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Multifaceted Roles of Serotonin in Plants

Aryadeep Roychoudhury[1]
[1]Department of Biotechnology, St. Xavier's College (Autonomous), 30,
Mother Teresa Sarani, Kolkata-700016, West Bengal, India.

Abstract

Serotonin (5-hydroxytryptamine) is one of the well studied indoleamine neurotransmitters in vertebrates. This molecule has also been reported from a wide range of plant species in almost all plant families, proving that serotonin is a ubiquitous molecule. Serotonin accumulation has been detected in different parts of the plants like roots, stems, leaves, fruits and seeds; however, the quantity varies in these different tissues. Serotonin in plants is synthesized via two-step process, where tryptophan is first catalyzed into tryptamine by tryptophan decarboxylase, followed by the catalysis of tryptamine by tryptamine 5-hydroxylase to serotonin. Serotonin is an ancient indoleamine that was presumably part of the life cycle of the first prokaryotic life forms on Earth, millions of years ago, where it functioned as a powerful antioxidant to combat the increasingly oxygen-rich atmosphere. Such antioxidative potential of serotonin has been largely exploited in the development of stress tolerance and resistance in plants. Serotonin plays diverse roles in plants including growth and development, energy acquisition, seasonal cycles, modulation of reproductive development, control of root and shoot organogenesis, delay of senescence, and responses to abiotic and biotic stresses. The present article provides an overview of the occurrence and metabolism of serotonin and its multifaceted roles in regulating plant morphogenesis and multiple physiological functions in plants.

Keywords: Serotonin; Antioxidant; Growth and Reproduction; Photomorphogenesis; Physiological Functions; Abiotic and Biotic Stress.

Introduction

Serotonin is a physiologically active and ubiquitous indoleamine, serving as a mitogenic factor and an essential neurotransmitter in the central nervous system, affecting sleep, mood and anxiety, as well as acting like a hallucinogenic drug in mammals. It also plays important roles in many disease processes, particularly in neurological disorders including depression, Alzheimer and Parkinson disease. It was initially identified as 5-hydroxytryptamine in mammalian systems in the 1930′s that acts as a potent vasoconstrictor substance in the blood serum. It was then named as enteramine due to its presence in enterochromaffin cells of the gut where it induced smooth muscle contraction (Veenstra-VanderWeele et al. 2000). Although serotonin is commonly regarded as an animal metabolite, it was discovered as early as 1950 in the legume, *Mucuna pruriens* (a medicinal herb), commonly known as cowhage. In course of time, serotonin was reported from ~42 plant species from 20 families, with the highest levels (25–400 mg/kg) found in walnuts (*Juglans regia*) and hickory (*Carya* sps.). Moderate levels of serotonin (3–30 mg/kg) were reported in banana, pineapple, plantain, plums, tomato and kiwifruit (Ramakrishna et al. 2011). The widely used technique for serotonin quantification is high performance liquid chromatography (HPLC) on reverse phased or cation exchange analytical columns. Liquid chromatography-tandem mass spectrometry has been recommended for accurate analysis of serotonin which can be fluorimetrically assayed at excitation and emission wavelengths of 394 nm and 505 nm, respectively after incubation (75°C, 30 min) with ninhydrin (Kele et al. 1996). Serotonin is quite an ancient molecule playing diverse roles across all kingdoms of life. Despite the increasingly apparent role of serotonin in plants, its functions in plants remain elusive and the mechanism of action also remains ambiguous. Initial researches were mostly focused on exploiting the medicinal property of serotonin and enhancing its production through plant tissue culture to generate pharmaceutically-active compounds (Erland et al. 2016). Serotonin has now been demonstrated to exert an array of physiological functions in plants that are related to growth regulation, flowering, xylem sap exudation, ion permeability and plant morphogenesis. It plays vital roles as plant growth regulator in every stages of plant life: germination, vegetative phase, reproduction and senescence. It is labeled as a defensive or anti-stress chemical, having an antioxidative role. The present review aims to provide an overview of the occurrence and synthesis of serotonin in plants and its significant beneficial roles in plants.

Occurrence and localization of serotonin in plants

Serotonin has been identified in over 90 plant species and 37 plant families. Its level is found to vary with families of plants, species, cultivars, developmental stages and types of tissues. Plant species like *Juglans cinerea*, *Carya ovata*, *Solanum lycopersicum*, *Vaccinium* spp., *Zea mays*, *Zingiber officinale*, *Griffonia simplicifolia*, *Urtica dioica*, etc. have been shown to have moderate to high levels of serotonin. However, the extraction methods and analytical tools used for serotonin quantification should be properly revisited to have a more realistic picture regarding the comparison of serotonin levels among plant species. Fruits, vegetables and seeds are the major tissues with abundant serotonin. Serotonin content has been found to vary between cultivars of the same species. Comparison of the four cultivars, viz., ‘Serr’, ‘Hartley’, ‘Chandler’ and ‘Howard’ of *J. regia* showed that the cultivar ‘Serr’ accumulated higher levels of serotonin (Tapia et al. 2013). Significant variability was noted in the edible tissues from eight cherry cultivars (*Prunus avium* L.). Higher levels of serotonin are found in the aerial tissues of plants, compared to those growing underground for potato. Differences in serotonin levels between tissue types, i.e. pulp and peel, for edible parts of banana, plantain, pineapple, kiwi fruit, and tomato are reported. Serotonin levels also fluctuate within specific tissue types during different stages of ripening or maturity. Serotonin levels were found to decrease in ripened pineapple. In *Griffonia simplicifolia* leaves, high quantities of serotonin accumulated in the reproductive period, whereas in the vegetative period, the accumulation was much lower. Serotonin levels in walnut increased as the seed matured, most notably when the endosperm degenerated into the seed coat (Murch et al. 2009). Significantly greater serotonin levels were found in the endosperm, compared to the embryo. Serotonin accumulated with age in the roots of rice and was abundantly synthesized in senescent rice tissues (Erland et al. 2016). Serotonin is regarded to be abundant in the vascular parenchyma cells, including companion and xylem cells of rice, suggesting its involvement in maintaining the cellular integrity for facilitating efficient nutrient recycling from senescing leaves to sink tissues. Serotonin has also been detected in the vascular bundles of the fruit wall of banana and accumulated in the protein bodies of cotyledons of developing embryos of *Juglans regia*. Serotonin is also likely to be high in rapidly dividing and differentiating tissues, based on its role in morphogenesis, reproduction and germination (Ramakrishna et al. 2011).

Serotonin metabolism in plants

Serotonin in plants is synthesized via two-step process where tryptophan is first catalyzed into tryptamine by tryptophan decarboxylase, followed by the catalysis of tryptamine by tryptamine 5-hydroxylase to serotonin. The level of tryptamine is highly connected with adequate serotonin synthesis as found in rice seedlings. However, there are some plants like *Hypericum perforatum* where serotonin biosynthesis resembles that in animals. Tryptophan is first converted by tryptophan hydroxylase to 5-hydroxytryptophan, which is eventually decorboxylated by aromatic L-amino acid decarboxylase to yield serotonin (Schroder et al. 1999; Murch et al. 2000). Serotonin undergoes catabolic breakdown by hydroxytryptamine acetyl transferase to N-acetyl serotonin, which is then methylated to 5-methoxy N-acetyl tryptamine (melatonin), having diverse physiological roles, including growth, reproduction, photoperiodic response, antioxidant and defense mechanism. There also exist alternative routes such as methylation of serotonin to form 5-methoxytryptamine, which involves the action of the phenylpropanoid biosynthetic enzyme, caffeic acid-O-methyltransferase. Several alkaloids such as bufotenine (as in *Piptadenia peregrina*), psilocin and psilocybin (as in *Psilocybe aztecorum*) are formed from serotonin (Ramakrishna et al. 2011). Serotonin may also act as a precursor for other plant metabolites, including the stress-related hydroxycinnamic acid amides that result from conjugation of serotonin to phenolic acids (Macoy et al. 2015). Serotonin biosynthesis occurs in the chloroplasts and mitochondria of diverse tissue types, as supported by the generation of high level of reactive oxygen species (ROS) in these tissues. By virtue of its antioxidative role, serotonin continues to play the same role in these modern organelles as it did in their ancient ancestors through detoxification of ROS, allowing the organism to thrive better in the oxygenated world.

Physiological roles of serotonin in plants

Serotonin in regulating growth and morphogenesis

Serotonin is regarded as a non-traditional plant growth regulator with cytokinin-like activity, capable of enhancing lateral root development in a dose-dependent manner by stimulating the development of preexisting lateral root buds. It is involved in diverse growth processes, notably root and shoot organogenesis and patterning, cell division and differentiation, biomass production and modulation of germination, somatic embryogenesis and senescence. The morphogenetic effects of serotonin were investigated in the medicinal plant *Hypericum perforatum* (L.). High levels of serotonin were associated with increased shoot production, and inhibition of serotonin receptors led to an inhibition in shoot production. Serotonin has also been found to be effective in promoting shoot production in *Mimosa pudica* L. where treatment with serotonin significantly increased shoot number, shoot height, root number, and total fresh weight of in vitro cultured explants (Erland et al. 2015). These effects were reversed by treatment with the serotonin receptor inhibitors, viz., p-chlorophenoxyacetic acid and fluoxetine (Prozac). Calcium signaling was found to play a major role in serotonin-mediated somatic embryogenesis in coffee. Application of calcium inhibitors retarded the growth induced by serotonin, while calcium supplementation restored the growth. Treatment of *Echinacea purpurea* (L.) leaf explants with thidiazuron led to an increase in the endogenous serotonin content, associated with an increase in callus production in the tissues. The importance of serotonin during embryo growth and development is demonstrated by its capacity to promote germination, increase coleoptile weight, overall biomass and hypocotyl elongation during germination. Serotonin was shown to regulate both hypocotyl and primary root length in sunflower seedlings after 2 and 4 days of growth, as well as promoting root production in walnut cuttings. In case of Arabidopsis, at low concentrations (10–160 µM), serotonin enhanced the lateral root formation, while at concentrations greater than160 µM, lateral root formation, primary root growth and root hair development were inhibited, although adventitious root formation was enhanced. Though rooting is promoted by serotonin, its function as an auxin-inhibitor is also reported in some plant species. The balance between melatonin and serotonin dictates the morphogenetic responses, since decreased melatonin reduced the root organogenesis, while increased serotonin level enhanced the shoot organogenesis in presence of exogenous auxin (Murch et al. 2001). Silencing of SNAT in rice seedlings resulted in inhibition of the conversion of serotonin to melatonin, thereby enhancing the serotonin content in these plants. These seedlings showed increased coleoptile growth, but slower seedling growth. This is in contrast with a study by Kang et al. (2007) who found that overexpression of tryptophan decarboxylase (TDC), resulting in the increased serotonin levels had no significant effect on phenotype, though serotonin levels were raised by 11–25 fold depending on the tissue type. Involvement of serotonin in root growth and development in rice, and germination of radish seeds or *Hippeastrum hybridum* pollen grains is also reported. The benefits with respect to radicle growth have also been observed in barley seeds inoculated for 72 h with 10^{-8} M serotonin.

Serotonin in regulating photomorphogenesis and circadian rhythm

Serotonin stimulates phosophoinositide (PI) turnover, which is found to mimic the red light effect in enhancing the *nitrate reductase* transcript levels and inhibiting *phyI* transcript accumulation in maize. Low light intensity was found to recover serotonin level better than light-supplemented conditions. The relative ratio of serotonin to melatonin plays role in light-mediated responses in plants. Serotonin concentration was found to exhibit a striking diurnal rhythm, remaining at a maximum level during the daylight hours and falling by more than 80%, soon after the onset of darkness (Ramakrishna et al. 2011). Serotonin has been implicated as an activator of phytochrome, for example. in corn (*Zea mays* L.), serotonin is capable of serving as a substitute for far red light during direct induction of phytochrome signaling, likely through the activation of nitrate reductase and enhancement of calcium uptake, which in turn leads to a modification of downstream phosphatidylinositol turnover (Chandok and Sopory 1994). Serotonin has been found to be a potent mediator of the action of phytochrome, the key factor driving the circadian rhythm in plants.

Serotonin in delaying senescence

Because of its antioxidative potential, serotonin protects xylem parenchyma and companion cells from senescence-induced oxidative damages, enabling nutrient recycling from senescent leaves into sink tissues (Kang et al. 2007). Accumulation of serotonin in senescent rice leaves facilitated the lowering of ROS level and membrane lipid peroxidation. The synthesis is closely coupled with transcriptional and enzymatic induction of the tryptophan biosynthetic genes as well as TDC. Transgenic rice plants that overexpressed TDC accumulated higher levels of serotonin than the wild type and showed delayed senescence of rice leaves. However, transgenic rice plants, in which the expression of TDC was suppressed through RNA interference mechanism, produced lesser serotonin and senesced faster than the wild type, suggesting that serotonin is involved in attenuating leaf senescence (Kang et al. 2009). Serotonin relieves the accumulation of the toxic metabolite, tryptamine and maintains the reducing potential of the cells through its powerful antioxidant activity in the senesced leaves.

Serotonin in detoxifying excess ammonia

The exact role of serotonin during seed development is not well understood yet; however, tracer studies utilizing ^{15}N in walnut suggested that accumulation of serotonin helps to protect the embryo through detoxification of the surrounding environment from ammonium (NH_4^+). In case of walnut, proteolysis and deamination of amino acids occur during fruit abscission, thereby accumulating NH_4^+ ions. This problem is overcome by glutamine synthase which assimilates ammonia, together with glutamic acid, via the synthesis of glutamine, which directly serves as a substrate for tryptophan synthesis. Since serotonin structure consists of an amine group, it is likely that serotonin can help detoxify ammonium-rich environment by acting as a nitrogen store, while the presence of the electronegative indole ring and oxygen groups may accept excess protons from the surrounding environment, thereby neutralizing an acidic environment (Grosse and Artigas 1983; Zhou et al. 2015).

Serotonin in reproductive development

Serotonin improved the tolerance of bud to chilling during dormant stages in apple. It contributed to bud dormancy by helping plants to tolerate low temperature during winter months. Serotonin level was the highest during the flowering stage and lowest during pre-flowering. In case of walnut flowers, serotonin levels increased significantly during early stages of flowering (Cooke et al. 2012; Endo et al. 2016). Serotonin may help to regulate flowering time through interactions with the phytochrome photoreceptor. With respect to the role of serotonin during pollen allelopathy, research suggests that serotonin may regulate microspore development, potentially through the modulation of cAMP signaling (Roshchina and Melnikova 1998). Serotonin may exhibit their stimulatory effects upon microspore development, via interactions with G-coupled receptors at the cell surface which in turn cause a conformational change to ion channel subunits. These events then lead to the modulation of cytoskeletal elements via actin and tubulin binding, as well as regulate downstream effects within specific organelles through either mechanical or electrical waves. Serotonin also acts as a protective compound in the developing embryo.

Serotonin in regulating photosynthesis

Since serotonin is believed to be definitively localized in the chloroplast, there is a strong evidence for its potential roles in the maintenance of photosynthetic tissues. Studies in isolated chloroplasts of pea (*Pisum sativum* L.) showed that serotonin was capable of enhancing efflux of magnesium and calcium. Serotonin also appears to be capable of mediating light sensing in plants via modulation of phytochrome activity and downstream signaling networks (Roshchina 1990; Chen and Chory 2011). Serotonin levels increased significantly under longer wavelength treatments of green, yellow, and red after 12 h of exposure, whereas after 24 h and 7 d, an increase was only observed under full dark (both 24 h and 7 d), green (24 h), and red (7 d) light exposure.

Serotonin in overcoming environmental stress

Serotonin plays a crucial role as an antioxidant by scavenging ROS and shows strong in vitro antioxidant activity through interactions with the phenylpropanoid pathway via modulation of polyphenol oxidase (PPO) and the formation of phenolic conjugates with hydroxycinnamic acids like 4-coumaroylserotonin and feruloylserotonin. Exposure of germinating beans of *Vicia faba* L. to varying levels of X-ray radiation (200 R-400 R) showed that secondary root growth was inhibited in a dose-dependent manner, with no secondary roots appearing at 400 R. Interestingly, application of serotonin in conjunction with 400 R X-ray radiation led to secondary root growth after a lag phase of 6–8 days. Prata bananas (*Musa acuminata* × *Musa balbisiana*) exposed to cobalt-60 radiation (1.0, 1.5 and 2.0 kGy) using a 220 gamma cell showed that serotonin degraded quicker within irradiated samples compared to the control (Byeon et al. 2015). Application of serotonin in presence of NaCl in sunflower seedlings increased primary root growth by 20%. In addition, accumulation of serotonin was also observed in roots, following NaCl treatment, suggesting a potential role of serotonin in salt stress amelioration (Mukherjee et al. 2014). Serotonin modulates the transport of specific ions across biological membranes in plants. Exposure of 4-week old rice plants to 0.2 mM $CdCl_2$ showed significant down regulation of *SNAT* gene which helped to maintain high levels of serotonin (Lozeron et al. 1964). The exposure of *Datura* flower to cold stress significantly increased the concentration of serotonin.

Serotonin in overcoming mechanical wounding, herbivory and pathogen infection

Application of serotonin to cut fruit slices can act as an anti-browning compound in apple (*Malus domestica* Borkh) cultivars 'Gala' and 'Fuji' through reduction of polyphenol oxidase activity. Serotonin acts as a substrate for the phenylpropanoid biosynthetic enzyme, caffeic acid O-methyltransferase. As already mentioned, serotonin interacts with the phenylpropanoid pathway by serving as an amine substrate for the formation hydroxycinnamic acid amides: 4-coumarolylserotonin and feruloylserotonin (Bajwa et al. 2015). 10-day old rice seedlings subjected to a methanol/water solution (0–2.5% methanol) demonstrated a dose-dependent increase of 4-coumarolylserotonin and feruloylserotonin in leaves, as well as elevated the activity for serotonin N-hydroxycinnamoyl transferase, the enzyme responsible for catalyzing the synthesis of coumarolylserotonin and feruloylserotonin. Hence, methanol acts as a signaling molecule during wounding, herbivory and pathogen attack (Dorokhov et al. 2012). High levels of serotonin, along with the neurotransmitters histamine and acetylcholine, were responsible for stinging effect in stinging nettle (*Urtica dioica* L.) which has evolved as a mechanism of defense. Plants subjected to herbivory had a significantly greater number of trichomes, and wounding of leaves increased trichome density. In rice plants, serotonin is involved in mediating a hypersensitive response. In rice sekiguchi lesion (sl) mutants, which lack a cytochrome P450 oxygenase catalyzing the conversion of tryptamine to serotonin, exogenous application of serotonin increased resistance of plants to rice blast disease [*Magnaporthe grisea* (T.T. Hebert) M.E. Barr] (Fujiwara et al. 2010). Similarly, sl rice mutants challenged with *Bipolaris oryzae* were more susceptible to infection, exhibited decreased lesion browning and did not produce serotonin. Increased serotonin content and expression of serotonin biosynthetic genes was also found in the rice mutant spl5 (spotted leaf 5), which exhibits hypersensitive-like lesions on leaves and demonstrates greater resistance against the pathogens. Serotonin may act as a phytoalexin in wheat against the pathogen *Stagonospora nodorum* through interference with trehalose synthesis, and promotion of the production of the mycotoxin, alternariol. Though serotonin appears to play important roles in the survival of pathogen in diverse species, such responses are specific to both the species of the pathogen and host plant (Fall and Solomon 2013).

Conclusion and future perspectives

Though serotonin research in plants is still underrepresented, there is growing interest among the plant scientists to study the regulatory effect of this molecule in various plant systems. This is because serotonin plays diverse roles like promotion of proper growth and development and mitigating the challenges faced from a wide array of abiotic and biotic stresses. Since serotonin also regulates morphogenesis, research in this area will have implications in better understanding of plant regeneration through tissue culture. The antioxidant potential of serotonin is also being investigated in depth. Serotonin may represent a critical antioxidant in many applied processes, notably in the field of conservation and cryobiology which are increasingly taking advantage of its unique antioxidant species, to work towards preservation of species at risk (Ramakrishna et al. 2011). However, there are still some unresolved issues which need to be properly addressed in future. It is not specifically known, in which part of the plant, serotonin synthesis mostly occurs or whether seasonal variations in day length influence serotonin levels. Moreover, variations in the serotonin levels of plants grown at different latitudes should be studied. The possible implication of serotonin catabolites in plant responses should also be clearly elucidated. The studies pertaining to the pathways of serotonin uptake and transport, its possible conjugated compounds, its catabolic pathway(s) and also its interaction with auxin metabolism would be interesting. The cross-talk between serotonin and phytohormones and possible presence of specific serotonin receptors will open up new perspectives in the possible role of serotonin in plant morphogenesis, flowering, dormancy and stress tolerance. The protective role of serotonin during different stresses, data on apical dominance and role in tropisms (photo-, geo- and others) needs to be investigated. Given that the plants have both serotonin-dependent, as well as to a much more limited extent, serotonin-independent pathway for the biosynthesis of melatonin, serotonin may have been conserved in plants for reasons beyond its role as biosynthetic precursor of melatonin. This issue also needs to be further analyzed. Overall, our understanding of the function of serotonin in plants is still in its infancy and we cannot ignore that its occurrence throughout the plant kingdom may be due to being an energetically favorable intermediate for the biosynthesis of indoleamines as well as regulator for other secondary metabolite pathways. Only future research will be able to throw light on the fact whether the signaling mechanisms involving antioxidant activity and hormonal interactions work independently or in a synergistic fashion.

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