISM

As we demonstrated, the local serotonergic network within the female reproductive system represents the location of closest contact between maternal tissues and the zygote, and season-dependent serotonin production by a maternal organism, has likely mediated the transmission of 5-HT-based signals to progeny.

Indeed, summer and autumn embryos and juveniles varied in specific sets of characters. A *Lymnaea* embryo develops within the egg capsule and there it passes cleavage, gastrulation, premetamorphic larvae stages (trochophore, veliger, and hippo), and undergoes metamorphosis and hatches as a miniature adult-like snail (Meshcheryakov, 1990). The summer generation demonstrates the accelerated speed of embryo rotation within the egg capsule, developmental dynamics with faster premetamorphic and metamorphic phases, and hatch 1–2 days earlier than the representatives of the autumn generation. Juvenile *Lymnaea* snails leave the egg cocoon using intense terrestrial locomotion, and after hatching utilize both gliding and terrestrial locomotion to inspect their novel environment. Summer juveniles moved about two times faster than autumn individuals, prefer vertical surfaces, and often exhibit negative geotaxis, thus leaving the water and creeping onto the bank margin. They can survive drying and stay alive longer with low oxygen. On the contrary, autumn juveniles spend more time on horizontal surfaces underwater, and approach the water surface for respiration episodes only. Contrary to summer individuals they spend more time feeding and grow faster. Nevertheless, summer and autumn generations become reproductively active simultaneously. Moreover, summer individuals produce more eggs than autumn ones.

Such a combination of features makes the summer-born generation exceptionally efficient at dispersion. They preferentially search for new habitats and demonstrate the "migrants" complex of behavior features described above. In contrast, the snails that hatched during the autumn tend to remain in their local environment and demonstrate "resident" behavioral characters.

Previously, it has been shown that juveniles of gastropod snails may disperse under natural conditions to distant water habitats by riding on the feathers and inside the gut of waterfowl and similar birds (Kawakami et al., 2008; Boag, 1986; van Leeuwen et al., 2012). In such a case, the "migrant" strategy with a negative geotaxis, a tendency to crawl to the water surface, combined with the fast locomotion of summer-born juveniles, increases their chances to cling to the bird's feathers or be swallowed. Usually, birds do not migrate large distances during summer, so juvenile snails have a chance to be successfully transferred to new water habitats. On the contrary, spring and autumn are the times when birds migrate long distances to their final location. And in this case, the "resident" strategy of juvenile snails with more time deep in the water ensures their better survival in their original habitat.

Interestingly, the pharmacological treatment of the mother can switch the natural season-dependent phenotype of progeny. The application of 5-HTP to an autumn mother-snail (with low natural serotonin) enhanced serotonin levels within the local network and resulted in the "summer" phenotype appearance in the originally autumn generation. And vice versa, the depletion of serotonin in the mother organism during summer (the season with originally high serotonin) leads to loss of active summer phenotype and the appearance of progeny with autumn characteristics (Ivashkin et al., 2015).

It should be noted that the modulations of serotonin levels had an effect on the development and behavior of progeny only if that occurred early at embryogenesis: at zygote or during cleavage stages (Voronezhskaya et al., 2012). This fact indicates that possible mechanism(s) underlying the phenomenon of described long-term serotonin-mediated changes utilizes the non-canonical way of serotonin action.

Recently a novel mechanism explaining such prolonged serotonin actions has been found. It has been shown that in addition to the classical pathway via binding to membrane receptors, serotonin can modify the intracellular proteins. This process of covalent serotonin binding to glutamine residues of the target protein is mediated by transglutaminase (TGase) and has been termed "serotonylation" (Walther et al., 2003). Not only can serotonin be a substrate for TGase-mediated transamidation but also other monoamines (Hummerich et al., 2012). This novel posttranslational proteins modification has an impact on such important physiological processes as platelet activation, insulin release, smooth muscle contraction, and even the regulation of transcription (Muma and Mi, 2015; Bader, 2019; Farrelly et al., 2019).

In our experiments, we demonstrated that *L. stagnalis* zygote and cleaved blastomeres have all the necessary biochemical machinery to perform serotonylation. They can transport serotonin inside the cells using the membrane transporter SERT or synthesize it from the precursors (Voronezhskaya et al., 2012). The basic level of serotonylation occurs naturally for a specific set of proteins in cleaved blastomeres, and it is enhanced and modified in response to an increased serotonin level (Ivashkin et al., 2015). Notably, among these modified molecules some nuclear proteins serve as a substrate for transglutaminase-mediated serotonylation as well (Ivashkin et al., 2019). The specific pattern of serotonylated proteins can be modified by enhanced serotonin during the zygote and early cleavage stages, but not at veliger and post-metamorphic embryos. Accordingly, TGase inhibition prevents the formation of serotonylated proteins at the early developmental stages as well as negating the delayed effects of enhanced serotonin level on progeny development and behavior. That confirms the involvement of the serotonylation mechanism in the long-term effect of serotonin in the formation of behavioral characters in molluscan progeny.

Summarizing the role serotonin played during early *Lymnaea* development, we can conclude that oocyte, zygote, and cleaved blastomeres are the targets for serotonin released by the mother-snail local serotonergic networks. Serotonin deposited within the embryonic cells can modify specific sets of intracellular and nuclear proteins in differentiating blastomeres which give rise to numerous tissues and organs (Ivashkin et al., 2019). Finally, the modulation of early serotonin level leads to modification in developmental dynamics and behavior of progeny (Ivashkin et al., 2015).

The presence of 5-HT elements in gonads and the reproductive tract has been found in representatives of various molluscan species: in the bivalve *Patinopecten* (Matsutani and Nomura, 1986), in nudibranchs *Pleurobranchaea* and *Tritonia* (Moroz et al., 1997), in opisthobranch *Asperspina* (Delgado et al., 2012). In many bivalves, the application of 5-HT stimulates oocytes maturation, induces spawning, or stimulates parturition (Fong et al., 1994; Fong, 1998). Serotonin level in parent organisms is highly variable and reflects the animal particular physiological states and certain environmental conditions. The serotonin level is different in starved and satiated animals (Hernádi et al., 2004), changes after intense locomotion (Aonuma et al., 2020) or under anxiety and stress conditions (Fossat et al., 2014). Our experiments with molluscs clearly demonstrate that all these physiological states and changes may influence the future generation in case they are happening in a specific time window (early cleavage) during embryonic development.

The effect of maternally-derived serotonin on germ cells has been shown also for nematode *Caenorhabditis elegans.* Serotonin released by maternal neurons during stress acts through conserved signal transduction pathways and enables the transcription factor HSF1 to alter chromatin in soon-to-be fertilized germ cells. This mechanism ensures the viability and stress resilience of future offspring (Das et al., 2020).

We do not know yet all the players and certain pathways which link the modification of proteins within *L. stagnalis* blastomeres, and the formation of neuronal networks underlying juvenile molluscs' behavior. However, we clearly see the phenomenon of maternal serotonin-mediated phenotypic adjustments providing more efficient survival skills and effective dispersion of progeny (**Figure 1**).

PARENTAL CHEMICAL SIGNAL AND SEROTONIN-MEDIATED CHANGES IN DEVELOPMENTAL TEMPO AND JUVENILE BEHAVIORAL CHARACTERISTICS

Like many representatives of aquatic biosystems, freshwater gastropod molluscs have a biphasic life cycle with embryo and adult forms occupying greatly different ecological niches. Adult *Lymnaea* and *Helisoma* release egg cocoons to the external environment and then leave their progeny to develop. The embryonic snail passes larval stages and metamorphosis inside the egg capsule and then hatches as a young juvenile snail. So, in molluscan development, there are no further contacts with the mother organism and the embryo after the egg cocoon was formed. Maternal effects are known to be of particular importance for species in aquatic systems. They not only form a link between the phenotypes of different generations, but the biphasic life cycle of most marine organisms suggests that maternal effects also link the phenotypes of populations (Marshall et al., 2008). In our experiments, we revealed adult-to-embryo chemical signaling, which regulates larval development in freshwater gastropods. We also proved that serotonin is a molecule mediating the adult-derived chemical signal with embryonic developmental tempo and juvenile's behavioral characteristics (Voronezhskaya et al., 2004, 2007).

When the adult or young juvenile *Lymnae*a and *Helisoma* face unfavorable environmental conditions like starvation or crowding they start to release water-borne chemical cues (with a still unidentified chemical structure). In response to those signals, early embryos retard or even stop their development (Voronezhskaya et al., 2004), while metamorphic embryos accelerate developmental tempo, and hatchlings as well as young juveniles demonstrate more active locomotion, feeding and cardiac activity (Voronezhskaya et al., 2007; Glebov et al., 2014). Such an adaptive strategy allows the early embryos to leave its nutrients and wait out inside the egg until the external situation will be improved. On the contrary, the late embryo already used up the egg's nutrients supply and a more adaptive strategy will be to hatch as soon as possible and leave an unfavorable environment (**Figure 1**).

The chemical signal (which is certainly not serotonin itself) is emitted by adult snails under conditions of starvation or crowding, and is sensed by specific larval neurons. These neurons are two apical cells that appear early during development at the trochophore stage and contain serotonin in the case *of Helisoma,* and dopamine and serotonin in *Lymnaea*. These early cells are bipolar neurons bearing sensory cilia at their apical dendrite and emitting basal axons with numerous varicosities. The morphology and transmitter content of these cells indicate their homology with the apical sensory organ of other invertebrates (Voronezhskaya et al., 2004; Voronezhskaya and Croll, 2015). Upon sensing the water-born chemical signal from conspecific adults, apical cells activate their transmitter content (serotonin in case of *Helisoma*, and serotonin and dopamine in case of *Lymnaea*) production and release. Using *Helisoma trivolvis* embryo we demonstrated how one and the same transmitter—serotonin—can cause the manifestation of opposing adaptive programmes (retardation or acceleration of developmental tempo) stage-dependently, and prove involvement of various serotonin receptors in this regulation (Voronezhskaya et al., 2008; Glebov et al., 2014).

According to the classical view, the diverse physiological functions of serotonin are mediated via membrane serotonin receptors, coupled G-proteins and respective intracellular pathways. Serotonin receptors constitute the largest class of G protein-coupled receptors (GPCRs) which include 16 big families depending on the activation of $Na^+/K^+/Ca^{2+}$ ion channel, respective G-protein (G_s, $G_{i/o}$, $G_{q/11}$), activation or inhibition of adenylate cyclase (AC), and phospholipase C

(PLC) (Tierney, 2001). We found at least four types of 5-HT receptors in *Helisoma* embryos. Activation of 5-HT_1- and 5-HT_5-like receptors and respective coupled Gi-protein induce acceleration of development, while activation of 5-HT_4- and 5-HT_7-like and respective Gs-protein results in retardation. While all types of serotonin receptors are expressed during both the early and late stages of embryonic development, their proportions vary stage-dependently. The 5-HT receptors and respective G-proteins whose activation induces developmental retardation (5-HT_4-like, 5-HT_7-like, Gs) prevails at the early stages. Vice versa, that 5-HT receptors and G-proteins whose activation induces developmental acceleration (5-HT_1-like, 5-HT_5-like, Gi) preferentially expressed at late stages. Thus the serotonin released from the apical neurons in response to the water-born chemical cue (which is not serotonin but the chemical substance emitted by the adult snail in unfavorable conditions) retards developmental tempo at early stages and accelerated it at later stages, depending upon a certain combination of 5-HT receptors expressed at a particular developmental stage in the embryonic tissues (Glebov et al., 2014).

Our results demonstrated that adult and juvenile snails sufficiently inform their encapsulated larvae about the unfavorable environmental conditions they will be faced with after hatching. The embryo or metamorphic larvae sense the emitted chemical signal by apical neurons. Serotonin released from apical neurons modulates the embryo developmental tempo and juvenile behavior via activation of a certain poll of serotonin receptors located in the embryonic tissues at the current developmental stage. The opposite reactions of the molluscan embryo to the same water-born environmental cues at early and late developmental stages provide an adaptive response at the level of individual organism and better survival of the whole generation.

CONCLUSION AND FUTURE PERSPECTIVES

Gastropod molluscs are very successful species with incredible flexibility of life strategies that inhabit a wide variety of marine, freshwater, and terrestrial habitats distributed between the two poles, and ranging from alpine meadows down to the depths of the oceans. In this mini-review we just slightly disclosed one of the possible mechanisms underlying the prosperity of two freshwater gastropod species. We revealed that serotonin appears to be a key molecule playing both hormonal (during cleavage stages) and neurohormonal (during larval stages) roles during *Lymnaea* and *Helisoma* embryonic development. Classical receptor-mediated regulation and non-canonical protein modification (serotonylation) underlie serotonin effects. Via these pathways serotonin links the environmental signals received by adults and respective changes in progeny developmental tempo, hatching time, and behavioral characteristics of juveniles. The benefits of such maternal serotonin-driven progeny phenotypic adjustments includes more efficient dispersion, feeding, survival skills, and fertility rates. That features are tuned in to the next-generation according to the different environmental factors the parents experienced.

The possible directions of this field of investigation may be devoted to the following topics: (1) the distribution of serotonin-mediated shaping of life strategy in other species; (2) involvement of other monoamines in maternal regulation of progeny characteristics; (3) the detailed mechanism of serotonin-induced changes in development and behavior from the first step in oocyte till the differentiation of neuronal networks underlying behavior (including transcription regulation). Each of the mentioned tasks can include the field study of the behavior and developmental characteristics in different natural populations, as well as laboratory investigations of the underlying molecular mechanisms of the discovered phenomena in model animals.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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