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Research review paper

Serotonin: An ancient molecule and an important regulator of plant processes

Lauren A E Erland [1], Christina E Turi [1], Praveen K. Saxena *

Gosling Research Institute for Plant Preservation, Department of Plant Agriculture, University of Guelph, 50 Stone Road E, Guelph, Ontario N1G 2W1, Canada

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ABSTRACT

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. First identified as a neurotransmitter signaling molecule in mammals, it is ubiquitous across all forms of life. Serotonin was discovered in plants many years after its discovery in mammals; however, it has now been confirmed in almost all plant families, where it plays important roles in plant growth and development, including functions in energy acquisition, seasonal cycles, modulation of reproductive development, control of root and shoot organogenesis, maintenance of plant tissues, delay of senescence, and responses to biotic and abiotic stresses. Despite its widespread presence and activity, there are many questions which remain unanswered about the role of serotonin in plants including the mode of signaling and receptor identity as well as the mechanisms of action of this important molecule. This review provides an overview of the role of serotonin in plant life and their ability to adapt.

Contents

Abbreviations: 5-HT, serotonin; 5-HTP, 5-hyroxytryptophan; AADC, amino acid decarboxylase; ASMT, acetylserotonin methyltransferase; CS, coumaryl-serotonin; EGTA, ethylene glycol(beta-aminoethyl ether)-N,N,N′,N′-tetraacetic acid; FS, ferulyl-serotonin; GABA, gamma-aminobutyric acid; HCAA, hydroxyl cinnamic acid amide; p-CPA, p-chloropheylalanine; PPO, polyphenol oxidase; Pfr, phytochrome far red; Pr, phytochrome red; ROS, reactive oxygen species; SHT, serotonin *N*-hydroxycinnamoyl; SNAT, serotonin *N*-acetyltransferase; T-5-H, tryptamine-5-hydroxylase; TDC, tryptophan decarboxylase; TDZ, thiadiazuron; TPH, tryptophan hydroxylase.

* Corresponding author.
E-mail address: psaxena@uoguelph.ca (P.K. Saxena).

[1] Authors contributed equally to this work.

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1. Introduction

Serotonin (5-hydroxytrytamine) is an ancient indoleamine produced in close association with melatonin (*N*-acetyl-5-methoxytryptamine) by the first unicellular life forms on Earth as a means to cope with the oxygenated atmosphere consequent to the evolution of photosynthetic organisms (Bajwa et al., 2015; Manchester et al., 2015; Tan et al., 2009). This is due to the strong antioxidant potential of these compounds, though the antioxidant potential of serotonin is only now being investigated in depth (Bajwa et al., 2015). Serotonin was first identified in mammalian systems in the 1930′s and named enteramine due to its presence in enterochromaffin cells of the gut where it induced smooth muscle contraction (Vialli and Erspamer, 1937). It was later named serotonin, which had also been identified and investigated by a separate lab since the 1940′s, after the compounds were found to be the same (Erspamer and Asero, 1952; Whitaker-Azmitia, 1999). Since these initial investigations, serotonin has been established as an essential neurotransmitter in the central nervous system playing important roles in many disease processes, particularly in neurological disorders including depression, Alzheimer and Parkinson disease (Izzati-Zade, 2008; Levy, 2006; Olivier, 2015; Yasin, 2009).

Although significant attention has been directed towards understanding the role of serotonin in humans for regulating mood and behavior, far less is known about the function of serotonin in plants. To complicate matters further, serotonin's role as a precursor to melatonin has created much confusion within the literature, as a majority of scientific works place greater emphasis upon investigating the role of melatonin. Though its function in plants has remained more elusive than in animals, serotonin was identified in plants shortly after its discovery in animals, having been found in the medicinal herb *Mucuna pruriens* (L.) DC (cowhage) in the 1950′s (Bowden et al., 1954). Initially efforts were made to enhance production of serotonin in several plant species through tissue culture in hopes of providing source materials for pharmaceutically relevant compounds (Berlin et al., 1993; Csaba and Pal, 1982; Sasse et al., 1982). Interest in the role of serotonin in plants, however, slowly followed and was greatly encouraged and supported by the discovery of its downstream biosynthetic product melatonin in plants in the mid 1990′s (Dubbels et al., 1995; Hattori et al., 1995). Though the body of knowledge on serotonin function is increasing, it is still often considered secondary to its product melatonin, making an investigation of the literature difficult as its presence is often only mentioned as a minor comment in studies which focus on its trendier relative. In order to highlight serotonin's importance as a modulator of fundamental processes governing plant growth and development, this review summarizes current understanding of the role of serotonin in plants.

2. Biosynthesis and localization

Serotonin is produced by two primary pathways, though both are derived from the aromatic amino acid L-tryptophan (Fig. 1). In the plant pathway, tryptophan is decarboxylated to form tryptamine by tryptophan decarboxylase (TDC) and then hydroxylated by tryptamine-5-hydroxylase (T-5-H) to form serotonin (Berlin et al., 1993; Kang et al., 2008; Murch et al., 2000). In animals the carboxylation and hydroxylation steps are reversed with 5-hydroxytryptophan (5-HTP) being produced by tryptophan hydroxylase (TPH), and 5-HTP then being decarboxylated to form serotonin by aromatic acid decarboxylase (AADC) (Tanis et al., 2008).

A major factor determining serotonin biosynthesis is availability of its precursor tryptophan, whose biosynthesis from chorismate is under relatively tight feedback control by anthranilate synthase (Kang et al., 2008). Tryptophan, in addition to serving as a precursor for serotonin, is a precursor for many essential plant metabolites including proteins and auxin as well as non-essential metabolites such as the indole alkaloids (Avery and Berger, 1943; Dubouzet et al., 2013; Sherwin and Purves, 1969); this makes competition for tryptophan an important factor. Within the plant serotonin biosynthetic pathway the rate limiting step is TDC, which controls flow of tryptophan into the pathway and is under transcriptional control, showing strong differences in expression patterns with developmental stage and age while T-5-H has been found to be constitutively expressed (Kang et al., 2008). Additionally, the activity of TDC is inhibited by serotonin, suggesting a negative feedback loop in this pathway (Kang et al., 2007). Several studies with transgenic plants have also shown that carbon flux through the pathway can further be enhanced by transformation with a constitutively expressed TDC (Berlin et al., 1993; Kang et al., 2007; Yao et al., 1995). Another factor affecting the serotonin pool in tissues is activity of the enzymes that convert serotonin to other metabolites, most notably melatonin. The conversion of serotonin to *N*-acetylserotonin, which is controlled by serotonin *N*-acetyltransferase (SNAT), is the main regulatory point in the melatonin biosynthetic pathway via transcriptional control, and which has also been found to be capable of utilizing tryptamine as a substrate further affecting serotonin levels in tissues (Byeon et al., 2014; Kang et al., 2013; Lee et al., 2014). Regulation of serotonin biosynthesis, though an active field of research in mammals, requires greater attention in plants to better elucidate further controls, which may include feedback inhibition or calcium signaling as observed in mammalian systems (Sawada and Nagatsu, 1986; Tanis et al., 2008). It is worth noting, that the diversity of information available for mechanisms controlling serotonin biosynthesis and actions in mammals may be useful information for plants, particularly in the development of diverse inhibitors of these processes which have been utilized to understand these processes in plants (Murch and Saxena, 2004; Murch et al., 2001; Ramakrishna et al., 2009, 2011).

In plants the underlying mechanisms governing serotonin signaling remains largely unknown, while in vertebrates and invertebrate serotonin signaling is believed to be mediated through serotonin receptors. Seven classes of serotonin receptors have been reported: 5-HT$_1$, 5-HT$_2$, 5-HT$_3$, 5-HT$_4$, 5-HT$_5$, 5-HT$_6$, and 5-HT$_7$ in mammals. With the exception of 5-HT$_3$ a ligand-gated ion channel, all the above are G-coupled receptors which can be further divided into multiple sub-classes. Over the